Critical Issues in Head and Neck Oncology

Key Concepts from the Fifth THNO Meeting

Jan B. Vermorken
Volker Budach
C. René Leemans
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Brian O'Sullivan *Editors*

Springer

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Preface

Trends in Head and Neck Oncology (THNO) is an educational program that started in 2007, initially under a different name, but recognized as such since 2011. Its concept is to promote multidisciplinarity and updated knowledge and, consequently, its leadership has a multidisciplinary signature. The realization of this educational program has been made possible by the support of Pharma and the practical logistical support of CongressCare. The organizers are grateful to our colleagues of Merck KGaA, who were the single sponsor at the commencement of the program in 2007. THNO-5 is the first THNO meeting with strong support and input of local colleagues into the case presentations in order to underscore the goals of this meeting. It is also the first time that the Proceedings have made available to the wider medical community.

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Contents

Part VII Quality of Life and End of Life Issues

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Part I
The Make Sense Campaign

Chapter 1
The "Make Sense Campaign": An Initiative of the European Head and Neck Society

C. René Leemans and Jan B. Vermorken

Recently, several actions have been planned by a Think Tank (Make Sense) to make head and neck cancer (HNC) more recognisable to health care providers and the general public. This Think Tank came together for the first time in January 2012 in London at the invitation of the European Head and Neck Cancer Society (EHNS) in collaboration with and support of Merck, previously Merck Serono (Darmstadt, Germany). Not only oncology professionals of different backgrounds were involved in this, but also representatives of European Cancer Leagues, the European Cancer Coalition (ECPC), patient groups, the European School of Oncology (ESO), the Roy Castle Lung Cancer Foundation, coworkers of Merck and a journalist. The background and evolution of this initiative is subject of this presentation.

The European Head and Neck Society (EHNS)

The EHNS, established in 2006, is a multidisciplinary body that brings medical experts together from many disciplines, including head and neck cancer specialists, oral and plastic surgeons, radiation therapists, medical oncologists, and imaging specialists and pathologists. The society also brings together other stakeholders,

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C. René Leemans, Jan B. Vermorken and the Make Sense Secretariat, on behalf of the Make Sense steering committee

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including speech therapists, cancer nurses, psychologists, physiotherapists, dieticians, social workers, and basic scientists and patient organisations involved in any aspect of HNC.

In order to help drive awareness and understanding of HNC among the general public, patients, caregivers and healthcare professionals (HCPs), the EHNS engages in a number of activities. This work began with a pan-European survey series called 'About Face', which revealed a worrying lack of awareness about HNC across Europe and a need for further education. In response to the needs uncovered in this survey, the 'Make Sense Campaign' was, in turn, created to help address some of these key challenges and needs.

'About Face' Research Series

The 'About Face' research series consists of two pan-European surveys that were conducted in 2008 and 2009 and that were planned by the EHNS; also these surveys were made possible by support from Merck, previously Merck Serono, of Darmstadt, Germany. The surveys aimed to gauge current awareness and understanding of HNC and its associated risk factors among the general public, as well as those from patients. A major objective was to determine whether there are significant differences between countries that need to be addressed.

'About Face I'

In Europe, the reported incidence and mortality rates of HNC at the time of this study were approximately 143,000 and 68,000 per year, respectively, although there were significant differences between individual countries. Despite this, the general public's awareness of HNC was thought to be very low across Europe. To find out more, the pan-European 'About Face I' survey aimed to gauge current awareness and understanding of HNC, with a focus on whether there are significant differences between countries that need to be addressed.

A total of 7520 Omnibus Internet interviews were conducted with members of the general public in seven European countries between 18 and 25 September 2008:

- France ($n = 1062$)
- Germany ($n = 1078$)
- Italy ($n = 1104$)
- The Netherlands ($n = 1101$)
- Spain ($n = 1090$)
- Sweden ($n = 1083$)
- UK ($n = 1002$)

The official census data were used to develop the survey sampling plan, with predetermined quotas for the number of responses required based on the gender, age and geographical distribution of the overall population of each country. Where

necessary, survey data were weighted to ensure that responders were representative of the overall population.

Results

The ‘About Face I’ survey revealed a worrying lack of awareness among the general public across Europe about HNC. There is some evidence that awareness may arise as a result of knowing someone with the disease, rather than from information distributed by healthcare professionals. Moreover, there were significant differences between individual countries, which should be investigated further. In some countries (e.g. the UK), a simple increase in awareness of the disease in general is required, whereas educational activity in countries such as Italy and Spain may need to focus more on increasing awareness of symptoms of HNC. Many potential symptoms and known risk factors of HNC are not recognised by the majority of the general public, which could lead to delays in symptom recognition and diagnosis, and – as a result – poor prognosis. The survey found a clear need for further education among the general public about HNC, its symptoms and its risk factors. Details of key findings are noted below and were presented at the ECCO/ESMO congress in Berlin, Germany in 2009 [1].

Awareness of HNC and the Locations That It Affects Was Low

More than three-quarters (77 %) of respondents were unaware of the term ‘head and neck cancer’ across Europe (Fig. 1.1). Lack of awareness fluctuated significantly across the countries surveyed (i.e. ranging from 89 % in the UK to 61 % in Italy); however, there was no apparent correlation with the incidence of disease and awareness.

Although the majority of respondents recognised that HNC affects the pharynx and larynx, other sites were poorly recognised and a number of sites were wrongly identified (Fig. 1.2). Swedish respondents were more likely to identify body parts affected by HNC correctly, whereas Italian respondents were the least likely.

Interestingly, although knowledge of the body parts affected by HNC was unsurprisingly higher among those respondents working in the medical profession, 57 % of this group of respondents still indicated incorrectly that the brain is categorised within HNC. This is important as the treatment regimens are different for HNC and brain tumours.

Symptom Recognition Was Highly Varied

Recognition of symptoms was highly varied based on the symptom and the country. The majority of symptoms were identified by only less than half of respondents, and many incorrectly thought that symptoms occurring in the head and neck region (e.g. hair loss, tooth ache) were indicative of the disease. Respondents from Italy and Spain had a lower level of knowledge of the symptoms of HNC than other countries, namely the UK and Germany (Fig. 1.2).

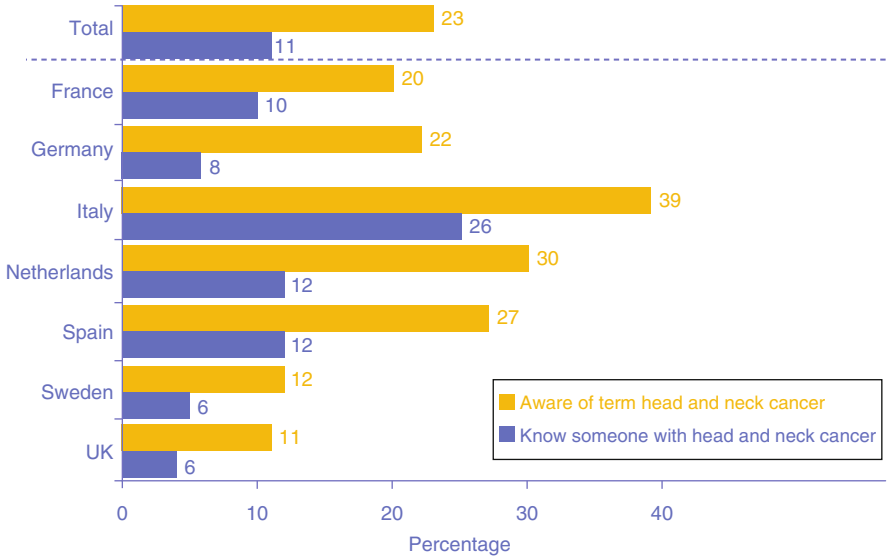


Fig. 1.1 'About Face I' survey responses to question, "Are you familiar with the term head and neck cancer?"

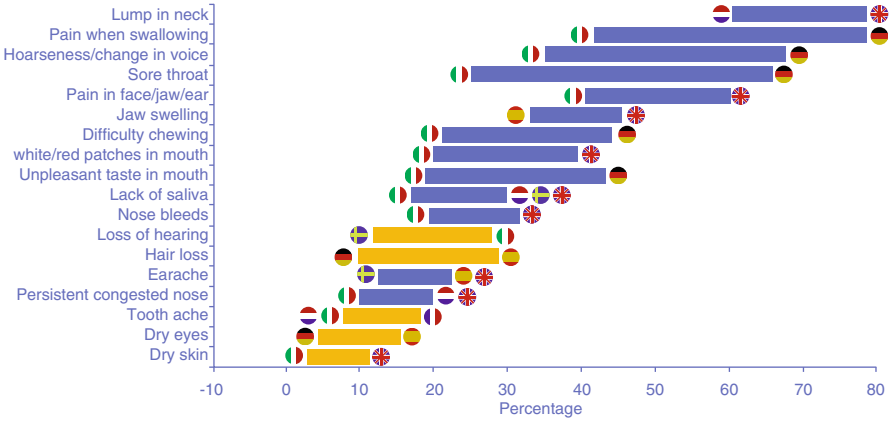


Fig. 1.2 'About Face I' survey responses to question, "Which of the following do you think are symptoms of HNC?"

Low Awareness of Risk Factors Beyond Smoking and Alcohol

There was general consensus across all countries that lifestyle factors may increase the risk of developing HNC. Although the majority of the respondents recognised the link between HNC and smoking or high alcohol intake – a common risk factor for many cancers – far fewer were aware of the role of excessive sun exposure, human papillomavirus (HPV) infection or gender in disease aetiology (Fig. 1.3).

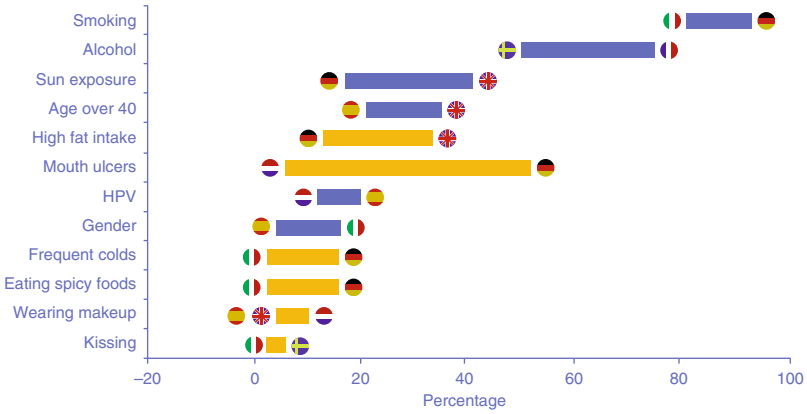


Fig. 1.3 ‘About Face I’ survey responses to question, “Which of the following do you think might be risk factors for developing HNC?”

Excluding consideration of lifestyle-related risk factors that can lead to HNC, awareness that the disease can occur spontaneously was generally less than 50 % across the countries surveyed. It was noted that there was less than 10 % awareness that sexual habits, including a higher number of orogenital partners may increase the risk of HNC, and only 20 % of respondents knew of the link between HPV and HNC.

‘About Face II’

The second study in the ‘About Face’ series focused on gaining an understanding of the profiles and emotional needs of patients living with HNC in order to inform future programmes for patients.

A total of 104 patients with HNC participated in face-to-face interviews across six countries: France, Sweden, Spain, Italy, Portugal and Belgium. The survey population was representative of the gender and age distribution of the disease, and the majority of respondents were males aged 50–70 years. Questions focused on the patient journey and recall of experiences at pre-diagnosis, diagnosis, treatment and post-treatment. Respondents were asked to consider the impact of the disease (rational vs emotional) and their quality of life [2].

Results

The ‘About Face II’ study revealed that patients want better communication and understanding of the disease and process at every stage of the journey. The survey uncovered unmet needs at key junctures of the patient journey from pre-diagnosis, at diagnosis, at treatment and post-treatment.

The ‘About Face II’ survey made it clear that more education and information are needed for not only the public, but also for healthcare professionals, in order to ensure appropriate detection and management of the disease.

It was revealed that patients who have been diagnosed with HNC also need additional education and information to help deal with the realities of their condition. HNC is a debilitating and cosmetically recognisable disease and can negatively affect self-esteem and image. As a result, patients reported that they experienced a wide range of emotions with the disease throughout their journey, especially after treatment; at times, they experienced a plethora of negative feelings. These negative feelings need to be addressed.

Pre-diagnosis Stage

During the pre-diagnosis stage, patients were positive about their health and felt that their health concerns were not at the forefront of their minds. There was a general feeling that life was ‘wonderful’ before diagnosis, as well as a lack of knowledge or awareness about the signs and symptoms relating to HNC. These types of feelings and lack of awareness can lead to delayed diagnosis.

Diagnosis Stage

The diagnosis stage brought with it a wider range of emotions – from denial, anger, fear and even mental ‘paralysis’. There was a strong fear associated with death as a result of the disease and a lack of understanding of treatment options. Generally speaking, the reaction of patients at diagnosis mirrored what their response to grief would be (Fig. 1.4).

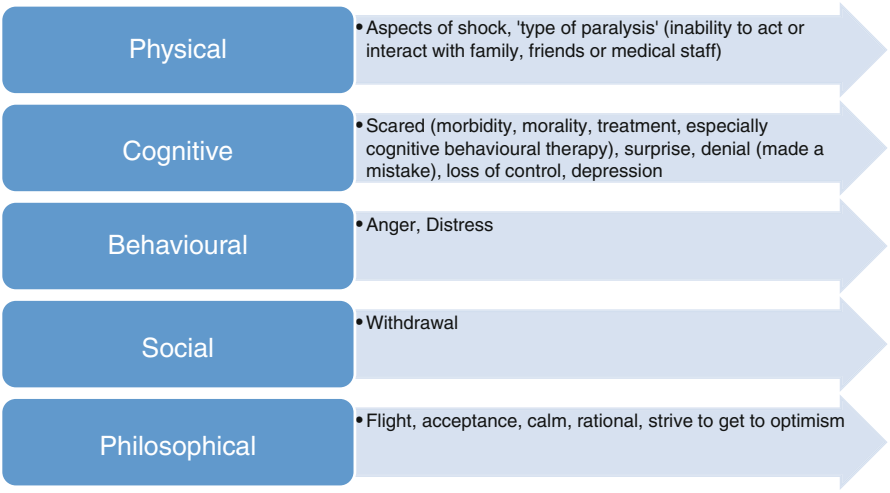


Fig. 1.4 Patients’ reactions to diagnosis mirror the response to grief

During diagnosis, patients expect a certain level of support, education and information from their physician, family and friends. In many cases, they felt that some psychological and emotional support was given; however, many of their expectations were not met around information, education and communication (Fig. 1.5).

Importantly, patients are looking for moral and emotional support to help develop coping mechanisms, including:

- Encouragement to cope with diagnosis, treatment and its after effects
- Emotional support, outside of family and friends. Patients are looking for someone else with the same disease
- Psychological support

Treatment and Post-treatment Stages

The treatment stage brings a mixture of hope and fear for patients: hope for a positive outcome, but fear about the possible personal and social consequences of treatment. Different treatment options also brought about different levels of fear, with many patients initially being more fearful of chemotherapy than radiotherapy due to the associated hair loss. Patients also expressed the need to tailor information specifically to their situation; this information includes all aspects that need to be considered, along with different treatment options.

Expectation	*Were the expectations met?*	*Future needs*
Practical information	No	• Patient-friendly information on condition, prognosis and treatment that is not frightening • Supportive and non-directional, which will help them to feel that they are making choices and taking control • Also to educate inform HCPs how to: o Facilitate early diagnosis • Select appropriate therapy
Education	Not well enough	
Communications	Not well enough	• HCPs should improve methods of communicating: talking to patients/families, atmosphere of care and understanding
Psychological support	Yes, but not always/not provided everywhere	• Those that need it should have access to it
Moral/emotional support	Yes– family (but lack of knowledge)	• Need an informed stranger

Fig. 1.5 Patient expectations around information, education and communication healthcare professional

Although some patients felt hopeful throughout the diagnosis to treatment stage, post-treatment was different, and patients expressed the need for a lot of support services. Mainly, patients felt that the disfigurement and pain was extremely difficult to live with and looked to someone else with the disease to provide clarity and understanding. After treatment, a new sense of normality and comfort is important and patients are looking for a new way forward.

Taking the Next Step After 'About Face': The First Steps Towards 'Make Sense'

As mentioned earlier, inspired by the results of the 'About Face' research series, the EHNS gathered experts from across Europe in 2012 to participate in a 'Think Tank Meeting' to tackle some of the issues uncovered.

The Think Tank group concluded that there was an urgent need for:

- Broader multidisciplinary healthcare professional knowledge of the disease, and the skills to communicate effectively about it
- Improved awareness of HNC symptoms across all stakeholder groups – HEALTHCARE PROFESSIONALS, patients and caregivers
- An integrated network of patient advocacy groups (PAGs) and healthcare representatives
- Greater emotional support for patients

Based on the recommendations proposed by the Think Tank group, the EHNS finalised a formal disease awareness campaign action plan, including a mission statement, ambassadors, taskforces and mandates, and the 'Make Sense' Campaign was born.

Make Sense Campaign

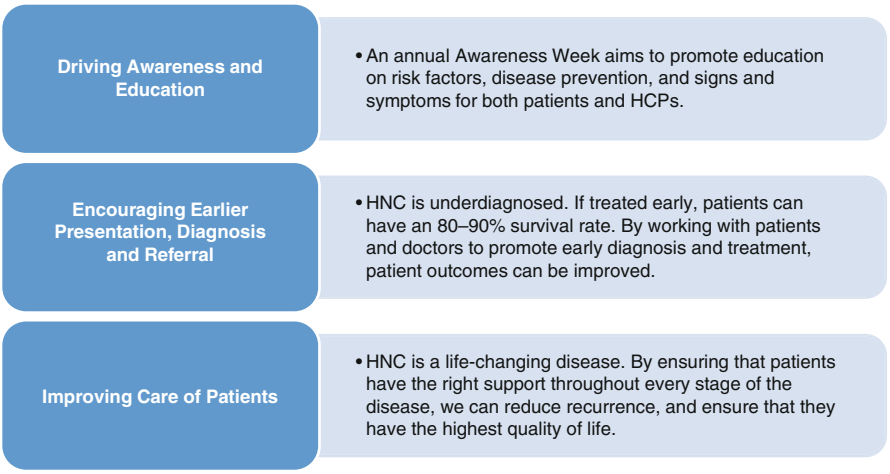
Based on the clear need to identify and treat HNC earlier to provide patients with the greatest likelihood of survival, the EHNS established and formally launched the *Make Sense* Campaign (MSC) in 2013, with Merck, previously Merck Serono, as a founding collaborator.

Make Sense Campaign Mission Statement
To raise awareness of HNC and to ultimately improve outcomes for patients with the disease

Based on the insights that there was a lack of clarity of the signs and symptoms of HNC and that successful interventions would require effective pan-European strategies, the *Make Sense* Campaign was created to:

1. Raise awareness of HNC among the general public and healthcare providers across Europe to support earlier diagnosis and to ultimately improve patient outcomes
2. Provide healthcare professionals and the general public across Europe with information about HNC
3. Build partnerships and engage with policy-makers and patient advocacy groups to support patients with HNC

These aims would be addressed through the following key aspects of the campaign: driving awareness and education; encouraging earlier presentation, diagnosis and referral; and, improving care of patients.



Laying the Foundations and Drawing on Expertise

With the goal of the *Make Sense* Campaign being a long-term, evolving initiative, the EHNS established an expert steering committee, Secretariat and four taskforces to research/address the key challenges in managing HNC.

Each taskforce was formed to address an identified unmet need – lack of awareness among the general public, lack of education for healthcare professionals about the signs and symptoms of HNC, lack of attention to patient care at a government level and lack of patient support resources.

Each taskforce agreed to conduct activities that would contribute to delivering on the *Make Sense* Campaign mission statement.

Awareness Raising Taskforce

Taskforce mandate: *to increase awareness of HNC among the general public and the media*.

The Awareness Raising taskforce aims to raise awareness of HNC among the general public and the media. It does this through a detailed programme of activities that aim to encourage a healthy lifestyle, earlier presentation, diagnosis and referral to healthcare professionals which culminates in an annual pan-European Awareness Week that is held in September.

Healthcare Professional (HCP) Education Taskforce

Taskforce mandate: *to raise awareness of the signs and symptoms of HNC among general practitioners* (*GPs*) *and to encourage improved patient care*.

The HCP Education taskforce aims to develop educational tools to reach primary care physicians, professional groups and other referring clinicians. These tools will aid the earlier presentation, diagnosis and referral of patients with HNC and ultimately achieve a universal understanding of the signs and symptoms healthcare professionals should look for when diagnosing HNC.

Partnership Building Taskforce

Taskforce mandate: *to expand relationships with European and national-level members of parliament*, *as well as supporting the exchange of knowledge across patient groups*.

The Partnership Building taskforce aims to work closely with European members of parliament to increase HNC on the European health agenda and to support groups for the exchange of knowledge among each other and other relevant European stakeholders. This will facilitate the ultimate aim of encouraging earlier presentation, diagnosis and referral of patients with HNC.

Emotive Support Taskforce

Taskforce mandate: *to raise awareness of the importance of psychological support tools for patients with HNC*.

The Emotive Support taskforce aims to review current data/clinical practice to better understand the emotive support that is available to patients with HNC. The group will develop recommendations for important improvements that need to be made at a European level to support the patient journey.

Make Sense Campaign Activities

All campaign activities have been supported by various industry partners at various times, including Merck, Transgene, Boehringer Ingelheim and Roche. All industry partners have acted in the absence of commercial bias, with the EHNS retaining all decision-making power over this campaign.

Awareness Raising Taskforce

The Awareness Raising taskforce works to increase the awareness of HNC among the general public and the media. The taskforce spans all countries involved, with the Secretariat being responsible for the coordination of activities and consistent messaging.

The taskforce meets regularly to provide a forum to share local plans and discuss key learnings, challenges/opportunities and anything of priority with the Secretariat.

The Secretariat develops and shares materials in line with the designated theme for localisation and implementation. Materials and platforms that have been developed include the *Make Sense* website (makesensecampaign.eu), educational resources spanning all aspects of the patient journey and information about HNC, white papers on key issues in HNC and media materials. All materials are available for download in various languages on the website.

Each year, the EHNS decide on an overarching theme for the campaign, which gives a specific focus for all activities. The themes for the past 3 years have been:

- 2013: Encouraging Early Diagnosis ('1for3' signs and symptoms)
- 2014: Advocating for Care that *Makes Sense*
- 2015: Seeking Excellence for Patients

Awareness Week

In order to achieve the overarching objectives of the campaign, the EHNS provide participating countries with a unified week that is dedicated to the various aspects of HNC that need attention. All activities conducted throughout the week ensure consistent messaging and provide accurate resources, which are easily accessible for physicians and patients. The first Awareness Week occurred in 2013, and the campaign is looking towards a successful fourth year in 2016.

In order to support all campaign objectives, the Awareness Week provides a platform for each taskforce by having a dedicated theme for each day of the week:

Monday (*Launch Day*): the launch of the annual Awareness Week begins with media events and activities at a pan-European and local-county level in order to generate interest and awareness of the week.

Tuesday (*Parliamentary Activities*): led by the Partnership Building taskforce, the focus of Tuesday's activities is to raise awareness of HNC and the importance of improved patient care among local and European Parliament.

Wednesday (*Early Diagnosis Day*): led by the Awareness Raising taskforce, Wednesday's activities focus on the importance of early diagnosis and referral. Participating countries are encouraged to work with local healthcare professionals and medical centres to hold a day of free screening. The general public is encouraged to come for a screening, potentially giving them a chance of an earlier diagnosis and a better understanding of risk factors.

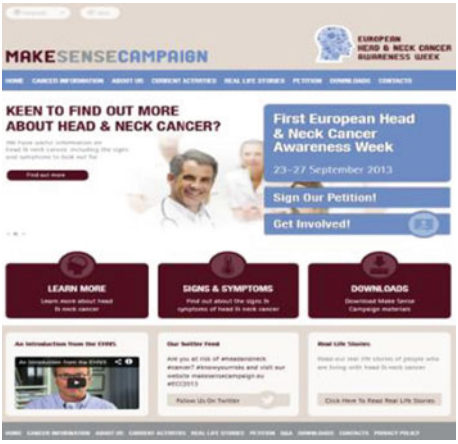
Thursday (*Young Adult Local Education Day*): led by the Awareness Raising taskforce, Thursday's activities focus on raising awareness of disease signs and symptoms, as well as preventative methods among young adults and youth.

Friday (*HCP Education Day*): led by the HCP Education taskforce, Friday's activities are dedicated to educating general practitioners and other healthcare professionals about the signs and symptoms of HNC and encouraging patient referral to a specialist.

2013 Awareness Week: Encouraging Early Diagnosis

The first European Head and Neck Cancer Awareness Week took place on 23–27 September 2013, with a total of 13 European countries involved, via the EHNS network.

The 2013 Awareness Week launched with the *Make Sense* website in 13 languages, achieving more than 10,000 views during its first week. Across Europe, more than 1100 pieces of media coverage were generated in order to garner interest and to spread the word of the campaign.



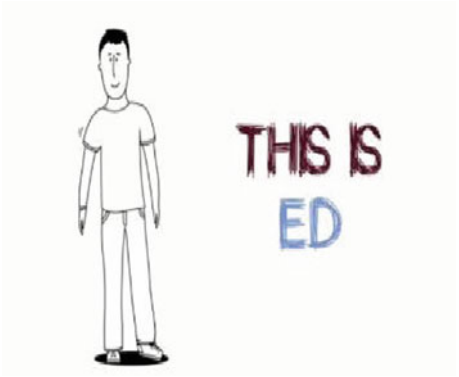
Make Sense Campaign website

Almost 100 free clinics in Germany, Poland, Portugal, Russia, Spain, the UK, France and Italy were open to the public during the Early Diagnosis Day, which was held on the Wednesday. More than 5000 patients were screened, including almost

3500 patients in Russia, which led to 250 referrals. To increase participation and interest in the day, media were invited to cover the various clinics, thereby ensuring that campaign and disease messaging were reaching a broader audience.

Patient receiving a screening during one of the Early Diagnosis Day clinics

Youth Education Days took place to inform Europe’s young adults of the signs and symptoms, as well as prevention methods, of HNC. To support activities, a video entitled ‘This is Ed’ was developed and translated into 12 languages to allow for localisation and retention of messaging. The video was an animation of the specific actions that individuals can take to help prevent HNC.



‘This is Ed’ video developed for the first Awareness Week

Country Activities

The Awareness Week is only as successful as the success of the countries taking part. The EHNS recognises that messages of prevention and early diagnosis should be disseminated on a country level to ensure that they resonate with its intended audience.

The 2013 campaign saw participation from: Belgium, France, Germany, Italy, The Netherlands, Poland, Portugal, Russia, Finland, Spain, Turkey and the UK. Each

country made use of the campaign materials provided, but also developed their own materials using the *Make Sense* branding.

2013 Awareness Week: Local Spotlight

*Belgium***:** A Belgium-specific website was created and launched, linking directly to the European *Make Sense* website. It also housed two patient testimonial videos that were used to support various local activities, such as media engagement and parliamentary activities.

Belgium website launched for the first Awareness Week

*Germany***:** A radio campaign was executed to raise awareness of HNC, broadcasting across 47 radio stations, which generated more than two million impressions.

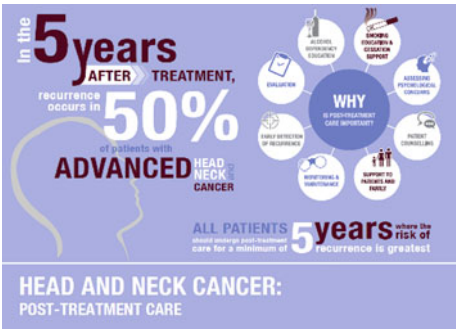
Portugal: Media coverage was generated by conducting interviews with a number of key opinion leaders. A Portuguese parliamentary event was held to increase the importance of HNC on the health agenda.

2014 Awareness Week: Advocating for Care That Makes Sense

Based on the engagement and excitement generated during the first Awareness Week, the 2014 Awareness Week aimed to build and expand on this success. Emphasis was placed on the importance of a multidisciplinary team approach to care, post-treatment care and the emotional impact of the disease. The message was more heavily targeted towards healthcare professionals.

Building on the success of the first Early Diagnosis Day in 2013, the 2014 Awareness Week allowed for another 12,000 people to receive free screening in seven countries, including Germany, Poland, Portugal, Russia, Spain, France and The Netherlands.

Continuing to work with young adults, the Youth Education Day saw lectures and corresponding activities in schools and universities in The Netherlands and Poland. The video produced in 2013 was used once again and rolled out across the network.



Post-treatment care infographic developed in 2014

In addition to traditional means of reaching key audiences, the campaign kicked off its social media presence during the 2014 Awareness Week, with the creation of the *Make Sense* Campaign Twitter feed (@MakeSenseCmpn). Using social media allowed the campaign to reach more of the general population with widespread messaging about HNC.

Country Activities

In 2014, three additional countries joined the campaign: the Czech Republic, Denmark and Slovenia. Country activities increased and became more unique to ensure that messages resonate with key audiences.

2014 Awareness Week: Local Spotlight

Italy: The development and launch of the first app to assist patients with squamous cell carcinoma of the head and neck with communication. The app was developed in Italian and allows patients to describe the level, type and area of body in which pain is occurring. This is particularly helpful if patients are unable to communicate due to their disease.

My Voice App developed by the Italian team for the second awareness week

Germany: EHNS representative, Professor Andreas Dietz, participated in a series of media interviews that resulted in television coverage across the country that was focused on HNC.

Spain: A press event – *Brunch de los Sentidos* – took place featuring a roundtable with key thought leaders in HNC and covered the importance of early diagnosis.

Poster for Brunch de los Sentidos, an event in Spain, during the second Awareness Week

2015 Awareness Week: Seeking Excellence for Patients

In 2015, the Awareness Week activities had a strong focus on elevating the voices of advocates for HNC, with the launch of a social media programme: *UnitingVoices*. *UnitingVoices* aimed to unite voices across Europe to speak up for improved care, while providing patients with a sense of community.

A key element of *UnitingVoices* was the creation of a ‘virtual choir’. As HNC in the pharynx, larynx, oral cavity and tongue can impact a patient’s voice, people around the world were encouraged to give their voice to support patients with HNC.

Poster for countries to adapt and to encourage participation in the UnitingVoices social media campaign

The song, *You’re the Voice*, by Australian singer/songwriter, John Farnham, was chosen as the song for the virtual choir. People were encouraged to film themselves singing this song and to submit their video. The videos were ultimately compiled to create a visual and acoustic representation of the impact of united voices around the world.

There was also the option to join the ThunderClap, a social media activity that allows many people to send out a message in support of a cause at any one time. In addition, people were encouraged to submit video testimonials that were also shared on the campaign’s social media channels and linked using a hashtag

(#UnitingVoices); these were then used more than 368,400 times leading up to and during the week.

Overall, *UnitingVoices* was a success, with all social media efforts and messages reaching more than 5,010,260 people. Patient advocacy groups, healthcare professionals and European Members of Parliament all engaged in *UnitingVoices* through online posts and videos. A total of 270 videos were developed by campaign supporters, including patient testimonials, uniting voices and virtual choir videos.

Still image of the UnitingVoices virtual choir

In its third year, the Early Diagnosis Day clinics continued to gain momentum, with 190 clinics open across France, Germany, Poland, Russia, Kazakhstan and the UK. More than 12,000 patients were screened, with a referral rate of between 8.5 and 30 % across countries.

Education Days were held in schools across Poland, Portugal and the UK. Youth pamphlets were developed in Portuguese to effectively communicate to the elementary school audience.

Country Activities

This year, two additional countries joined the campaign: Ireland and Kazakhstan. Kazakhstan was one of the first countries outside of Europe to meet the EHNS criteria for joining the society. The participants in Kazakhstan were enthusiastic and were dedicated to ensuring that campaign messages reached key audiences throughout the week. Ireland joined the campaign through its participation in the patient advocacy network.

2015 Awareness Week: Local Spotlight

Portugal: The Portuguese Football Federation, including all of its 151 football clubs, showed their support for the campaign by having all 3000 players, including referees, wear the campaign t-shirt; hundreds of thousands of people were in attendance and watching from home. Additionally, the Real Madrid and Portuguese football player, Pepe, posted a supportive campaign video on Facebook, which received more than 110,000 views!

Real Madrid player, Pepe, shows his support with a video posted to his own social media accounts

Poland: Attention and interest in the Early Diagnosis Day clinics was so high in Poland that it shut down the *Make Sense* website for a short period. The team also translated the ‘Second Voice’ app so that it could be used in this country. The app is a communication tool that is aimed at patients with HNC who have lost the ability to speak.

Kazakhstan: The latest country to join in Awareness Week efforts held seminars on the importance of a multidisciplinary team approach to care.

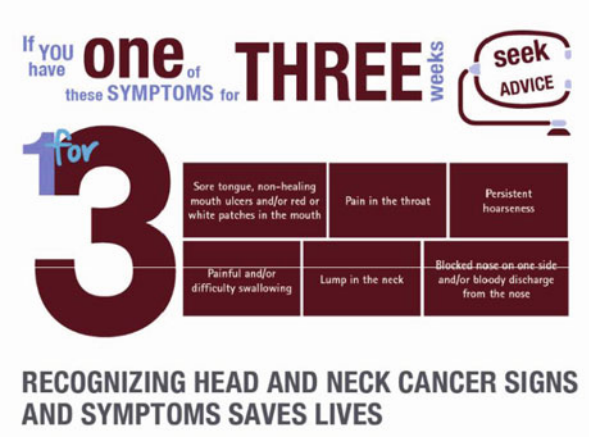
Healthcare professionals in Kazakhstan speak to the media during the awareness week

HCP Education Taskforce

The HCP Education taskforce advocates for a universal understanding of the signs and symptoms of HNC, the importance of referring patients to a specialist and educating other healthcare professionals on the multidisciplinary team approach to care. This taskforce had a pivotal role in the lead up to the official launch of the campaign in 2013 by convening experts to develop core statements and materials on aspects of importance, such as signs and symptoms and the importance of multidisciplinary care.

The result was the '1for3' concept: if you experienced at least one symptom for a period of 3 weeks, then you should seek medical advice.

The taskforce then looked for opportunities to educate and spread the educational message of the signs and symptoms, but also post-treatment care and the multidisciplinary team approach to care. The HCP Education taskforce's activities culminated on the Friday of the Awareness Week each year. The campaign has a presence at the leading European Oncology Congress, ESMO, with a booth in the exhibition hall. During this time the *Make Sense* campaign Secretariat was able to engage with healthcare professionals about the importance of recognising signs and symptoms and the campaign itself, as well as handing out leaflets.



Signs and symptoms of HNC, as defined by the EHNS and its 1for3 concept

The taskforce also works to engage with country-level general practitioner societies. As HNC is rare, general practitioners may only see two to three cases in their entire careers. As HNC can be curable in 80–90 % of cases when caught early, it is important to encourage the learning of symptoms and encouraging early diagnosis.

HCP taskforce newsletter

Keeping in mind the amount of information that GPs receive, the HCP Education taskforce aims to provide quick, useful information that will be well received. Through materials and newsletters, they focus on bringing attention to the different aspects of patient care to this important audience.

Partnership Building Taskforce

The objective of the Partnership Building taskforce is to work with parliament, at a European and country level, and patient groups to unite and address the lack of attention paid to HNC.

Since the inception of the campaign, various activities have been put into place to raise awareness of HNC at the EU level among key politicians and parliaments via different white papers, meetings, debates and specific activities within the EU parliament.

White Paper

Head and neck cancer: *The* 'curable' *cancer that kills over half of all sufferers – it is time to do something about it.*

The *Make Sense* Campaign white paper was developed as a thought-provoking and action-orientated call to drive change for patients with HNC in Europe.

Call-to-Action
There is little awareness of HNC among the general public and the healthcare community in Europe, resulting in the majority of diagnosed cases being late stage. Consequently, treatment outcomes for patients are poor and chances of survival are significantly reduced. This must be changed, but is only possible with your help.

The white paper centred on recommendations for a multidisciplinary team approach to care and the importance of this approach in order to improve outcomes for patients. It was launched at an EU Parliament meeting during the 2013 Awareness Week.

EU Parliament Launch Meeting

On Tuesday 24 September 2013, as a part of the Parliamentary Activities Day of the Awareness Week, a meeting was held in EU parliament to launch the *Make Sense* White Paper. The meeting was an opportunity for the Campaign to gain support for improved care for patients with HNC from Members of the European Parliament (MEPs). The meeting was attended by 10 MEPs, as well as more than 30 other key stakeholders from across Europe, including physicians and patients.

Energetic discussion was led by sponsor Daciana Sarbu, an MEP from Romania and Vice-Chair of the Committee on the Environment, Public Health and Food Safety (ENVI Committee). The meeting also included endorsement via a moving video testimonial, from the ex-President of Brazil, Lula Da Silva, who is himself a survivor of HNC. The call-to-action of the white paper was signed by 12 MEPs and was then passed on to EU Commission.

Daciana Sarbu, MEP from Romania and Vice-Chair of the Committee on the Environment, Public Health and Food Safety (ENVI Committee)

Oral Question and the ENVI Committee Debate

The Partnership Building taskforce continued to work closely with the European Cancer Patient Coalition (ECPC) and developed an oral question for discussion at the European Parliament. The question focused on the need for better care for rare cancers and focused specifically on HNC. The oral question had the support of Vice-Chair of the ENVI Committee, Daciana Sarbu, and was debated among European Parliament members at the ENVI Committee meeting in November 2015. The meeting touched on a number of key aspects relating to rare cancers, and HNC in particular. Key conclusions from the meeting were that more work could be done to expedite the policy issues related to HNC and rare cancers in general.

Patient Advocacy Group (PAG) Network

Working closely with patient groups is another important aspect of the taskforce. Engaging with patients to ensure that campaign messaging is resonating and aligned with how patients really feel is imperative. As such, the development of the ‘Make Sense’ PAG network came to fruition on 26 September 2015 through an inaugural meeting in Madrid. The meeting involved a total of 10 PAGs, who pledged to officially form the first-ever HNC patient network. The group has met twice in 2015 and members are in close contact as they work together to consult and provide guidance for patient-specific materials.

Emotive Support Taskforce

The Emotive Support taskforce aims to increase the understanding of the importance of psychological support tools needed for patients with HNC, as well as making improvements to the support that patients receive following their diagnosis and during the subsequent treatment.

In order to reach these objectives, the taskforce began working on a manuscript focusing on the emotive support that is required throughout the journey of patients with HNC. A series of planning meetings were held to gain alignment on the most important aspects to be included. Topics covered were emotional problems encountered by patients with squamous cell carcinoma of the head and neck (SCCHN), the type of support that patients require from their physicians and how the physician should react to specific situations. The manuscript, entitled *Best practices in the management of the psycho-oncologic aspects of head and neck cancer patients: recommendations from the European Head and Neck Cancer Society Make Sense Campaign*, was published in *Annals of Oncology* in May 2014 [3].

The Emotive Support taskforce continues to work on additional materials and manuscripts to help address the evolving needs of patients with this disease.

Looking Towards the Future

The *Make Sense* Campaign has been imperative in driving general disease awareness, encouraging early presentation and educating on the signs and symptoms of HNC. To keep spreading awareness of the disease and advocating for better care, the campaign will continue to build on this successful foundation.

In its fourth year, the campaign will focus on new and different ways to amplify this message by reaching new countries, addressing important and evolving aspects of the disease, making a deeper impact with practitioners at a country level and continuing to increase parliamentary attention on HNC.

Reaching New Countries with Make Sense

The EHNS recognises the impact that HNC has on communities outside of Europe. As such, a set of criteria has been developed to aid in the inclusion of countries outside of Europe. In 2016, the campaign is looking to include more countries in Europe, as well as to expand to Asia and the Americas.

Expanding Messaging to Include the Impact That HPV Has on the Disease

The prevalence of HPV as a factor in HNC has been increasing in recent years. This year, the campaign will aim to help physicians to engage in their conversations with patients around this link. HPV-associated tumours tend to occur in a somewhat younger patient group, preferentially (but not only) in the oropharynx, may implicate additional risk factors beyond the usual ones, but can occur in all socioeconomic classes. Awareness and education will focus on this. The campaign will work to encourage HPV testing and HPV vaccinations, as well as other preventable measures for both men and women.

Increase Relationships with General Practitioners on a Country-Level Basis

As an ongoing objective, the campaign is looking for additional ways to reach the general practitioner population. This year, and in coming years, the campaign will strengthen its relationships with local societies and work to develop materials that resonate and are considered to be useful.

Expanding Our Presence in European Parliament Supported by European-wide Research

The EHNS is working with a number of European Commission-backed research organisations, including Rare Care and the Joint Action on Rare Cancer. The results from these research projects will provide the head and neck community with comparative research and evidence about HNC care throughout Europe, providing the groundwork for further action to be taken in European Parliament. The collaborative research projects will build a broader network of support, but also provide the HNC community with useful and important information.

The EHNS would like to thank the many partners that have come together to make the Make Sense Campaign possible. We continue to grow the campaign year after year thanks to this support. If you are interested in participating or learning more, please visit our website makesensecampaign.eu or contact the Secretariat at secretariat@makesensecampaign.eu.

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Part II
Head and Neck Cancer: A Changing Disease

Chapter 2
New Epidemiologic Aspects in Head and Neck Cancers

Gemma Gatta and Laura Botta

Introduction

Head and neck cancers (H&N) are rare diseases. Each of the entities (lip, oral cavities, oropharynx, nasal cavities, major salivary glands, salivary gland type tumours, hypopharynx and larynx) which contributed the group of H&N has an annual incidence rate lower than 6 per 100,000 and also a prevalence lower than 5 per 10,000. The two thresholds are of the RARECARE definition of rare cancers [1] and of the European definition for rare diseases [2]. H&N, as all the rare cancers, suffer of difficulties in making correct diagnosis, definition of appropriate treatment, problems in research for the low number of cases and in the organisation of the patients management.

The objective of the paper is to provide an update on H&N burden in Europe.

All the epidemiological information reported in this paper are collected from three major and easily accessibly tools: (i) the GLOBOCAN project http://globocan.iarc.fr/; (ii) EUROCARE project (Surveillance of Cancer Patients in Europe) www.eurocare.it; and (iii) RARECAREnet (Information network on rare cancers) http://www.rarecarenet.eu/rarecarenet/.

Incidence

In Europe, according to GLOBOCAN [3], in 2012 H&N cases are 4 % of all malignant cancer diagnoses, with a higher proportion in men (6 %) than in women (2 %) (Fig. 2.1). In men for oral cavities and pharynx, incidence was highest in Portugal,

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DOI 10.1007/978-3-319-42909-0_2

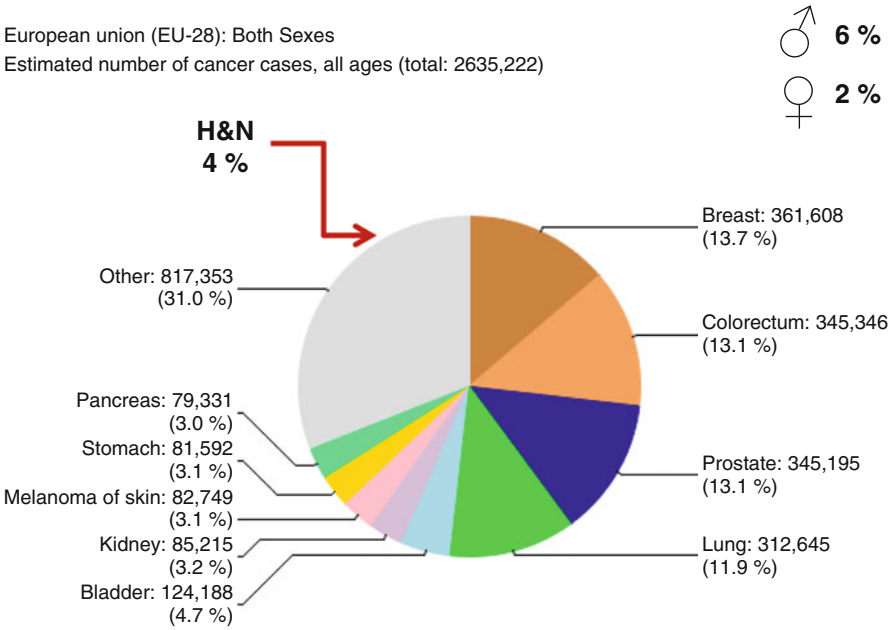


Fig. 2.1 Europe, 2012, head and neck cancers incidence. H&N = lip, tongue, oral cavity, pharynx, larynx, salivary glands, nasopharynx and nasal cavities (GLOBOCAN 2012 (IARC) – 2.11.2015)

several eastern countries, France and Germany (>18 per 100,000/year) (Fig. 2.2). For laryngeal cancer (Fig. 2.3), rates remained high in Portugal, Eastern countries and Spain (≥9.7 per 100,000/year). Cancer of nasopharynx was more common in the Southern European countries: the annual incidence rates were 0.7 per 100,000 and lowest in the Northern countries (0.2 per 100,000). [http://www.rarecarenet.eu/rarecarenet/].

From 1995 to 2007, incidence rates increased significantly for lip, oral cancer, oropharynx and larynx cancers and it remained stable for all the other H&N (Table 2.1) [http://www.rarecarenet.eu/rarecarenet/].

Figure 2.4 shows incidence and mortality rates for laryngeal cancer in the 20 highest, for incidence, European countries. The mortality incidence ratio was lowest in the Eastern countries, which are at high incidence rates. However, for other countries at high incidence, as Portugal, Spain and Belgium incidence mortality ratio was high, suggesting that in these countries management of patients with laryngeal cancers reached good outcome, differently from the Eastern countries. The same pattern was reported for the other H&N, for Europe.

Survival

In Europe, survival was analysed from about 240,000 H&N cases diagnosed in 1999–2007 collected by 86 population-based cancer registries, in 29 countries [4].

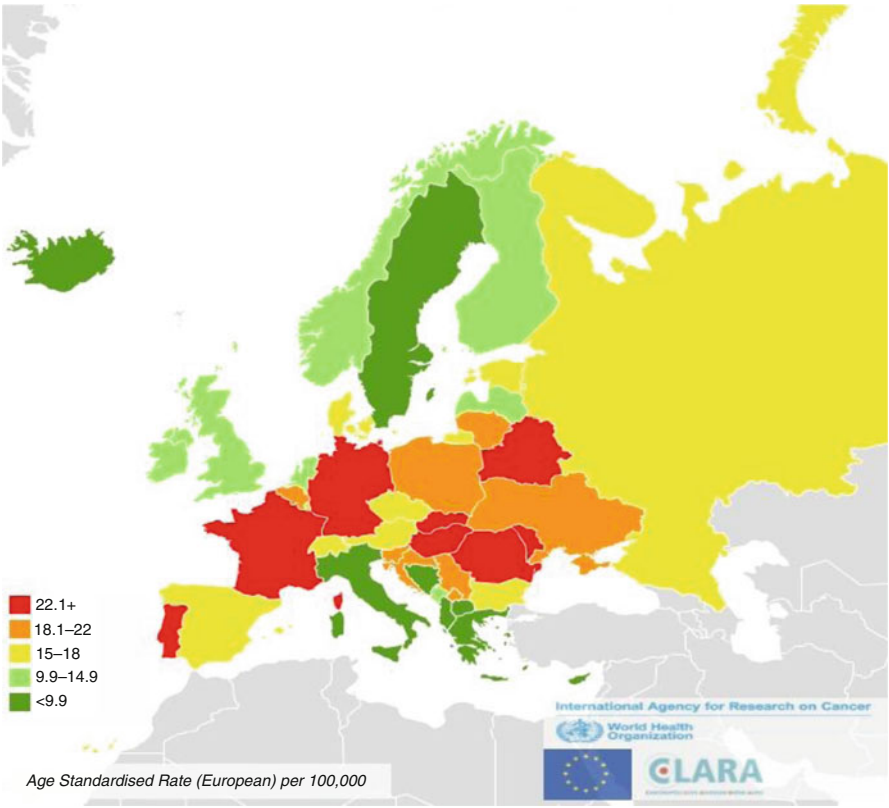


Fig. 2.2 Estimates incidence from cancer of lip, oral cavity, and pharynx in men, 2012

There are some differences between clinical and population-based survival studies.

- Survival analyses from clinical series are crucial to evaluate the effectiveness of a specific treatment, whereas population-based studies evaluate the effectiveness of the heath care systems in a country or region.
- In clinical studies, there is a selection of patients by hospital, age, stage, co-morbidity, etc., while in population-based studies, all cancer patients belonging to a demographically defined population (country, region, local area, etc.) are included.
- Population-based survival studies estimate the average survival actually achieved in the general population. Clinical studies indicate the highest achievable survival in selected patient groups.

For the above reasons, descriptive survival figures are more properly taken from population-based than from clinical studies.

In population-based studies, the definition of cause of death cannot be easily assured, and survival is commonly expressed as *relative survival*, to assure a proper comparison across populations. Relative survival can be considered as the

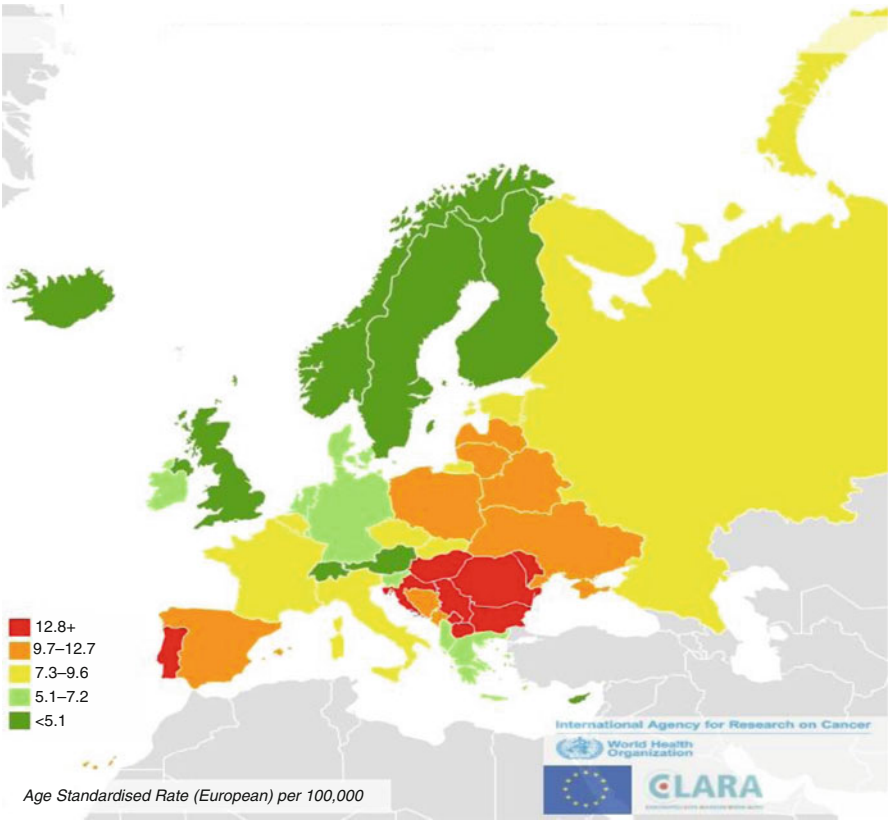


Fig. 2.3 Estimates incidence from laryngeal cancers in men, 2012

Table 2.1 Head and neck cancers annual incidence rates (rate per 100,000), trend, 1995–2007, Europe

	Age-adjusted incidence rate per 100,000/ year		
	Period of diagnosis		
Cancer entity	1995–1998	1999–2002	2003–2007
Epithelial tumours of nasal cavity and sinuses	0.36	0.37	0.37
Epithelial tumours of nasopharynx	0.41	0.41	0.40
Epithelial tumours of major salivary glands and salivary-gland type tumours	1.12	1.12	1.14
Epithelial tumours of hypopharynx	0.90	0.95	0.93
Epithelial tumours of larynx[a]	3.90	3.85	3.58
Epithelial tumours of oropharynx[a]	2.12	2.41	2.73
Epithelial tumours of oral cavity[a]	2.65	2.80	2.94
Epithelial tumours of lip[a]	0.97	0.84	0.69

Source: RARECAREnet project
[a]Statistically significant, period 2003–2007 versus period 1995–1997

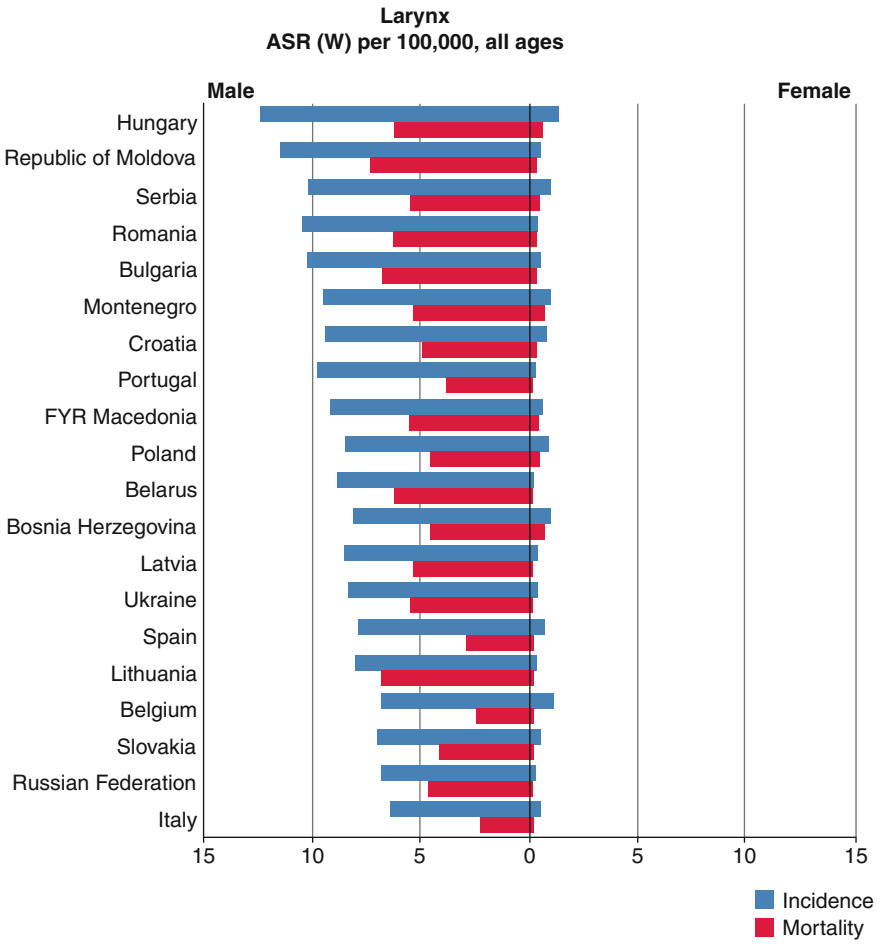


Fig. 2.4 Incidence and mortality, 20 highest in Europe, Larynx (GLOBOCAN 2012 (IARC) (4.11.2015)). *ASR* age-standardised rate (world)

population-based counterpart of cause specific survival in clinical studies and is calculated as the ratio of observed survival to the survival that the patients would have experienced if they had had the same probability of dying as the general population, having the same age and sex. All the survival figures provided in this chapter are relative survival estimations and are taken from the recent results of EUROCARE-5 project. Furthermore, since populations can differ by age, and age is a prognostic factor, survival figure are standardised by age.

From Figs. 2.5, 2.6, and 2.7, 5-year relative survival is given by cancer site (tongue and lingual tonsil, oral cavity, oropharynx, nasopharynx, hypopharynx and larynx) and by country. Countries are ordered according to geographical region from North Europe to UK and Ireland, Centre, South and East of Europe, and different regions are highlighted by different grade of blue. Cases included in the analyses are those diagnosed between 2000 and 2007.

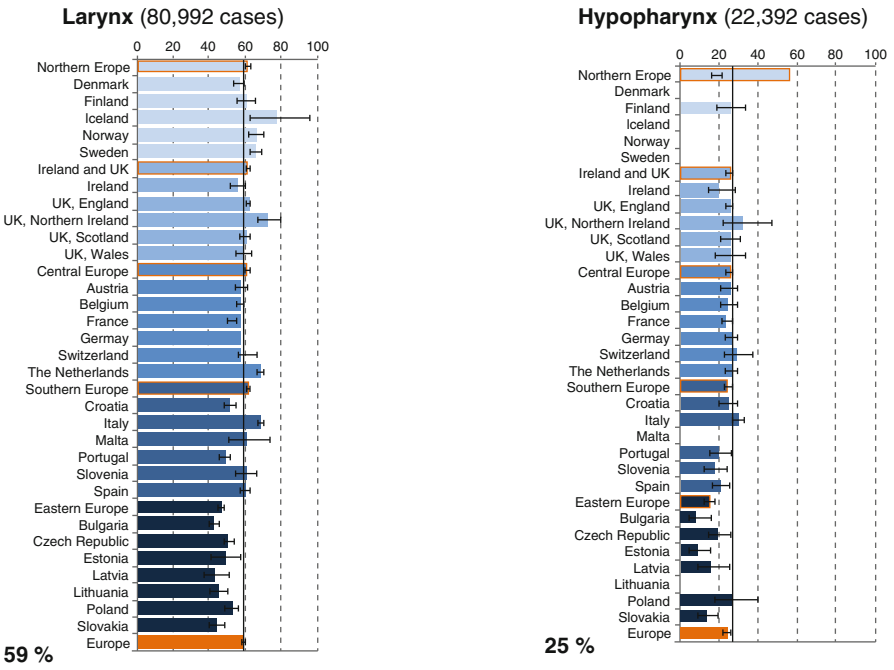


Fig. 2.5 Age-standardised 5-year relative survival for larynx and hypopharynx cancer cases diagnosed in 2000–2007, by European region, country and overall (Source: Gatta et al. [4])

Five-year survival was the poorest for hypopharynx and the highest for larynx cancers, 25 % and 59 %, respectively (Fig. 2.5). Survival for tongue or oral cavity cancer patients were similar, 43 % and 45 %, respectively (Fig. 2.6). Five-year survival was slightly better for nasopharynx (49 %) and worse for oropharynx (39 %) (Fig. 2.7). For all these H&N, survival significantly reduced with the increasing age: from 56 % in the youngest age group of 15–44 years of age to 34 % in the oldest age group 75 and more years old (Table 2.2). Five-year survival was significantly better in female than male: 36 % and 50 %, respectively (Table 2.3).

H&N survival disparities were reported in Europe: for all the considered cancers, 5-year survival was low in the Eastern countries (Figs. 2.5, 2.6, and 2.7).

Five-year survival increased for some of the H&N. Between 1999 and 2007, survival significantly improved for hypopharynx, tongue, oral cavity, oropharynx (Figs. 2.8, 2.9, and 2.10). Improvement was marginally significant for nasopharynx (Fig. 2.10); for larynx, 5-year survival remained stable (Fig. 2.8).

To understand the impact on geographical differences of anatomical sub-site of origin of the lesion, the relative excess risk of dying (RER) was estimated by a model which included age, sex, country and sub-site. Tables 2.4, 2.5, and 2.6 show that for mouth-pharynx and larynx, after the inclusion of sub-site, as covariate, geographical disparities between countries slightly reduced. For larynx, with

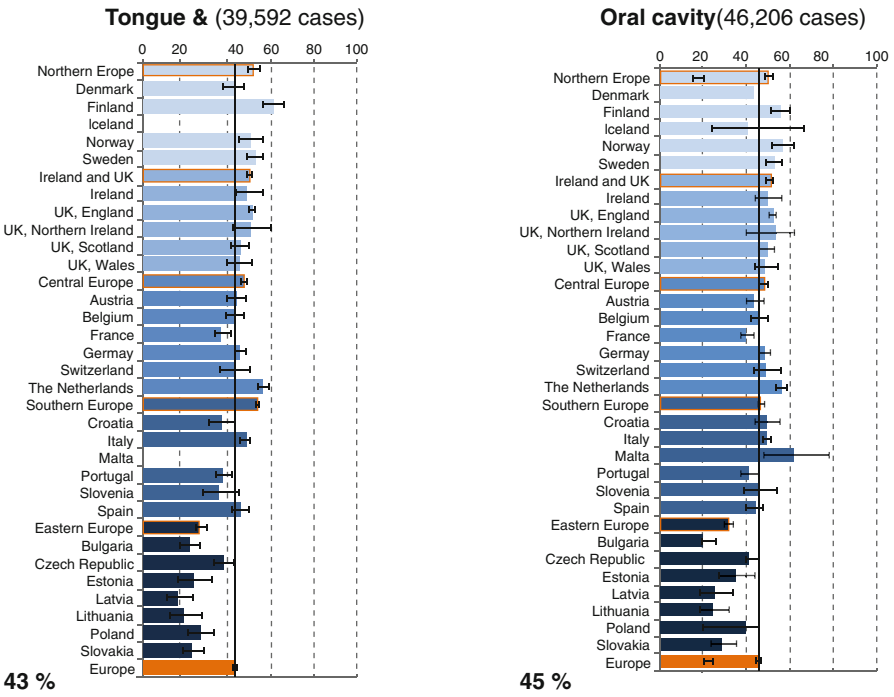


Fig. 2.6 Age-standardised 5-year relative survival for tongue and lingual tonsil, and oral cavity cancer cases diagnosed in 2000–2007, by European region, country and overall (Source: Gatta et al. [4])

England as reference, all the northern countries, Germany, the Netherlands, Scotland, Italy, Slovenia and Spain were at lower risk, while Ireland and all the Eastern countries were at higher risk. For mouth-pharynx, the Nordic countries, Germany, Switzerland, the Netherlands and Italy were at lower, and Belgium, France, Slovenia, Spain and all the Eastern countries were at higher risk, again, considering England as reference. High risk was estimated, when comparing subsites, for hypopharynx, oropharynx and pharynx NOS, postcricoid region, with RER of 1.52, 1.53 and 1.62, respectively, with respect to the base of tongue, valecular, and lingual tonsil (taken as reference) and the lowest for cheek plus vestibule of mouth (0.61) (Fig. 2.8). For larynx, all the anatomical sub-sites considered in the model (sovra- and sub-glottis), RERs were about three times higher than reference (glottis) (Fig. 2.9).

Thirty-six percent of patients were diagnosed in localised stage, ranging from 14 % for hypopharynx to 56 % for larynx (Table 2.7). Five-year survival for localised and metastatic cancer patients were, respectively, 69 % and 9 % for oral cavity, 65 % and 9 % for tongue, 58 % and 12 % for oropharynx, 42 % and 4 % for hypopharynx and 74 % and 7 % for larynx. Five-year RS was intermediate for regional and unknown stage (34 % and 47 % for H&N combined, respectively).

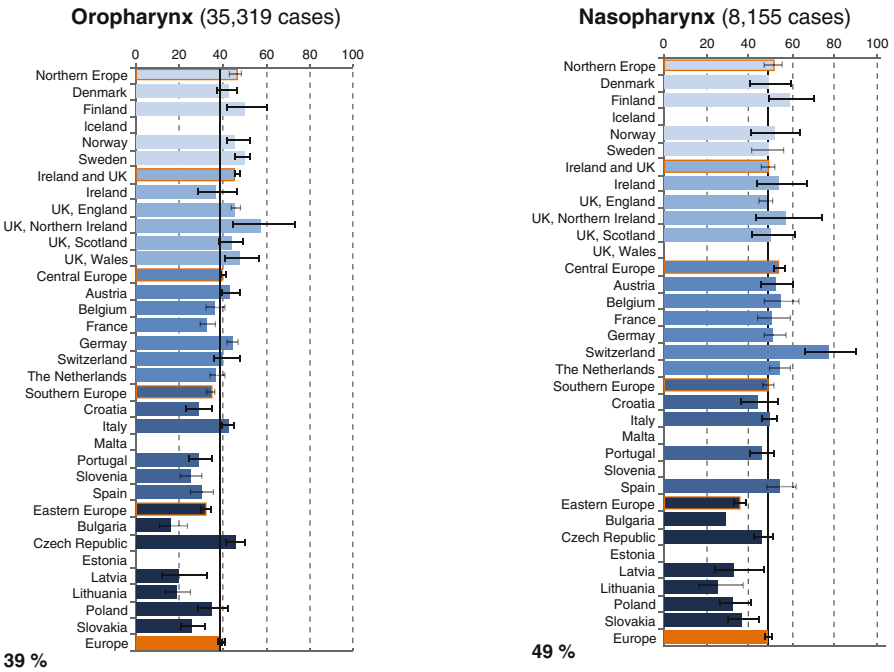


Fig. 2.7 Age-standardised 5-year relative survival for oropharynx and nasopharynx cancer cases diagnosed in 2000–2007, by European region, country and overall (Source: Gatta et al. [4])

Table 2.2 Head and neck cancers survival (%) by age, cases diagnosed 2000–2007 in Europe

All cases	Numbers of cases	1 year	3 years	5 years
15–44	11,745	81.8	61.7	55.8
45–54	37,457	76.1	52.4	44.6
55–64	43,612	73.4	49.7	41.6
65–74	33,978	68.5	45.8	38.4
75+	22,728	59.4	39.5	34.3
All adults	154,520	68.8	46.7	39.9

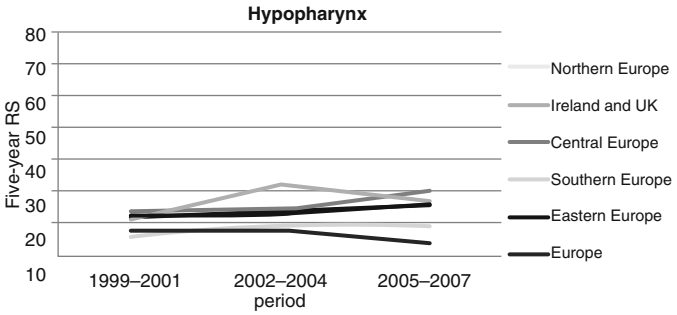
Source: Gatta et al. [4]

The epithelial nasal cavities tumours and the major and minor salivary glands type tumours were analysed in the framework of RARECAREnet project according to the combination of morphology and topography codes. Geographical survival variation was present with the same pattern as all the other H&N. Figures 2.11 and 2.12 show survival trend between 1999 and 2007 by nasal cavities and salivary glands. There was a significant improvement in nasal cavities carcinoma (Fig. 2.11), while progress was modest for salivary glands cancers (Fig. 2.12).

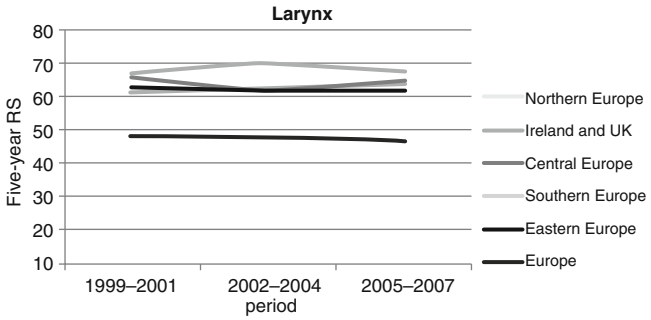
Table 2.3 Head and neck cancers survival (%) by age and sex; cases diagnosed 2000–2007 in Europe

Male (74%)		1 year	3 years	5 years
15–44	8547	79.5	58.1	51.7
45–54	30,043	74.9	50.0	42.1
55–64	38,185	71.8	47.2	38.8
65–74	24,860	66.3	42.1	34.5
75+	12,161	57.6	35.9	30.3
All adults	113,796	67.0	43.6	36.4
Female (26%)				
15–44	3198	88.8	72.4	68.0
45–54	7414	81.5	63.1	56.1
55–64	10,427	81.0	61.4	54.3
65–74	9118	76.0	57.4	50.8
75+	10,567	62.2	45.0	40.1
All adults	40,724	74.7	56.5	50.3

Source: Gatta et al. [4]

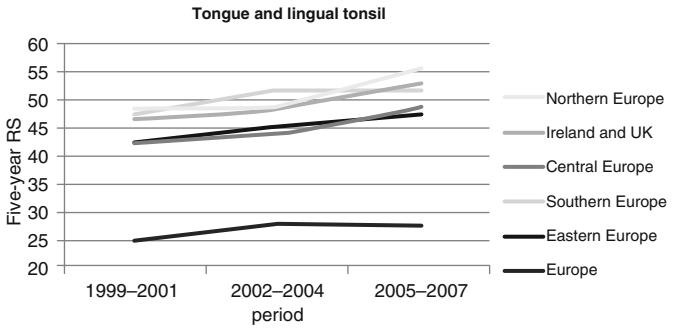


	1999–2001	2002–2004	2005–2007	*p*-value
Northern Europe	15.5	19.3	19.7	0.055
Ireland and UK	22.2	22.6	26.6	0.011
Central Europe	24.1	24.8	29.6	0.017
Southern Europe	21.2	31.1	26.9	0.053
Eastern Europe	18.0	18.1	14.3	0.112
Europe	21.7	24.6	25.6	0.004

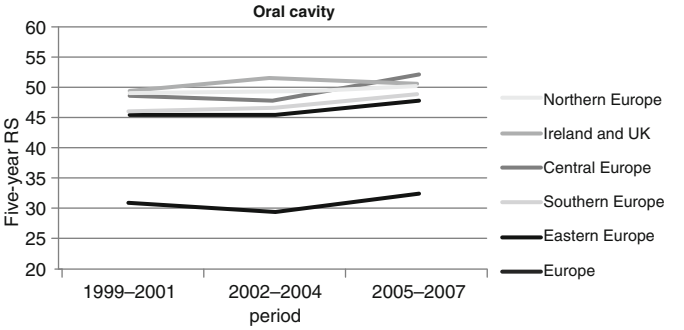


	1999–2001	2002–2004	2005–2007	*p*-value
Northern Europe	63.4	60.9	62.1	0.255
Ireland and UK	60.7	61.8	61.7	0.155
Central Europe	65.9	62.2	64.5	0.196
Southern Europe	66.8	70.1	67.6	0.327
Eastern Europe	47.7	48.0	46.8	0.299
Europe	62.4	61.8	62.0	0.307

Fig. 2.8 Time trend in age-standardised relative survival (RS, %) for hypopharynx and larynx cancer patients across European regions, period 2005–2007 versus period 1999–2001 (Source: Gatta et al. [4])

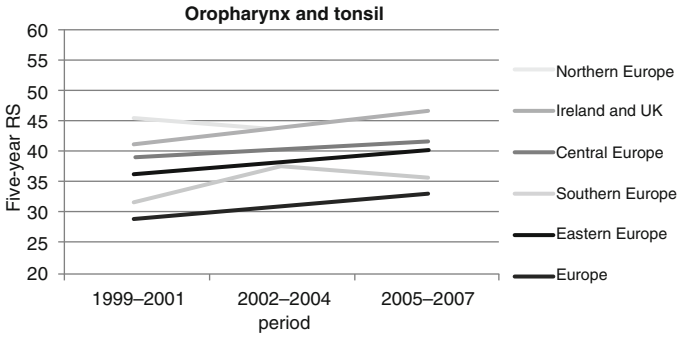


	1999–2001	2002–2004	2005–2007	*p*-value
Northern Europe	48.2	48.6	55.1	0.003
Ireland and UK	46.0	48.3	52.7	0.000
Central Europe	46.8	51.3	51.4	0.018
Southern Europe	42.1	43.4	48.4	0.020
Eastern Europe	25.2	27.7	27.4	0.209
Europe	42.3	45.2	47.4	0.000

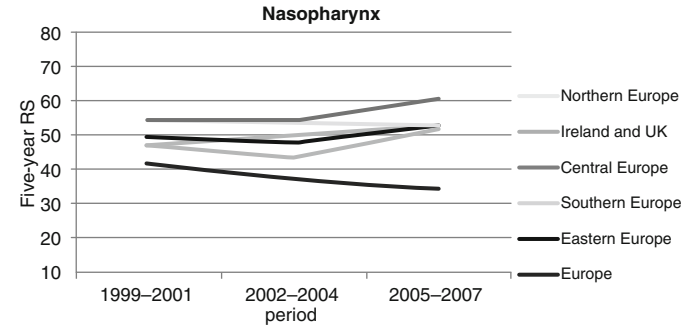


	1999–2001	2002–2004	2005–2007	*p*-value
Northern Europe	49.3	49.5	51.0	0.193
Ireland and UK	49.6	51.5	50.7	0.189
Central Europe	48.8	47.9	52.0	0.045
Southern Europe	46.2	46.8	48.7	0.181
Eastern Europe	30.8	29.8	32.9	0.216
Europe	45.6	45.5	48.1	0.012

Fig. 2.9 Time trend in age-standardised relative survival (RS, %) for tongue and lingual tonsil, and oral cavity cancer patients across European regions, period 2005–2007 versus period 1999–2001 (Source: Gatta et al. [4])



	1999–2001	2002–2004	2005–2007	*p*-value
Northern Europe	45.4	43.8	46.2	0.390
Ireland and UK	41.4	44.2	46.7	0.005
Central Europe	39.5	39.9	41.8	0.172
Southern Europe	32.0	37.3	35.8	0.108
Eastern Europe	28.9	31.5	33.4	0.056
Europe	36.7	38.8	40.1	0.006



	1999–2001	2002–2004	2005–2007	*p*-value
Northern Europe	54.3	52.3	51.8	0.287
Ireland and UK	47.4	43.9	51.7	0.060
Central Europe	54.5	54.3	60.1	0.079
Southern Europe	46.7	50.0	51.8	0.129
Eastern Europe	41.4	37.3	34.4	0.023
Europe	49.6	49.0	52.5	0.080

Fig. 2.10 Time trend in age-standardised relative survival (RS, %) for oropharynx and tonsil, and nasopharynx cancer patients across European regions, period 2005–2007 versus period 1999–2001 (Source: Gatta et al. [4])

Table 2.4 Relative excess risks (RERs) of death by country for all mouth-pharynx sites by age and sex (Model 1) and by age, sex and sub-site (Model 2) compared with UK, England

	Model 1		Model 2	
Country	RER of death	95 % CI	RER of death	95 % CI
Northern Europe				
Norway	0.88	0.83–0.95	0.89	0.84–0.96
Sweden	0.86	0.81–0.90	0.87	0.83–0.91
Ireland and UK				
Ireland	1.04	0.96–1.11	0.99	0.92–1.07
UK, England	*1 (reference)*		*1 (reference)*	
UK, Northern Ireland	0.96	0.87–1.07	0.93	0.84–1.03
UK, Scotland	1.02	0.97–1.07	0.99	0.95–1.04
UK, Wales	1.00	0.93–1.07	1.00	0.93–1.07
Central Europe				
Belgium	1.12	1.08–1.17	1.07	1.03–1.12
France	1.20	1.15–1.25	1.08	1.04–1.12
Germany	1.02	0.99–1.05	0.92	0.89–0.94
Switzerland	0.98	0.90–1.06	0.91	0.84–0.98
The Netherlands	0.92	0.89–0.95	0.91	0.88–0.94
Southern Europe				
Italy	0.95	0.91–0.99	0.90	0.86–0.94
Slovenia	1.34	1.27–1.43	1.24	1.17–1.31
Spain	1.15	1.09–1.22	1.06	1.00–1.12
Eastern Europe				
Bulgaria	2.76	2.65–2.88	2.68	2.57–2.79
Czech Republic	1.37	1.32–1.42	1.32	1.27–1.37
Latvia	2.43	2.27–2.60	2.08	1.94–2.22
Slovakia	1.94	1.87–2.02	1.79	1.72–1.85
Poland	1.67	1.57–1.79	1.63	1.53–1.75

Source: Gatta et al. [4]
Based on 108,728 cases diagnosed in 2000–2007
CI confidence interval

Table 2.5 Relative excess risks (RERs) of death by sub-site relative to base of tongue plus vallecula plus lingual tonsil (reference) with age, sex and country as covariates

Sub-site	ICD-O-3 code	%	RER of death	95% CI
Base of tongue, vallecula and lingual tonsil	C01.9, C02.4, C02.8, C10.0	11.2	1 (reference)	
Tongue, other parts	C02.0–C02.3, C02.9	16.8	0.73	0.70–0.75
Gum	C03.0–C03.9	5.5	0.75	0.72–0.79
Floor of mouth	C04.0–C04.9	11.7	0.83	0.80–0.86
Palate	C05.0–C05.9	6.4	0.67	0.64–0.70
Cheek and vestibule of mouth	C06.0–C06.1	3.2	0.61	0.58–0.65
Retro-molar area	C06.2	2.4	0.73	0.69–0.78
Mouth, NOS	C06.8–C06.9	2.5	0.88	0.83–0.93
Tonsil	C09.0–C09.9	16.4	0.73	0.71–0.75
Anterior surface of epiglottitis	C10.1	0.4	0.72	0.62–0.83
Lateral wall of oropharynx	C10.2, C10.8	2.5	1.30	1.23–1.37
Posterior wall of oropharynx	C10.3	0.6	1.24	1.12–1.37
Oropharynx and pharynx, NOS	C10.9, C14.0, C14.8	6.0	1.53	1.47–1.59
Pyriform sinus and posterior wall of hypopharynx	C12.9, C13.2	7.6	1.26	1.22–1.31
Aryepiglottic fold	C13.1	0.7	0.87	0.79–0.97
Postcricoid region	C13.0	0.8	1.62	1.49–1.76
Hypopharynx, NOS	C13.8–C13.9	5.4	1.52	1.46–1.58

Source: Gatta et al. [4]
Based on 108,728 cases diagnosed in 2000–2007
ICD-O-3 International Classification of Diseases for Oncology, 3st revision, *CI* confidence interval, *NOS* not otherwhise specified

Table 2.6 (A) Relative excess risks (RERs) of death by country for laryngeal cancer by age and sex (Model 1) and by age, sex and sub-site (Model 2) compared with England. (B) RERs of death by sub-site relative to glottis (reference) with age, sex and country as covariates. Based on 52,461 cases diagnosed in 2000–2007

	Model 1		**Model 2**	
(A) Country	**RER of death**	**95 % CI**	**RER of death**	**95 % CI**
Northern Europe				
Norway	0.79	0.69–0.90	0.86	0.76–0.98
Sweden	0.82	0.74–0.91	0.89	0.80–0.99
Ireland and UK				
Ireland	1.10	0.98–1.23	1.22	1.09–1.36
UK, England	*1 (reference)*		*1 (reference)*	
UK, Northern Ireland	0.60	0.5–0.74	0.62	0.51–0.75
UK, Scotland	0.95	0.88–1.03	0.90	0.83–0.98
UK, Wales	0.97	0.86–1.09	1.03	0.91–1.16
Central Europe				
Belgium	1.03	0.96–1.10	0.97	0.91–1.04
France	1.04	0.96–1.14	0.97	0.89–1.06
Germany	0.91	0.86–0.97	0.84	0.79–0.90
Switzerland	0.88	0.77–1.01	0.88	0.76–1.00
The Netherlands	0.71	0.67–0.75	0.79	0.75–0.85
Southern Europe				
Italy	0.66	0.61–0.70	0.66	0.62–0.71
Malta	0.80	0.57–1.12	0.99	0.71–1.38
Slovenia	0.98	0.86–1.11	0.88	0.77–0.99
Spain	0.92	0.86–0.99	0.79	0.74–0.85
Eastern Europe				
Czech Republic	1.28	1.21–1.36	1.19	1.12–1.27
Estonia	1.47	1.27–1.69	1.26	1.09–1.45
Slovakia	1.60	1.49–1.73	1.39	1.29–1.50
(B) Sub-site	**ICD-O-3 code**	**%**	**RER of death**	**95 % CI**
Glottis	C32.0	53.2	*1 (reference)*	
Supraglottis	C32.1	24.6	3.31	3.19–3.45
Subglottis	C32.2	1.8	2.88	2.61–3.18
Overlapping lesion of larynx	C32.8	4.5	3.47	3.24–3.71
Larynx, NOS	C32.9	15.8	3.28	3.13–3.42

Source: Gatta et al. [4]
ICD-O-3 International Classification of Diseases for Oncology, 3st revision, *CI* confidence interval, *NOS* not otherwise specified

Table 2.7 Frequency distribution of stage (%) and 5-year relative survival (RS), by head and neck (H&N) cancer site, country and European region

	Local			Regional			Metastatic			Unknown		
	%	RS	95% CI	%	RS	95% CI	%	RS	95% CI	%	RS	95% CI
Tongue and lingual tonsil	36.0	64.9	62.9–66.9	52.0	33.4	31.9–34.9	3.0	9.1	5.4–14.0	9.0	39.4	35.4–43.3
Oral cavity	39.0	69	67.3–70.7	47.0	33.6	32.2–35.0	3.0	8.8	5.8–12.7	11.0	50.8	47.6–54.0
Oropharynx and tonsil	19.0	57.6	55.0–60.2	69.0	38.2	36.9–39.5	4.0	12.4	9.3–16.0	8.0	33.1	29.2–37.0
Hypopharynx	14.0	41.8	38.0–45.6	72.0	23.6	22.3–25.0	7.0	3.9	2.0–6.6	7.0	20.2	16.3–24.4
Larynx	56.0	74.4	73.1–75.6	31.0	37.8	36.3–39.4	2.0	7.2	4.5–10.7	11.0	61.4	58.6–64.1
All H&N	36.0	68.7	67.9–69.5	50.0	33.7	33.0–34.3	4.0	8.2	6.9–9.8	10.0	47.3	45.7–48.9
Northern Europe												
Norway	34.3	74.4	70.3–78.0	42.2	41.7	38.4–44.9	4.4	12.8	7.2–19.9	19.1	59.8	54.6–64.7
Central Europe	37.7	73.0	72.0–73.9	47.7	38.8	38.0–39.7	3.5	9.5	7.7–11.5	11.1	49.0	47.2–50.9
Austria	29.7	69.5	67.1–71.9	52.5	39.8	38.0–41.5	4.8	10.9	7.6–15.0	13.0	37.4	33.8–40.9
Germany	30.0	70.2	68.5–71.9	49.0	37.7	36.5–39.0	4.0	11.0	8.2–14.2	17.0	51.0	48.7–53.4
The Netherlands	50.0	75.2	73.8–76.6	43.8	38.2	36.8–39.6	2.3	4.5	2.2–8.0	3.9	55.1	50.1–59.9
Southern Europe												
Slovenia	31.7	70.80	66.5–74.7	65.2	31.7	29.2–34.3	2.1	2.8	0.3–11.4	1.0	13.40	2.7–32.7
Eastern Europe	34.2	53.50	51.6–55.3	56.9	20.70	19.6–21.8	4.0	5.00	3.0–7.6	5.0	28.70	24.6–32.8
Estonia	49.3	50.20	45.1–55.1	45.9	21.8	18.0–25.8	3.6	N.A	N.A	1.2	32.70	92–59.2
Lithuania	36.5	48.90	45.3–52.4	45.8	16.4	14.3–18.7	3.4	0.0	N.A	14.4	29.00	24.3–34.0
Poland	65.1	56.30	50.0–62.1	27.7	26.7	19.4–34.5	7.2	6.6	1.3–18.3	0.0		
Slovakia	27.8	56.40	53.7–59.0	66.0	21.6	20.3–22.9	4.0	6.2	3.6–9.7	2.1	27.00	19.7–34.8

Source: Gatta et al. [4]
13 registries in 9 countries, only
RS 5-year relative survival, *Stage local* confined to the site of origin, *regional* spread to adjacent tissue or nodes+, *metastatic* spread to distant organ, *CI* confidence interval, *NOS* not otherwise specified

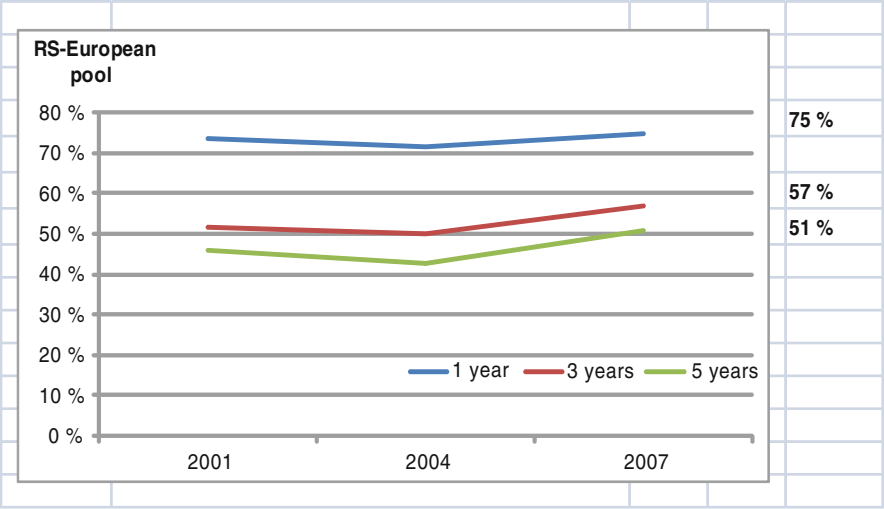


Fig. 2.11 Time trend in age-standardised 1-, 3-, 5-year relative survival (RS, %) for nasal cavities cancer patients, period 1999–2007 (Source: RARECAREnet project)

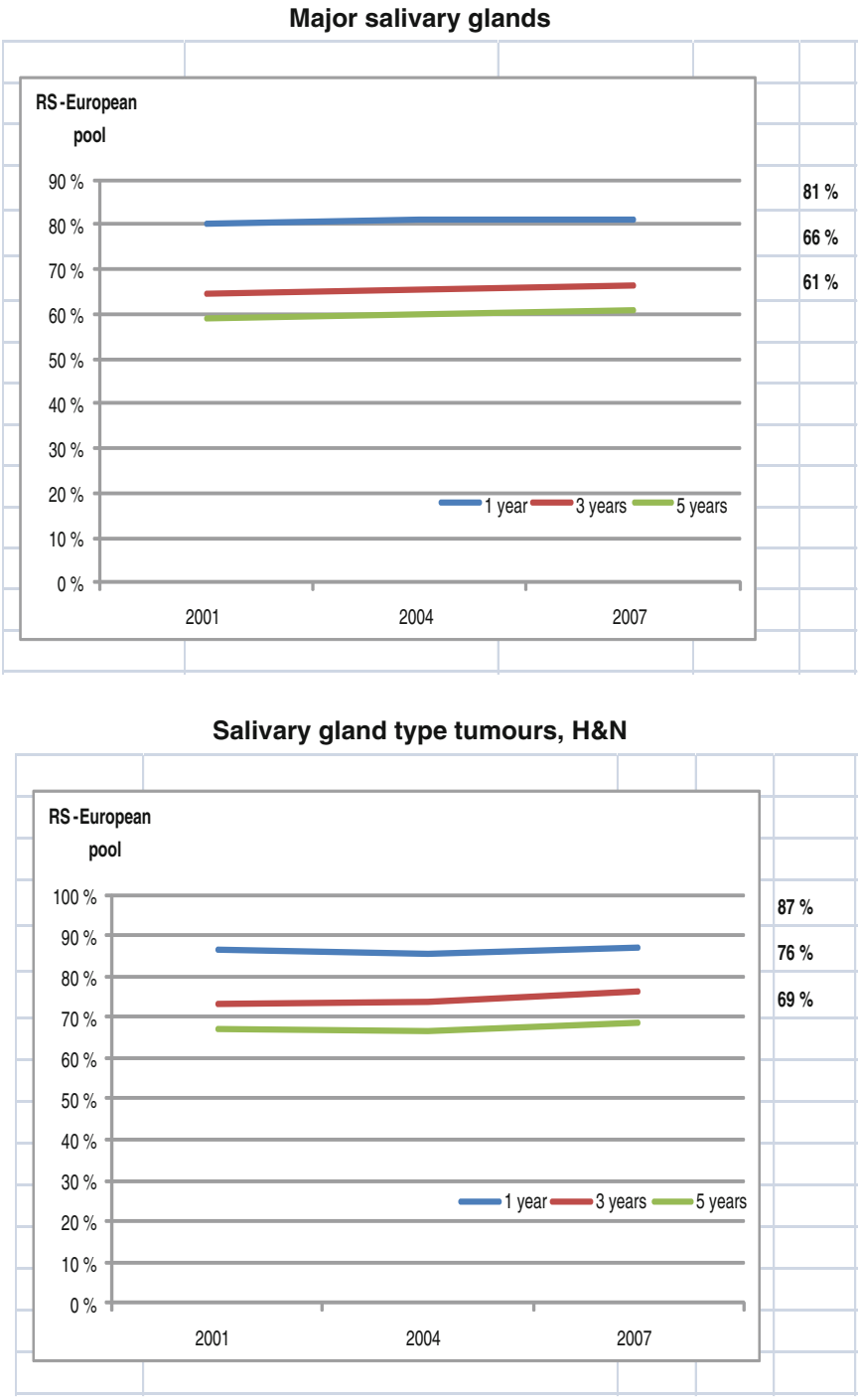


Fig. 2.12 Time trend in age-standardised 1-, 3-, 5-year relative survival (RS, %) for major salivary glands and salivary gland type cancer patients, period 1999–2007 (Source: RARECAREnet project)

Conclusions

According to both European definition of rare diseases and RARECARE project, all H&N can be considered as rare. Their major risk factors are well known, being tobacco, alcohol, diet responsible of a substantial fraction of cases [5, 6]. Virus are specifically involved in a causal association with two H&N cancers: EBV is for nasopharynx and, particularly, HPV is for oropharynx [7, 8]. Occupational exposures are also relevant for all the H&N [9]. Knowledge of risk factors implies the possibility to act with preventive programmes. Most of these risk factors are also involved with other more common cancers; thus, preventive plans can be effective against a larger fraction of cancers. Furthermore, some risk factors are also prognostic factors that in some cases (tobacco and alcohol) can be responsible of recurrences or while in other cases (as the HPV) are associated with less aggressive cancers [10–14]. The application of preventive plans may save a fraction of the cost presently needed to care H&N patients and are definitely more comfortable for the citizen. However, preventive programmes have to be rigorously evaluated.

Survival progress have been reported for quite all H&N; however, about 50 % of patients present at diagnosis with advanced stage; survival is poor in the elderly and, as for the great majority of cancers, survival is better in women than in men, possibly due to more favourable risk/prognostic factors distribution. Geographical survival disparities are partly due to not homogeneous distribution of sub-site in European countries [15].

However, sub-site explained only a part of the differences, and it should be crucial to involve population-based cancer registries to collect more clinical variables, in *ad hoc* studies, in order to analyse hypotheses of disparities. Such studies are only possible in collaboration with clinicians.

Management of H&N is complex and multimodal and requires a multidisciplinary approach. The access to appropriate treatment is therefore not easy. Early detection is difficult to achieve due to the un-specificity of symptoms and signs, but effective programmes for increasing the awareness of key physicians (dentists, general practitioner, etc.) should be implemented and evaluated. Actually, one of the most pressing questions is why the majority of H&N cancers are diagnosed late. Delay of treatment for H&N cancers is still one of major reasons of negative patient outcomes [16]. Studies demonstrated the value of being treated in large-volume H&N centres [17], and we believe that the benefits of high-volume centres must be made accessible to all patients with H&N for optimal outcomes to be achieved. However, small or local centres, close to home, should be linked to high-volume centres in a network arrangement to avoid patient discomfort.

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Chapter 3
The Biology of Head and Neck Cancer

Kevin J. Harrington

Introduction

Cancer is a genetic disease that arises when the information in cellular DNA is corrupted, leading to abnormal patterns of gene expression. As a result, the effects of normal genes that control normal cellular functions, such as growth, survival and invasion/motility, are enhanced and those of genes that act to suppress these effects are repressed. The main mechanism of genetic alteration is through the accumulation of mutations, but it is increasingly clear that non-mutational (epigenetic) changes that affect patterns of gene transcription play a key role in the process. In addition to effects that occur in cancer cells, there is a growing understanding of the influence of changes in the so-called tumour microenvironment (TME) on the biological behaviour of cancers.

The entire genetic code consists of about 3.2×10^9 bases and contains approximately 20,000–25,000 genes, whose function is to make proteins. Alternate splicing of messenger RNA transcripts of approximately 70 % of human genes allows different proteins to be produced from the same gene. On average, genes produce about four alternatively spliced mRNAs, such that the human genome encodes about 100,000 different proteins. Cancer is driven by two classes of genes – oncogenes and tumour suppressor genes (TSGs) – each of which provides essential functions in normal cells. Oncogenes are derived from mutated versions of normal cellular genes (called proto-oncogenes) that control cell proliferation, survival and invasion/motility. In normal cells, expression of proto-oncogenes is tightly regulated to prevent uncontrolled cell growth. In cancer, activating mutations of proto-oncogenes

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cause uncontrolled cell division, enhanced survival (including in response to anti-cancer treatments) and tumour spread. Oncogenes can be activated through: gain-of-function activating mutations; genetic amplification to produce multiple copies of a normal gene that is overexpressed; and gene translocation to bring a proto-oncogene under the control of a new, highly active promoter or to create a novel, fusion protein with enhanced biological activity. TSGs function to inhibit cell proliferation and survival. They are frequently involved in controlling cell cycle progression and programmed cell death processes.

In recent years, The Cancer Genome Atlas (http://cancergenome.nih.gov/) programme has catalogued the specific genetic alterations in an increasing number of tumour types, including squamous cell cancers of the head and neck (SCCHN) [1]. These data have highlighted a number of genes that are important drivers of the biology of SCCHN and have shown that there are specific genetic differences between human papillomavirus (HPV)-positive and HPV-negative tumours. More than 80 % of SCCHN have abnormalities in *TP53* function, potentially rendering them vulnerable to targeted therapies that act selectively in certain phases of the cell cycle (see below). Inactivating mutations of *CDKN2A* (p16) have also been shown to be present in about 20 % of cases. Both of these events are selectively present in HPV-negative, as opposed to HPV-positive, tumours. In HPV-positive tumours, activating mutations of *PIK3CA* have been found to be common and, again, this represents a potential therapeutic target in these cases. Other genetic abnormalities appear to be present in both HPV-negative and HPV-positive cases and are, as yet, of uncertain biological and therapeutic significance. For example, approximately one-third of SCCHN have mutations in genes that control squamous differentiation (*NOTCH1*, *IRF6*, *TP63*) and approximately 10 % have abnormalities in *CASP8*, which is involved in signalling in the extrinsic apoptotic pathway. Further research in this area is likely to provide greater insights into the biology of SCCHN and pinpoint important new therapeutic targets.

Key Biological Processes in Cancer

Hanahan and Weinberg described six fundamental changes in cancers (growth factor independence, evading growth suppressors, avoiding cell death, maintaining replicative potential, angiogenesis, invasion/metastasis) that, at the time, were thought to explain their malignant behaviour [2]. This description was subsequently updated in 2011 with the incorporation of two emerging hallmarks (reprogramming energy metabolism, evading immune destruction) and two enabling characteristics (genomic instability, inflammation) [3].

Although it is likely that each of these processes plays an important role in almost all SCCHN, it would appear that certain hallmarks and enabling characteristics are more important than others. In the rest of this chapter, the discussion will focus on the following key biological processes that, at present, appear to hold the greatest prospect for changing the way that we treat SCCHN: (i) deregulated growth factor

signalling; (ii) toleration of DNA damage and avoidance of cell death; (iii) promotion of invasion and metastasis; and (iv) evasion of immune destruction.

Deregulated Growth Factor Signaling

A general scheme for the function of growth factor receptors and their ligands in promoting cell growth (and other effects) is shown in (Fig. 3.1). SCCHN very often show upregulated epidermal growth factor receptor (EGFR) signalling. EGFR is a member of the c-erbB family of receptor tyrosine kinases, which comprises four members (EGFR/c-erbB-1/HER1, c-erbB-2/neu/HER-2, c-erbB-3/HER-3, c-erbB-4/HER-4 [4]. These proteins share a common structure, consisting of a glycosylated extracellular ligand-binding domain, a hydrophobic trans-membrane component and an intracellular domain with tyrosine kinase activity. When the specific, cognate ligand binds to its ligand-binding site, it causes receptor dimerisation and activation of the intracellular kinase domain. This, in turn, triggers phosphorylation of target proteins which causes a cascade of intracellular secondary

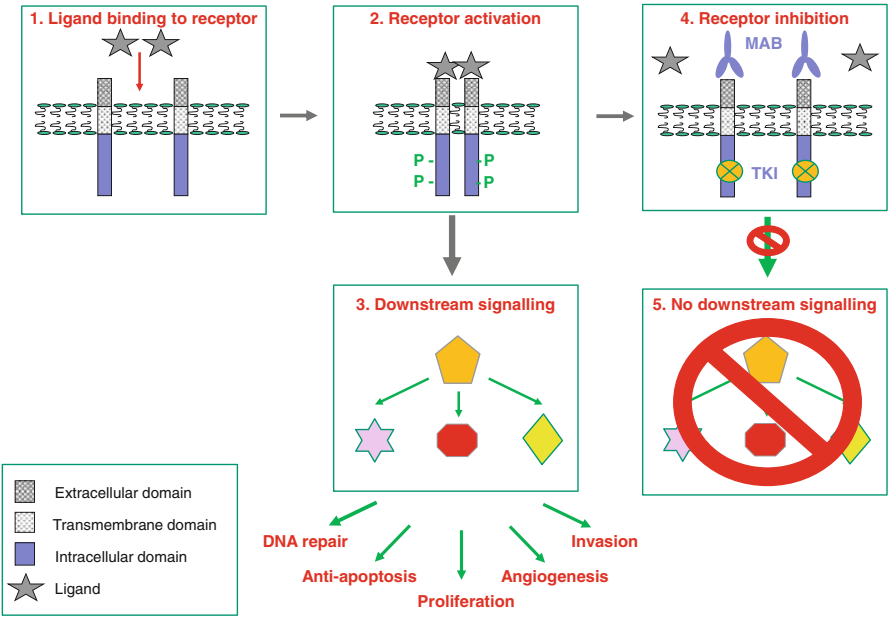

Fig. 3.1 Growth factor independence leads to sustained signalling in pathways that control essential biological functions. Binding of ligand to the extracellular ligand-binding domain leads to receptor dimerisation and activation of the kinase function in the intracellular domain. This mediates receptor phosphorylation, triggering recruitment of adaptor molecules and activation of downstream signal transduction pathways, leading to altered patterns of gene expression. Ultimately, this leads to altered biological behaviours which are characteristic hallmarks of cancer

messengers that trigger altered patterns of gene expression. In this way, binding of a protein on the cell surface can influence the cell's behaviour. Signalling through c-erbB receptors governs the activity of a number of cellular processes that can be associated with normal growth/wound healing, but which are frequently subsumed as a cancer develops (Fig. 3.1).

Normally, activation of growth factor receptors is very tightly regulated – as is the synthesis and release of the ligands that stimulate them. Cancer cells almost ubiquitously deregulate normal growth factor signalling pathways and use them to promote unrestrained cell division [4]. It is important to note that there is no ligand for the c-erbB2/HER2 receptor and that the c-erbB3/HER3 receptor has no kinase activity. Nonetheless, these receptors are able to participate in signalling by dimerising with appropriate partners (e.g. c-erbB-2:c-erbB-3 (HER2/HER3) heterodimers exploit ligand binding to the HER3 component and kinase-mediated signalling from the HER2 component).

Cancer cells achieve self-sufficiency in growth factors by three main mechanisms: (1) they make and release growth factors to stimulate their own (autocrine) and neighbouring cells' (paracrine) receptors; (2) they alter the number, structure or function of growth factor receptors on their surface so they are primed to relay a growth signal to the nucleus (even without binding of cognate ligand); and (3) they deregulate signalling pathways downstream of the receptor to turn it on permanently (constitutive activation). In contrast to other tumour types, in which EGFR gene amplification or mutation is frequent (e.g. lung adenocarcinoma), overexpression of the receptor, without gene amplification, is the dominant process whereby EGFR influences the pathobiology of SCCHN. Previously, a mutated, truncated form of EGFR (EGFR variant III) was believed to be expressed in many head and neck cancers [5], but recent reports have cast doubt on this as a major driver in SCCHN [6]. The roles of c-erbB-2, c-erbB-3 and c-erbB4 in SCCHN remain unclear. However, it is known that c-erbB-2:c-erbB-3 (HER2/HER3) heterodimers are potent inducers of the PI3-kinase anti-apoptotic pathway [7] and this may be relevant to particular subsets of SCCHN, including human papillomavirus (HPV)-related disease [1].

c-erbB receptors are attractive therapeutic targets in SCCHN. Two main classes of drugs, monoclonal antibodies (MAB) and small molecule tyrosine kinase inhibitors (smTKI), have been developed. MAB are large molecules directed against the extracellular domain of the receptor, while smTKI inhibit the receptor's intracellular kinase domain. A number of EGFR-targeted MAB, differing in terms of their species of origin (murine, chimeric (part human/part murine) or fully human) and the specific part (epitope) of the EGFR protein to which they bind, have entered clinical trials. The main agents to consider in the context of SCCHN are: cetuximab (C225, Erbitux), zalutumumab and panitumumab (Vectibix). Cetuximab has been shown in randomised phase III trials to be effective in combination with radiation [8, 9] (but not chemoradiation [10]) in newly diagnosed locally-advanced disease. In addition, it has been shown to improve survival when combined with platin and 5-fluorouracil chemotherapy in the context of first-line treatment for relapsed/metastatic disease [11]. The other anti-EGFR MABs have not established a role in the treatment of

SCCHN, either as part of radiation/chemoradiation (RT/CRT) combinations [12–14] or in the relapsed/metastatic setting (first- or second-line) [15, 16]. Small molecule TKIs have, as yet, failed to find a place as standards-of-care in the management of SCCHN. Gefitinib, erlotinib and lapatinib have been evaluated in combination with RT/CRT in patients with newly diagnosed locally-advanced SCCHN and in relapsed/metastatic disease, without clear evidence of benefit [17–26]. In the context of relapsed/metastatic disease, only one agent (afatinib) has shown a positive result in a randomised trial [27]. Afatinib is an irreversible inhibitor of EGFR, c-erbB2/HER2 and c-erbB4/HER4 that is currently being investigated in a number of settings in SCCHN. In the primary treatment setting, it is being tested in combination with CRT (NCT01732640), and as adjuvant therapy after definitive CRT in high-risk patients (phase III LUX2 study NCT01345669) or after surgery (GORTEC 2010–02, EudraCT 2010-023265-22). Afatinib has been assessed in the phase III LUX head and neck-1 study in 583 patients receiving second-line therapy for relapsed/metastatic SCCHN [27]. Afatinib significantly increased median progression-free survival (2.6 versus 1.7 months, $p=0.03$) but did not improve median overall survival (6.8 versus 6.0 months) relative to methotrexate. In an integrated analysis of quality of life, afatinib showed a delay in deterioration of global health status, pain and swallowing problems (all $p \leq 0.03$). These modest benefits mean that it is unlikely that afatinib will be approved for use in patients with relapsed/metastatic SCCHN.

Toleration of DNA Damage and Avoidance of Cell Death

During cell division, as cells duplicate their DNA, they assess their genomic integrity and check for errors in the DNA sequence. If errors are present, they can arrest at cell cycle checkpoints and engage DNA repair pathways. There are four cell cycle checkpoints: at G1/S transition, during S phase, early in G2 phase and late in G2 phase.

Two of these checkpoints are particularly relevant to the cellular response to RT/CRT in SCCHN [28]. The G1/S checkpoint allows diploid (2n, 46 chromosomes) cells to pause before entering synthesis (S) phase, during which the entire DNA complement is duplicated to create a cell with 4n DNA content before mitosis. The tumour suppressor genes *TP53* and retinoblastoma (*RB1*) are essential for the G1/S checkpoint. *TP53* pathway mutation or inactivation is very common in SCCHN. Smoking-induced SCCHN shows almost universal loss-of-function mutations of the p53 pathway, with 84 % of tumours showing *TP53* mutation [1]. In contrast, just 3 % of HPV-negative SCCHNs have mutated *TP53*, but in these tumours the pathway is inactivated through interactions between viral E6 and E7 proteins with p53 and Rb proteins, respectively. As a consequence of aberrant G1/S checkpoint status, most SCCHN are highly reliant on a functional G2/M checkpoint.

RT/CRT induces a number of lesions in DNA, ranging from purine and pyrimidine lesions to single-strand (SSB) and double-strand breaks (DSB) in the DNA. DSB are the most lethal DNA lesions induced by RT/CRT and therapies that

can prevent their repair/resolution have the potential to act as radiosensitisers. As might be expected, there are specific mechanisms to detect and repair radiation-induced abnormalities in DNA structure: DSBs are repaired by non-homologous end-joining (NHEJ) repair during G1 phase of the cell cycle and by high-fidelity homologous recombination (HR) in S and G2 phases; SSBs and base damage are repaired through the base excision repair pathway (reviewed in 28).

Normal (and cancer) cells continually assess their viability by auditing the balance of pro- and anti-survival signals that they receive. In normal cells, endogenous (during replication) or exogenous (from genotoxic events such as RT/CRT) DNA damage leads to cell cycle arrest and attempted DNA repair. If the extent of damage exceeds the capacity for repair, the balance of pro- and anti-survival signals shifts and the cell triggers cell death pathways (apoptosis, autophagy, necroptosis, necrosis). This mechanism protects the organism against generating and perpetuating genetic damage. In contrast, loss of normal cell death pathway signalling is extremely common in cancer (including SCCHN). Indeed, two of the best known cancer-associated genes (*TP53* and *BCL-2*) are intimately involved in cell death signalling. Cancer cells frequently evade apoptosis by ignoring signals sent through the extrinsic pathway or by resetting the balance of intracellular pro- and anti-survival molecules in favour of inhibition of apoptosis. By avoiding apoptosis, cancer cells can sustain DNA damage without it causing cell death (unless the damaged gene is absolutely necessary for cell survival). Thus, cancer cells that bypass normal apoptotic signalling are more likely to have unstable genomes and to be intrinsically resistant to anti-cancer treatments.

Although there are obvious advantages in cancer cells switching off normal cell cycle checkpoint controls and cell death signalling pathways, it also exposes them to significant risks. As discussed above, most SCCHN (both HPV-negative and HPV-positive) lack a normal p53-mediated G1/S checkpoint and, thus, become highly dependent on the ATR-Chk1 pathway (Fig. 3.2) to mediate S and G2/M arrest to allow repair of DNA damage following RT/CRT. As such, G2/M checkpoint control can be seen as a particularly attractive target for cancer-specific radiosensitisation [reviewed in 28]. p53-defective cancer cells exposed to RT/CRT will not be able to arrest at the G1/S checkpoint, rendering them highly vulnerable to drugs that inhibit the G2 checkpoint. Cancer cells treated in this way will proceed into mitosis before repairing their RT/CRT-induced DNA damage and, as a result, will run a significant risk of mitotic catastrophe and cell death. This activity of G2/M checkpoint inhibitors in p53-defective tumour cells is an example of so-called synthetic lethality and represents a promising prospect for developing cancer-selective radiosensitising drugs (Fig. 3.3).

A number of G2/M-targeted radiosensitisers are under development and are beginning to enter clinical trials. ATR inhibitors (VE-821, VE-822, AZD6738) are showing promise in preclinical models and are in early-phase clinical trials both as monotherapy and combined with radiotherapy, chemotherapy or immunotherapy [NCT02223923, NCT02264678] [29–33]. Early Chk1 inhibitors (UCN-01, AZD7762) have been tested in clinical trials, but their development was stopped

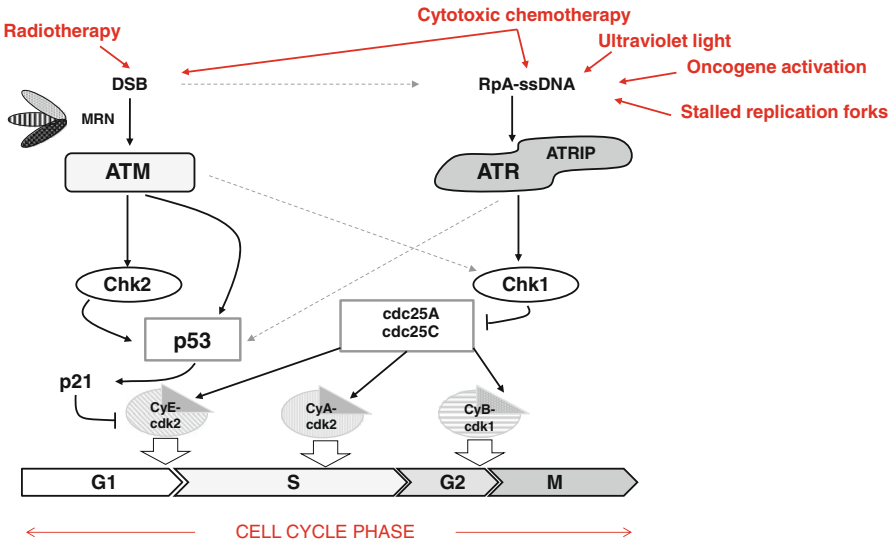

Fig. 3.2 DNA damage leads to activation of DNA damage response and cell cycle arrest pathways. The frequent loss of p53 function in head and neck cancers leads to reliance on G2/M cell cycle arrest and DNA repair pathways that operate in G2 phase of the cell cycle

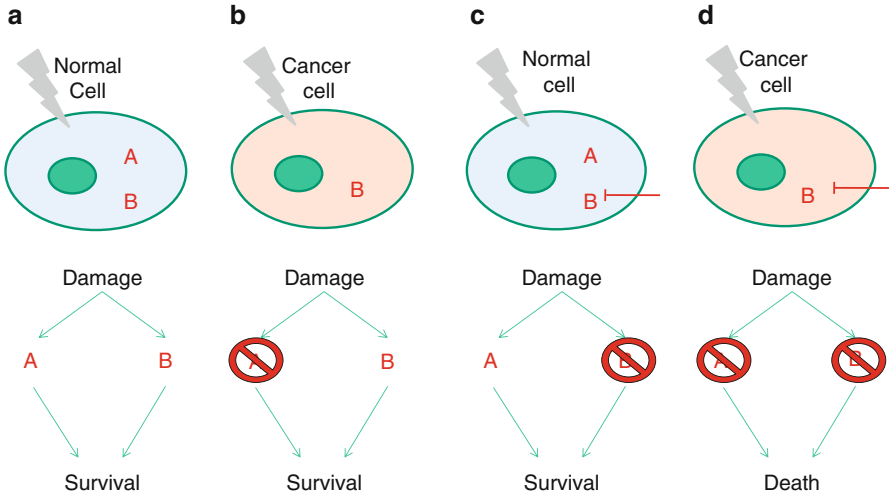

Fig. 3.3 The concept of synthetic lethality as applied to G2/M-targeted drugs in tumours that lack p53-mediated G1 checkpoint control

because of concerns about lack of efficacy or toxicity [34–38]. However, newer orally bioavailable agents, such as CCT245737 [39], are now in clinical trials and would appear to offer significant promise as targeted chemo-/radiosensitisers.

Invasion and Metastasis

Distant metastases cause 90 % of cancer deaths and are emerging as an increasing problem in SCCHN as we improve our ability to secure locoregional control with advanced RT/CRT and surgical approaches. Invasion and metastasis involves orchestrating a sequence of complex biological processes [40]. These include: (1) detachment of the tumour cell from its immediate neighbours and stroma at the local site; (2) enzymatic degradation of the extracellular matrix followed by specific directional motility (as single cells or in co-operative groups); (3) penetration (intravasation) of blood or lymphatic vessels and tumour embolisation; (4) survival of tumour cells in the circulation until arrival at the metastatic site that may be "chosen" on the basis of its ability to provide a favourable supply of appropriate growth factors; (5) attachment to the endothelium of blood vessels at its destination and extravasation from the vessel; and (6) proliferation and invasion of its new location and recruitment of a new blood supply.

This general scheme has been understood for some years, but a number of recent observations have shed new light on the process of invasion and metastasis. In an in vitro culture system that attempted to recapitulate the physiological situation (surface exposed to a gaseous interface, base in contact with a matrix of fibrillar collagen I, laminin, collagen IV), Gaggioli et al. (2007) [41] showed that the movement of malignant head and neck cancer cells through the extracellular matrix was a collective process that enlisted the help of cancer-associated fibroblasts. Using imaging and molecular biology techniques, it was shown that fibroblasts generate tunnels in the extracellular matrix, by enzymatic (protease) digestion and force-mediated matrix remodelling, through which carcinoma cells follow. The carcinoma cells use Cdc42 and MRCK (myotonic dystrophy kinase-related CDC42-binding protein kinases) to regulate intracellular myosin light chain as a means of controlling their directional motility behind invading fibroblasts. Some of these signaling events are controlled by proteins which may be druggable targets, offering the prospect of developing specific agents that inhibit the ability of malignant cells to invade normal tissues. Such studies are ongoing.

The process by which tumour cells escape from the primary tumour and establish metastatic colonies in biologically favourable secondary tissues has also been the subject of much research. This work has completely changed our understanding of the biology of tumour metastasis. For example, studies have shown that far from being a passive game of chance whereby an aspiring metastatic cell has to trust fortune to carry it to what Paget called "congenial soil", it is now clear that metastasis involves a degree of forward planning and preparation on the part of the tumour. In breast cancer models, it has been shown that metastasis is facilitated by the formation of "pre-metastatic niches" in target organs. This occurs through the activities of bone marrow-derived cells that accumulate at metastatic sites in advance of tumour deposits and condition the environment to make it favourable to tumour cells that subsequently arrive and establish a secondary colony. The process is initially triggered by hypoxic tumour cells secreting an enzyme, lysyl oxidase (LOX),

into the circulation. LOX accumulates at pre-metastatic sites where it mediates the cross-linking of structural proteins in the extracellular matrix [42]. Specifically, LOX catalyses oxidative deamination of the primary amines of lysine and hydroxylysine in proteins such as collagen and tropoelastin to generate peptidyl-α-aminoadipic-δ-semialdehyde, an aldehyde that spontaneously condenses to form both inter- and intra-chain cross-links. Consequently, LOX regulates maturation of proteins in the extracellular matrix, thereby modifying its tensile strength and function and playing an important part in connective tissue remodelling. LOX-mediated tissue remodelling is an essential prerequisite for subsequent recruitment of CD11b+myeloid cells which adhere to crosslinked collagen IV and produce matrix metalloproteinase-2, which cleaves collagen and increases the invasion and recruitment of bone marrow-derived cells and metastasising tumour cells. Elevated LOX expression is associated with the formation of metastases but it is also required for their continued survival and growth. Importantly, it has been shown that inhibiting LOX can prevent CD11b+cell recruitment and, thus, prevent metastatic growth. Le et al. (2009) have validated LOX as a biomarker of metastasis in head and neck cancer patients [43]. They studied 66 head and neck cancer patients from a single institution and 306 of 1113 patients treated in the RTOG 90–03 trial. LOX expression predicted time to metastasis in the initial 66 patient cohort. In the RTOG 90–03 study, multivariate analysis, controlling for significant parameters such as nodal stage and performance status, revealed LOX expression was a statistically significant independent predictor for time to metastasis, time to progression and overall survival. These fundamental discoveries have resulted in drug discovery programmes that seek to generate chemical inhibitors of LOX activity, with the goal of reducing the establishment of metastatic deposits and attacking those that have already come into being.

Evading Immune Destruction

The theory of immune surveillance maintains that the immune system is constantly vigilant against the emergence of premalignant and frankly malignant cells. The observation that patients with chronic immunosuppression (e.g. after organ transplantation) are prone to specific cancers, especially those of viral origin, is frequently cited as evidence in favour of this theory. There is also evidence that the immune system acts as a significant barrier to non-virally-induced cancers in immunocompetent patients. Therefore, the occurrence of tumours can be viewed as a failure of the immune system to recognise, reject and destroy tumour cells that express altered self-antigens. As part of this process, it is thought that selection of less immunogenic cancer cells (through immunoediting) and active recruitment of immunosuppressive components of the immune system (e.g. regulatory T cells, myeloid-derived suppressor cells and suppressive macrophages) to some cancers ultimately allows tumours to escape from immune surveillance, grow and spread without becoming targets for immune attack [44, 45].

For decades, scientists and clinicians sought to understand how they could use immunotherapies as active anti-cancer agents. Much of this work focussed on using immune-activating cytokines (e.g. interleukin-2, interferon-α, interferon-β) as single-agent treatments or as part of biochemotherapy cocktails. In the main, those efforts proved to be fruitless. It is only in recent years that immunotherapy has emerged as a major new modality in the treatment of a wide variety of solid cancers, including SCCHN [44]. Renewed interest in immunotherapy has been underpinned by significant advances in our understanding of the fundamental biological principles that govern the activity of the immune system. In particular, specific immune checkpoints have been discovered that act as integral components of normal immune responses. In normal health, these checkpoints function to inhibit T cells and prevent them from becoming chronically activated or aberrantly directed against normal tissues. Effectively, they serve the function of negative regulators or "brakes" on the normal immune response. Many cancers exploit these inhibitory pathways in order to break free from immunosurveillance. Therefore, by activating brakes on the immune system, cancer cells are able to emerge from elimination/equilibrium phase and escape from immune detection and/or immune-related attack [45].

Proteins that are expressed on activated T cells, such as cytotoxic T-lymphocyte-associated protein 4 (CTLA4) and programmed death 1 (PD1), are key players that allow many cancers to evade anti-tumour immunity by disrupting the activation and effector phases of immune responses, respectively. CTLA4 is an important control mechanism that influences the activation phase of the immune response. When a specific tumour-associated antigen is presented by an antigen-presenting cell (APC) to a T cell that expresses a T-cell receptor capable of recognising it, there are two possible outcomes. In the first outcome, if the T cell also receives a co-stimulatory signal via B7 on the APC binding to CD28 on the T cell, the T cell will become activated and capable of dividing to generate a clone of T cells that can mediate an anti-tumour effect. However, in becoming activated, the T cell upregulates CTLA4 on its surface and this is able to out-compete CD28 for binding of B7 on the APC. The net effect is that the T cell can be switched off or anergised. Therapeutic monoclonal antibodies that target CTLA4 (e.g. ipilimumab, tremelimumab) can block this negative interaction and enhance T cell activation. In the effector phase of the immune response (Fig. 3.4), an activated T cell can be prevented from engaging with and killing a tumour cell if the tumour cell expresses the negative regulatory ligand programmed death ligand 1 (PD-L1) on its surface (either constitutively or in response to interferon-gamma secreted by an activated T cell). This negative interaction between T cell and tumour cell can be interrupted by administration of specific monoclonal antibodies that block either PD-1 on the T cell surface or PD-L1 on the tumour cell surface.

In addition to these two pathways, a large number of other checkpoints have been described at the so-called immune synapse. Some of these checkpoints lead to inhibition (e.g. TIM3, LAG3, VISTA), and others to activation (e.g. OX40, CD137/4-1BB, GITR) of immune responses. Many new therapeutic agents are currently in preclinical or clinical development and it is probable that some of these will enter the clinic in the next few years.

Both anti-CTLA4 and anti-PD1/PD-L1 monoclonal antibodies have demonstrated significant activity in a range of non-SCCHN tumour types, including melanoma, lung, bladder and mismatch repair-deficient bowel cancer. Interestingly, the chance that a patient will benefit from immunotherapy appears to correlate directly with the mutational burden and, hence, the neoantigenic load within their tumour [46]. This

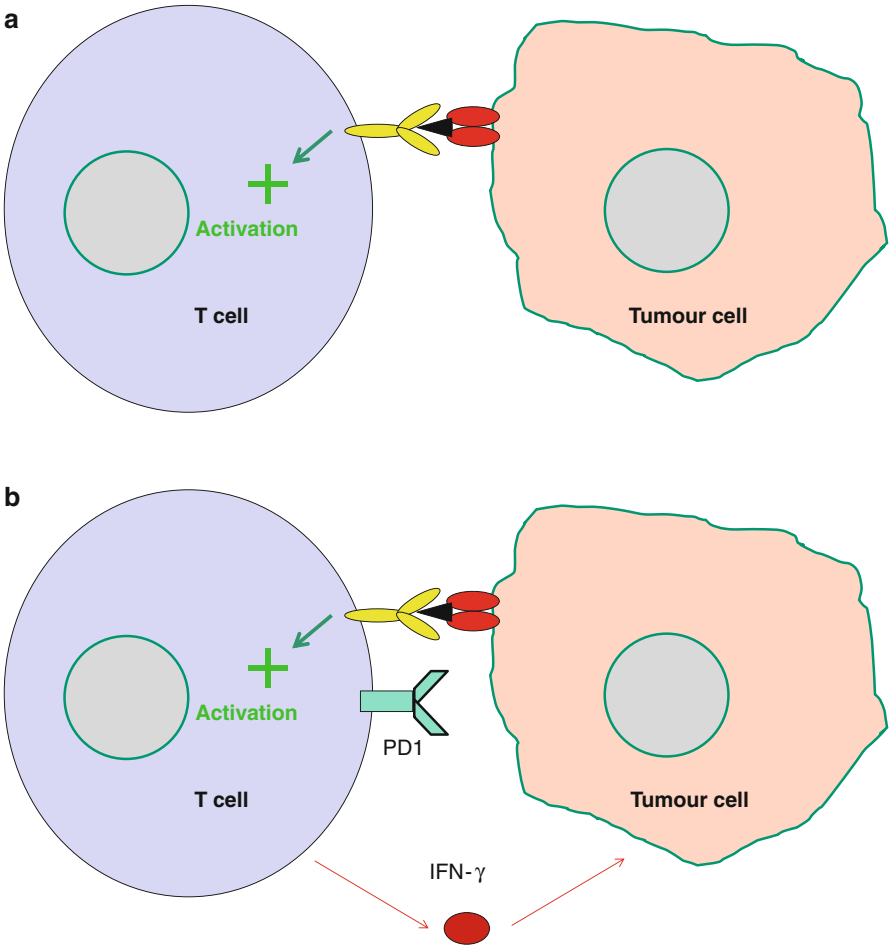

Fig. 3.4 Mechanisms of immunotherapy based on PD1/PD-L1-targeted therapies. PD-1/PD-L1-mediated immune evasion by cancer can be overcome by immune checkpoint-inhibiting MAB therapy (using either anti-PD1 or anti-PD-L1 therapy). (**a**) T cells may be able to recognise tumour-associated antigens loaded on major histocompatibility (MHC) class I molecules. (**b**) In doing so, T cells become activated and upregulate expression of programmed death 1 (PD-1) receptors on their surface and secrete interferon-γ (IFN-γ). (c) In response, tumour cells express programmed death-ligand 1 (PD-L1), which can bind to PD-1 on T cells and turn them off. (**d**) Treatment with either anti-PD-1 or anti-PD-L1 MAB can block the interaction between PD-L1 on tumour cells and PD-1 on T cells and, as a result, reactivate T cell efficacy against tumour cells

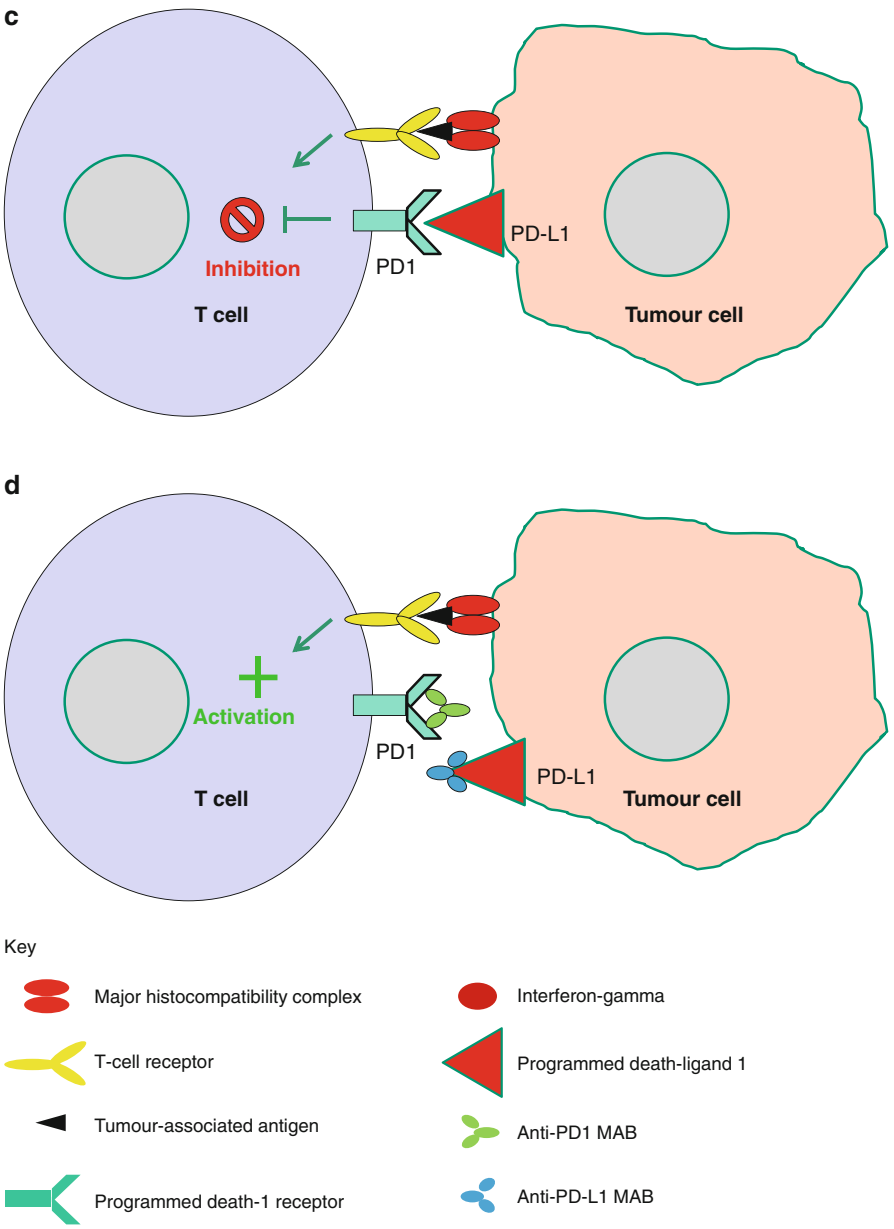

Fig. 3.4 (continued)

mutational load appears to be greatest in melanoma, but head and neck cancers (especially HPV-negative tumours) are also associated with a very large number of mutations.

In the setting of SCCHN, there have been initial reports of single-agent activity in patients with relapsed/metastatic disease. One of the largest early experiences

with anti-PD1 therapy was derived in single-agent therapy with the anti-PD1 monoclonal antibody, pembrolizumab. In KEYNOTE-012 (NCT01848834), patients with PD-L1-positive (>1 % staining of tumour cells) tumours were divided into HPV+ and HPV− cohorts and treated with 10 mg/kg of pembrolizumab every 2 weeks. Overall, 26 of 51 patients had a reduction in tumour burden and 20 % satisfied standard radiological criteria (RECIST v1.1) for response [47]. In a subsequent study, a larger group of 132 patients was treated with a flat dose of pembrolizumab (200 mg) every 3 weeks. Patients were included irrespective of PD-L1 status. Only 7.6 % of patients experienced grade 3 or greater adverse effects. Of 99 patients who were evaluable for the preliminary analysis, 18.2 % showed a response (all partial responses) and 31.3 % of patients had stable disease [48]. There are a number of ongoing or recently accrued randomised phase II and III clinical trials with both anti-PD1 and anti-PD-L1 agents (pembrolizumab [KEYNOTE-040 NCT02252042, KEYNOTE-048 NCT02358031], nivolumab [CHECKMATE-141 NCT02105636], durvalumab/MEDI4736 [HAWK NCT02207530, EAGLE NCT02369874, KESTREL NCT02551159]) in patients with relapsed/metastatic disease that are likely to be reported in the next 2–3 years.

In early 2016, the pivotal phase III trial of nivolumab in platin-resistant SCCHN was terminated prematurely because an assessment conducted by the independent Data Monitoring Committee (DMC) concluded that the study met its primary endpoint, demonstrating superior overall survival in patients receiving nivolumab compared to the control arm (investigator's choice chemotherapy). This is the first indication of a positive outcome for immunotherapy in relapsed/metastatic head and neck cancer and the first trial ever to report a survival advantage in the second-line setting. These data suggest that immunotherapies are likely to find a place in the management of patients with relapsed/metastatic SCCHN. In addition, it is important to appreciate that a number of studies are being planned in which immune-oncology agents will be combined with RT/CRT in the radical setting in patients with newly diagnosed SCCHN.

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Part III
Diagnostic Challenges

Chapter 4
The Changing Role of the Pathologist

Philip Sloan

Molecular Pathology

The advent of molecular pathology is leading to a transformation of pathology services, moving from the provision of traditional remote histopathology and cytopathology written reports to the creation of more clinically apposite integrated reports for precision medicine. Increasingly, pathologists are playing an expanded role in the oncology clinical team, having greater responsibility for integration of molecular testing with morphological interpretation. Through attendance at tumour boards or multi-disciplinary team meetings, pathologists can also provide interpretation of pathology testing in the clinical context, alongside imaging and other investigations.

Molecular pathology is driving the integration of pathology services that have traditionally been provided by small laboratories, often on disparate sites. Formation of a large 'hub' laboratory provides many advantages, largely around the handling of human tissue samples. A single laboratory database facilitates more efficient exchange of information and a single sample reception enables optimal use of human tissue for histopathology, cytopathology, cytogenetic analysis, molecular testing and biobanking. This is particularly important because there are clinical drivers for smaller biopsies with less patient morbidity and, at the same time, the need to arrive at a fully informative diagnosis avoiding the need to re-biopsy wherever possible.

Large hub laboratories can sustain the management cohort necessary for continuous improvement and monitoring programmes that are essential to achieve accreditation for quality assurance. Additionally hub laboratories for pathology are

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ideally placed to host biobanks, as the single laboratory database can act as a LIM system to enable sample tracking. This facilitates working with researchers and industrial partners who often require well characterised stratified collections of tissue samples with proper patient consent in place. Larger laboratories can also develop an efficient skill mix, making better use of non-medical staff for specimen trimming, sampling and even reporting of less complex biopsy material.

At the same time as molecular pathology is driving rapid change, the introduction of digital pathology is altering the field of diagnostic pathology. Slide scanning technology is now available in most pathology laboratories and high-resolution images suitable for centralised reporting can be generated. Such systems can avoid the intrinsic delays and risks associated with transporting human tissue samples and can be used to obtain specialist opinions when rare or diagnostically challenging cases are encountered. Integration with the hub laboratory database makes for greater safety and minimises errors due to labelling or mismatch. Margins, tumour thickness and other tumour parameters that might partly determine clinical interventions can be measured with greater accuracy. Image analysis systems can be used to quantify tissue cellularity and provide an accurate multi-parameter dataset for analysis. A key requirement for modern molecular pathology is the assurance of high quality tissue for immunohistochemistry and molecular testing. This involves being able to track and record times for samples taken in theatre through transport, fixation and processing, or rapid freezing of samples, to permit the refinement of protocols for optimal sample handling.

Over the next few years, whole exome or whole genome sequencing is likely to become more widely available and cost effective, though bioinformatic algorithms will need to be developed to enable the data to be clinically useful. In future, diagnostic challenges that cannot be met by a combination of histological or cytological morphological interpretation with cytogenetic and/or limited molecular testing may be resolved through a molecular pathology MDTM meeting. Whole genome/exome sequencing or molecular profiling may serve to stratify patients with greater precision, for example those with HPV positive oro-pharyngeal cancers who have other mutations due to smoking or alcohol abuse (see next section). In order to take advantage of the opportunities offered by deep sequencing in the future, pathology services need to develop effective protocols for the collection of fresh tumour samples. Preservation of DNA integrity is an important issue, and in the United Kingdom, the 100,000 Genomes project has established the importance of collection pathways and in particular the need to keep tissue at 4 °C from theatre to pathology. Beyond whole genome sequencing, RNA analysis is likely to come into play, requiring even more stringent sample collection protocols.

If these major changes to pathology services are to be implemented, then molecular pathology must form part of the training programme for pathologists, as well as continuing education for established pathologists. Change in pathology must involve on-going dialogue with clinical teams, in particular oncologists in relation to precision medicine biomarkers for stratification and companion drug tests. Groups such as CM-Path in the United Kingdom seek to bring pathologists, oncologists, scientists and industry together to develop molecular pathology testing for the future.

Diagnosis of Oro-pharyngeal Cancer HPV

The discovery that a significant proportion of oro-pharyngeal cancers are driven by high-risk human papilloma virus (types 16, 18 and related genomes) and the demonstration that HPV positive carcinomas have better clinical outcomes [2] has led to the introduction of HPV testing for oro-pharyngeal cancers in most diagnostic centres providing a head and neck service. The prognosis of oro-pharyngeal carcinoma is currently based on HPV status, smoking history, tumour stage and nodal stage.

- Low-risk: HPV-positive tumours, a smoking history of 10 or fewer pack years and N0 to N2a nodal disease
- Intermediate-risk: HPV-positive tumours, a smoking history of more than 10 pack years, and N2b–N3 disease; or, HPV-negative tumours, a smoking history of 10 or fewer pack years, N2b or N3 disease, or T2–3 tumours
- High-risk: HPV-negative tumours and a smoking history of more than 10 pack years; or a smoking history of 10 or fewer pack years, and T4 disease

The choice of laboratory test for detection of high-risk HPV is critical for stratification of patients. At present, HPV status alone is not a determinant of therapeutic choice, but when clinical trial data such as De-ESCALate and RTOG 1016 become available, this is likely to change. Current guidelines require testing of metastatic squamous cell carcinoma in neck lymph nodes for high-risk HPV and EBV, as this aids the localisation of clinically silent primary lesions to the oropharynx and nasopharynx, respectively. Further, it is well established that high-risk HPV is a useful prognostic marker for oropharyngeal cancer.

The finding that a significant proportion of oral potentially malignant disorders that typically show the distinctive features of koilocytic atypia (high grade dysplasia with mitosoid bodies) are high-risk HPV positive [7] suggests that the virus may play an important role in the pathogenesis of oral squamous cell carcinoma, though active viral signatures are found in only a very small proportion of oral carcinomas, suggesting that HPV may be cleared during transformation.

Human papilloma virus is a double stranded DNA virus and there is chronological expression of early (E) and late (L) genes. The early genes E6 and E7 interact with major tumour suppressor pathways involving retinoblastoma and p16 and their expression can be used as a signature for biologically relevant high-risk HPV in squamous carcinoma. Hence the gold standard for laboratory HPV testing for oropharyngeal cancer is demonstration of E6/E7 mRNA by PCR in fresh frozen tissue.

Immunohistochemistry for the cell cycle protein p16 (CDKN2A) often shows overexpression in HPV positive tumours. However, p16 immunohistochemistry lacks specificity and a positive result may be seen in tumours that lack HPV genome. Immunohistochemistry for p16 is a relatively inexpensive test and is widely available. In one series, p16 positive oro-pharyngeal carcinomas that lacked HPV were found to behave as HPV negative tumours [8]. In many pathology laboratories, in situ hybridisation for high-risk HPV DNA is available. This test is highly specific

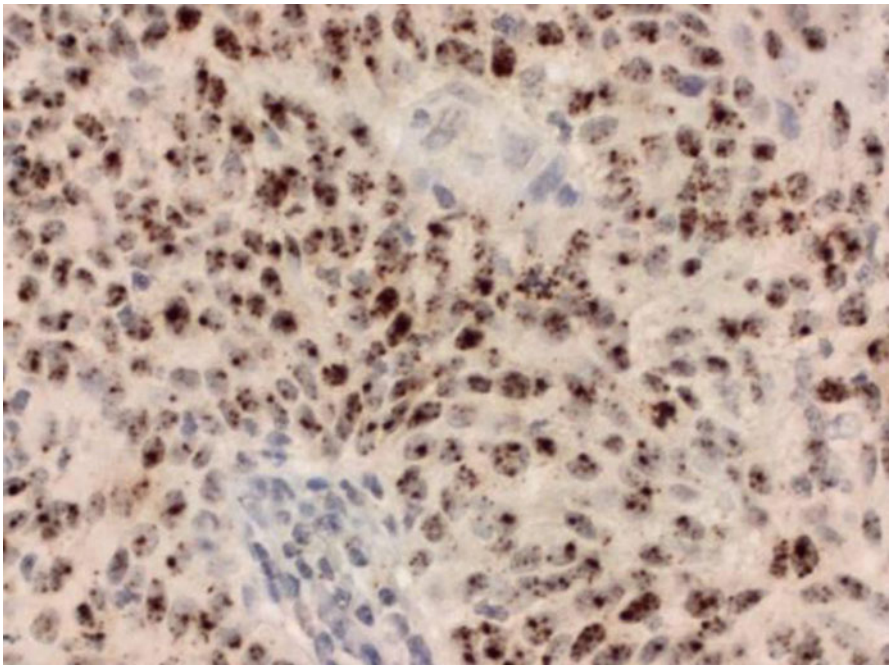

Fig. 4.1 Detection of high-risk HPV using RNAscope. Multiple nuclear dot-like signals are present in the neoplastic cells whilst the stromal cells are unlabeled

Table 4.1 The performance of RNAscope in testing oro-pharyngeal squamous cell carcinomas

Diagnostic test	Sensitivity (%) [95 %CI %]	Specificity (%) [95 %CI %]	PPV (%)	NPV (%)
HR-HPV RNAscope	97 [84–99]	93 [82–98]	91	98
p16 IHC	97 [85–99]	82 [67–91]	80	97
HR-HPV DNA ISH	94 [80–98]	91 [79–96]	89	95
Combined p16/HR-HPV DNA ISH	94 [80–98]	91 [79–96]	89	95
DNA qPCR	91 [76–97]	87 [74–94]	83	93
Combined p16/DNA qPCR	91 [76–97]	93 [82–98]	91	93

Adapted from Schache et al. [10]

but lacks sensitivity, often in part due to sampling because the signal may be very focal in its distribution. PCR methods can be used in conjunction with p16 immunohistochemistry, but are highly sensitive and lack specificity because contaminants or incidental virus may amplify resulting in false positive results.

The most accurate laboratory method currently available for HPV testing of oropharyngeal carcinoma is detection of E6/E7 mRNA by in situ hybridisation (Fig. 4.1). The method is at least equivalent, and arguably even outperforms, the gold standard method of PCR on fresh frozen tissue (Table 4.1). The advantage of

working in formalin fixed paraffin embedded tissue is that small tumours or even areas of carcinoma in situ may be located that would be hard to find in fresh frozen tissue, increasing sensitivity in routine practice. It is not practical or effective to swab or collect washings of tonsillar type tissues for detection of HPV. In clinical practice, small primary oropharygeal carcinomas may be difficult to visualise and are often located by the pathologist microscopically. Thorough sampling is required using serial blocks from tonsillectomy samples or robotic tongue base excisions to reliably detect and characterise occult primary lesions.

There is accumulating evidence that HPV positive oro-pharyngeal carcinomas have a better prognosis than HPV negative tumours [2, 9]. However, whole genome and whole exome sequencing, as well as clinical factors can identify additional subgroups of HPV positive and HPV negative types, enabling more precise stratification [6].

Molecular and Cytogenetic Testing for Salivary Gland Cancers

The histopathological diagnosis of salivary gland tumours is based largely on morphological criteria, often supplemented by histochemistry to identify mucins and to a limited extent by immunohistochemistry. Gene fusions and somatic mutations have been described and have recently opened up the possibility of using targeted therapies for some salivary malignancies [1]. In addition, molecular markers can be used to refine histological diagnosis, for example the t(12;15)(q13;q25) translocation resulting in fusion of the ETV6 and NTRK3 (or other unknown partner), distinguishes secretory carcinoma from acinic cell carcinoma. Identification of this signature fusion has contributed to the evidence leading to inclusion of a new salivary tumour in the classification scheme.

Carcinoma Arising in Pleomorphic Adenoma

Invasive carcinoma that has arisen in pleomorphic adenoma (carcinoma ex PA) is most frequently high grade and often shows undifferentiated or salivary duct carcinoma patterns, though any salivary malignancy may arise. Carcinoma arising in pleomorphic adenoma may exhibit the same gene fusions as pleomorphic adenoma, including PLAG1 and HMGA2 fusions. Unfortunately, PLAG1 fusions (including cryptic fusions, [4]) are only found in a proportion of pleomorphic adenomas. Multiple copy number alterations are typically seen in high-grade carcinomas and there may be amplification of HMGA2 and MDM2. In relation to therapy for unresectable or metastatic carcinoma ex PA, molecular typing for HER2 and AR where salivary duct carcinoma arises can be performed and may inform targeted therapy.

Adenoid Cystic Carcinoma

Although slow growing, adenoid cystic carcinoma typically spreads by perineural invasion and lacks an immune stromal response. Local recurrence is common and distant metastasis may occur late in the course of the disease. The MYB-NFIB fusion is the genomic hallmark of adenoid cystic carcinoma, and activation of MYB and MYBL1 by increased copy number or proximity to other genes is thought to be the major driver. Mutation frequency in other genes is low [5]. Both KIT and EGFR may be overexpressed but are rarely mutated and therapy against these tyrosine kinase inhibitors is not effective.

Mucoepidermoid Carcinoma

The biological behaviour of mucoepidermoid carcinoma has a broad spectrum and histological grading has prognostic utility (WHO in press). The hallmark genomic events in mucoepidermoid carcinoma are translocations involving the transcriptional coactivator genes MAML2 and CRTC1/3. Additionally, mutations of HRAS have been found in around 20 % of mucoepidermoid carcinomas, most often in high grade tumours. Mucoepidermoid carcinomas that are MAML2-CRTC1/3 fusion positive have a more favourable outcome than fusion negative tumours [3]. Genomic studies can subdivide fusions positive mucoepidermoid carcinomas into two subgroups; those with a low copy number have a good prognosis whilst those with numerous copy number alterations pursue an aggressive clinical course and show poor outcomes. Precise histological classification of high grade salivary carcinomas is difficult and some MAML2 and CRTC1/3 fusion negative carcinomas that were currently classified as poorly differentiated mucoepidermoid carcinoma may in reality fit better into the adenocarcinoma NOS type.

Mammary Secretory Analogue Carcinoma

Secretory carcinoma arising is salivary glands (MSAC) shares common histological and genomic features to the breast counterpart. Previously these tumours were diagnosed mostly as acinic cell carcinomas with paucity of DPAS positive cytoplasmic granules. The genomic signature of secretory carcinoma is the ETV6-NTRK3 fusion, though a subset involve ETV6 fusions with as yet unidentified partners. As for acinic cell carcinoma, most secretory carcinomas are low grade, but a few high-grade examples have been reported. Current histological grading systems are not predictive for acinic cell or secretory carcinoma, though histological atypia, necrosis, Ki67 greater than 15 % and invasive growth are worrying features.

Salivary Duct Carcinoma

Arising mostly in the parotid gland, salivary duct carcinoma may occur de novo or as the malignant component of carcinoma ex pleomorphic adenoma. No signature gene fusions have been described. The majority of salivary duct carcinomas show increased copy number or overexpression of androgen receptor, and anti-androgen therapy has resulted in some patient benefits in small series. A proportion of salivary duct carcinoma shows amplification of HER-2 and patients with progressive disease may benefit from anti-HER-2 therapy. Genomic studies of salivary duct carcinoma show wide heterogeneity, and profiling may be the best approach to make individual choices for therapy.

Polymorphous Low-Grade Adenocarcinoma

The genomic signature of polymorphous low-grade adenocarcinoma is a high frequency of activating mutations of PRKD1. Such mutations are a useful diagnostic biomarker in the positive subset, because they have not been found in other salivary neoplasms. The exception is the cribriform adenocarcinoma of minor salivary glands that often shows alterations of PRKD1 family genes suggesting common molecular pathways of pathogenesis for the two tumour types.

Hyalinising Clear Cell Carcinoma

The clear cell carcinoma is a low grade tumour that arises in minor glands particularly in the base of tongue and palate. Frequent stromal hyalinisation is present and a nested arrangement of clear cells may be seen. The genomic hallmark is the EWSR1-ATF1 fusion that has also been found in other tumours characterised by cytoplasmic clearing including clear cell sarcoma, myoepithelial, and odontogenic tumours.

Conclusion

Advances in molecular pathology are driving change in the provision of pathology services. More accurate diagnosis is possible through the use of new diagnostic markers. As more targeted therapies are developed for clinical practice, so new companion tests will be needed to ascertain which patients can benefit from them. Precision medicine requires the integration and interpretation of complex datasets. It may be anticipated that stratification of head and neck cancer will be refined and individualised therapeutic regimes will emerge over the next years.

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Chapter 5
Molecular Imaging in Head and Neck Squamous Cell Carcinoma Patients

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Introduction

Molecular imaging allows visualization of tumor biology in vivo [1]. Different processes can be visualized, such as glucose metabolism, proliferation, and hypoxia. But also numerous ligands for receptors and other relevant targets in the tumor microenvironment have been labeled to be used as a tracer for molecular imaging. For positron emission tomography (PET) and single photon emission computerized tomography (SPECT) imaging, ligands are labeled with a radioactive nuclide, while for optical imaging ligands are labeled with a fluorescent dye. Also for magnetic resonance imaging (MRI), computerized tomography (CT), and ultrasound, specific contrast agents are available for molecular imaging [2–4]. Head and neck squamous cell carcinoma (HNSCC) is diagnosed in more than 500,000 patients worldwide per year. Many patients present with locally advanced disease, which has a poor prognosis with around 50 % 5-year survival. Adequate staging and tumor delineation could enhance precision of surgery and radiotherapy, which may lead to a reduction of recurrences. PET imaging has great potential to improve staging, while optical imaging is investigated for its ability to improve tumor delineation. Furthermore, molecular imaging can be used to visualize specific tumor characteristics that can be used for targeted treatment. Therefore, this chapter will focus on PET imaging and optical imaging in HNSCC.

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PET Imaging

Next to a role in diagnosis, staging, and response evaluation when combined with CT or MRI, PET imaging maybe useful for prognostication and radiotherapy treatment planning. Furthermore, PET imaging can be used during drug development by demonstrating the distribution of a drug or treatment target [5]. The role of PET in the management of head and neck cancer patients has been summarized in an excellent review by Cammaroto et al. [6]. Radionuclides that are frequently used for PET imaging in patients are fluor-18 (^{18}F), copper-64 (^{64}Cu), zirconium-89 (^{89}Zr), and iodine-124 (^{124}I), which differ among others in half-life (1.8 h, 12.7 h, 78.4 h, and 100.2 h, respectively). The half-life of the SPECT tracer indium-111 (^{111}In) is 67.4 h. Antibodies have long half-lives of 1–3 weeks, which requires the use of radionuclides that also have long half-lives [7].

^{18}F-Fluorodeoxyglucose PET

In HNSCC patients, many PET tracers have been tested but only ^{18}F-fluorodeoxyglucose (FDG)-PET is incorporated in management guidelines. FDG-PET enables visualization and quantification of glucose metabolism which is enhanced in most tumors, but also in areas of inflammation. The National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines for head and neck cancer (version 1, 2015) recommend the use of FDG-PET/CT for patients with lymph node metastasis in the neck of a squamous cell carcinoma (SCC), adenocarcinoma, and anaplastic or undifferentiated epithelial tumors of an unknown primary site [8]. For patients with stage III and IV HNSCC, FDG-PET is considered optional because it may alter treatment decisions by upstaging patients. For response evaluation after chemoradiotherapy or radiotherapy alone, FDG-PET is recommended 12 weeks after completion of treatment in patients with a clinical response, to guide the decision on neck dissection. A meta-analysis of mainly single center small studies demonstrated a high negative predictive value of FDG-PET/CT after chemoradiotherapy for persistent/recurrent disease [9]. A recent phase III trial compared FDG-PET/CT guided active surveillance with planned neck dissection for HNSCC patients with locally advanced disease treated with primary radical chemoradiotherapy. The study showed that overall survival was equivalent. Moreover, in the surveillance arm only 20 % of the patients underwent a neck dissection, which resulted in fewer complications, better cost effectiveness, and similar quality of life [10].

Quantification of tumor FDG uptake may also have prognostic value. A meta-analysis suggested that a low tumor standardized uptake value (SUV) is associated with a better disease free survival, a better overall survival, and improved local control [11]. In a large retrospective study from Denmark, tumor FDG uptake was shown to be an independent prognostic factor in patients who received radiotherapy as primary treatment, with high tumor SUVmax corresponding to a worse failure free survival [12].

Finally, FDG-PET is under investigation as a tool to improve radiotherapy (RT) treatment planning. The observation that local recurrence after radiotherapy

frequently occurs in the area with the most intense FDG uptake has boosted trials that investigate FDG-PET based radiotherapy dose painting [13]. Two different strategies are applied: dose painting by contours, where a higher uniform RT dose is delivered to a target volume based on PET imaging; and dose painting by numbers, where on a voxel scale SUV is used to calculate RT dose.

Non-FDG PET Tracers

Apart from FDG, more than 20 PET tracers have been tested in HNSCC for imaging hypoxia, proliferation, amino acid metabolism, and other cellular processes and tumor characteristics (see Table 5.1). Especially imaging of tumor hypoxia is an area of active research.

Table 5.1 Examples of studies with non-FDG PET tracers in HNSCC patients

Tracer	First author, year	Type	Target/process
^{18}F-FMISO	Rajendran, 2006 [14]	Nitroimidazole	Hypoxia
^{18}F-FAZA	Mortensen, 2012 [15]	Nitroimidazole	Hypoxia
^{18}F-HX4	Zegers, 2015 [16]	Nitroimidazole	Hypoxia
^{18}F-EF5	Komar, 2014 [17]	Nitroimidazole	Hypoxia
^{62}Cu-ATSM	Sato, 2014 [18]	Copper semicarbazone	Hypoxia
^{64}Cu-ATSM	Grassi, 2014 [19]	Copper semicarbazone	Hypoxia
^{18}F-FLT	Hoeben, 2013 [20]	Nucleoside	Proliferation, DNA synthesis
^{11}C-4DST	Ito, 2015 [21]	Nucleoside	Proliferation, DNA synthesis
^{11}C-MET	Wedman, 2009 [22]	Amino acid	Amino acid metabolism
^{18}F-FAMT	Kim, 2015 [23]	Amino acid	Amino acid metabolism
^{18}F-FET	Pauleit, 2006 [24]	Amino acid	Amino acid metabolism
^{18}F-FMT	Burger, 2014 [25]	Amino acid	Amino acid metabolism
^{11}C-Choline	Ito, 2010 [26]	Phospholipid precursor	Phospholipid biosynthesis
^{18}F-FCH	Parashar, 2012 [27]	Phospholipid precursor	Phospholipid biosynthesis
^{15}O-H_2O	Komar, 2014 [17]	Water	Perfusion
^{68}Ga-DOTATOC	Schartinger, 2013 [28]	Octreotide	Somatostatin receptor expression
^{18}F-BPA	Tani, 2014 [29]	Boron-amino acid	Replicating cell/boron accumulation
^{18}F-5-FU	Hino-Shishikura, 2013 [30]	Cytotoxic chemotherapy	Replicating cell/drug distribution
^{89}Zr-Cetuximab	Heukelom, 2013 [31]	Antibody	EGFR expression, drug distribution
^{89}Zr-U36	Börjesson, 2009 [32]	Antibody	CD44v6 expression
^{124}I-F16SIP	Heuveling, 2013 [33]	Mini antibody	Fibronectin/angiogenesis

Hypoxia Imaging

Tumor hypoxia is associated with poor prognosis and resistance to treatment. Tumor hypoxia can be analyzed directly by measuring oxygen tension with an electrode, but this is an invasive procedure which does not take into account tumor heterogeneity. Hypoxia imaging on the other hand allows serial noninvasive assessment of tumor hypoxia, both of the primary tumor and of lymph node metastases. Multiple hypoxia PET tracers have been developed, mostly based on a nitroimidazole structure. These molecules freely diffuse through cell membranes but get trapped into cells in the presence of a low oxygen level [34, 35]. The most used hypoxia PET tracer is ^{18}F-fluoromisonidazole (^{18}F-FMISO) which has recently been reviewed by Rajendran and Krohn [36]. Several, generally small single center, ^{18}F-FMISO PET studies have been published in HNSCC patients over the last 10 years (Table 5.2). In these studies, different parameters for quantification were used, but also different reference tissues, different treatment schedules, and different timing of follow up imaging. This complicates interpretation and hampers robust conclusions. However, several studies showed that patient with more hypoxic tumors had a worse outcome [14, 37, 41, 44, 46, 50]. Furthermore, early reoxygenation during chemoradiotherapy appears to be associated with a lower risk of recurrence [46, 50].

Where prognostic markers provide information about outcome of patients independent of treatment, predictive markers give information on the effect of a specific treatment strategy [51]. The prognostic value of hypoxia PET can potentially be used to guide treatment de-escalation in patients with nonhypoxic tumors with favorable prognosis and/or treatment escalation in patients with hypoxic tumors (Fig. 5.1). Currently a treatment de-escalation study is ongoing in patients with human papillomavirus (HPV) positive oropharynx cancers that are nonhypoxic at baseline or show early re-oxygenation on repeat imaging (ClinicalTrials.gov Identifier: NCT00606294). On the other end of the spectrum, in silico studies have demonstrated the feasibility of increasing radiotherapy dose to hypoxic tumor subvolumes [53–57]. Currently two randomized studies are comparing standard chemoradiotherapy with chemoradiotherapy using an increased radiation dose to hypoxic tumor subvolumes (ClinicalTrial.gov. Identifiers: NCT02352792 and NCT01212354).

Several therapeutic strategies have been developed to reduce tumor hypoxia during radiotherapy, including carbogen and nicotinamide, tirapazamine, and nimorazol [58–60]. Hypoxia PET may have predictive value by identification of patients who benefit from hypoxia targeting treatment. This could be investigated by using a biomarker stratified study design (Fig. 5.2). Data from a sub study using ^{18}F-FMISO PET suggested that patients with hypoxic tumors derived benefit from treatment with tirapazamin, a cytotoxic drug with selective toxicity towards hypoxic cells [38]. Currently an international randomized phase III trial comparing chemoradiotherapy plus nimorazol with chemoradiotherapy plus placebo in patients with locally advanced HNSCC uses a hypoxic gene signature as stratification factor but also tests predictive value of hypoxia PET in a subset of the patients (ClinicalTrials.gov Identifier: NCT01880359). However, nimorazole

Table 5.2 ^{18}F-FMISO PET studies in HNSCC patients

Author	Year	Pt N	Treatment	Timing	Quantification parameters	Reference tissue	Prognostic value	Predictive value
Thorwarth [37]	2005	15	(C)RT	Baseline	TAC, TRP, perfusion, SUVmax, FHV	Blood	Yes	NA
Rajendran [14]	2006	73	(C)RT / surgery ± PO(C)RT	Baseline	HV, TBRmax	Blood	Yes	NA
Rischin [38]	2006	45	RT + tirapazamin vs. CRT	Baseline, week 4/5	Qualitative > background	NR	No	Yes
Eschmann [39]	2007	14	(C)RT	Baseline, 30 Gy	TAC, mean SUV, TMR	Muscle	NR	NA
Nehmeh [40]	2008	20	NR	Baseline 2×	FHV	Blood	NR	NA
Dirix [41]	2009	15	CRT	Baseline, week 4	HV, TBRmax	Blood	Yes	NA
Lee [42]	2009 [43]	20	CRT	Baseline, week 4	Qualitative > background	NR	No	NA
Kikuchi [44]	2011	17	NAC followed by surgery or (C)RT	Baseline	SUVmax, TMR	Muscle	Yes	NA
Yamane [45]	2011	14	NAC	Before + after NAC	SUVmax, TMR, HV	Muscle	NR	no
Zips [46]	2012	25	CRT	Baseline week 1, 2, 5	HV, baseline HF, SUVmax, TBRmax	Muscle	Yes	NA
Bittner [43]	2013	16	CRT	Baseline, week 2	HV	NR	NR	NA
Henriques [47]	2013	15	RT	Baseline	TBRmax, FHV 3×	NR	NR	NA
Okamoto [48]	2013	11	NR	Baseline 2×	SUVmax, TMR, TBR, HV	Muscle Blood	NR	NR

(continued)

Table 5.2 (continued)

Author	Year	Pt N	Treatment	Timing	Quantification parameters	Reference tissue	Prognostic value	Predictive value
Sato [49]	2014	22	NAC followed by surgery	Before surgery + before/during/after NAC	SUVmax	TMR	NR	Yes
Wiedenmann [50]	2015	16	CRT	Before, week 2, 5	TBRmax, HV	Blood	Yes	NA

(*C*)*RT* (chemo)radiotherapy, *FHV* fractional hypoxic volume, *Gy* Gray, *HV* hypoxic volume, *NA* not applicable, *NAC* neoadjuvant chemotherapy, *N* number, *NR* not reported, *PO*(*C*)*RT* postoperative (chemo)radiotherapy, *Pt* patient, *SUVmax* maximum standardized uptake value, *TAC* time activity curve, *TBR* tumor-to-blood ratio, *TBRmax* maximum tumor-to-blood ratio, *TMR* tumor-to-muscle ratio, *TRP* tracer retention potential, *wk* week

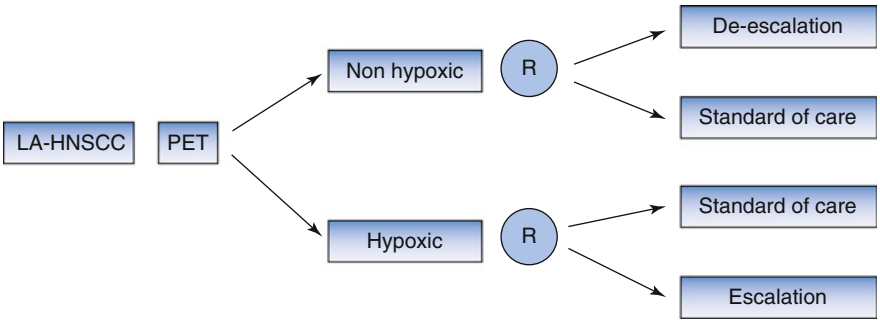

Fig. 5.1 Study design using hypoxia PET as prognostic marker. *LA-HNSCC* locally advanced head and neck squamous cell carcinoma, *PET* positron emission tomography, *R* randomization. Patients with LA-HNSCC undergo hypoxia PET imaging before start of treatment. Patients with nonhypoxic tumors are randomized between standard of care and an experimental treatment de-escalation regimen. Patients with hypoxic tumors are randomized between standard of care and an experimental treatment intensification regimen. Double enrichment design (After Freidlin et al. [52])

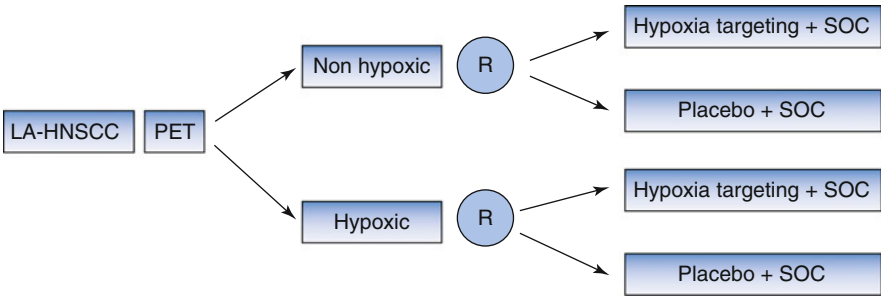

Fig. 5.2 Study design testing hypoxia PET as predictive marker. *LA-HNSCC* locally advanced head and neck squamous cell carcinoma, *PET* positron emission tomography, *R* randomization, *SOC* standard of care. Patients with LA-HNSCC undergo hypoxia PET imaging before start of treatment. Patients with nonhypoxic tumors as well as patients with hypoxic tumors are randomized between standard of care plus a hypoxia targeting drug and standard of care plus placebo. Biomarker stratified design (After Freidlin, et al. [52])

is a cheap drug with limited side effects, therefore it is doubtful if hypoxia PET is going to be implemented as predictive marker even if the positive and negative predictive values are high.

PET Imaging Using Radiolabeled Antibodies

PET imaging with radiolabeled monoclonal antibodies, also called immuno-PET, can potentially be used to select patient for targeted treatment and for drug development [5]. For HNSCC, the epidermal growth factor receptor (EGFR) blocking

antibody cetuximab is the only targeted therapy shown to be effective, in combination with radiotherapy and in combination with chemotherapy [61, 62]. EGFR, also known as human epidermal growth factor receptor 1 (HER1), is a member of the human EGFR (HER) family that further consists of HER2, HER3, and HER4.

Preclinical research has shown that activation of HER3 after dimerization with HER2 limits activity of EGFR inhibition in HNSCC and that dual inhibition of EGFR and HER3 can overcome resistance to radiation and to EGFR inhibition [63, 64]. Several agents targeting HER3 are currently under investigation in clinical trials, including monoclonal antibodies directed against HER3, dual inhibitors of EGFR and HER3, and pan-HER monoclonal antibody mixtures and tyrosine kinase inhibitors. Immuno-PET using radiolabeled antibodies against EGFR and HER3 could be useful to provide information on availability of the drug target and distribution of therapeutic antibodies in HNSCC patients.

EGFR Imaging

EGFR expression determined by immunohistochemistry has prognostic value in HNSCC, but is not a predictive biomarker for efficacy of cetuximab [65]. This may be related to heterogeneity in EGFR expression but also to accessibility of the tumor to EGFR inhibitors. Tumor drug delivery is not solely dependent on expression of the target, but also determined by perfusion, permeability, interstitial pressure, and drug characteristics including size [66, 67]. Two preclinical studies investigating ^{64}Cu-cetuximab PET imaging in xenograft models reported a correlation between tumor uptake of ^{64}Cu-cetuximab and EGFR expression [68, 69]. A third study with ^{89}Zr-cetuximab PET imaging in tumor bearing mice showed tracer uptake in EGFR positive tumors, but no correlation between tracer uptake and EGFR expression was found [70]. This may however be related to the tracer dose used [71].

Antibodies have a long half-life which implicates that in order to achieve a good tumor-to-background ratio and tumor-to-blood ratio, the optimal timing of imaging is around 7 days after tracer injection. To allow imaging within 24 h and repeat imaging early after start of treatment, antibody fragments of cetuximab (cetuximab-F(ab')$_2$) have been developed and radiolabeled for SPECT and PET imaging [72, 73]. Imaging studies in head and neck cancer xenograft models using ^{111}In-cetuximab-F(ab')$_2$ SPECT have shown that localization of the tracer correlates with EGFR expression and that the model with the highest uptake was the most sensitive to cetuximab treatment [72, 74]. Furthermore, increased tumor tracer uptake was found after radiotherapy in a cetuximab sensitive HNSCC xenograft model, which was accompanied by translocation of EGFR to the tumor cell membrane [75]. On the other hand, in a cetuximab resistant tumor model, no increase in tumor tracer uptake after radiotherapy occurred. Finally, treatment of human HNSCC xenograft models with radiotherapy alone, cetuximab alone, or the combination demonstrated reduced tracer uptake in responding tumors while in resistant tumors an increase in tumor tracer uptake was found [75]. Therefore, translation of this molecular imaging technique to

the clinic offers a promising tool for selecting patients who will benefit from treatment with cetuximab but it could also be useful as an early read-out of treatment efficacy. Three clinical studies have started using ^{89}Zr-cetuximab PET imaging, one in HNSCC and two in colorectal cancer patients (ClinicalTrials.gov Identifiers: NCT01504815, NCT02117466, NCT01691391) [31, 76]. The head and neck cancer trial was initiated as a randomized phase II study comparing cisplatin with cetuximab and standard radiotherapy with redistributed radiotherapy in a two by two factorial design. One of the objectives was to evaluate the predictive value of ^{89}Zr-cetuximab tumor uptake on a pretreatment PET scan [31]. Unfortunately the trial design has been changed and cetuximab treatment and cetuximab imaging are no longer part of the protocol (https://clinicaltrials.gov/archive/NCT01504815/2014_08_21/changes).

HER3 Imaging

The HER3 antibodies lumretuzumab and patritumab have been labeled for PET imaging [77, 78]. In a phase I study, 13 patients with solid tumors expressing HER3, determined by immunohistochemistry, underwent imaging with ^{89}Zr-lumretuzumab PET before start of treatment with the same antibody [79]. Two patients with HNSCC were included in this study. The aim of the imaging part was to determine in vivo biodistribution and the ability of the antibody to target the tumor. In all patients, tracer uptake in tumor lesions was seen. Metastases in the bone and brain that were unknown were detected in three patients. Results of serial imaging during treatment to assess HER3 saturation are awaited. In another phase I study, dosimetry of ^{64}Cu-DOTA-patritumab and receptor occupancy after a therapeutic dose patritumab were investigated [78]. Three out of six patients in the receptor occupancy cohort had a negative PET scan, likely because patients were not preselected for HER3 tumor expression. In the remaining patients, receptor occupancy was ~42 %. Larger studies are needed to assess predictive value of immuno-PET for efficacy of antibody therapy and/or for selecting the right treatment dose.

PET Imaging of Tumor Immunity

Cancer immunotherapy with immune checkpoint inhibitors has been a great breakthrough for melanoma, non–small cell lung cancer and other tumor types and has shown very promising early results in head and neck cancer [80, 81]. Antibodies directed at programmed death 1 (PD-1) and its ligand PD-L1 are currently investigated in phase III trials in HNSCC. To date there are no biomarkers that predict efficacy of immune checkpoint inhibition, although in some tumor types expression of PD-L1 using immunohistochemistry is associated with a higher response rate. Expression of relevant targets for immunotherapy may vary between and within tumor lesions, and over time. Molecular imaging offers a noninvasive platform for

serial assessment of whole body target expression and antibody distribution. PET imaging of tumor immunity is in an early phase of development with no clinical data available yet. One imaging study is currently ongoing in patients with triple negative breast cancer, bladder cancer and non–small cell lung cancer using ^{89}Zr-atezolizumab (PD-L1 antibody) PET before treatment with the same antibody (ClinicalTrials.gov Identifier: NTC02453984). Two preclinical studies already demonstrated feasibility and specificity of radiolabeled antibodies for PD-L1 imaging in tumor bearing mice [82, 83].

Another interesting strategy is to use molecular imaging as an early read-out of treatment response. PD1 and PD-L1 antibodies are supposed to act by augmenting the activity of tumor infiltrating cytotoxic T lymphocytes. Activated T lymphocytes express interleukin-2 (IL-2) receptor. SPECT imaging with radiolabeled IL-2 (^{99m}Tc- IL2) has successfully been used in patients for visualization of activated T lymphocytes in atherosclerotic plaques and in melanoma [84, 85]. For IL-2 PET imaging, which allows more sensitive and more precise quantification than SPECT, ^{18}F-IL2 has been developed and validated preclinically [86, 87].

The subset of lymphocytes that can eliminate tumor cells are CD8 expressing cytotoxic T cells. Antibody fragments against murine CD8 have successfully been labeled with ^{64}Cu and showed specific uptake in lymph nodes and spleen of antigen positive mice [88]. If this technique can successfully be translated to the clinic, it would allow to study in vivo tumor T cell infiltration which appears to be a prerequisite for immunotherapy to be effective.

Another important class of immune cells affecting tumor behavior are the tumor associated macrophages (TAMs). The subset of M2 macrophages appears to have a tumor promoting and cytotoxic T cell suppressive effect [89]. Macrophage depleting drugs are currently investigated in clinical trials. M2 macrophages specifically express the macrophage mannose receptor (MMR). Radiolabeled antibody fragments targeting MMR have been developed for PET imaging and showed specific uptake in tissues and tumors expressing MMR in mice [90]. MMR imaging could be helpful in the process of drug development, for patient selection, and as a read out for treatment efficacy.

Optical Imaging

Optical molecular imaging is a much more recent field of research, and evidence from clinical studies is still scarce. Optical imaging techniques use illumination with light of different wave lengths, ranging from safe ultraviolet range (350–400 nm), and the visible spectrum (400–750 nm) to infrared regions (750–1000 nm). Penetration of light is limited due to scattering and absorption, which vary substantially in different target tissues. Generally, in the range of 350–1000 nm, light penetration is deeper with increasing wavelength. Near-infrared (NIR) fluorescence imaging can visualize structures up to 8 mm below the surface, depending on the optical properties of the target tissue [91]. Several optical spectroscopy and imaging technologies have been and are currently investigated in HNSCC, including Raman spectroscopy, narrow band imaging, autofluorescence and exogenous fluorophore

imaging, optical coherence tomography, confocal laser endomicroscopy, and confocal reflectance microscopy [92]. Optical imaging is currently investigated for its potential to differentiate malignant lesions from normal tissue, and from benign and premalignant lesions. Optical imaging can be used during endoscopy but also intraoperatively to guide surgical resection margins. However, in cancer diagnosis, most optical techniques are either difficult to apply in vivo (i.e., Raman spectroscopy) or have not shown to yield sufficient specificity to support routine clinical use. Only in certain fields optical imaging techniques have shown to aid the clinician in diagnostic procedures. For instance, narrow band imaging helps to identify (pre)malignant lesions in head and neck cancer [93]. Here we present examples of molecular optical imaging using fluorescently labeled molecules that target specific tumor characteristics to improve the contrast between cancer and non-cancer tissue.

EGFR Imaging

In the first clinical trial on molecular optical imaging in HNSCC patients, cetuximab labeled with the NIR fluorescent dye IRDye800 was systemically injected 3–4 days before surgery in a dose finding study [94, 95]. Wide field NIR imaging was performed at day 0, day 1, and immediately before surgery, and closed field NIR imaging of fresh tissue slices of 4–5 mm was done. After histologic preparation, a corresponding slide was analyzed with a fluorescence scanning system for comparison with immunohistochemistry. Cetuximab-IRDye800 specifically accumulated in tumor lesions with a sharp demarcation of the tumor border. The mean fluorescence intensity signal was highly correlated with EGFR expression (Fig. 5.3) [94].

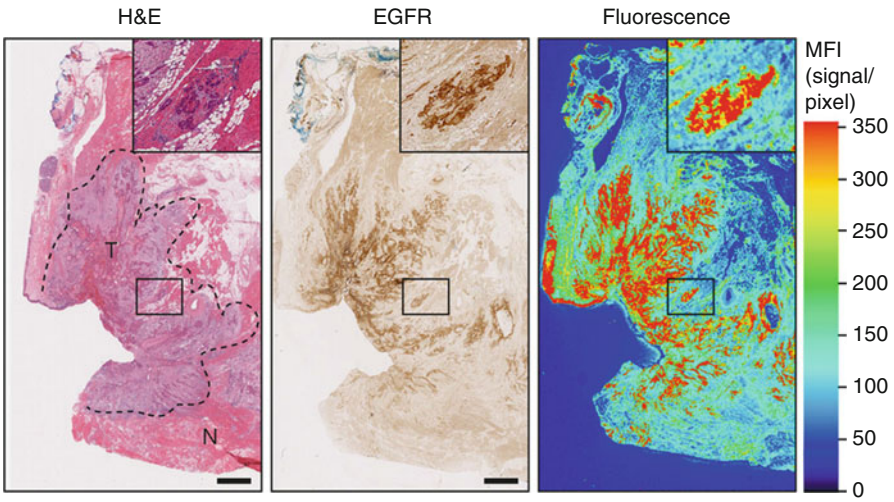

Fig. 5.3 Co-localization of fluorescence signals of cetuximab-IRDye800CW and epidermal growth factor receptor (*EGFR*) expression. Representative hemotoxylin/eosin (*H&E*) image indicating tumor (*T*) and normal (*N*) with corresponding EGFR expression immunohistochemistry stain and fluorescence image [94]

However, in tumor areas with necrosis and in areas with mature, differentiated keratinizing cancer cells, fluorescence was low despite high EGFR expression. The latter might be explained by loss of ligand binding affinity of EGFR during maturation [94]. Of interest, the highest tracer dose (62.5 mg/m^2) suggested receptor saturation according to the authors, because the tumor-to-background ratio seemed to have reached a plateau. This raises the question whether the standard therapeutic cetuximab loading dose of 400 mg/m^2 followed by weekly doses of 250 mg/m^2 might be too high, and imposes unnecessary off-target effects. However, tumor-to-background ratio may also be reduced due to a higher background fluorescence which occurs by increasing the cetuximab-IRDye800 dose. The study also revealed cetuximab-IRDye800 localization in sebaceous glands and basal cells which might be related to the skin toxicity that is frequently seen during cetuximab therapy. This novel imaging technique is an interesting tool for intraoperative use to lower the rate of involved or close surgical margins. Next to this, studying the localization of the cetuximab-IRDye800 in histological slides of the excised tumor may add another dimension to the pathology report which could be useful in determining postoperative strategies.

In a xenograft study of human oral cavity squamous cell carcinoma, fluorescent optical imaging was used to investigate whether tumor uptake of the cetuximab-IRDye800 could be improved by pretreatment with bevacizumab, a monoclonal antibody targeting human vascular endothelial growth factor A (VEGF-A) [96]. Neoadjuvant bevacizumab administration but not simultaneous bevacizumab increased cetuximab-IRDye800 tumor accumulation. This was accompanied by a higher pericyte coverage of tumor blood vessels compared to mice that did not receive bevacizumab, which suggests vascular normalization. Translating such a study design to the clinic could provide important information on effective treatment combinations and schedules.

Quantum dots (QDs) are semiconductor nanocrystals with a wide excitation and a small emission spectrum that can be conjugated to antibodies and peptides for molecular optical imaging. The size of QDs determines emission wave length, which can vary from the UV to the NIR range. A NIR QD800-EGFR antibody has been used for in vivo imaging of mice with a human orthotopic oral cavity squamous cell carcinoma [97]. Specific binding to tumor cells with a high signal-to-noise ratio up to 6 h after intravenous injection was demonstrated.

Another interesting development is topical application of a fluorescently labeled EGF peptide (EGF-Alexa 647) for early detection of oral neoplasia [98]. Immediately after excision, oral neoplastic lesions and paired normal tissue biopsies were incubated with EGF-Alexa 647 showing a consistently higher fluorescent signal in lesions which corresponded with EGFR immunohistochemistry. Clinically applicable conjugates are under development.

Integrin $\alpha_v\beta_3$ Imaging

Integrin $\alpha_v\beta_3$ is expressed by endothelial cells during angiogenesis in many cancers, including HNSCC, and by some tumor cells. Peptides containing an arginine-glycine-aspartic acid (RGD) sequence bind to $\alpha_v\beta_3$ integrin. A tetravalent RDG

peptide labeled with a NIR fluorescent molecule (AngioStamp800) is commercially available for preclinical optical imaging. Using this probe in an $\alpha_v\beta_3$ expressing orthotopic HNSCC xenograft model, Atallah et al. operated 12 mice with the use of integrin $\alpha_v\beta_3$ imaging and 12 mice with visual guidance only [99]. In the first group, after visual complete resection, tumor beds contained fluorescent spots in all mice, and 35 out of 37 specimens of these fluorescent spots contained tumor foci. Furthermore, recurrence free survival after 2 months was 75 % in mice that had $\alpha_v\beta_3$ integrin imaging guided surgery compared to 25 % in mice resected without optical imaging. In a second study by the same group, mice were followed for lymph node recurrence after resection of orthotopic HNSCC [100]. Intraoperative integrin $\alpha_v\beta_3$ imaging correctly identified clinical and subclinical lymph node metastases in these mice.

Quantum dots conjugated with RGD (QD800-RGD) have also been used for integrin $\alpha_v\beta_3$ imaging in mice bearing HNSCC. The xenografted human oral squamous cell carcinoma cell line did not express integrin $\alpha_v\beta_3$ but specific targeting of tumor vessels in this mouse model resulted in clear tumor fluorescence with the highest tumor-to-background ratio 6 h after intravenous injection of QD800-RGD [101].

Other Optical Imaging Targets

Cancer cells display aberrant glycosylation of cell surface proteins and lipids with increased sialic acid content. This has been exploited for optical imaging using topical application of wheat germ agglutinin (WGA) conjugated with fluorophores in the UV range (Alexa Fluor 350) and NIR range (Alexa Fluor 647)[102]. Ex vivo imaging of tumor and normal mucosa biopsies of patients with HNSCC demonstrated a satisfactory signal-to-noise ratio.

Another characteristic of many cancers is overexpression of cyclooxygenase-2 (COX-2). Fluorocoxib, a COX-2 targeted NIR probe, has been developed for optical imaging [103]. Specific uptake in COX-2 overexpressing human HNSCC xenografts was demonstrated with an optimal signal-to-noise ratio at 7 days post injection in mice.

Interestingly, also a NIR dye conjugated PD-L1 antibody was successfully tested in tumor bearing mice [83].

Finally, also tumor M2 macrophage recruitment has been visualized with optical imaging using an antibody against MMR (αCD206) conjugated with NIR dyes in a murine breast cancer model [104, 105].

Future Perspectives

Molecular imaging with radiolabeled ligands for PET imaging provides whole body information on distribution of targets and/or drugs with low resolution. Optical imaging gives local information with very high resolution but with limited

penetration. These complementary techniques can be used simultaneously by injecting molecules labeled with a fluorescent dye and a radionuclide [106].

Furthermore, for optical imaging, several tumor characteristics have already been analyzed simultaneously by using probes with different excitation wavelengths in preclinical studies [107].

Molecular imaging cannot replace anatomical imaging or biopsies but can potentially provide additional information to improve diagnosis and treatment of HNSCC. Before implementation, large well powered clinical studies are needed to assess its added value. Alternatively, data from multiple small studies can be combined which could be facilitated by creating ware houses with imaging data. The currently publicly available databases for genomics could serve as a role model in this respect. However, standardization of techniques and endpoints is critical for combined analysis.

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Part IV
Multidisciplinary Decision Making and Head and Neck Tumor Boards

Chapter 6
Multidisciplinary Decision Making and Head and Neck Tumor Boards

Jan B. Vermorken

Squamous Cell Carcinoma of the Head and Neck: Introduction

A Changing Population

The incidence of head and neck cancer (HNC) is still increasing, now being the fifth most common tumor worldwide, with an estimated 688,000 new cases in 2012 [1]. The incidence of squamous cell carcinoma of the head and neck (SCCHN) peaks between the fifth and seventh decades of life and the proportion of elderly (65+) patients is expected to rise in the coming years [2]. Surveillance, epidemiology, and end results (SEER) data in the United States indicated that this category of patients comprised 54 % of all malignant HNC (larynx + oral cavity + pharynx) and that the incidence of HNC among these older patients is expected to increase with 37 % by 2020 and even with 63 % in 2030 [3]. The clinical profile of the elderly is somewhat different from that in the younger patients with respect to sex ratio, tobacco and alcohol (ab)use, primary disease site, disease stage, survival, and human papillomavirus (HPV) infection (see Chap. 16 on "Treatment in the Elderly").

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A Changing Disease

In the general SCCHN population, the prevalence of tobacco and alcohol consumption is over 70 % of the patients, and tobacco still is the single most important risk factor for this disease worldwide. However, HPV has now been recognized as one of the primary causes of oropharyngeal squamous cell cancer (OPC), and the incidence of HPV-associated OPC is on the rise. Oncogenic HPV infection is a risk factor for OPC both in smokers and in nonsmokers and in fact is the strongest prognostic factor in this disease [4, 5]. The proportion of SCCHN caused by HPV varies widely but is particularly rising rapidly in the Western world. HPV-positive and HPV-negative tumors appear to be distinct entities based on different clinical and molecular presentations [6]. Clinically, HPV-positive OPC patients generally are younger, generally have a better performance status, more frequently consume less alcohol and tobacco, and more frequently have a history of multiple sex partners. However, it should be understood that HPV-associated OPC may occur also in individuals with few sexual partners and 8–40 % of the interviewed patients with HPV-positive tumors indicated they never had oral sex [6, 7]. HPV-positive OPC frequently presents with a smaller primary tumor associated with multiple lymph nodes relative to HPV-negative OPC, is more responsive to chemotherapy and radiation than HPV-negative disease, and overall has a better outcome ([8]; see also Chap. 10 on viral-associated head and neck cancer).

Changing Treatments (Innovations)

Innovations have occurred in all areas. The field of head and neck surgery has gone through numerous changes in the past two decades, whereby microvascular free flap reconstructions largely replaced other techniques. In addition, organ sparing surgical techniques, and in particular more recently transoral robotic surgery, are getting major attention. In the field of radiotherapy, dramatic advances have occurred in optimizing dose fractionation schedules, improving target delineation for staging and radiotherapy simulation/planning using anatomical and functional imaging, improving accuracy of radiotherapy delivery using daily image-guidance, as well as the emergence of new radiation techniques (rotational intensity-modulated radiotherapy, stereotactic radiotherapy, and particle therapy). Innovations in combining radiation and systemic agents have also taken place including with cytotoxic chemotherapy, hypoxic cell modifiers, and targeted agents [9].

Standard Treatment Options in SCCHN

Taking the above into account, the present standard treatment options for early disease (stage I–II) include either a radiotherapeutic approach or a surgical approach, depending on patient and disease factors [10, 11]. With such approaches, the expected 5-year survival figures range from 60 to 90 %. Patient factors, such as lifestyle habits, will have a major impact on the outcome.

Treatment approaches for locoregionally advanced disease include surgery (in patients with resectable disease) followed by radiation or chemoradiation, depending on the results reported in the pathology specimen (positive margins, extracapsular extension). In case surgery is not the selected primary option, there are different possibilities to choose from with different levels of evidence, i.e., concurrent chemoradiotherapy (CCRT), hypoxic modification of radiotherapy (standard in Denmark, not yet standard outside Denmark) and altered fractionation radiotherapy (all level IA evidence), and bioradiotherapy (BRT) with cetuximab or induction chemotherapy (ICT) followed by radiation alone, CCRT, or BRT. The latter two options do not reach level IA evidence and in fact ICT followed by CCRT or BRT is still considered investigational [12, 13]. Mainly because of disease factors there is a wide range in the expected outcome with 5-year overall survival ranging from 20 to 80 % (see also Chap. 11 on "Patient and Treatment Factors in Concurrent Chemoradiotherapy").

For patients with recurrent and/or metastatic SCCHN, the most unfavorable group of patients, there are several treatment options depending on the presentation. In case of locoregionally recurrent disease, without distant metastases, surgery is the first choice and should always be considered, and patients are then treated with a curative intent. According to a meta-analysis of 32 studies with a total of 1,080 patients reported by Goodwin, a survival rate of 39 % can be expected at 5 years after salvage surgery [14]. Unfortunately, that will be possible only in a minority of patients (see also Chap. 12 on "Salvage Surgery of Head and Neck Cancer"). Postoperative radiotherapy might be indicated in some instances [15]. Reirradiation should also be considered in patients with unresectable recurrences and primary tumors arising in a previously irradiated area. However, retreatment is associated with an increased risk of serious toxicity and impaired quality of life (QoL). Therefore, a proper selection of patients based on disease-related factors, current comorbidities, and preexisting organ dysfunction for such treatment is essential. If so done, a meaningful survival in the range of 10–30 % at 2 years can be expected [15]. Patients with locoregional recurrence only who are not candidates for salvage surgery or reirradiation might be candidates for systemic therapy. The latter is also the case for patients with distant metastases with/without a local and/or regional recurrence. When in a good condition (Eastern Cooperative Oncology Group [ECOG] performance status [PS] 0/1), patients are candidate for platinum/5-FU plus cetuximab (the EXTREME regimen), the new standard chemotherapy regimen since 2008; patients with PS 2 are candidates for treatment with less aggressive regimens, which is commonly a single-agent therapy; for patients with PS 3 best supportive care only is advisable. At all times, patients should be offered the option of participating in a clinical trial, as results with so-called standard therapy in the recurrent/metastatic disease setting are still disappointing [12].

Multidisciplinary Team Meetings

Cancer care is undergoing an important paradigm shift from a disease-focused management to a patient-centered approach, in which increasingly more attention is paid to psychological aspects, quality of life, patients' rights and empowerment, and survivorship [16]. In this context, multidisciplinary teams have emerged as a practical necessity for optimal coordination among health professionals and clear

communication with patients. A new definition addressing the role of multidisciplinary teams was put forward in 2013 by the healthcare working group of the European Partnership for Action Against Cancer (EPAAC): "*Multidisciplinary teams* (*MDTs*) *are an alliance of all medical and health care professionals related to a specific tumour disease whose approach to cancer care is guided by their willingness to agree on evidence-based clinical decisions and to co-ordinate the delivery of care at all stages of the process*, *encouraging patients in turn to take an active role in their care*" [16]. The importance of MDTs in cancer care is becoming widely recognized as shown by international adoption of mandatory guidelines or legislation. This is illustrated by the fact that in Belgium, France, and the Netherlands, the use of MDTs is mandatory with make-up of multidisciplinary teams clearly defined. The United Kingdom, Canada, and Australia all have national or state-defined guidelines for the use of MDTs in cancer care [17]. In Italy and Germany, it is mandatory for cancer patients to be treated in expert centers.

Goals and Benefits of MDTs

The primary goal of an MDT is to improve the care management for individual patients. The early implementation of the discussion process in the pathway of an individual patient can prevent unnecessary diagnostic investigations and save valuable time. Ruhstaller et al. suggested that one multidisciplinary discussion with all the involved specialties is more effective and the joint decision more accurate than the sum of all individual opinions [18]. They also stressed that in such meetings, patients will be treated according to the same guidelines and to the same standard regardless to whom the patient was initially referred to. In principle, when treated in Europe the decision-making process should preferably be consistent with evidence-based European clinical practice guidelines, if available. Moreover, during MDT meeting discussions, guidelines should be tailored to the type of tumor and the specific condition of the patient, including comorbidities and frailty. Treatment decision, which impact patients' QoL to varying degrees, should not be made without information on patients' preferences for treatment and/or care [16]. Next to these positive elements in decision-making, there are some additional benefits of MDTs; for instance multidisciplinary discussed patients are more likely to be included in clinical trials; MDTs lead to a better understanding of the roles, possibilities, and limitations of each discipline and lead to a better communication between different specialties. MDTs are also an ideal learning opportunity for junior doctors or other health care professionals [18].

MDT Management in Head and Neck Cancer Patients

Because HNCs are a complex, heterogeneous group of malignancies, which require multifaceted treatment strategies and the input of a number of specialities, they are an ideal example to benefit from MDTs. Moreover, as mentioned earlier, the HNC

population is changing, there are new entities in HNC coming up with different biology, presentation, and outcome, and there is a tremendous evolution in treatment possibilities, both in surgical and nonsurgical approaches. Molecular biology has proven to be vital in our understanding of the disease; at the same time we start to understand now that the molecular characteristics of no two tumors are identical. Nevertheless, a more personalized approach is coming closer and closer. Smarter drugs are needed to make optimal use of the specific genetic make-up of a patient's tumor [19]. In addition to this development, a spectacular revival in immunology and evolution of immunological therapies in oncology in general but in particular also in HNC is ongoing [20]. During the MDTs, all these aspects have to be taken into account in order to make an optimal choice of treatment for an individual patient. Basically, it means that we should take into account: (1) disease factors, i.e., site, stage, biology (HPV, epidermal growth factor receptor [EGFR]), specific risk factors for locoregional or distant relapse; (2) patients factors, such as age sex, performance status, nutritional status, comorbid chronic disease, oral health, lifestyle habits, socioeconomic status, etc.; (3) treatment factors (surgery, radiotherapy, chemotherapy, targeted therapy, immunotherapy with all the possible side effects they may induce); and (4) adequate communication with and information to the patient, giving sufficient support, taking into account the wish of the patient. It has become increasingly apparent that patients need emotional support to navigate their cancer journey and successfully integrate back into society and daily life. Emotional support is vital as many people who have been through SCCHN, in particular younger patients, may have impaired physical and psychological well-being.

MDT for head and neck cancer patients should include a surgical oncologist (head and neck surgeon), a radiation oncologist and a medical oncologist, a pathologist, a radiologist, a plastic (reconstruction) surgeon, an otolaryngologist, an oncologic dentist or oral oncologist, a speech therapist, an audiologist, a dedicated oncology nurse, and preferably a datamanager involved in all ongoing trials in HNC and a case manager. In addition, MDTs may be enriched by a variety of other care professionals, such a physical therapist, a social worker, a dietician, and a psychologist and/or psychiatrist and for elderly patients a geriatrician.

The attendance in such meetings of primary care physicians (general practitioners) should be promoted, as they know their patients best and are able to provide advice on comorbidities and a holistic health assessment of their patients' care needs [16]. The case manager, which could be an expert nurse or a qualified staff member, should provide case management throughout the care process, acting as a point of contact for both patient/families and the team. Some of the most important tasks assigned to this case manager is giving expert clinical advice to patients, exchanging key patient information and care recommendations with the physicians, attending MDT meetings, and ensuring that diagnostic and treatment times are consistent with the targets set in this regard [16]. Case managers can also play an important role in the emotional support that the patients need throughout their journey, i.e., from diagnosis, during treatment, and posttreatment. Reich et al. defined emotional support in this context as a sensitive, empathic, and understanding approach to patients to help them to cope with their disease and to allow patients to express and communicate their concerns and feelings [21]. Figures 6.1 and 6.2, derived from that article, are summarizing the expected emotions and reactions from the SCCHN

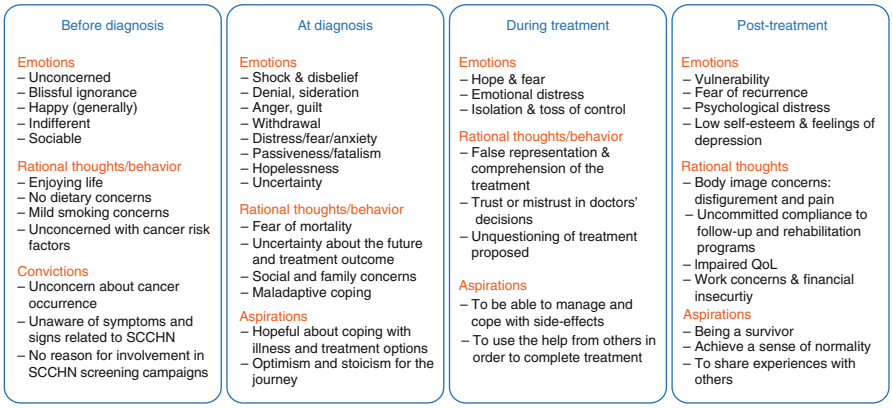

Fig. 6.1 Expected emotions and reactions for the SCCHN patient

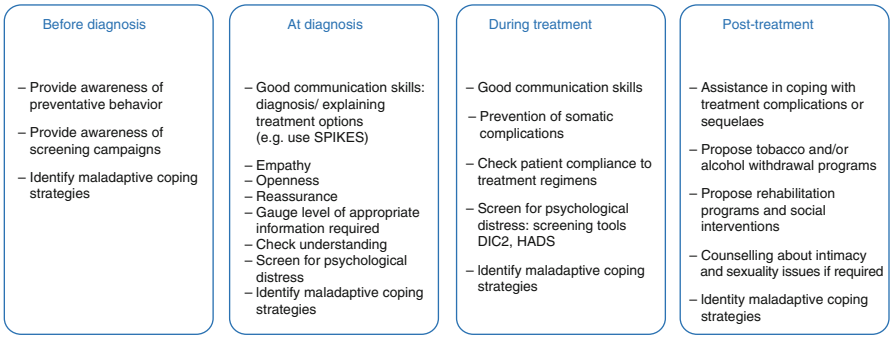

Fig. 6.2 Recommended actions for the healthcare professional. *DIC2* Distress Inventory for Cancer version 2, *HADS* Hospital Anxiety and Depression Scale, *SCCHN* squamous cell carcinoma of the head and neck, *QoL* quality of life (From Reich et al. [21], reproduced with permission)

patients and the recommended actions that need to be taken by the health care professional.

Do MDT Meetings Impact on Diagnosis, Treatment Decision, and Outcome?

It seems self-evident that the variety of specialist team members with their combined knowledge and expertise will improve decision-making and therefore ultimately patient management and outcome. Although that is very likely so, evidence for that has not been easy to demonstrate because, as outlined above, over time cancer care is changing, there is improvement in staging and diagnosis, and more

effective treatments become available. These aspects are, of course, confounding factors in retrospective studies where one looked at whether the introduction of MDT meetings had any impact on outcome (so-called "before and after" studies). Prades et al. undertook a literature search in the Medline database for peer-reviewed articles (partly retrospective, partly prospective) published between November 2005 and June 2012 that examined multidisciplinary clinical practice and organization in cancer care [22]. MDTs resulted in better clinical and process outcomes for cancer patients with evidence of improved survival among colorectal, head and neck, breast, esophageal, and lung cancer patients in this study period. However, unfortunately the two studies in that survey that concerned HNC were both retrospective [23, 24].

Friedland et al. [23] analyzed the outcomes of 726 cases of primary HNC patients managed between 1996 and 2008, including 395 patients managed in a multidisciplinary clinic or team setting and 331 managed outside of an MDT by individual disciplines. Data were collected from the Hospital Based Cancer Registry (HBCR) and a database within the Head and Neck Cancer Clinic of the Sir Charles Gairdner Hospital, Perth, Australia. The MDT patients were younger by about 2 years of age on average ($p=0.046$), which is a potential source of bias. On the other hand, patients seen in the multidisciplinary clinic were more likely to have advanced disease ($p<0.001$). The authors reported a better outcome for the patients in the MDT group (for all patients with stage I–IV a hazard ratio [HR] of 0.79, $p=0.024$), but this was mainly due to a different outcome in the stage IV patients (HR = 0.69, $p=0.004$). There was no difference observed in stage I–III, although the numbers in each of these stages were too small to provide statistical power. Over time there was an increasing incidence in the use of CCRT (2.1 % in 1996 and 42.5 % in 2008; test for trend $p<0.001$) and at the same time a decline in the use of radiotherapy alone (27.1 % in 1996 and 15 % in 2008; test for trend $p<0.001$). Patients in the multidisciplinary clinic were significantly less likely to receive radiotherapy alone for positive nodes or surgery alone for their cancer and positive nodes. The MDT group used significantly more CCRT ($p=0.004$) and the non-MDT group significantly more radiotherapy alone ($p=0.002$).

Wang et al. [24] reported on a study performed in Taiwan, where the incidence of oral cavity cancer is very high (about 60 % of all HNC). They used for their study the National Health Database (2004–2008) and applied matching based on propensity of receiving MDT care. After the propensity score matching, 3099 MDT care participants and 6198 non-MDT care participants were included in the study. The relative risk of death was lower with MDT care than for those without MDT care (HR = 0.84; 95 % CI 0.78–0.90, $p<0.001$). The effect of MDT care was stronger for older patients.

In two prospective studies, treatment plan changed in about one third of cases after MDT. The first study was performed at the Department of Otolaryngology-Head and Neck Surgery of the University of North Carolina Hospital in North Carolina, in the USA, and concerned 120 new patients (84 with malignant, 36 with benign tumors) whose clinical findings were presented for review at the MDT meeting between December 2009 and February 2010 [25]. Approximately 27 %

(32/120) had some change in either tumor diagnosis or treatment plan due to the input from the multidisciplinary tumor board. Three (9 %) of these 32 patients had changes in both diagnosis and treatment, 19/32 (59 %) had a change in their treatment plan without a change in diagnosis, and 10/32 (31 %) had a change in diagnosis without a change in treatment. Approximately 7 % of patients required further diagnostic workup before definitive treatment planning. The second study was executed at the Sydney Head and Neck Cancer Institute at the Royal Prince Alfred Hospital, a tertiary care hospital in Central Sydney, Australia [26]. One hundred seventy-two patients with head and neck tumors (160 malignant, 12 benign) were discussed in 39 meetings over the period from December 2011 until October 2012. The proposed management plans were documented before the MDT meeting, and the MDT meeting recommendations and potential changes to the initial plan were recorded after the meeting. The changes were categorized as major or minor: changes were considered major when they concerned a change in treatment modality, while changes were considered minor when they comprised alterations in the extent of a chosen modality, the addition of diagnostic tools or research decisions. Compliance with MDT recommendation was evaluated after completion of treatment. Of the 172 patients, 52 (30 %) had management changes, 35 (67 %) of which were considered major and 12 (33 %) considered minor. Interestingly, a significant association was found between the frequency of changes in treatment plan and the referring consultant's specialty (more likely in case referrals by medical oncologists or radiation oncologists than by surgical oncologists), the initial treatment plan (when the treatment plan did not include surgery) and the histological tumor source (least likely in case of mucosal tumors). The recommendations of the MDT meeting were followed in 132 (84 %) of the 158 patients on which data were available. Of the 26 cases where the treatment plan was not followed, a more aggressive plan was chosen by the treating physician in 50 %, in 40 % it was less aggressive, and in 10 % the modality changed (surgery replacing RT or vice versa). Reasons for this noncompliance were variable: unexpected findings in the surgical specimen, patient preference, and/or change in functional status between the MDT meeting and the actual start of the treatment. Given the complex and mutilating nature of SCCHN treatments and the advanced age and frequent comorbidities in HNC patients, the authors considered the compliance to the recommendations in this study high (84 % overall, 70 % for patients with changes). On the other hand, still worrisome is the fact than in 15 % of cases the treatment agreed upon was not carried out.

A disadvantage of MDT meetings that sometimes has been mentioned by some authors is that this might potentially lead to delay in starting treatment [26]. However, this will be particularly the case when the interval between MDT meetings are long. In most institutions, MDT meetings take place at weekly intervals. However, the point is well taken. It is very well known that treatment delay is associated with a less favorable outcome [27, 28]. A recently performed systematic review with meta-analysis of ten studies showed that the estimated relative risk (RR) of mortality related to any diagnostic delay (either patient or professional delay) was 1.34 (95 % CI, 1.12–1.61) [29]. Therefore, studies that investigate how to reduce time intervals are of interest. One such initiative was taken by the Danish

group and showed that a fast-track program through logistic changes, employment of a full-time case manager, strengthening the multidisciplinary tumor board, and giving higher priority to HNC patients (by introducing a hotline for referrals, having prebooked slots in the outpatient clinic, having faster pathology reports and imaging procedures), the overall time from first suspicion of cancer until treatment start could be reduced from 57 calendar days to 29 calendar days [30].

Conclusions

Head and neck cancer management is a typical example of a complex treatment involving multiple disciplines. There is not much doubt that multidisciplinary care is needed for an adequate coordination of the multidisciplinary care pathway with respect to logistics, reducing any treatment delays, and communication with the patient. MDT meetings have a positive effect on decision making and management, as in about one third of cases the initial proposed management will be changed in these meetings. A case manager seems to play a crucial role in this whole process, and although prospective trials on the impact of MDTs on outcome are lacking, because having a valid control group is almost impossible, the expectation is that it does have an impact on outcome. Therefore, not only centralization of care for HNC patients is a major issue, but within this MDT meetings nowadays are considered standard of care.

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Part V
Locoregionally Advanced Head and Neck Cancer

Chapter 7
Pros and Cons of Endoscopic Surgery

Francesca Del Bon, Alberto Paderno, Alberto Schreiber, Nausica Montalto, Cesare Piazza, and Piero Nicolai

Introduction

Transoral laser microsurgery (TLM), transoral robotic surgery (TORS), and transnasal endoscopic surgery (TES) can be considered three of the most innovative techniques introduced during the last decades in head and neck surgical oncology. The aim of these technologies is to provide patients with treatments associated with the same outcome in terms of local control compared to traditional surgical techniques or radiation/chemoradiation (RT/CRT), but with less morbidity and decreased hospitalization time. The value of TLM, TORS, and TES in the management of early-stage lesions is widely recognized, while the debate is still ongoing on their role in the treatment of selected intermediate/advanced tumors.

If we specifically look at laryngeal/hypopharyngeal and oropharyngeal intermediate/advanced cancers, treatment options more commonly include surgery via an external approach (with or without the need for reconstruction) or CRT. Meta-analysis data have demonstrated a significant rate of treatment-related toxicities, particularly acute mucositis, xerostomia, and long-term swallowing dysfunction, in case of nonsurgical organ preservation protocols [1–4]. The rate of gastrostomy tube (GT) dependence for patients treated with CRT has been reported as typically between 9 and 39 % [5, 6]. CRT does not avoid the need for temporary/permanent tracheotomy [6] and does not guarantee functional preservation. In fact, Hanna et al. observed no significant difference between total laryngectomy and primary CRT in speech and swallowing–related quality of life scores [7]. In case of locally advanced laryngeal cancer, there is still debate about the oncological comparability of organ

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preservation protocol and surgery in real-world clinical settings [8–13]. On the other hand, when considering the therapeutic strategy for locally-advanced hypopharyngeal squamous cell carcinoma (SCC) (surgery vs. organ preservation protocols), there are no significant differences between the two groups in relation to survival outcomes. In the advanced stage setting, concurrent CRT is frequently proposed for patients with low to moderate volume disease in which functional status has not been irreversibly compromised. Otherwise, a primary surgical approach followed by postoperative RT is typically adopted [14–16]. In this scenario, TLM and TORS may be considered good options in well selected cases of locally intermediate/advanced cancer, where, in view of the extent and location of the lesion, tumor resection within free margins may be expected with less morbidity compared to external approaches.

Transoral Laser Microsurgery

Laryngeal Cancer

In the last 25 years, several experiences have demonstrated the oncological reliability of TLM for early laryngeal tumors (Tis, T1, and T2), comparable to more traditional approaches. The excellent results reported led to a gradual expansion of the indications to include locally advanced tumors (T3–T4a), traditionally managed by open-neck surgery (either partial or total laryngectomies), and nonsurgical organ preservation protocols [17–31]. The main advantage of TLM is the ability to perform individualized surgery according to the size and location of each tumor, thus preserving the maximal amount of healthy tissue [32]. From a technical point of view, tumor resection in a single piece ("excisional biopsy" generally applicable for Tis-T1 and most T2) is not always possible for advanced or bulky lesions. In this scenario, the tumor must be divided into multiple blocks ("multibloc technique"), with the great advantage of visualizing the deep and inferior extent of the tumor (Figs. 7.1 and 7.2) [33–35]. General absolute contraindications to TLM are the impossibility to adequately expose the larynx, involvement of the posterior commissure, cricoid cartilage invasion, extensive subglottic involvement, and massive extralaryngeal tumor extension [33, 36–39]. Furthermore, suboptimal exposure, anterior commissure involvement in the cranio-caudal plane, thyroid cartilage erosion, arytenoid fixation, and massive infiltration of the preepiglottic and paraglottic spaces represent the most controversial scenarios for management of glottic and supraglottic tumors by TLM [38]. If all laryngeal subsites are not appropriately visualized, misdiagnosis, incomplete resection, or unnecessary need for adjuvant therapy can be encountered [36, 38, 39]. Tumors affecting the anterior commissure represent a controversy for TLM because of a reduced local control compared to external partial techniques, even in case of negative margins [40–44]. It is extremely important to differentiate between tumors affecting the anterior commissure in the horizontal plane (T1b) from those that grow along a cranio-caudal direction,

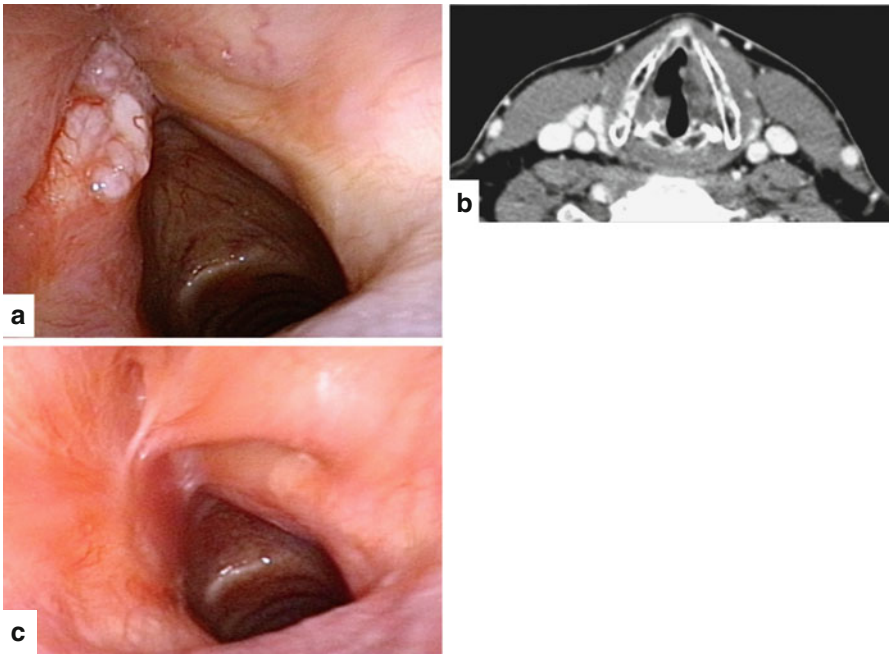

Fig. 7.1 (**a**) Endoscopic view of a squamous cell carcinoma (SCC) of the left vocal fold. (**b**) Preoperative CT scan of the same lesion showing the invasion of the left anterior paraglottic space. (**c**) Endoscopic view 3 years after TLM

affecting the supra- and/or subglottis (T2–T3 transcommissural lesions), in which endoscopic dissection may be more troublesome [45–50].

For some authors [39], radical control of disease by a transoral approach cannot be achieved when the lesion involves the laryngeal framework and/or tends to grow outside the laryngeal box. The efficiency of CT or MRI to preoperatively diagnose minimal cartilaginous involvement is around 60–80 %; [44, 51] therefore, cartilage infiltration is often an intraoperative finding, accompanied by the impossibility to obtain frozen sections on cartilaginous tissue. The removal of a cartilage window or extensive vaporization of the involved thyroid laminae recommended by some authors [32–34] is not a guarantee of good oncologic results [38, 39, 52, 53].

Vocal cord mobility is another crucial issue: vocal fold fixation (associated or not with arytenoid fixation, [33, 38]) represents an independent risk factor for local recurrence in patients treated by TLM, with 5-year local control ranging between 50 and 70 % [54]. As proposed by Holsinger et al., tumors with complete fixation of the arytenoid and vocal cord should be classified as T3b, while tumors with scarce mobility or cord fixation, but with a functional cricoarytenoid joint, should be categorized as T3a. Only the latter are amenable to partial or subtotal removal of the arytenoid [55]. Although it is technically possible to perform total arytenoidectomy, this extreme endoscopic procedure has functional limitations, with frequent secondary aspirations.

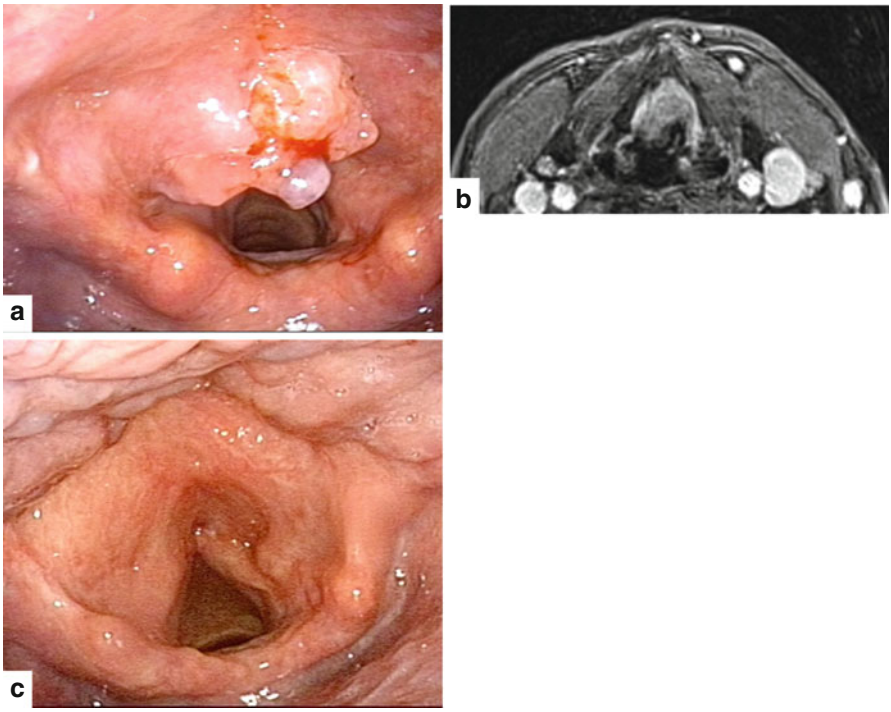

Fig. 7.2 (**a**) Endoscopic view of an SCC invading the infrahyoid portion of the epiglottis. (**b**) Preoperative MRI showing partial involvement of the preepiglottic space without infiltration of the thyroid cartilage. (**c**) Endoscopic view 2 years after TLM

Moderate infiltration of the paraglottic and preepiglottic space can be managed by TLM: however, the narrow space of work in the posterior crico-thyro-arytenoid corner, in comparison with the relatively wider view allowed at the supraglottic level, may be crucial in determining a higher failure rate [39].

Another matter of debate is the decision of skipping neck dissection in cases of a clinically and radiologically negative neck (cN0). During conventional open surgery, neck dissection is generally performed at the same time as the primary resection. Many authors recommend to perform neck dissection 2 weeks after TLM as a second-stage procedure, thus decreasing the risk of laryngeal edema (and, consequently, tracheotomy) and fistula, and allowing reevaluation of the surgical field in view of the definitive histopathology [29, 37, 56]. In case of a wait-and-see policy, strict clinical examination every 2–3 months in the first 2 years, with periodic ultrasound examinations of the neck, is mandatory to identify positive nodes at an early stage in order to perform delayed neck dissection without compromising survival. Oncologic outcomes of TLM in locally-advanced glottic and supraglottic tumors are summarized in Tables 7.1 and 7.2, respectively.

From a functional point of view, the possibility to tailor the TLM resection allows various structures to be maintained. Preservation of the laryngeal framework,

Table 7.1 Review of published data on oncologic results of TLM for advanced glottic cancer

Author(s)	Number of patients	pT	Treatment	LC with TLM (follow-up)	Final LC (follow-up)	DSS (follow-up)	OS (follow-up)
Ambrosch et al. (2001) [57]	167	T3	TLM	68 % (5 y)	87 % (5 y)	62 % (5 y)	–
Motta et al. (2005) [58]	51	T3	TLM	65 % (5 y)	–	72 % (5 y)	64 % (5 y)
Grant et al. (2007) [30]	10	T3–4	TLM ± RT	45 % (4 y)	–	–	62 % (4 y)
Peretti et al. (2010) [24]	11	T3	TLM	71.6 % (5 y)	–	100 % (5 y)	–
Vilaseca et al. (2010) [54]	51	T3	TLM	47.1 % (5 y)	88.2 % (5 y)	86.3 % (5 y)	73.1 % (5 y)
Blanch et al. (2011) [44]	26	T3 (AC+)	TLM	–	80.4 % (5 y)	–	–
Peretti et al. (2013) [59]	30	T3	TLM ± RT/CRT	55 % (5 y)	–	–	–
Canis et al. (2014) [60]	122	T3	TLM ± adjuvant RT/CRT	71.5 % (5 y)	83 % OP (5 y)	84.1 % (5 y)	58.6 % (5 y)
Pantazis et al. (2015) [13]	19	T3	TLM ± adjuvant RT/CRT	52.6 % (5 y)	73.7 % (5 y)	63.2 % (5 y)	63.2 % (5 y)

AC anterior commissure, *CRT* chemoradiation, *DSS* disease specific survival, *LC* local control, *OP* organ preservation, *OS* overall survival, *RT* radiotherapy, *TLM* transoral laser microsurgery, *y* years

Table 7.2 Review of published data on oncologic results of TLM for advanced supraglottic cancer

Author(s)	Number of patients	pT	Treatment (follow-up)	LC with TLM (follow-up)	Final LC (follow-up)	DSS (follow-up)	OS (follow-up)
Iro et al. (1998) [27]	48	3–4a	TLM ± ND ± RT	83.3 % (5 y)	–	–	–
Rudert et al. (1999) [29]	17	3–4a	TLM ± ND ± RT	–	–	–	47 % (5 y)
Ambrosch et al. (2001) [57]	50	3–4a	TLM ± ND ± RT	86 % (5 y)	91 % (5 y)	71 % (5 y)	–
Motta et al. (2004) [61]	18	3	TLM	77 % (5 y)	–	81 % (5 y)	81 % (5 y)
Grant et al. (2007) [62]	10	3–4a	TLM ± ND ± RT	T3 100 % (3 y) T4 80 % (4 y)	–	–	T3 67 % (3 y) T4 75 % (4 y)
Cabanillas et al. (2008) [63]	15	3	TLM ± ND ± RT	70 % (5 y)	–	80 % (5 y)	–
Peretti et al. (2010) [24]	20	3	TLM ± ND ± RT/CRT	83 % (5 y)	–	–	–
Vilaseca et al. (2010) [54]	96	3	TLM ± ND ± RT	69.8 % (5 y)	91.7 % (5 y)	61.8 % (5 y)	45.8 % (5 y)
Canis et al. (2013) [35]	104	3	TLM ± ND ± RT/CRT	77.3 % (5 y)	92 % OP (5 y)	84.2 % (5 y)	66.5 % (5 y)
Pantazis et al. 2015 [13]	24	3	TLM ± ND ± RT/CRT	87.5 % (5 y)	91.7 % OP (5 y)	91.7 % (5 y)	87.5 % (5 y)

CRT chemoradiation, *DSS* disease specific survival, *LC* local control, *ND* neck dissection, *OP* organ preservation, *OS* overall survival, *RT* radiotherapy, *TLM* transoral laser microsurgery, *y* years

infrahyoid musculature, superior laryngeal nerves, pharyngeal constrictor muscles, and hyoid bone limits the consequences on postoperative swallowing mechanisms [59, 64–69]. This leads to a reduced need for tracheotomy or feeding tube, faster rehabilitation, and reduction of more than 50 % in hospital stay compared with open-neck procedures [59, 60, 68–70].

In studies including advanced cancers, complications have been significantly correlated with tumor size, surgeon experience, and tumor location [71]. The most significant complications reported are postoperative bleeding, aspiration pneumonia, cervical emphysema, dyspnea, local infection, and cervical fistula. Postoperative hemorrhage is the most common and feared complication due to the vital risk for patients generally without tracheotomies [33], with a similar incidence to open approaches (3–14 %) [71]. The second most frequent complication, especially in case of supraglottic laryngectomy, is aspiration pneumonia: temporary aspiration rate favorably compares with data reported after open partial approaches (32–89 %) and CRT organ preservation protocols (up to 84 %) [72–74]. In the study by Vilaseca et al., the reported rate of aspiration pneumonia in a cohort of patients with T3–4a supraglottic carcinomas treated by TLM was 6.5 % (only 1.3 % of patients had repeated pneumonia) [34].

Peretti et al., in a cohort of glottic pT2 and selected pT3, reported that postoperative subjective satisfactory swallowing was significantly better (95.7 %) compared to data reported in the literature after supracricoid partial laryngectomy (59.8 %) and CRT (61.9 %). The same trend was confirmed by objective evaluation of swallowing, with the majority of patients presenting normal function after TLM. Hospitalization time was significantly shorter compared to RT protocols (8.3 vs. 20–24 days). Moreover, reduction in perioperative morbidity following TLM seems to fit better with the overall general frail conditions of elderly patients and those with poor pulmonary function (both at higher risk of aspiration pneumonia) [59, 71].

Oropharyngeal Cancer

The majority of studies investigating the role of TLM in the treatment of oropharyngeal cancer have recruited a limited number of patients with a short follow-up [75–77]. However, a multicenter study by Haughey et al. [78] analyzed a series of 204 patients undergoing TLM for high-stage oropharyngeal cancer, 34 % with T3–T4 tumors. After resection, 117 (58 %) patients received adjuvant RT alone, whereas 33 (16 %) received adjuvant CRT. The authors documented a statistically significant difference in survival in T1–T2 vs. T3–T4 tumors ($p=0.025$), with a risk of death that was twofold greater (HR 2.0–2.3) in higher T categories. Furthermore, the group with negative margins had fewer T3–T4 cases than the positive margins group (34 vs. 50 %), but the difference did not reach statistical significance. In this series, the 3-year overall survival was 86 %, locoregional control 93 %, and the long-term GT rate approximately 4 %. Similar results have been reported for a cohort of 71 patients, including 32 % of T3–T4 lesions,

Table 7.3 Summary of survival outcomes in recent series on TLM and TORS for advanced oropharyngeal cancer

Author(s)	Number of patients	Stage	Survival (follow-up)	Local control (follow-up)
TLM				
Haughey et al. (2011) [78]	204	III–IV	*Stage III+IV* (*3 y*) OS: 86 % RFS: 88 %	LC 97 %
Canis et al. (2013) [80]	102	I–IV	*Stage III+IV* (*5 y*) OS: 56 % RFS: 60 %	*T3–T4a* (*5 y*) LC 75 %
TORS				
Weinstein et al. (2010) [81]	47	III–IV	*Stage III–IV* (*2 y*) DSS: 90 %	*Stage III–IV* (*2 y*) LC 98 %

DSS disease specific survival, *LC* local control, *OS* overall survival, *RFS* recurrence free survival, *TLM* transoral laser microsurgery, *TORS* transoral robotic surgery

who underwent CRT [79]. Three-year overall survival was 83 %, locoregional control rate 90 % (including salvage surgery), but a GT rate of 35 % was observed. A similar study by Canis et al. [80] confirmed the efficacy of TLM, demonstrating 75 % 5-year locoregional control and 56 % 5-year overall survival for tonsillar pT3 and pT4a. Only 3 % of patients needed a permanent GT after surgery and adjuvant treatment. In this view, while maintaining comparable oncologic results (Table 7.3), TLM offered better functional outcomes than CRT.

Hypopharyngeal Cancer

Approximately 70–85 % of patients affected by hypopharyngeal SCC reported in large series have stage III–IV disease at presentation, and the 5-year overall survival rate is reported to range from 15 to 45 %. In such a scenario, nonsurgical organ preservation protocols have been largely incorporated [6], but minimally invasive organ and function preserving surgery such as TLM has been investigated in the attempt to reduce CRT-related morbidities [82, 83]. However, in locally advanced tumors (T3–T4), experience with TLM is still limited and only a few institutions have treated a reasonably large cohort of patients [82, 84, 85]. Generally, TLM in hypopharyngeal SCC is the least established transoral laser procedure, even though in selected cases it has progressively replaced open partial pharyngectomies, especially in view of the better results achieved in chronic aspiration and pneumonia (Fig. 7.3) [86]. Furthermore, TLM has no age limit and tracheotomy is usually not required [87]. Tumors of the lateral pharyngeal wall are generally accessed with ease, while in tumors involving the retrocricoid area, an endoscopic approach is only suitable for lesions without cartilage or arytenoid joint involvement. In tumors of the medial wall and the apex of the piriform sinus, the absence of anatomical

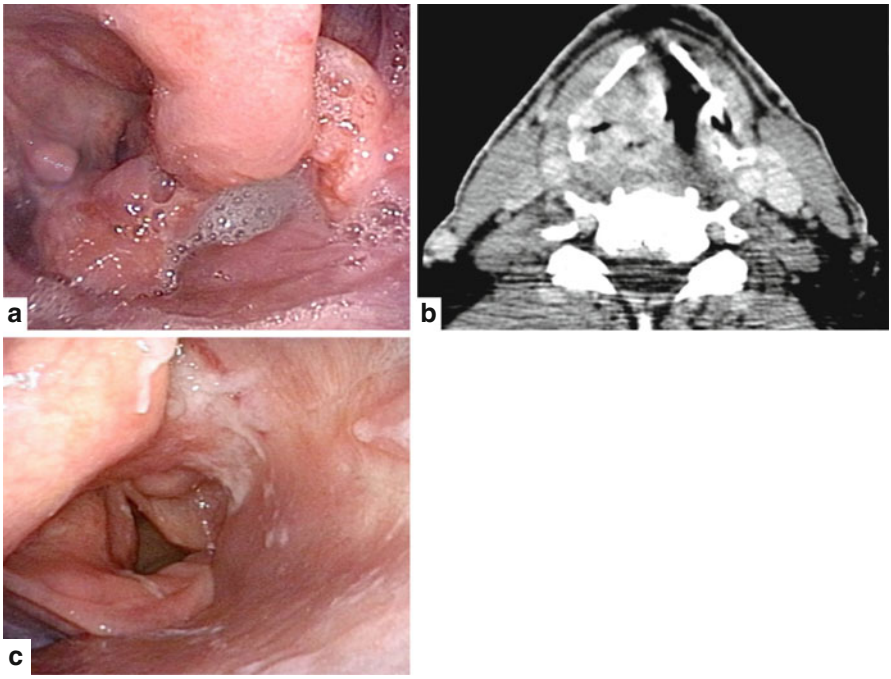

Fig. 7.3 (**a**) Endoscopic view of a T4a hypopharyngeal SCC of the right pyriform sinus and supraglottis. (**b**) Preoperative CT scan showing infiltration of the thyroid cartilage and adjacent tissues. (**c**) Endoscopic view 4 years after TLM and adjuvant CRT

barriers to the supraglottic larynx and paraglottic space allows rapid invasion of these areas. In addition, the ipsilateral supraglottis and paraglottic space lateral to the vestibular fold should be included in the resection. A contraindication to TLM for hypopharyngeal cancer is invasion of the paraglottic space lateral to the true vocal cord [86].

Most patients affected by stage III-IV disease receive adjuvant RT/CRT and local control rates are better than those obtained with nonsurgical treatment alone [88]. In such a scenario, the question is whether the intensity of adjuvant treatment should be reduced after TLM, thus making the surgery worthwhile or, on the contrary, will only increase side-effects. On one hand, surgery gives the possibility to have objective pathologic data about the true tumor extension and neck involvement. On the other, the risk of distant disease supports the use of CRT regimens as adjuvant treatment. In any case, these treatments are expensive, may increase toxicity, and reduce the possibility of its use in the not uncommon event of a second primary which may then not be treated by TLM [87]. In summary, the oncologic results of TLM in hypopharyngeal cancer appear comparable with open approaches, with a 5-year overall survival (OS) of about 40–50 % in stage III and IV, and 5-year disease specific survival (DSS) around 60 %. Higher rates of laryngeal preservation in these selected cases are also reported (Table 7.4).

Table 7.4 Oncologic results of TLM for advanced hypopharyngeal cancer

Author(s)	Number of patients	Stage	Survival (follow-up)	Local control
Steiner et al. (2001) [84]	129	III–IV	*Stage III+IV* (*5 y*) OS: 47 % RFS: 69 %	–
Vilaseca et al. (2004) [85]	28	II–IV	*Stage II+IV* (*4 y*) OS: 43 %	LC T3 56.2 % (*n*=49) LC T4 100 % (*n*=1) OP 79 %
Martin et al. (2008) [82]	172	III–IV	*Stage III* (*5 y*) OS: 64 % DSS: 86 % *Stage IV* (*5 y*) OS: 41 % DSS: 57 %	LC T3 75 % (*n*=75) (82 % plus adjuvant RT vs. 66 % without) LC T4 57 % (*n*=28)

DSS disease specific survival, *LC* local control, *OP* organ preservation, *OS* overall survival, *RT* radiotherapy, *RFS* recurrence free survival

Transoral Robotic Surgery

Laryngeal Cancer

The current size and rigidity of instruments commonly used in TORS can render a transoral robotic approach to the larynx and hypopharynx cumbersome; [89–91] furthermore, tracheotomy is often required [92]. New instruments and surgical systems that are not limited by "a straight line approach" (the Flex System, the Robo-ELF, and the MicroRALP system) [93, 94], can potentially overcome these challenges, but applicability in surgical procedures of the larynx has not yet been shown in a clinical setting [95–97].

TORS has mainly found three applications in cancer of the larynx: supraglottic laryngectomy [98, 99], total laryngectomy [100], and cordectomy [101]. When glottic cancer is considered, there are no reports on treatment of locally advanced tumors by TORS. Even for early lesions there is a lack of data on long term oncologic outcomes, while functional results (in terms of tracheotomy rate and nasogastric feeding tube) tend to be suboptimal compared to TLM [102–105].

Similarly, series on TORS supraglottic laryngectomy predominantly include early tumors (T1–T2), even though T3 lesions, based on preepiglottic space extension, are also amenable to this technique. Up to now, the overall small number of patients reported does not allow realistic comparison with other types of treatment, also considering the wide range of tracheotomy and GT rates in the different series [106–110]. Furthermore, Mendelsohn et al. described tumor stage as an important predictor of functional recovery, with low-T categories (pT1–pT2) having significant earlier return to swallowing, than more advanced ones (pT3) [111].

The rationale behind robotic total laryngectomy, although technically demanding and more costly, is to decrease postoperative morbidity and reduce recovery times [112], with a smaller pharyngotomy and maximally mucosa-sparing incisions, which minimize lateral dissection and preserve fascial barriers between the neopharynx and carotid sheaths. The indications for the procedure are yet to be well-defined and its main advantage seems to be experienced in salvage laryngectomy for functional reasons after CRT. However, to date, there are no data showing better results than open total laryngectomy [113–115].

Oropharyngeal Cancer

Before considering the potential applications of TORS for the treatment of advanced oropharyngeal squamous cell carcinomas (OPSCCs), it is essential to mention that the current staging system has relevant limitations in regard to stage grouping. For example, stage IV groups together patients with totally different disease, such as T1N2a and T4N2c. Therefore, it appears more reasonable to stratify indications for treatment based on T and N categories.

Especially in advanced tumors, the first-line approach has typically been CRT, in view of the good response and nonnegligible morbidity, even in the best hands, of conventional surgery. However, data published in the last decade have emphasized the remarkable late effects of CRT. At the same time, the striking increase of human papillomavirus (HPV)-related OPSCCs, which typically affect young patients not exposed to traditional risk factors such as smoking and alcohol, and associated with a better prognosis, have fostered the search for treatments that minimize functional sequelae without jeopardizing the disease control.

TORS have emerged in this context, showing promising potential especially for treatment of early OPSCC, but with less evidence in advanced tumors (Fig. 7.4). In this view, optimal treatment should find a balance between oncologic outcomes and functional results: on one hand, undertreatment can increase the risk of recurrence; while on the other, overtreatment can lead to worse functional results without improving survival. In high-stage OPSCC, the right balance is generally a dual-modality treatment (i.e., CRT or surgery + RT) or, in selected cases, a single-modality treatment (i.e., RT alone, or surgery alone). In some situations, TORS exposes the patient to a risk of overtreatment (i.e., triple-modality treatment: surgery + CRT) in case of positive margins or extracapsular extension at final histopathology. For this reason, in patients in whom preoperative staging reveals in advance the postoperative need for adjuvant CRT, TORS may not be the ideal choice of treatment. On the other hand, TORS provides both a therapeutic and diagnostic step that allows for assessment of pathologic findings and de-intensification of adjuvant treatment, thus avoiding chemotherapy in approximately 40 % of patients, with 10 % requiring no RT/CRT or allowing for utilization of standard postoperative RT dosages.

Taking into consideration recent data concerning the treatment of OPSCC, Lorincz et al. [116] developed a decisional algorithm including TORS, conventional

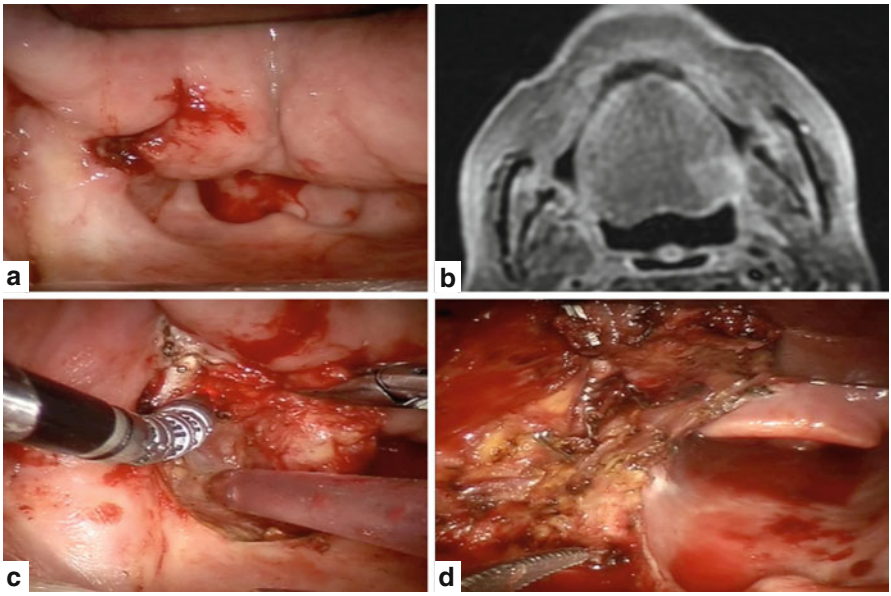

Fig. 7.4 (**a**, **b**) Intraoperative view and preoperative MRI of a T4a SCC of the left base of tongue and glossotonsillar sulcus. Deep infiltration of the tongue into the extrinsic muscles is depicted by MRI. (**c**, **d**) Intraoperative view during TORS and after tumor resection

surgery, RT, and CRT. In their evaluation, TORS + neck dissection is considered as a valuable choice in tumors with low T categories (T1 or T2) and without radiologic signs of lymph-node extracapsular extension, reserving surgery + postoperative RT (60 Gy) in N2 and N3 patients. In fact, while different authors have reported optimal outcomes even in tumors with high T classification, there is no evidence of the reproducibility of such results outside these very selected series.

To date, there is limited data on oncologic outcomes of locally advanced tumors treated by TORS, since most series prevalently include T1–T2 neoplasms, with T3–T4 approximately accounting for only 20 % of cases [101, 117–119]. In a single series, compared directly to open approaches, TORS for T1–T3 tonsillar cancer was seen to have a higher rate of negative margins and more rapid functional recovery [120], showing its potential even in moderately advanced tumors. In a study by Weinstein et al. [81], excellent disease-free survival at 1 (96 %) and 2 years (79 %) was reported in 47 patients with stage III or IV OPSCC treated by TORS (Table 7.3). Regarding the need for adjuvant therapy, 39 % each required RT or CRT. However, comparison with CRT is difficult because of the heterogeneity of the different series, with TORS patients being generally characterized by lower stage and higher prevalence of HPV positive tumors. Furthermore, morbidity is often overestimated in the nonsurgical group used for comparison. In fact, in an "all stages" MSKCC cohort treated mainly (88 %) with concurrent CRT, the authors reported GT dependency in 7 % of patients at 1 year, which compares favorably with the significantly higher

rates of functional complications after CRT reported in other studies [121–123]. Moreover, in this light, data from MSKCC are similar to those on chronic GT dependence after TORS, which in a systematic review by Hutcheson et al. [124] ranged from 0 to 7 % (mean follow-up, 11–26 months).

Transnasal Endoscopic Surgery

TES was introduced in the 1980s for treatment of inflammatory diseases of the nose and paranasal sinuses. The indications rapidly expanded to include first the management of benign tumors and subsequently the resection of malignant lesions of the sinonasal tract and nasopharynx.

The first experiences in the treatment of naso-ethmoidal malignancies were limited to lesions of different histology not encroaching the anterior skull base [125, 126]. However, with the refinement of duraplasty techniques, endoscopic surgeons started to approach even tumors eroding the skull base, invading the dura, or with limited extension to the brain (T3–T4a-b) [127–130]. The indications for TES in nasopharyngeal carcinoma vary in relation to histology. Based on the WHO classification [131], TES can be considered an alternative to re-irradiation in residual/recurrent T1, T2, and very selected T3 nasopharyngeal carcinomas or a reasonable primary treatment option in the more rarely observed salivary gland-type carcinomas or papillary adenocarcinoma.

Malignant Lesions of the Sinonasal Tract

Malignancies of the sinonasal tract are rare, accounting for 3 % of all cancers of the head and neck. Their major peculiarity is the extreme histological variability, which is frequently associated with variable natural history and response to different treatments. For a long time, surgery followed by RT or CRT has been invariably considered the standard of care for management of advanced lesions. The major advancement in surgery was the introduction in the 1960s of anterior craniofacial resection (ACR), a technique providing a reasonably good local control even to lesions encroaching on the anterior skull base. A multicenter collaborative study analyzing 1307 patients (with a reasonable number of patients in each histology group), who underwent ACR followed in most cases by radiotherapy, provided an excellent dataset on survival and morbidity outcomes to be used as a benchmark for future comparisons with alternative treatments [132, 133].

When TES was proposed for treatment of selected malignancies of the naso-ethmoidal complex, it was considered heresy, mainly for the impossibility in most cases to perform the resection according to an “en bloc” principle. However, from the beginning the philosophy guiding endoscopic surgery was to obtain radical resection of the tumor in free margins similar to external procedures. In view of the

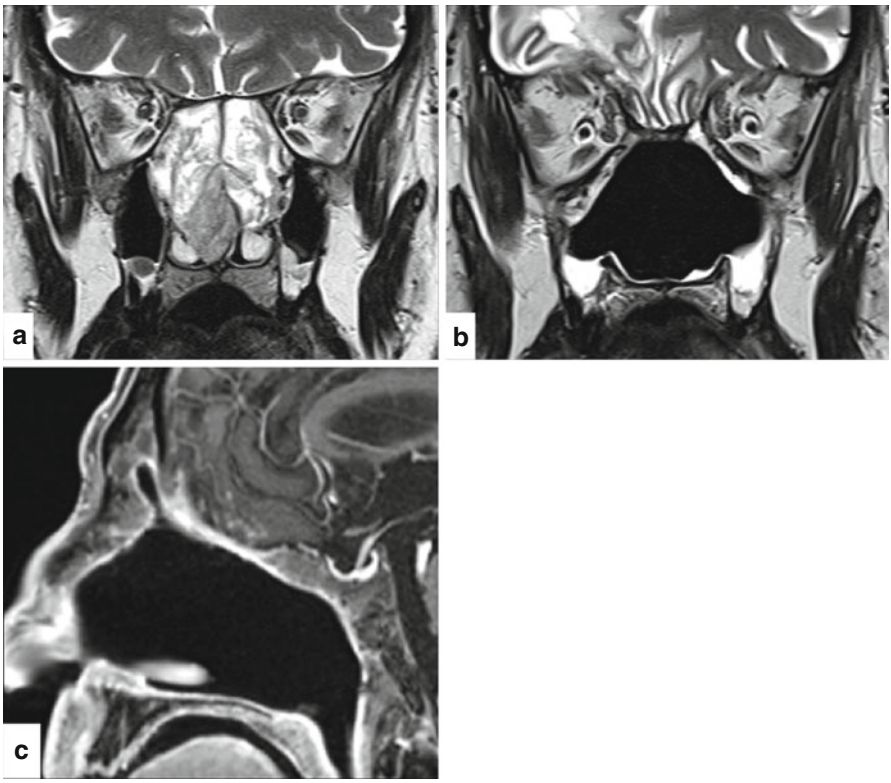

Fig. 7.5 Sinonasal adenoid cystic carcinoma in a 55-year-old man. (**a**) Coronal T2 weighted MRI sequence showing the lesion, which involves both nasal cavities with no evidence of orbital or transdural spread. Endoscopic resection with transnasal craniectomy and three-layer skull base reconstruction with iliotibial tract was performed. Histologic examination of the surgical specimen demonstrated microscopic infiltration of periobit and dura (pT4bN0M0G2). The patient underwent adjuvant RT. (**b**) Coronal T2 weighted and (**c**) contrast-enhanced sagittal T1 weighted MRI sequences show no evidence of disease and perfect healing of skull base reconstruction at 4 years after treatment

narrow access through the nostril(s), a new principle of resection ("tumor disassembling"), starting from the endonasal portion of the tumor and progressively removing in a centrifugal fashion different layers of tissue (mucoperiosteum of the naso-ethmoidal cavity on the most involved side; septum, if required; mucoperiosteum of the contralateral side; periorbit and/or dura, in relation to tumor extent), was introduced [127]. When dura of the anterior cranial fossa is resected, duraplasty is performed preferably with autologous material, with a multilayer technique [134] (Figs. 7.5, 7.6 and 7.7).

There are still "anatomic" contraindications for the use of TES in malignant tumors of the sinonasal complex. Basically, this technique is not suitable for lesions of the maxillary sinus, apart the very rare cases limited to its medial wall, and finds its main playground in naso-ethmoidal tumors. Contraindications within this group

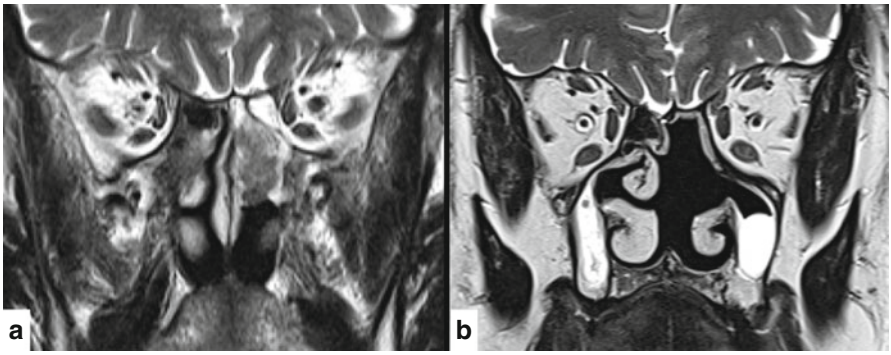

Fig. 7.6 Sinonasal intestinal-type adenocarcinoma in a 64-year-old male woodworker. (**a**) Coronal T2 weighted MRI sequence shows the lesion localized in the posterior ethmoid and confined to the left nasal cavity. Endoscopic resection with unilateral transnasal craniectomy and two-layer skull base reconstruction was performed. Histologic examination of the surgical specimen was consistent with intestinal-type adenocarcinoma pT2N0M0G2. No adjuvant radiotherapy was added. (**b**) Coronal T2 weighted MRI sequence shows no evidence of disease and regular healing of the surgical cavity 2 years after treatment

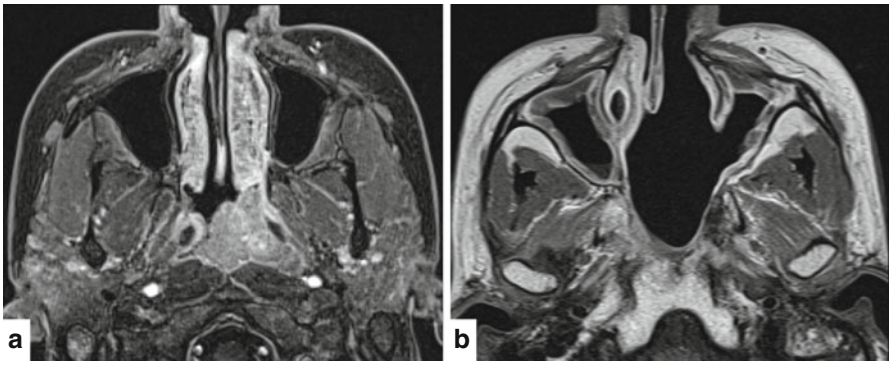

Fig. 7.7 Nasopharyngeal adenoid cystic carcinoma in a 32-year-old woman. (**a**) Contrast-enhanced axial T1 weighted MRI sequence shows the lesion centered in the left nasopharynx with contralateral extension along the posterior wall. Bilateral type III nasopharyngeal endoscopic resection was performed as primary treatment. Histologic examination of the surgical specimen confirmed the histologic diagnosis and showed the presence of perineural spread. The patient underwent adjuvant RT. (**b**) Axial T2 weighted MRI sequence shows no evidence of disease at 7 years after treatment

include infiltration of nasal bones and palate, massive involvement of the frontal sinus, gross invasion of the lacrimal pathway, extension into the infratemporal fossa, involvement of the orbital content, extension of dura involvement beyond the meridian of the orbit, and massive invasion of brain parenchyma. These situations require a combination of endoscopic and external approaches.

Other than the extent of tumor to critical areas, which limits the indications for TES, there are biologic features of the tumor itself, which in general suggest

adopting a nonsurgical treatment strategy, such as concomitant CRT, or use of neoadjuvant chemotherapy to select the next step (CRT or surgery followed by CRT). This approach seems applicable in high-grade tumors (i.e., poorly differentiated SCC, sinonasal undifferentiated carcinoma, neuroendocrine carcinoma, NUT midline carcinoma) [135, 136], which are associated with a high risk of distant metastasis and are frequently diagnosed at an advanced local stage requiring extensive and mutilating surgery.

Twenty-five years after TES was proposed as an alternative to ACR, it is time to try to compare the two techniques with regards to survival and morbidity outcomes. However, there are factors which include the rarity of the disease, histologic heterogeneity, and the length of follow-up in relation to the propensity of some tumors to recur many years later, which made it difficult to accrue large series with sufficient follow-up to make statistically robust comparisons [130]. The three major series (Table 7.5), collected at two Italian Tertiary referral centers, at the M.D. Anderson Cancer Center in Houston, and at the Royal National Throat Nose & Ear Hospital in London, respectively, include a number of patients ranging from 120 [128] to 184 [127]. In spite of the different distribution by histology, with a prevalence of olfactory neuroblastoma in the series from the USA [128] and UK [130], and adenocarcinoma in the Italian study, the results in terms of oncologic outcomes are similar, with 5-year OS varying from 76 to 84 %, and DSS from 82 to 87 %. When morbidity is considered, it is noteworthy that complications occurred in 9–11 % of patients, and no death in the postoperative period was observed. Although the comparison with the results of the collaborative study on ACR is hindered by the different distribution of patients by stage, with a higher rate of advanced tumors in the ACR group, the reported 5-year OS and DSS of 54 % and 60 %, respectively [132], a 36.3 % complication rate, and 4.7 % mortality rate [133] suggest that ETS may favorably compete with ACR in specific indications.

This assumption was confirmed by the results of a very recent paper, which compared the outcomes of endoscopic and open surgery in 82 and 42 patients, respectively, by using a propensity score matching analysis to normalize the differences in comorbidities for the comparison [137].

In the attempt to overcome the limitations related to histologic diversity, several studies have concentrated on the results of ETS in specific histotypes. At the same time, some speculations on the indications for adjuvant therapy have been offered.

Olfactory neuroblastoma is most likely the tumor with the highest number of specific reports [138–142]. A recent systematic review and meta-analysis of 36 studies on 609 patients comparing the results of open surgery vs. ETS concluded that the two techniques have comparable results in relation to long-term survival and oncologic outcomes [143]. However, the rate of intracranial and overall complications was significantly higher in the external surgery group, 20.1 % vs. 7.5 % and 52.9 % vs. 28.1 %, respectively [143]. Following the first extensive review on treatment results of olfactory neuroblastoma [144], the recommended treatment is surgery followed by RT. Since that time, the situation is relatively unchanged, even in view of the nonnegligible tendency of the tumor to metastasize to lymph nodes [145], with the need to include the first echelons in the irradiation plan. Notwithstanding,

Table 7.5 Characteristics of the three largest sinonasal malignant tumors endoscopic resection series to date

	Nicolai et al. (2008) [127]	Hanna et al. (2009) [128]	Lund et al. (2015) [130]
Number of cases, *n*	184	120	140
Reporting period	1996–2006	1992–2007	1996–2014
Mean age, years	59	53	63
Male sex, *n* (%)	117 (64)	65 (54)	68 (49)
Surgical approach, *n* (%)			
Endoscopic	134 (73)	93 (77)	140 (100)
Cranioendoscopic	50 (27)	27 (23)	–
Prior treatment, *n* (%)	52 (28)	70 (58)	25 (22)
T stage, *n* (%)			
1	52 (28)	30 (25)	57 (41)
2	26 (14)	30 (25)	27 (19)
3	32 (17)	25 (21)	41 (29)
4	52 (41)	35 (29)	17 (11)
Histology, %			
Esthesioneuroblastoma	22 (12)	20 (17)	36 (26)
Adenocarcinoma	68 (37)	17 (14)	19 (14)
Squamous cell carcinoma	25 (14)	16 (13)	9 (6)
Mucosal melanoma	17 (9)	17 (14)	33 (24)
Adenoid cystic carcinoma	13 (7)	8 (7)	1 (1)
Others	39 (19)	42 (29)	42 (29)
Adjuvant treatment, *n* (%)	86 (47)	60 (50)	95 (68)
Complications, *n* (%)	16 (9)	13 (11)	14 (10)
CSF leak	8 (4)	4 (3)	3 (2)
Mean follow-up, months	34	37	60
Survival results, %			
5 year	82 (DSS)	87 (DSS) 76 (OS)	−84 (OS)
10 year	– –	80 (DSS) 50 (OS)	−69 (OS)
Site of recurrence, *n* (%)			
Local	28 (15)	18 (15)	14 (11)
Regional	2 (1)	7 (6)	10 (7)
Distant	13 (7)	6 (5)	12 (9)

DSS disease specific survival, *OS* overall survival

future studies should address if adjuvant RT is actually indicated in early cases, Hyams grade I–II, treated with aggressive surgery (unilateral resection of the anterior skull base and olfactory bulb), negative margins, and no intracranial extension at definitive pathologic examination.

Adenocarcinoma has been extensively studied in Europe where the large majority of cases are intestinal-type adenocarcinomas (ITAC) [146–148], a disease typically

affecting wood and leather workers. Based on the analysis of the results of three studies which included treatment outcomes in 451 patients [146–148], Nicolai et al. [148] concluded that there is evidence-based support for the use of ETS, when planned according to precise indications and contraindications, as the surgical treatment of choice for ITAC. The missing link in the comparison between the efficacy of external and endoscopic approaches was provided by a recent single institution, retrospective, comparative study [149]. By analyzing two groups of patients with ITAC that were homogeneous in terms of stage, histologic findings, and adjuvant therapy, treated with an external ($n=31$) or endoscopic ($n=43$) approach, Grosjean et al. [149] observed a 3-year OS of 61.3 % and 76.7 %, respectively. Similarly to the majority of the other histologies, adjuvant RT has been always recommended in adenocarcinoma. However, a recent retrospective case-control study comparing results in two cohorts of patients with T1–T2 adenocarcinoma receiving ETS, with or without adjuvant RT, suggests that RT can be spared in patients with low-grade tumors resected in free margins [150].

Malignant mucosal melanoma is the second or third most prevalent malignancy in the major series of tumors treated by ETS (Table 7.5). Specific studies on this very aggressive tumor are rare [151–155], and all group together patients treated with different surgical approaches. In spite of the many limitations which affect comparison of the results, at least in three studies [152–154] the conclusion is that ETS is not associated with an increased risk of death. Five-year OS is in the range of 28–38 % [152, 154]. Although the role of adjuvant RT is controversial, some data suggest benefits in local control of disease, without, however, any benefit on OS [155].

Malignant Lesions of the Nasopharynx

Surgery has always played a limited role in management of nasopharyngeal malignancies in view of the difficulty in accessing an area located in the center of the skull and the otherwise good response, in particular of NPC, to RT and CRT. External approaches, such as the infratemporal [156] and maxillary swing [157], which have been proposed for the treatment of selected residual/recurrent lesions, have gained limited popularity because of related sequelae and potential complications. The first report on the use of ETS to treat nasopharyngeal carcinoma was by Yoshizaki et al. [158]. As expected in relation to the epidemiological distribution of the tumor, which is endemic in southeast China and Hong Kong, most studies are from this geographic area [159–161] and only a few from Europe [162] and USA [163]. There is general agreement that endoscopic resection is one of the treatment options together with re-irradiation and external surgery in residual/recurrent nasopharyngeal carcinomas (NPC) (T1–T2 and selected T3 with minimal bone erosion involving the floor of the sphenoid sinus). Additional indications include primary treatment of papillary adenocarcinoma or salivary gland-type carcinomas, which are well known to be less radiosensitive than NPC. Absolute contraindications for ETS are

Table 7.6 Characteristics of the four largest nasopharyngeal malignant tumors endoscopic resection series to date

	Chen et al. (2009) [159]		Ko et al. (2009) [165]		Castelnuovo et al. (2013) [162]		You et al. (2015) [160]	
Number of cases, *n*	37		28		36		72	
Reporting period	2004–2008		2004–2007		1997–2011		2001–2009	
Stage of primary tumors, *n*	–	–	–	–	9	5 T1 1 T2 2 T3 1 T4	–	–
Stage of recurrent tumors, *n*	37	17 rT1 18 rT2 2 rT3	28	12 rT1 16 rT2	27	12 rT1 1 rT2 13 rT3 1 rT4	72	32 rT1 27 rT2 13 rT3
Histology, *n* (%)								
NPC	37 (100)		28 (100)		23 (64)		72 (100)	
Adenoid cystic carcinoma	–		–		4 (11)		–	
Adenocarcinoma	–		–		4 (11)		–	
Others	–		–		5 (14)		–	
Positive margins, *n* (%)	13 (5)		3 (10)		3 (8)		–	
Median follow-up, months	24		13		33		49	
Survival results	2-y OS 84 % 2-y DFS 86 %		2-y OS 59 % 2-y DFS 58 %		5-y OS 75 % 5-y OS 58 %		5-y OS 77 % 5-y DFS 67 %	

DFS disease free survival, *m* months, *NPC* nasopharyngeal carcinoma, *OS* overall survival, *y* years

extensive erosion of the skull base, intracranial involvement, invasion of the orbital tissues, and intimate contact of the tumor with the internal carotid artery.

There are basically three different types of nasopharyngeal endoscopic resection (NER) [162, 164]. In Type 1 NER, the resection is limited to the posterosuperior nasopharyngeal wall, reaching the bony floor of the sphenoid sinus superiorly and the pharyngobasilar/prevertebral fascia posteriorly. Type 2 NER superiorly extends to include the anterior wall and the floor of the sphenoid sinus, as well as the rostrum. Type 3 NER is the most complex resection and requires a transmaxillary-transpterygoid approach to expose and remove the cartilaginous portion of the Eustachian tube and soft palate muscles (tensor and levator veli palatini). It is suitable for lesions laterally extending to the torus tubarius and the Rosenmuller fossa.

No prospective studies comparing survival outcomes of different surgical techniques or ETS and re-irradiation in recurrent NPC have been reported to date, and thus the present recommendations for treatment are based on studies with a low level of evidence (Table 7.6). A meta-analysis on 17 retrospective studies including 779 patients treated with surgery (open or ETS) for recurrent NPC reported that more than half of patients treated were salvaged by surgery. Interestingly, the overwhelming majority (83 %) were T1–T2 lesions. The 5-year OS and local

recurrence-free survival rates for the entire cohort were 51.2 % and 63.4 %, respectively. Multivariate analysis revealed that ETS offers better outcomes than open surgery for T3–T4 tumors in selected patients, and adjuvant re-irradiation provides an additional survival advantage over surgery alone [166].

Two recent Chinese studies from Sun Yat-sen University Cancer Center in Guangzhou have shed light on the role of ETS and its advantages compared with RT [160, 161]. The first is a retrospective analysis of 410 patients treated for recurrent NPC with IMRT, ETS, or 2D conventional RT [161]. Despite the authors' recognition that the distribution by T category was not homogeneous in the three treatment groups, with a significantly higher number of recurrent T1–T2 in the ETS group, subgroup analysis of T1–T2 showed that ETS was associated with better 5-year OS than IMRT and 2D conventional RT. In the subgroup of patients with recurrent T3–T4 NPC, although ETS still presented higher OS than IMRT and 2D conventional RT, all patients who received ETS were recurrent T3 and highly selected, with disease confined in the floor of the sphenoid sinus [161].

The second study went deeper further analyzed the results between ETS and IMRT in selected T1–T3 recurrent NPC by performing a retrospective case-matched analysis on 144 patients [160], 72 in each arm, which were well balanced in relation to prognostic factors based on propensity scores. Compared with IMRT, ETS was associated with significantly better 5-year OS (77.1 vs. 55.5 %, $P = .003$), quality of life conservation (mean global health status score 57.6 vs. 29.8 %; $P < .001$), significant decrease in posttreatment complications (12.5 vs. 65.3 %; $P < .001$) and, specifically, in complication-related deaths (5.6 vs. 34.7 %; $P < 0.001$). Medical costs of ETS were also significantly lower. Even though the conclusions are extremely important, the study suffers some limitations: neoadjuvant chemotherapy was delivered more frequently in the IMRT than in the ERS group; frozen sections were obtained in only some patients in the surgical group; and there is no mention of surgical margin status.

The possibility to use TORS to perform salvage nasopharyngectomy has also been described [167]. However, to increase the limited exposure enabled by the standard equipment via a transoral route, a longitudinal split of the soft palate has been recommended, which indeed increases the potential for complications related to the intervention. Another limitation of present technology is the impossibility to use drills or rongeurs to remove bony structures, which can be overcome by combining the use of ETS with TORS [168]. However, an important question arises: why two different tools, with an increase in costs, should be used in the nasopharynx if ETS at present shows better performance?

Conclusions

Technology is rapidly evolving and provides surgeons with new tools that arouse our curiosity, but which need to be judiciously tested in a preclinical setting and, subsequently, in clinical practice. The main goal is to offer patients treatments that can compete with standard nonsurgical and surgical methods considering survival

and morbidity. Appropriate evaluation of numerous outcomes pertaining to disease control, complications, quality of life possibly in the context of clinical trials together with analysis of costs is mandatory to provide evidence of the efficacy and efficiency of any "new method."

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Chapter 8
Oncologic Dentistry and Implants

Ross O.C. Elledge, Rokhsareh Elledge, Sat Parmar, and Stefan Edmondson

The aims of reconstruction in the head and neck cancer patients are:

1. Functional rehabilitation
   (a) Speech
   (b) Mastication
   (c) Deglutition
2. Aesthetics
3. Quality of life

Implant-supported facial and oral prostheses remain an important option in the armamentarium of the modern head and neck surgeon. They can be used with or without autologous reconstruction. However, they are particularly useful in critical sites such as the eyes, ear and nose where autogenous alternatives produce unpredictable results (Figs. 8.1 and 8.2).

Head and neck patients offer a unique set of challenges and relative contraindications to implant placement that include poor systemic health and nutritional status, poorly controlled metabolic diseases, ongoing or recent chemotherapy and/or radiotherapy and continued smoking.

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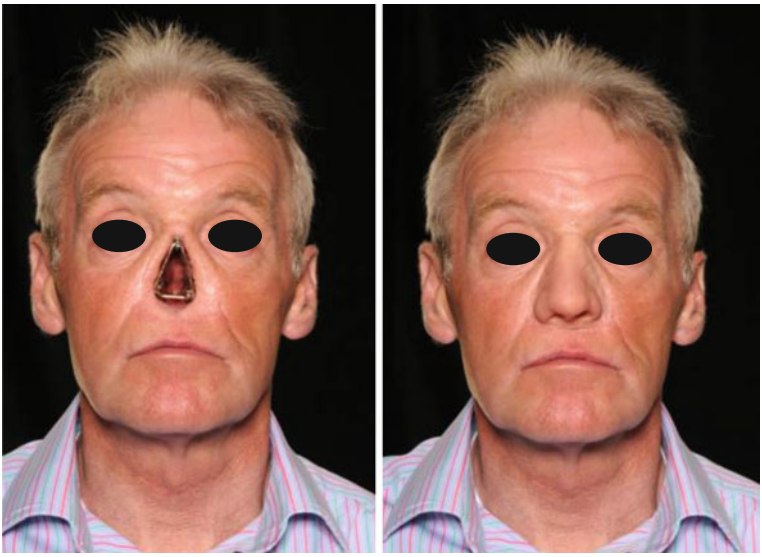


Figs. 8.1 and 8.2 A superior aesthetic result from an implant-supported prosthesis rivalling any potential result achievable with autogenous tissue transfer

Fundamentals of Maxillofacial Implantology

Implants have been employed in oral prosthodontic rehabilitation since the 1980s [1]. The history of dental implantology goes back much further to implantation of human teeth supported by gold strips by the Etruscans as early as 630 BC [2]. Much of what we know about implantology today hinges on work done by Branemark in the 1960s and the key observation of osseointegration of titanium fixtures to bone as a foundation for the science implantology has become today [3].

Successful implant placement is based on achieving osseointegration through good primary stability followed by secondary stability. Osseointegration is defined by Zarb and Albrektsson as "direct structural and functional connection between ordered, living bone and the surface of a load-carrying implant" [4]. Primary stability is the initial stability at the time of placement by mechanical engagement of an implant with the surrounding bone and is dependent upon bone density and implant design. Tapered implants, thinner drills and omitting pre-tapping (where the bone is grooved so the implant "screws" into the bone) are all strategies that can enhance primary stability [1]. Secondary stability is bone regeneration and remodelling to determine the bone implant contact and final osseointegration.

One can distinguish two different forms of osteogenesis in implant osseointegration: *contact osteogenesis* and *distance osteogenesis* [5]. The former is bone forming directly on the implant surface whilst in the latter instance bone is formed from pre-existing bone surfaces migrating towards the implant. Surface-treated implants with roughened surfaces tend to show more contact osteogenesis and better

short- and long-term outcomes, and the recent trend in implantology has been towards favouring these over machined, smooth-surface implants in view of these superior outcomes [6].

Criteria for successful implant integration have been described by Zarb and Albrektsson [4] as:

1. The implant allows for placement of planned functional and aesthetic prostheses.
2. The absence of pain, discomfort, altered sensation or infection.
3. Individual implants are immobile.
4. Mean vertical bone loss less than 0.2 mm/annum following the first year of function.

Implant-Supported Obturators and Removable Prosthodontic Devices

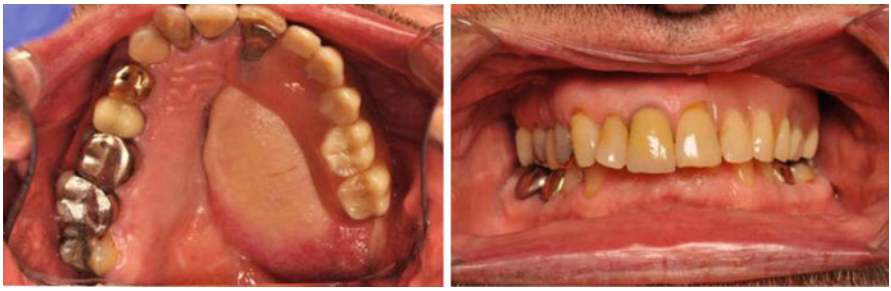
Obturators represent an attractive solution in terms of rehabilitating patients with partial and total maxillectomy defects. They allow for minimal surgical morbidity, obviating the need for free flap harvest and reconstruction and lengthy surgery whilst yielding good aesthetic and functional results as well as allowing for regular easy inspection of the ablative site to enable early detection of recurrence. However, patients with partial and total maxillectomy defects may present significant challenges that need to be addressed [7]:

1. Masticatory problems in partially dentate/edentulous patients
2. Hypernasality due to oro-nasal/oro-antral communication and speech defects
3. Difficulty in retaining removable prostheses
4. Facial disfigurement due to loss of maxillary support for overlying soft tissues
5. Dysphagia due to loss of velopharyngeal competence and safe swallow

Where a decision is made to provide an implant-assisted obturator, implants are usually placed in the premaxilla and tuberosity regions, as these areas of the maxilla often represent the best quality and volume of bone available [8]. A surgical guide can be used and pre-planned using software planning packages or stents fabricated on plaster models.

As highlighted by Roumanas and colleagues [8], we recognize that uniting implants with a precision-fitted bar directs occlusal forces along the axis of the implants to generate more favourable loading patterns and optimize survival of the implants.

In the absence of adequate bone in the maxilla, zygomatic implants can represent a useful alternative solution. In recent years we have placed less of these as our tendency in such situations in Birmingham is to place composite free flaps to provide adequate bone stock for standard implant placement (Figs. 8.3 and 8.4).



Figs. 8.3 and 8.4 An example of a removable implant-supported prosthesis on a osseocutaneous composite radial forearm free flap

We recognize the need to link implants again with bar devices, as we have seen higher failure rates when zygomatic implants are placed in isolation. In our own series of 53 implants in 42 sites, we have had six (9.5 %) failures [9]. Other authors have demonstrated similar outcomes for use of zygomatic implants for maxillary and midface defects [10, 11].

Implant Placement in Composite Flaps

Composite flap (bone with skin or muscle) reconstructions of the oral cavity aim to achieve adequate width and height of bone to replace horizontal and vertical deficiencies following ablative surgery. Selection of free flaps should take into account their ability to support implants as well as adequate pedicle length to avoid where possible the need for inter-positional vein grafts, sufficient bone to restore facial contour whilst always being mindful of the need to minimize donor site morbidity.

All flaps are not equal when it comes to considering their ability to support implants. Moscoso et al. have described different free flaps as having a relative implantability index, whereby the iliac crest is the most consistently implantable donor site, followed by the scapula, fibula and radius (83 %, 78 %, 67 % and 21 %, respectively) [12]. Free flap selection in orofacial reconstruction should take into account the potential volume of bone harvested to "replace like with like" and also provide sufficient bone stock to support implants as well as sufficient bone quality as described by Lekholm et al [13]. Implant survival rates of 93 % have been reported for fibula flaps in the literature, with a 98 % implant-supported prosthesis success rate, making outcomes predictable and safe [14, 15] (Figs. 8.5, 8.6 and 8.7).

We regularly employ computer-assisted design (CAD) in our more complex reconstructions. Using DICOM data from 3D computed tomograms (CT) of donor and recipient sites for composite flaps we construct stereolithographic (STL) models. The Object 3D printer we use provides highly accurate rendering at 27 μm per slice. Such STL models enable the manufacture of custom reconstruction plates (laser-welded titanium 2.0 mm locking plates), which are pre-fabricated in the laboratory, saving valuable intra-operative time and ensuring accurate results. STL

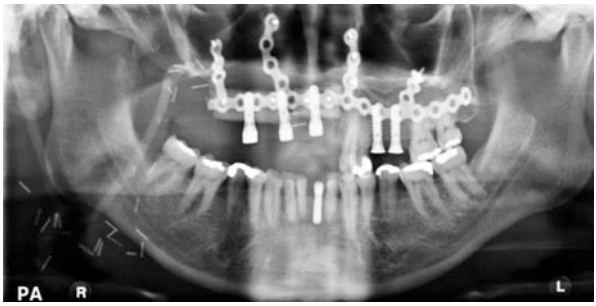
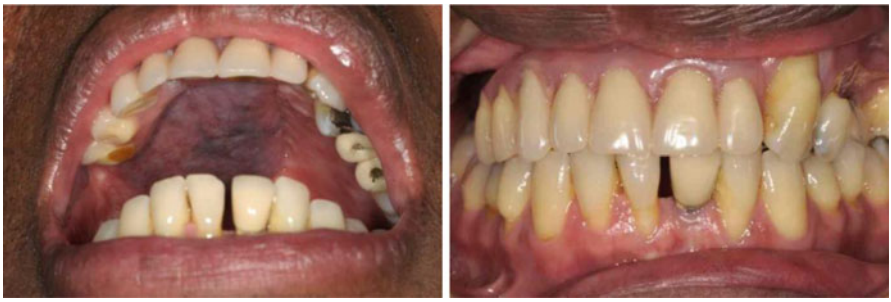


Fig. 8.5 Orthopantomogram (OPG) showing fibula flap used for reconstruction of partial maxillectomy defect incorporating pre-bent custom reconstruction plate and osseointegrated implants



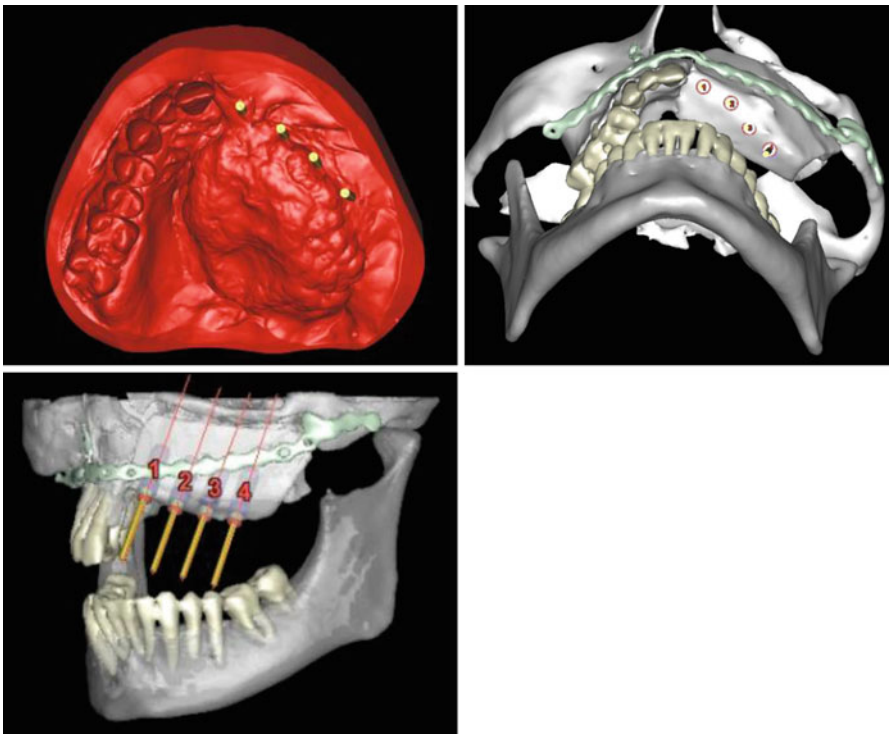
Figs. 8.6 and 8.7 Final aesthetic result of case shown in Fig. 8.3

models also enable the fabrication of cutting guides for donor sites such as the deep circumflex iliac artery (DCIA) free flap, fibula and scapula [16, 17] (Figs. 8.8, 8.9, 8.9, 8.10 and 8.11).

Such technology can equally be employed further down the line for custom made implant stents in conjunction with our restorative dentistry colleagues and maxillofacial prosthetists. The option exists, however, for implant placement at the time of ablative surgery using suitable custom stents, and this is well described in the literature [18, 19]. Jackson et al [14] have demonstrated no difference in placement at either the initial surgery or a separate second stage approach and this is our experience also (Fig. 8.12).

Implants for Facial Prostheses

The evidence is quite clear that patients prefer implant-retained facial prostheses to adhesive ones in particular with regard to ease of placement and removal, frequency of wear and quality of retention [20]. As with intra-oral obturators, facial prostheses promise a number of advantages in terms of reducing surgical time and morbidity as well as allowing regular inspection of ablative defects for detection of recurrence. All this coupled with superior results with dedicated maxillofacial prosthetists and modern materials translates into a tempting reconstructive option for challenging defects (Figs. 8.13 and 8.14).



Figs. 8.8–8.10 Computer-assisted design (CAD) planning for a deep circumflex iliac artery (DCIA) free flap reconstruction of partial maxillectomy defect

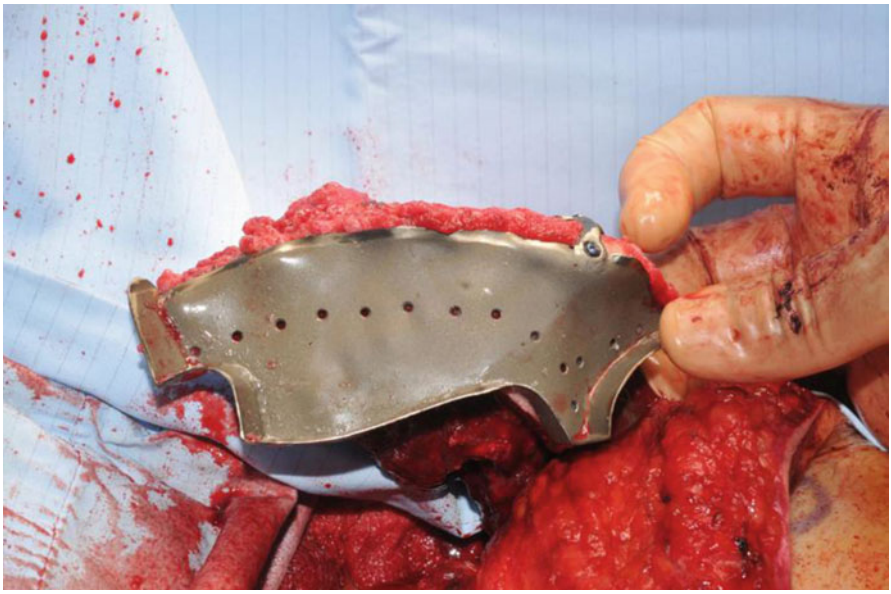


Fig. 8.11 A computer-designed custom cutting stent for a bespoke deep circumflex iliac artery (DCIA) free flap with holes for a pre-bent custom reconstruction plate

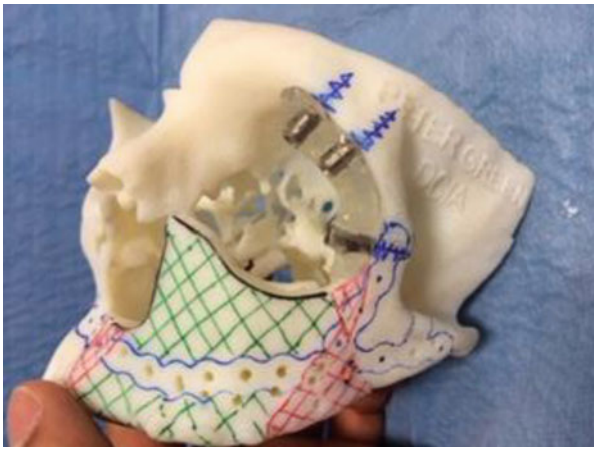
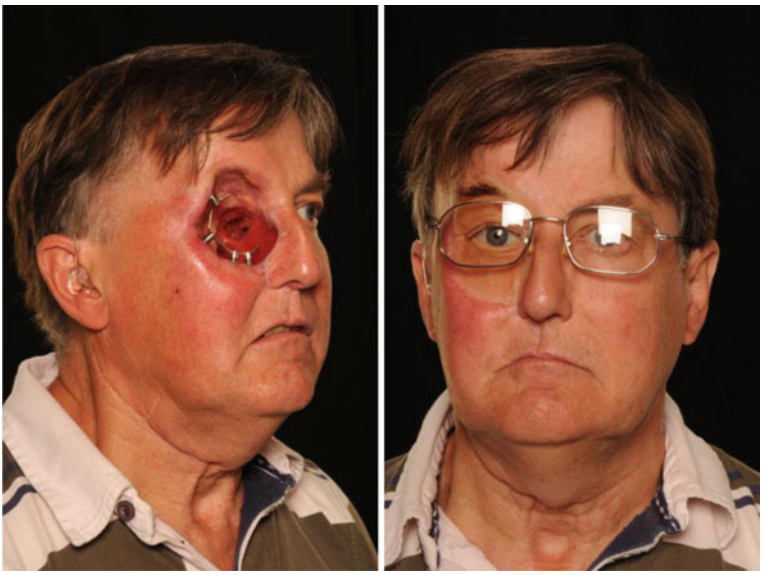


Fig. 8.12 A stereolithographic (STL) model with pre-planned bespoke composite flap and outline of custom plate along with stent for implant placement at orbital rim



Figs. 8.13 and 8.14 An example of an implant-retained orbital prosthesis with excellent aesthetics

We tend to place our implants for facial prostheses at the same time as ablative surgery with no detrimental effects on long-term outcomes. All cases are done in close conjunction with our maxillofacial prosthetists who see the patient at pre-operative planning, intraoperatively and post-operatively for ongoing care of facial prostheses and provisions of replacement when required. We have conducted a recent survey of 451 implants placed in our practice over a 10-year period, including 222 (49.2 %) auricular implants, 98 (21.7 %) nasal implants and 131 (29.0 %) orbital implants. We had 24 (5.3 %) implant failures. We tend to favour bar-clip attachments for our larger midfacial prostheses due to better retention but often use magnets for our orbital prostheses due to the ease of placement by patients who have lost stereoscopic vision and depth perception following orbital exenteration [21].

Implants and Radiotherapy

Radiotherapy has a significant impact on implant success rates, and this has been widely reported in the literature. Implant survival rates for extra-oral implants in non-irradiated bone typically range from 94.0 to 99.0 %, whilst those in irradiated bone return significantly poorer outcomes of 58.0–90.5 % [22–26]. Timing in relation to radiotherapy is controversial. Schoen et al. reported worse outcomes for implants pre-radiotherapy than those placed post-radiotherapy (85.7 vs. 90.5 %) [27]. It has been reported, however, that implants placed at the time of ablative surgery as a one-stage approach show higher survival rates than those placed afterwards as a second separate stage [26–29]. This has been our practice and our findings have been that whilst failure rates were higher for those implants placed in irradiated bone (10.9 vs. 2.2 %, χ^2 test $p<0.001$), timing of radiotherapy in relation to implant placement appeared to demonstrate little difference ($p=0.96$) [21].

The role for hyperbaric oxygen (HBO) therapy is controversial. The arguments for HBO find their roots in Marx's original theory concerning the development of osteonecrosis (ORN), and the modified Marx protocol of 20 sessions pre-surgery and 10 sessions post-surgery at 2.4 atm for 90 min/session has been advocated to reduce the likelihood of ORN and implant failure [30, 31]. The purported beneficial effects of HBO include:

1. Improved tissue healing
2. Stimulation of angiogenesis
3. Induction of fibroplasia and neo-cellularity
4. Promotion of differentiation and survival of osteoprogenitor cells
5. Promotion of formation of a functional periosteum

Granstrom [32] reported reduced implant failures with adjuvant HBO but recent evidence has called into question the place of HBO as a panacea. Schoen et al [33] found higher failure rates in patients given HBO, and Shaw and colleagues [34] demonstrated no apparent impact of HBO on success rates of implants in irradiated bone. Similarly, the only systematic review on the subject by Esposito and Worthington [35] showed no benefit from HBO, but acknowledged that there was a paucity of data on the subject, with only one suitable randomized-controlled trial.

A multicentre trial (the Hyperbaric Oxygen for the Prevention of Osteoradionecrosis or HOPON trial) is currently recruiting and underway, and the results of this may help settle this debate which is of considerable interest to all those undertaking implant placement in head and neck cancer patients requiring adjuvant radiotherapy [36].

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Chapter 9
Comprehensive Overview: Definitive Radiotherapy and Concurrent Chemoradiation in Locally Advanced Head and Neck Cancer

Volker Budach

Introduction

For many decades surgery and radiotherapy (RTX) were the only feasible treatment options in head and neck squamous cell carcinomas (HNSCC) until the 80s of the last century when concurrent chemoradiation (cCRTX) was established [1–3]. Until today, RTX and cCRTX are still considered standard of care for locally advanced (LAD) and inoperable HNSCC [4]. The detection of a viral pathogenesis in up to 70 % of HNSCC, especially for oropharyngeal cancer (OPC), changed considerably the landscape, since it leads to a significant better outcome [5–9]. Sequential chemoradiation, e.g. induction chemotherapy (CTX) and bio-radiation, has also been introduced for the treatment of HNSCC [10–12]. Since the implementation of genomics in HNSCC research, an increasing number of phase II/III clinical trials (RCT) were launched with integrated translational research elements aiming at the detection of predictive biomarkers for clinical outcome [13–15]. With the development of immune checkpoint inhibitors, additional perspectives are available which carry the chance of a substantial improvement of the therapeutic ratio in HNSCC during the next couple of years.

Definitive Radiotherapy (RTX)

For many decades high-dose two-dimensional fractionated RTX was the standard of care for HNSCC. With the advances in precision engineering, computer technology and radiation biology, 3-D conformal RTX and **I**ntensity **M**odulated **R**adio**T**herapy

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(*IMRT*) and **V**olumetric **A**rc **T**herapy (*VMAT*) were introduced into clinical practice. Standard fractionated (SF)-RTX using single fractions of 1.8–2.0 Gy up to a total dose of 70–72 Gy during 7–8 weeks was established long ago as standard for definitive treatment before altered fractionated (AFX) regimens were introduced during the 80s of the last century. Two major types of AFX have been explored, which is on the one hand hyperfractionation (HFX) with twice daily (bid) fractions of 1.0–1.3 Gy up to total doses of around 80 Gy. With improved loco-regional control (LRC) rates and equal or less late morbidities, HFX aims at an improvement of the therapeutic ratio. On the other hand, moderately accelerated fractionation (ACFX) regimens without and with total dose compromise used either single (qd) fractions of 2.0 Gy up to 7 days a week or bid fractions of 1.4–1.6 Gy in an attempt to reduce tumour cell proliferation, a major cause for loco-regional failures so far. For very accelerated regimes (vACFX) fraction sizes of 1.0–1.8 Gy twice or thrice daily (tid) to a total dose of 66–70 Gy were employed.

Rationale

HFX with a bid RTX approach maximally exploits the different fractionation sensitivities of tumours and normal tissues and critical organs at risk by using treatment intervals of up to 12 h between the two fractions. Hence, the rationale for AFX in terms of HFX is the improvement of LRC without enhanced late morbidities. For accelerated regimens the reduction of the overall treatment time (OTT) is the major focus of attention. Accelerated tumour clonogenic repopulation, which regularly occurs during fractionated RTX, is threatening LRC and ultimately overall survival (OS). During SF-RTX, this phenomenon called “accelerated tumour clonogen repopulation” might happen continuously from the beginning or stepwise starting around the third week of radiation therapy [16, 17]. The interfraction intervals with bid RTX regimens proved to be of outmost importance and should be kept to a minimum of 6 h [18]. By means of dose intensified regimens the results for definitive RTX alone for HNSCC – mainly in terms of LRC – could definitely be improved.

Selected Phase-III RCTs for Hyperfractionation (Table 9.1)

A selection of pivotal trials using AFX represents the experiences gained by the radiotherapeutic community worldwide. A small RCT of Pinto et al. (1991) treated 98 stage III/IV OPC patients using bid 1.1 Gy with interfraction intervals of 6 h up to 70.4 Gy vs. qd 2.0 Gy up to 66 Gy total dose, respectively. It could be shown that HFX was superior in terms of local control (LC; 84 % vs. 64 %, $p = .02$) and OS (27 % vs. 8 %, $p = .04$) at 3.5 year follow-up [19]. Acute mucosal and skin toxicities were similar but had an earlier onset with HFX. Late morbidity was not different between both arms.

Table 9.1 Selection of pivotal randomized clinical trials of altered versus standard fractionation in LAD HNSCC

Study/ author/year	No. patients	Sites/no. pts. OP/OC/HP/L	Stage (UICC)	Fractionation schedule	OTT (weeks)	Total dose in tt.-arms	LC/LRC (%)	PFS (%)	OS (%)	Acute toxicities	Late morbidities
Pinto et al. (1991) [19]	56	56/–/–/–	III/IV	HFX: 1.1 Gy bid	6.5	HFX: 70.4 Gy	LC: 84 % $p=.02$	25 % $p=.08$	8 % @ $p=0.03$	Same degree but earlier onset for HFX	No differences between tt.-arms
	56	56/–/–/–	ditto	CFX: 2.0 Gy qd	6.5	CFX: 66.0 Gy	LC: 64 % @ 3.5 yrs	7 % @ 3.5 yrs	27 % 3.5 yrs		
EORTC 22791	180	180/–/–/–	III	HFX: 1.15 Gy bid	7.0	HFX: 80.5 Gy	LC: 59 % $p=.02$	Not stated	39 %; $p=.08$	Diffuse mucositis: HFX: 67 %	No differences between tt.-arms
Horiot et al. (1992) [21]	176	176/–/–/–	ditto	CFX: 2.0 Gy qd	7.0	CFX: 70.0 Gy	LC: 40 %; @ 5 yrs	Not stated	30 % @ 5 yrs	CFX: 49 %; $p=.01$	
RTOG 09–03	211	160/26/28/49	II/III/IV	HFX: 1.2 Gy bid	7.0	HFX: 81.6 Gy	LRC: 54.4 % @ 2 yrs $p=.045$	37.6 % @ 2 yrs	54.5 % @ 2 yrs	All patients in the AFX treatment groups had enhanced acute toxicities	Feeding tubes @ 5 yrs in survivors: 4.8 % for HFX vs. 13 % for SFX, no differences in other late effects
Fu et al. (2000) [22] and Beitler et al. (2014) [23]	274	165/29/40/40	ditto	Split-ACF: 1.6 Gy bid	5.0	Split-ACF: 67.2 Gy	LRC: 47.5 % @ 2 yrs	33.2 % @ 2 yrs	46.2 % @ 2 yrs		
	268	165/24/39/40	ditto	Conc. Boost: 1.8 + 1.6	6.0	Conc. Boost: 72 Gy	LRC: 54.5 % @ 2 yrs $p=.05$	39.3 % @ 2 yrs	50.9 % @ 2 yrs		
	268	159/31/34/44	ditto	CFX: 2.0 Gy qd	7.0	CFX: 70.0 Gy	LRC: 46 % @ 2 yrs	31.7 % @ 2 yrs	46.1 % @ 2 yrs		

(continued)

Table 9.1 (continued)

Study/ author/year	No. patients	Sites/no. pts. OP/OC/HP/L	Stage (UICC)	Fractionation schedule	OTT (weeks)	Total dose in tt.-arms	LC/LRC (%)	PFS (%)	OS (%)	Acute toxicities	Late morbidities
DAHANCA 6&7 Overgaard et al. (2003) [24]	730	213/71/–/466	II/III/IV	ACFX: 2.0 Gy qd 6×/week	5.6	ACF 66-68 Gy	LRC: 70 % @5 yrs, $p = .0005$	73 % @ 5 yrs	52 % @ 5 yrs	Enhanced acute toxicities $p < .0001$	No differences $p = .16$
	755	222/62/–/442	ditto	CFX: 2.0 Gy qd 5×/week	6.6	CFX 66–68 Gy	LRC: 60 % @ 5 yrs	66 %; $p = .01$	50 %; n.s.		
CAIR Skladowski et al. (2013) [25]	173	56/16/17/83	II/III/IV	CAIR: 2.0 Gy qd 7 days/week	5.3–5.7	CAIR 66.6–72.0 Gy	LRC: 63 %/60 % @ 5/10 yrs	Not stated	40 %/25 % @ 5/10 yrs	Confluent mucositis 3°: 89 % vs. 86 %	Only 6 % for both tt.-arms
	172	61/13/15/82	ditto	CB: 2.0 Gy qd 5 days/ week	5.3–5.7	CB: 66.6–72.0 Gy	LRC: 65 %/60 % @ 5/10 yrs	Not stated	44 %/25 % @ 5/10 yrs		
CHART Dische et al. (1997) [29]	552	141/79/53/224	II/III/IV	CHART: 1.5 Gy td 12 days	1.8	CHART: 54.0 Gy	LRC: 45 % @ 5 yrs	42 % @ 4 years	40 % @ 5 yrs	73 % confluent mucositis	Less severe late reactions
	366	98/47/34/170	ditto	CFX: 2.0 Gy qd	6.6	CFX: 66.0 Gy	LRC: 44 % @ 5 yrs; n.s.	40 % @ 4 years; n.s.	40 % @ 5 yrs	43 % confluent mucositis	

EORTC 22851 Horiot et al. (1997) [30]	257	153/38/–/32[a]	II/III/IV	ACFX: 28.8 Gy tid, 14 d. split 72 Gy tid	5.0	ACFX: 72.0 Gy	LRC: 59 % @ 5 yrs; $p = .02$	Not stated	26 % @ 5 yrs	OMR[a] @ 6 weeks: 70 %	SAE-free @ 5 yrs: 53 %
	255	153/38/–/32[a]	ditto	CFX: 2.0 Gy qd 5×/week	7.0–8.0	CFX: 70.0 Gy	LRC: 46 % @ 5 yrs	Not stated	27 % @ 5 yrs	34 %	86 %
GORTEC Bourhis et al. (2006) [31]	137	107/19/7/4	III/IV	ACFX: 2.0 Gy bid	3.2	ACFX: 64.0 Gy	42 % @ 6 yrs	No difference in both tt.-arms	20 % @ 5 yrs	Increased dermatitis 3°; each $p < .0001$	No differences for both treatment arms
	129	98/17/8/6	ditto	CFX: 2.0 Gy qd 5×/week	7.0	CFX: 70.0 Gy	27 % @ 6 yrs $p = .009$		17 % @ 5 yrs n.s.		

Abbreviations: *OP* oropharynx, *OC* oral cavity, *HP* hypopharynx, *L* larynx, *NP* nasopharynx, *SFX* conventional fractionation, *HFX* hyperfractionation, *ACFX* accelerated fractionation, *CAIR* continuous accelerated fractionation, *CHART* continuous hyperfractionated accelerated radiotherapy, *bid* two fractions per day, *tid* three fractions per day, *RTX* radiotherapy, *OTT* overall treatment time, *LC* local control, *LRC* loco-regional control, [a]*OMR* objective mucosal reactions, *n.s* not significant, *SAE* severe adverse event, *ditto* the same like above, *no* number, *pts* patients, *confl* confluent, *yrs* years

[a]Only 93.5 % of patients classified

A large 3-arm RCT was carried out by Sanchiz et al., 1990, in 859 patients with LAD HNSCC [20]. In the first treatment arm, 299 patients were treated with SF-RTX of weekly 5 × 2.0 Gy up to 60 Gy. In the second arm, 282 patients received bid 1.1 Gy with a fraction interval of at least 3 h up to a total dose of 70.4 Gy, and the third treatment arm included 300 patients with 5 × 2.0 Gy up to 60 Gy in 6 weeks OTT with concomitant 5-FU of 250 mg/m^2 every other day. The acute mucosal and skin toxicity was moderate with 10 % grade 3 mucositis in the combined arm. Late morbidity was confined to moderate xerostomia in 42 %, bone necrosis in 11 % and cervical fibrosis in 19 % of all patients. Mean OS for group A (SFX) was 38.2 months vs. 84.0 months ($p < .001$) for group B (AFX). This study from the 1980s was hypothesis-generating for the development of subsequent RCT on AFX and concurrent CTX.

A large 2-arm trial investigating HFX was executed by the former EORTC Radiotherapy Group (Trial 22791) in 356 stage III OPC patients with fractions of bid 1.15 Gy vs. qd 2.0 Gy up to total dose levels of 80.5 Gy vs. 70.0 Gy, respectively [21]. At 5 years, an LRC benefit of 19 % (59 % vs. 40 %, $p = 0.02$) could be shown. A difference in acute toxicity was exclusively observed for grade 3 mucositis, which was dominant in the HFX-treatment arm with 66.5 % vs. 49 %. Late morbidity was not different between the two study arms.

Fu et al. published the by far largest trial addressing altered fractionation (RTOG 90–03) with a recruitment of 1073 stage II/III (≈30 %) and IV (≈70 %) patients, who were submitted to SFX, HFX, ACFX with split and moderately ACFX with concomitant boost (CB) during the fifth and sixth weeks of treatment by introducing a second fraction of 1.5 Gy in the afternoon [22]. The major involved sites were oropharynx (OP) ≈60 %, larynx ≈17 %, hypopharynx (HP) ≈13 % and oral cavity (OC) ≈10 %. The results at 2 years showed a statistically improved LRC for HFX ($p = .045$) and ACFX with CB ($p = .05$), however, no impact on disease-free (DFS) and OS. As in all AFX-trials the acute toxicities were enhanced, in some instances leading to treatment interruptions of 3–5 days. Late morbidities at 2 years of the experimental treatment arms were not different from those of the controls. An update of this trial with a maximum follow-up of 15 years reported by Beitler et al. 2014, showed only HFX to be superior to SFX in terms of a HR reduction for LRC of 21 % (HR: 0.79; $p = .05$) and for OS of 19 % (HR: 0.81) at 5 years [23]. Late morbidities grade 3–5 including use of feeding tubes were not statistically different in the whole study population. However, surviving patients at 5 years experienced with 13 % vs. 4.8 % for the ACFX-regimens a higher feeding tube dependence compared with HFX.

Selected Phase-III RCTs for Moderately Accelerated Fractionation (ACFX)

The DAHANCA 6 and 7 trials addressed in 1.485 patients the question of a superiority of a modest ACFX regimen of 66–68 Gy in 5.6 weeks vs. SFX using the same total dose with an OTT of 6.6 weeks in moderately advanced (ca. 50 %

stage III/IV) HNSCC with about two thirds of prognostic favourable laryngeal cancers. The experimental arm received six fractions of 2.0 Gy including Saturdays vs. five weekly fractions in the standard arm [24]. As a result of this moderate acceleration without a compromise in total dose the hazard of accelerated tumour clonogen repopulation, mainly during the weekends, could be minimized leading to an improvement of the LRC-rates by 10 % (70 % vs. 60 %; $p = .0005$). Moreover, primary tumour control was improved from 64 to 76 % ($p = .0001$) and voice preservation was successful in 80 % (ACFX) vs. 66 % (CFX; $p = .007$). DFS was also enhanced from 66 % to 73 % ($p = .01$), but not OS. The acute toxicities of ACFX were more pronounced; however, no differences in late morbidity were observed.

Another RCT in 345 patients compared a 7-days-a-week ("weekend-on") ACFX regimen (CAIR = **C**ontinuous **A**ccelerated **IR**radiation) with single fractions of 1.8 Gy against a 5-day concomitant boost (CB) regimen with 1.8 Gy qd on Monday, Wednesday and Thursday and bid 1.8 Gy on Tuesday and Friday ("weekend-off") to the same total doses depending on the initial T-stage (T2 = 66.6–68.4 Gy, T2/3 = 70.2–72.0 Gy) in 37–40 fractions during 5.3–5.7 weeks with moderately advanced HNSCC (60 % stage IV) [25]. LC at 5 and 10 years for CAIR was 63 % and 60 %, respectively, or 65 % and 60 % for the CB. Corresponding OS-figures were 40 % and 25 % for CAIR vs. 44 % and 25 % for CB at 5 and 10 years, respectively. Acute confluent mucositis developed as the major symptom with CAIR (89 %) and CB (86 %). The 5-year late radiation morbidity was low with 6 % in both treatment arms. This study clearly showed that the "weekend-on" regimen can be skipped in favour of a "weekend-off" regimen without losing on tumour control or survival. Without chemotherapy (CTX), a moderate acceleration of the OTT with weekly doses of 12 Gy is beneficial for the patients and well tolerated by normal tissues and organs at risk at the head and neck region.

Selected Phase-II/III RCTs for Very Accelerated Fractionation (ACFX)

These regimens involve a radical reduction of the overall treatment time from 7 to 8 to about 2 weeks or even less. It needs three fractions per day and a substantial reduction of the total dose to prevent excessive acute mucosal and dermal reactions. A considerable number of studies have focused on very accelerated regimens in order to attain an enhanced tumour cell kill and also to avoid accelerated tumour clonogenic repopulation. The most intensive continuous course regime was done by Perachia et al. 1981, who treated 22 patients with three fractions of 2 Gy with 4 h intervals to 48–54 Gy within only 9–11 days [26]. This led to intolerable acute reactions including 60 % severe necrosis and fistulas and some deaths soon after treatment.

Svoboda et al. treated 59 patients with thrice daily fractions of 1.7–2.3 Gy with intervals of at least 3 h to a total dose of 50–55 Gy in 1.5–2.0 weeks. The 3 years OS

of 44 % in LAD was notable; however, a rate of 15 % of late necrosis and stenosis also compromised the overall results [27].

Nguyen et al.1985, published on a rapid AFX in 178 patients with LAD HNSCC [28]. Patients in two cohorts were treated with initially 40 fractions of 0.9 Gy with 2 h interval up to 36 Gy during the first 5 days. After 2 weeks rest, a similar course was applied with reduced fields up to 72 Gy in an OTT of 24 days. For the second cohort the total dose was reduced to 60–66 Gy and the rest period extended from 2 to 4 weeks. At the end of these treatments, about two thirds of the patients had a complete remission; however, 56 % developed local recurrences during follow-up. The OS-rate at 2 years was only 13 %. The acute toxicity was severe in one third of the patients with extensive mucosal necrosis and bleeding. Also the rate of late complications with trismus, extensive cervical fibrosis and permanent laryngeal oedemas was enhanced. This indicates the critical role of an adequate interfraction interval as already mentioned above.

A pivotal RCT in terms of patients and acceleration was the CHART trial. This by far largest trial for **C**ontinuous **H**yperfractionated **A**ccelerated **R**adio**T**herapy (*CHART*) recruited at total of 918 patients for the experimental arm with thrice daily 1.5 Gy to a total dose of 54 Gy in 12 days versus the SFX using single doses of 2 Gy to a total dose of 66 Gy [29]. Despite a dose reduction from 66 to 54 Gy, the endpoints, e.g. LRC and OS, were not inferior for CHART. Acute toxicities, however, were more pronounced with CHART opposite to reduced late morbidities. This study clearly pointed out the considerable impact of repopulation as cause of recurrent disease in the absence of CTX or other tumour cell proliferation inhibitors.

An accelerated split-course RCT was investigated on an EORTC platform (EORTC 22851) in 512 patients with moderately advanced stage II–IV HNSCC [30]. Three fractions (tid) of 1.6 Gy were applied during 8 days to a dose of 28.8 Gy with a subsequent split of a fortnight. Thereafter the same schedule was continued with 27 fractions in 17 days to a total of 72 Gy in 5.2 weeks OTT. The SFX-arm used 35 fractions of 2.0 Gy in 7 weeks. The split-ACFX regimen was superior in terms of LRC with 59 % vs. 46 % ($p = .02$). However, OS showed no difference with 26 % vs. 27 %, respectively. For the split-ACFX arm, 70 % acute objective mucosal reactions vs. 34 %, respectively, and 5 % vs. 2 % life-threatening severe adverse events (SAE) were reported. Also late morbidity was significantly enhanced with only 53 % SAE-free survival vs. 86 % for SFX. Due to the high rates of acute and late radiation sequelae split course ACFX was no longer pursued.

The French collaborative head and neck group (GORTEC) carried out a RCT employing a very accelerated radiation regimen with a total dose of 62–64 Gy with bid 2 Gy in 31–32 fractions within 2.5 weeks vs. a SFX of 70 Gy with qd 2.0 Gy in 35 fractions in 268 patients [31]. The majority of patients (78 %) had OPC (≈78 %) and about 66 % UICC stage-IV tumours. With the very ACFX regimen the LRC rate could be significantly improved by 24 % at 6 years,

whereas DFS and OS were not different in both treatment arms. Acute WHO grade III/IV mucositis was enhanced with very ACFX up to 90 % vs. 51 % for the control arm. No difference in late effects between the two treatment arms was observed.

Altered Fractionated Radiotherapy – Results from Meta-Analyses

The abundance of available data from RCTs as partly cited above qualify for a comprehensive meta-analysis based either on published hazard ratios (HR) and survival curves or on the integration of updated data sets from individual patients.

A meta-analysis based on published OS probabilities of 4792 patients showed no OS-benefit at 2 years and no prolongation of the median survival nor a significant HR reduction for ACFX vs. SFX, respectively. In contrast, HFX vs. SFX led to a significant OS benefit of 12 % at 2 years ($n = 1523$) corresponding to a median OS prolongation of 14.2 months and a 14 % reduction of the HR for death [32].

An international collaborative group of primary investigators agreed to establish a collaborative meta-analysis group, which provided individual patients' data for AFX based on 7073 patients. This **M**eta-**A**nalysis of **R**adiotherapy in **C**arcinomas of **H**ead and Neck (*MARCH*) addressed AFX regimens like HFX and ACFX with or without (w/o) total dose reduction in comparison with SFX [33]. The majority of patients suffered from HNSCC of the OP and larynx in stage III and IV. Multiple endpoints like HRs for death and cancer/non-cancer death, LC, LRC, regional control (RC), metastatic control and corresponding survival figures were analysed (Figs. 9.1 and 9.2). The results at 5 years from four RCTs based on a total of 680 patients clearly favour HFX with an absolute OS-benefit of 8.2 % ± 2.6 % vs. 1.7 % ± 2.3 % and 2.0 % ± 1.7 % for ACFX w/o total dose reduction ($p = 0.003$), respectively. Cancer specific death was improved by 7.8 % ± 2.8 % in favour of HFX corresponding to a HR reduction of 22 % (95%CI: 10–32 %). HFX vs. SFX showed a benefit in PFS of 7.8 % ± 2.8 % (45 % vs. 36.9 %). LRC figures were also superior with 9.4 % ± 3.0 % at 5 years and interestingly also of 7.3 % ± 1.7 % for the ACFX without dose compromise ($p < .0001$). The HRs for death were reduced for HFX by 22 % (95%CI: 10–32 %) and for LRC by 24 % (95%CI: 11–34 %) as also for ACFX without dose reduction by 21 % (95%CI: 13–28 %). The benefit in LRC could exclusively be attributed to an improved LC with an overall relative HR reduction for the three treatment groups (HFX, ACFX w/o total dose reduction) by 23 % (95%CI: 17–29 %, $p < .0001$), but not to nodal control and DM. In terms of HRs for death a significant interaction with age after AFX compared with SFX was observed, which could not be established for sex, performance score, stage and site of the primary.

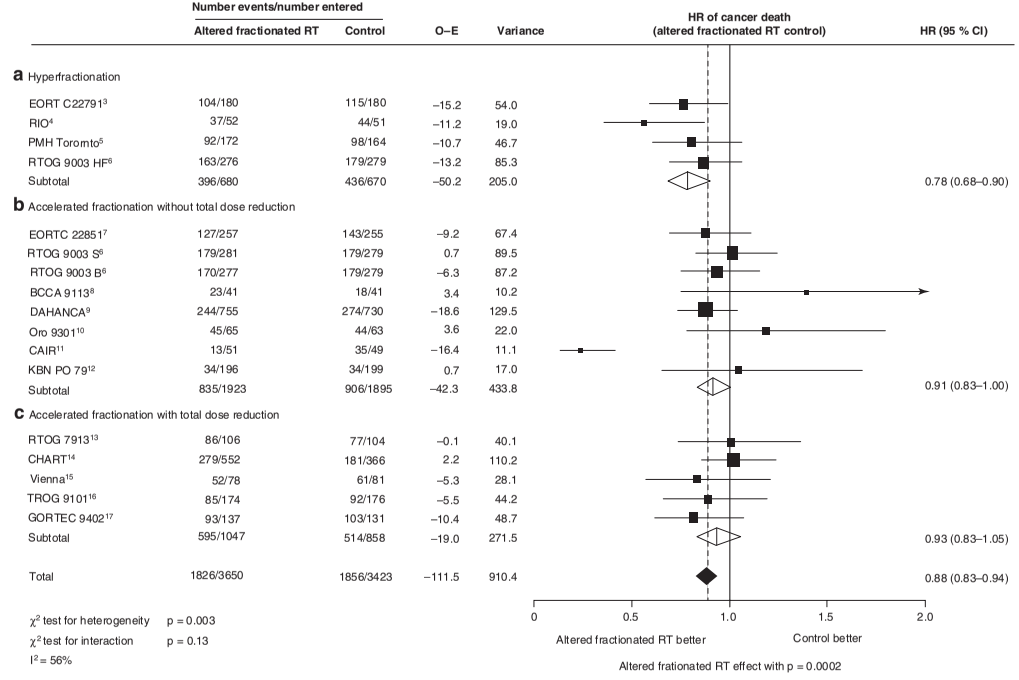
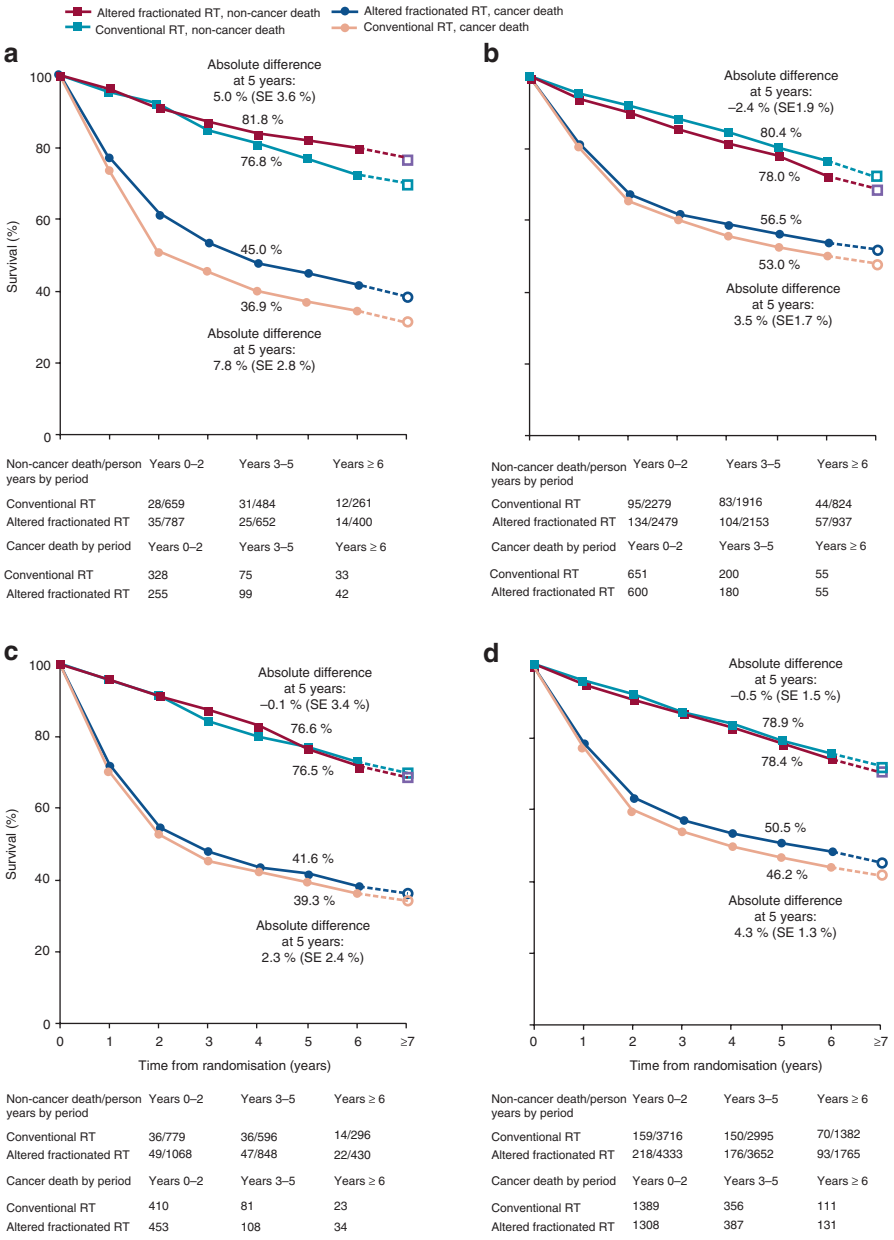


Fig. 9.1 Hazard ratio of head and neck cancer death with altered fractionated radiotherapy versus conventional radiotherapy. The centre of each square is the hazard ratio (HR) for individual trials and the corresponding horizontal line is the 95 % CI. The area of the square is proportional to the number of events from each trial. The broken line and centre of the black diamond is overall pooled HR and the horizontal tip of the diamond is the 95 % Cl. Open diamonds are the HR of different types of radiotherapy. *BCCA* British Columbia Cancer Agency, *CAIR* continuous accelerated irradiation, *CHART* continuous hyperfractionated accelerated radiation therapy, *DAHANCA* Danish Head and Neck Cancer Study Group, *EORTC* European Organisation for Research and Treatment of Cancer, *GORTEC* Groupe d'Oncologie Radiothérapie Tête et Cou, *KBN* Komiet Badan Naukowych (Committee for Scientific Research), *0-E* observed minus expected, *PMH-Toronto* Princess Margaret Hospital, Toronto, *RT* radiotherapy, *RTOG* Radiation Therapy Oncology Group, *TROG* Trans-Tansman Radiation Oncology Group



Non-cancer death/person years by period	Years 0–2	Years 3–5	Years ≥ 6
Conventional RT	28/659	31/484	12/261
Altered fractionated RT	35/787	25/652	14/400
Cancer death by period	Years 0–2	Years 3–5	Years ≥ 6
Conventional RT	328	75	33
Altered fractionated RT	255	99	42

Non-cancer death/person years by period	Years 0–2	Years 3–5	Years ≥ 6
Conventional RT	95/2279	83/1916	44/824
Altered fractionated RT	134/2479	104/2153	57/937
Cancer death by period	Years 0–2	Years 3–5	Years ≥ 6
Conventional RT	651	200	55
Altered fractionated RT	600	180	55

Non-cancer death/person years by period	Years 0–2	Years 3–5	Years ≥ 6
Conventional RT	36/779	36/596	14/296
Altered fractionated RT	49/1068	47/848	22/430
Cancer death by period	Years 0–2	Years 3–5	Years ≥ 6
Conventional RT	410	81	23
Altered fractionated RT	453	108	34

Non-cancer death/person years by period	Years 0–2	Years 3–5	Years ≥ 6
Conventional RT	159/3716	150/2995	70/1382
Altered fractionated RT	218/4333	176/3652	93/1765
Cancer death by period	Years 0–2	Years 3–5	Years ≥ 6
Conventional RT	1389	356	111
Altered fractionated RT	1308	387	131

Fig. 9.2 Non-cancer death and cancer death survival curves for all trials and for the three groups of trials according to the type of altered fractionated radiotherapy. (**a**) Hyperfractionation. (**b**) Accelerated fractionation without total close reduction. (**c**) Accelerated fractionation with total close reduction. (**d**) All three groups together. The slopes of the broken lines from year 6 to year ≥ 7 are based on the overall death rates in the seventh and subsequent years. *RT* radiotherapy

Take Home Message for Altered Fractionation, Part 1

- Altered fractionation vs. standard fractionation led to a small but significant absolute OS benefit of 3.4 % at 5 years in patients with LAD HNSCC corresponding to a HR reduction for death of 8 %.
- Hyperfractionation as a specific subtype of altered fractionation led to a highly significant absolute OS and LRC benefit of 8.2 % and 9.4 %, respectively, compared with standard fractionation corresponding to a HR reduction for death of 22 %, which was not observed for moderately and very accelerated fractionation regimens.
- Hyperfractionation results in the best overall survival benefit compared with other altered fractionation regimens like accelerated fractionation w/o total dose compromise.
- Hyperfractionation is a good alternative for definitive treatment of LAD HNSCC in patients who are not fit for concurrent chemoradiation or who have a high Charlson comorbidity score.

Take Home Message for Altered Fractionation, Part 2

- Despite level IA evidence, hyperfractionation as a resource-intensive treatment is currently not in widespread use and limited to patients with interlaced target volume and critical organs at risk, which needs to be spared by biological means.
- Hyperfractionated re-irradiation with bid 1–1.2 Gy to 66–70 Gy can be a treatment of choice in locally recurrent disease for a target volume >60 ml.
- Accelerated fractionation shows the best efficacy for primary tumours and to a lesser extent for nodal disease.
- Patients below the age of 70 years benefit from altered fractionation in terms of LRC and PFS. However, patients above 50 years of age have only marginal benefit in terms of overall survival from altered fractionation.

Concurrent Chemoradiation

Rationale and Caveats

The rationale for cCRTX is primarily the cooperation of cytotoxic effects leading to increased tumour cell kill and secondarily a dissociation of acute and late morbidities at the organs and tissues at risk, e.g. spinal cord, aiming at an improved therapeutic ratio [34–36]. Since the 80s of the last century the first RTX with concomitant CTX were carried out in LAD HNSCC [1, 3, 37]. At that period of time, drugs such as 5-FU, methotrexate, bleomycin, mitomycin C, cyclophosphamide, vincristine

and vinblastine were employed. Many studies used multidrug and others single-drug combinations. In 1987 the first concurrent chemoradiation (cCRTX) with platinum/5-FU was introduced by Toohill et al. 1987 [38]. Since then, a large number of RCTXs have been successfully carried out. In recent years, Carboplatinum and Taxotere were also introduced in clinical trials in HNSCC [39–41]. Consequently, cCRTX has been continuously improved during the last decades and is still considered standard of care for LAD and functionally inoperable HNSCC. Despite a clear level IB evidence for improvements of the major endpoints like OS, LRC and DFS, in clinical practice, these benefits were often achieved at the expense of enhanced acute or late treatment related sequelae, e.g. functional deficits hampering an improved therapeutic ratio (Table 9.2).

Selected Phase-III RCT for Concurrent Chemoradiation (Fig. 9.2)

Numerous RCTs trials with SFX or dose intensified ACFX or very ACFX-RTX regimens, but without the addition of CTX did emerge, which showed a definite improvement in LRC, but not in OS. To explore further on this issue, the French collaborative head and neck clinical trials group (GORTEC) carried out a pivotal comprehensive 3-arm RCT in 840 patients suffering from stage III/IV LAD HNSCC comparing SFX-CRTX ($n=279$) of 70 Gy/7 weeks (5×2.0 Gy/week) plus three cycles of concurrent Carboplatinum/5-FU vs. ACFX-CRTX ($n=280$) of 70 Gy/6 weeks (40 Gy of 5×2.0 Gy/week followed by bid 1.5 Gy to 70 Gy) plus two concomitant cycles of Carboplatinum/5-FU vs. very ACFX-RTX ($n=281$) alone of 64.8 Gy/3.5 weeks using a bid 1.8 Gy fractionation schedule (GORTEC 99–02) [41]. ACFX-CRTX offered no PFS-benefit over SFX-CRTX or very ACFX-RTX. Three years' PFS was 34.1 % with ACFX-CRTX vs. 37.6 % with SFX-CRTX and 32.2 % with very ACFX-RTX alone. For SFX-CRTX vs. very ACFX-RTX, a HR reduction could be observed for OS of 19 % (95%CI: 1–33 %; $p=.04$), for PFS of 18 % (95%CI: 1-33 %; $p=.041$) and for LR-failures of 23 % (95%CI: 1–41 %; $p=.045$), whereas distant metastases rates (LRF) were not different between both treatment arms. ACFX-CRTX showed no HR reduction compared with SFX-CRTX in terms of OS, DFS, DM and LRF. ACFX-CRTX vs. very ACFX-RTX was only superior in terms of LRF with a HR reduction of 24 % (95%CI: 2–41 %; $p=.033$). The highest acute mucosal toxicity (RTOG grade 3–4) was observed after very ACFX-RTX in 84 % of all patients vs. 76 % for ACFX-CRTX and 69 % for SFX-CRTX ($p=.0001$). Corresponding gastric feeding tubes were necessary in 70 %, 64 % and 60 % ($p=.045$), respectively. Despite a higher rate of feeding tube dependency in the very ACFX-RTX group ($p=.027$) late morbidities did not differ between the three treatment regimens after up to 5 years' follow-up. In summary, very accelerated ACFX-RTX-regimens cannot compensate for the absence of CTX in definitive treatment of LAD HNSCC.

Table 9.2 Selected pivotal randomized clinical trials with altered fractionated chemoradiation in LAD HNSCC

Study/author/year	Fractionation no. of pts.	Sites/no. pts. OP/OC/HP/L	Stage (UICC)	Fractionation schedule	OTT (weeks)	Total dose in tt.-arms	CTX drugs	LC/LRC (%)	Distant metastases rates (%)	Progression-free survival (%)	Overall survival (%)	Acute toxicities	Late morbidities
GORTEC 99–02 Bourhis et al. (2012) [41]	ACFX-CRTX 280	184/31/47/17	III/IV	2 Gy qd – 40 Gy bid 1.5 Gy	6.0	70.0 Gy	2 cycles Carbo/5-FU	Not stated	Not stated	34.1 %	Not stated	Muscositis RTOG 3/4° 76 %	
	Very ACFX-RTX 279	188/27/45/18	ditto	1.8 Gy bid	3.5	64.8 Gy	No CTX	Not stated	Not stated	32.2 %	Not stated	84 %	Tube feed. ↑@5 years, $p=.027$
	CFX- CRTX 279	183/28/49/17	ditto	2 Gy qd	7.0	70.0 Gy	3 cycles Carbo/5-FU	Not stated	Not stated	37.6 %	Not stated	69 % $p=.0001$	
RTOG 0129 Nguyen-Tan et al. (2014) [42]	ACFX-CRTX 371	217/18/27/98	III/IV	1.8 Gy qd -32.4 Gy, bid 2.8/1.5 Gy	6.0	72.0 Gy	2 cycles DDP	LRF 38.5 % @8 years	12.8 % @ 8 years	41.4 % @ 8 years	47.7 % @ 8 years	33.10 %	PEG-rates ↑ @1 year $p<.001$
	CFX-XRTX 372	216/24/31/90	ditto	2 Gy qd	7.0	70.0 Gy	3 cycles DDP	LRF 36.7 % @ 8 years; n.s.	15.2 % @ 8 years n.s.	42.1 % @ 8 years n.s.	47.6 % @ 8 years n.s.	39.1 % n.s.	PEG-rates ↑ 5 years, $p<.01$
Brizel et al. (1998) [43]	HFX alone 80	29/3/10/8/10[a]	III/IV	1.25 Gy bid	6.0	75.0 Gy	No CTX	LRC 70 % @ 3 years, $p=.01$	Not stated	61 % @ 3 years	55 % @ 3 years	Mucositis RTOG 3° 77 %	PEG-rate: 44 % @ 3 years
	HFX- CRTX 80	23/3/13/10/7[a]	ditto	1.25 Gy bid	5.6	70.0 Gy	2 cycles DDP/5-FU	LRC 41 % @ 3 years	Not stated	41 % @ 3 years $p=.08$	34 % @ 3 years $p=.07$	Mucositis RTOG 3° 75 %	PEG-rate: 29 % @ 3 years
ARO 95–06 Budach et al. (2005) [49]	C-HART 190	109/19/62/–	III/IV	2.0 Gy qd 30 Gy 1.4 Gy bid	6.0	77.6 Gy	No CTX	LRC 49 %/38 % @5/10 years	54 %/52 % @5/10 years	30 %/25 % @5/10 years	27 %/10 % @5/10 years	Mucositis 3/4° ↑ $p=.045$	No difference for 12 items like dysphagia and xerostomia
	HART 194	119/13/62/–	ditto	2.0 Gy–30 Gy 1.4 Gy bid	6.0	70.6 Gy	MMC 1st + 6th week + 5-FU 1st week	LRC 35/26 % @5/10 years, $p=.002$	55 %/48 % @5/10 years, n.s	25 %/18 % @5/10 years, $p=.03$	20 %/9 % @5/10 years, $p=.049$	Skin 3/4° $p=.002$ for HART	

SAKK 10–94 Ghadjar et al. (2012) [44]	HFX-CRTX 112	59/7/28/18	II/III/IV	1.2 Gy bid	6.0	74.4 Gy	DDP 5 × 20 mg/m^2 week 1+5	LC 55 % @ 10 years	44 % @ 10 years	55 % @ 10 years	28 % @ 10 years	60 % 3/4° mucositis 62 % dysphagia	Not significant difference between both tt.-arms
	HFX-RTX: 112	59/10/27/15	ditto	1.2 Gy bid	6.0	74.4 Gy	No CTX	LC: 34 % @ 10 years $p = .0007$	59 % @ 10 years $p = .02$	43 % @ 10 years $p = .03$	22 % @ 10 years n.s.	55 % 3/4° mucositis 46 % dysphagia	
Dobrowsky et al. (2000) [47]	V-CHART + MMC 80	30/25/14/11	III/IV	2.5 Gy d. 1 then bid 1.65 Gy	2.4	55.3 Gy	MMC 20 mg/m^2	LRC 48 % @ 4 years	6 % @ 4 years	Not stated	41 % @ 4 years	95 % 3/4° mucositis	n.s.
	V-CHART 78	34/21/15/8	ditto	2.5 Gy d. 1 then bid 1.65 Gy	2.4	55.3 Gy	No CTX	32 % @ 4 years $p < .05$	9 % @ 4 years	Not stated	31 % @ 4 years, $p < .05$	95 % 3/4° mucositis no hemat.	n.s.
	CFX 81	34/26/12/9	ditto	2.0 Gy qd	7.0	70.0 Gy	No CTX	31 % @ 4 years	13 % @ 4 years	Not stated	24 % @ 4 years	60 % gr. 3/4° muc.	n.s.
ARO 04-01 Budach et al. (2012) [50]	C-HART 182	106/76/–/–	IV	2.0 Gy–30 Gy then bid 1.4 Gy	6.0	72.0 Gy	Weekly DDP, 1st week 5-FU	LRC 59.1 % @ 5 years	66.8 % @ 5 years	47.2 % @ 5 years	39.1 % @ 5 years	No difference for seven items like dysphagia creatinine higher for DDP-arm	No difference in 12 items, e.g., dysphagia and xerostomia
	C-HART 182	107/75/–/–	IV	2.0 Gy–30 Gy then bid 1.4 Gy	6.0	72.0 Gy	MMC 1st+6th week+5-FU 1st week	LRC: 56.1 % @ 5 years, n.s.	53.5 % @ 5 years, $p = .04$	37.2 % @ 5 years, n.s.	32.8 %@ 5 years, n.s.		

Abbreviations: *OP* oropharynx, *OC* oral cavity, HP hypopharynx, *L* larynx, *NP* nasopharynx, *SFX* conventional fractionation, *HFX* hyperfractionation, *ACFX* accelerated fractionation, *CAIR* continuous accelerated fractionation, *CHART* continuous hyperfractionated accelerated radiotherapy, *bid* two fractions per day, *tid* three fractions per day, *RTX* radiotherapy, *OTT* overall treatment time, *LC* local control, *LRC* loco-regional control, *OS* overall survival, *OMR* objective mucosal reactions, *n.s* not significant, *SAE* severe adverse event, *ditto* the same like above, *prim* primary, *no* number, *pts* patients, *tt* treatment, *resp* respective, *DM* distant metastases, *PFS* progression-free survival

[a]Other sites

Another pivotal RCT compared in 743 patients with LAD HNSCC a concomitant boost ACF-CRTX with 72 Gy in 42 fractions vs. a SFX-CRTX of 70 Gy in 35 fractions of 2 Gy [42]. CTX consisted of platinum 100 mg/m^2 every 3 weeks for two cycles in the experimental arm and three cycles in the standard arm. At 8 years, all endpoints taken into account like OS (47.7 % vs. 47.6 %), PFS (41.4 % vs. 42.1 %), LRF (38.5 % vs. 36.7 %) and DM (12.8 % vs. 15.2 %) did not differ for ACFX-CRTX vs. SFX-CRTX, respectively. The only difference occurred in p16+ patients with an OS-benefit of 70.9 % vs. 30.2 % corresponding to a HR reduction of 70 % (95%CI: 58–79 %; p < .001). The acute and late toxicities grade 3–5 were also not significantly correlated with one of the treatment arms nor the p16-status. Both studies underline that moderately ACFX-CRTX regimens of 6 weeks OTT are not superior to CFX-CRTX of 7 weeks OTT and thus are not mandatory in cCRTX.

Brizel did a unique RCT using HF-CRTX vs. HF-RTX alone for stage III/IV LAD HNSCC in 122 patients, who received in the standard arm bid 1.25 Gy up to a total dose of 75.0 Gy in 6 weeks OTT and for the experimental arm the same bid fractionation up to 70 Gy/5.6 weeks plus two concurrent cycles of 5 × 12 mg/m^2 platinum and 5 × 600 mg/m^2 5-FU during weeks 1 and 6 of treatment [43]. Two additional adjuvant cycles of platinum/5-FU were applied for most of the patients. The results after 3 years showed a benefit for HFX-CRTX in terms of LRC (70 % vs. 41 %; $p = .01$), but only a trend for an improved PFS of 61 % vs. 41 % ($p = .08$) and OS of 55 % vs. 34 % ($p = .07$). The rates of confluent mucositis were high, but not enhanced by the addition of CTX (77 % vs. 75 %, respectively). This HFX-CRTX is an appealing approach; however, the difference in total dose and/or the number of patients might have been too small to reveal a significant benefit in PFS and/or OS.

Another RCT with HF-CRTX vs. HF-RTX alone in 224 patients with LAD HNSCC was executed by the Swiss Group for Clinical Cancer Research (SAKK). It compared bid 1.2 Gy up to 74.4 Gy in 6 weeks OTT with additionally two concurrent cycles of 5 × 20 mg/m^2 platinum during weeks 1 and 5 as experimental arm against in the same RTX regimen without CTX as standard arm [44]. The long-term results with a median follow-up of 9.5 years showed an improved LC at 10 years of 55 % vs. 34 % ($p = .0007$) and LRC (40 % vs. 32 %, $p = .049$), in favour of HF-CRTX. Distant metastases-free rates were 56 % vs. 41 % ($p = .02$) and CSS 55 % vs. 43 % ($p = .03$), respectively. An OS-benefit for HF-CRTX was not observed (28 % vs. 22 %; $p = .19$). Acute toxicities were similar in both treatment arms with 60 %/55 % and 62 %/46 % grade 3–4 mucositis and dysphagia, respectively. The results showed a benefit for two cycles of 5 days each of concurrent platinum with HF-RTX leading to a significant improvement of LC, LRC, DM and a trend for an improved OS.

RTX with mitomycin C (MMC, 15 mg/m^2 single shot) as hypoxic cell sensitizer was compared with RTX alone ($n = 120$), RTX, MMC and dicumarol ($n = 83$) or pofiromycin ($n = 128$) as new hypoxic cell sensitizer postoperatively or as definitive approach in stage III/IV HNSCC [45, 46]. MMC led to a significant benefit in terms of LC, LRC and DFS, however, not for OS with acceptable acute and late morbidities.

Another RCT used a SFX-RTX regimen on 239 patients with LAD HNSCC, which consisted of 70 Gy in 35 fractions of 2.0 Gy in 7 weeks. This regimen was compared with a very ACFX with 55.3 Gy in 33 fractions of 1.7 Gy in 17 consecutive days (V-CHART) and with the same RTX regimen with the addition of 20 mg/m^2 MMC on day 5 of treatment [47]. The LRC-rates were 31 % vs. 32 % vs. 48 % ($p < .05$) and the OS-rates 24 % vs. 31 % vs. 41 % ($p < .05$), for SFX, V-CHART and V-CHART/MMC, respectively. The major toxicity with very ACFX was a grade 3–4 confluent mucositis in 95 % of all patients. Eighteen percent of the MMC patients developed grade 3–4 thrombocytopenia, but no enhanced mucosal reactions. The results for CF-RTX and V-CHART are similar, whereas a significant benefit in LRC (+16 %) and OS (+10–17 %) was achieved with the addition of MMC to V-HART.

Budach et al. reported on the 5- and 10-years outcome of a RCT of the German Collaborative Clinical Trials Group (ARO 95–06) with 384 patients suffering from LAD HNSCC of the OP, OC and HP [48, 49]. The rationale of this study was to compare a maximally aggressive hyperfractionated accelerated RTX (HART) applying a total dose of 77.6 Gy in 6 weeks with a less aggressive HART of 70.6 Gy plus 10 mg/m^2 MMC in week 1 and 6 and 600 mg/m^2 5-FU in week 1 (C-HART) [43]. This study had a similar rationale like that of Brizel and coworkers above. The aim was to arrive at equivalent levels of acute and late normal tissues/organs at risk injuries and still achieve an improvement of the endpoints LRC, DM, DFS and OS. At 10 years, the LRC-rates were 38.0 % vs. 26 % for C-HART vs. HART ($p = .002$). For PFS and OS the corresponding values were 25 % and 10 % for C-HART vs. 18 % and 9 % for HART ($p = .042$ vs. $p = .033$), respectively. The association of the combined treatment and improved LRC was limited to OPC ($p = .003$) as compared with HPC or OCC (n.s.). The contribution of CTX in terms of radiation dose equivalent was calculated to be about 10 Gy in the C-HART arm, which would add up to a total equivalent RTX dose of 80.7 Gy thus probably explaining the superior outcome for C-HART. This RCT showed a significant improvement of the primary endpoint LRC and in univariate analysis also of OS, PFS and PFS, not, however, for DM indicating the absence of a systemic effect of 5-FU/MMC. In planned subgroup analyses, only for OP tumours a benefit in terms of LRC and OS, not for HP/OC-tumours, could be seen. Thus, since the acute and late radiation morbidity was not different in both treatment arms, an improvement of the therapeutic ratio for C-HART vs. HART despite a 10 % total dose reduction (70.6 Gy vs. 77.6 Gy) could be established.

Since no improvement in distant metastases rates was observed in the ARO 95–06 trial, the randomized clinical successor trial (ARO 04–01) was aimed at a reduction of distant metastases rates. A total of 364 patients suffering from LAD stage IV HNSCC of the OP and HP were randomized for C-HART with MMC/5-FU (MMC-HART; $n = 182$), the best arm of the ARO 95–06 trial vs. C-HART with weekly DDP/5-FU (DDP-HART; $n = 182$) [50]. With DDP-HART, 30 mg/m^2 on days 1, 8, 15, 22, 29 and 36 supplemented by continuous infusion 5-FU at a dose of 600 mg/m^2 days 1–5 was applied. The results at 5 years show a benefit in favour of DDP-HART for freedom from metastases (FFM) of 66.8 % vs. 53.5 % ($p = .044$). Corresponding LC-rates were 66.2 % vs. 65.9 % (n.s.) and regional control (RC)

was achieved in 77.3 % vs. 73.3 % (n.s.) of all patients, respectively. Ultimate OS was 39.1 % vs. 32.8 % (n.s.). A significant HR reduction of 36.7 % ($p = .023$) for MFS and of marginal significance of 26.1 % ($p = .051$) for DFS was observed. Seven items for acute toxicity were not different for both treatment arms except for creatinine level, which increased for DDP-HART. Nine items for late morbidity did not differ for both treatment arms. This trial showed level IB-evidence for a once weekly platinum/5-FU CRTX. Since acute and late morbidities were not significantly enhanced and the results were also comparable for the endpoints LC, LRC, RC, DFS and OS, an improvement of the therapeutic index would not have been established if MFS would not have been superior with DDP-HART. Thus, both treatment arms proved to be similarly effective, indicating MMC-HART as valuable alternative for platinum-resistant patients.

Concurrent Chemoradiation (cCRTX): Results from Meta-Analyses

A meta-analysis based on published OS probabilities for 32 RCTs with a total of 10.225 patients addressed CRTX regimens with SFX and AFX of 60–78 Gy total dose in both treatment arms enhanced by 5-FU, platinum, Carboplatinum or MMC, 5-FU/platinum or 5-FU/Carboplatinum [32]. The survival benefit at 2 years was 13.3 % ($n = 2197$) for CFX-RTX and 14.7 % ($n = 1301$) for AF-RTX. This corresponded to a gain in median survival of 12.0 months with both treatment regimens. Three RCTs with split-course or rapidly alternating CRTX and prolonged OTT showed a worse OS-benefit at 2 years of 8.1 % ($n = 502$) and a gain in median survival of 7.9 months. The drugs used in the trials had the strongest impact on a prolongation of the median survival for 5-FU (+24 months; $n = 887$), followed by platinum (+16.2 months; $n = 903$), Carboplatinum (+6.7 months; $n = 822$) and MMC (+4.0 months; $n = 1169$), respectively.

Analogous to the MARCH meta-analysis the international collaborative group initiated the **M**eta-**A**nalysis of **C**hemotherapy in **H**ead and **N**eck-**C**ancer (*MACH-NC*) and provided individual patients' data for the combination of RTX and CTX in a sequential and concurrent mode [51]. This analysis was based on 94 RCTs with a total of 17.246 patients (Fig. 9.3). The majority of patients suffered from OP (≅40 %), OC, HP and laryngeal cancer (each ≅ 20 %) and >90 % had stage IV-disease. For cCRTX a total of 9.615 patients were available for analysis. The absolute benefit of the addition of CTX irrespective of the timing was 4.5 % ± 0.8 % and for cCRTX 6.5 % ± 1.0 % corresponding to a HR reduction of death of 12 % and 19 %, respectively. For induction and adjuvant CTX no significant benefit for OS was observed (Figs. 9.3 and 9.4a). For cancer-specific survival at 5 years, an absolute survival benefit of 8.6 % ± 1.5 % was observed, whereas non-cancer deaths were not enhanced with the addition of CTX at 5 years (Fig. 9.4b). cCRTX reduced local failure rate by 9.3 % and DM by 2.5 % Fig. 9.5a). When looking at the different drugs, platinum-based regimens decreased the local failure rate by 13.5 %, however, DM rate only by 2.9 % (Fig. 9.5b). HR reductions for death of 21 % for platinum/5-

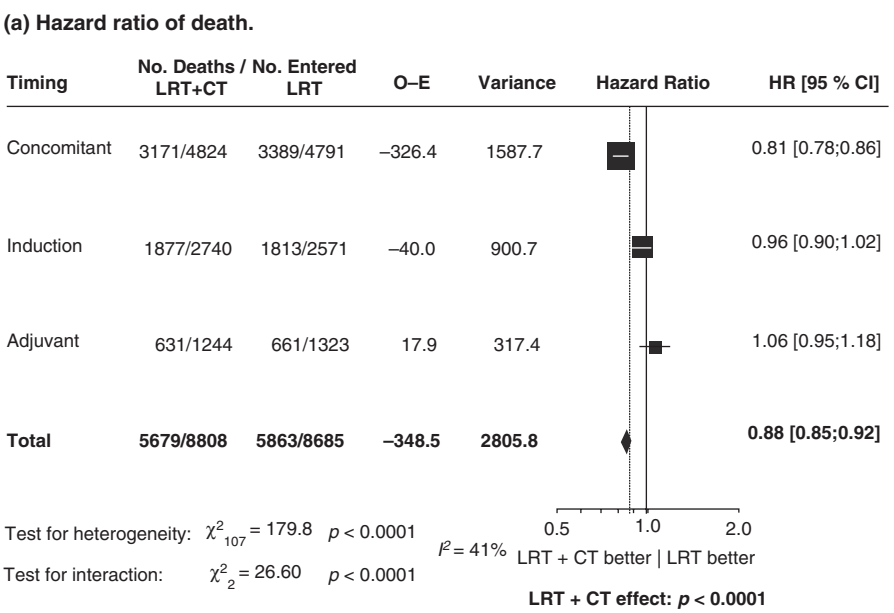


Fig. 9.3 Hazard ratio with loco-regional treatment plus chemotherapy versus loco-regional treatment alone by timing of chemotherapy. (**a**) Hazard ratio of death. The broken line and centre of the black diamond correspond to overall pooled hazard ratio (HR) and the horizontal tip of the diamond is the 95% confidence interval (CI). The centre of black square corresponds to the HR of different types of chemotherapies. The area of the square is proportional to the number of deaths in each trial (or groups of trials); *CT* chemotherapy, *LRT* loco-regional treatment, *RT* radiotherapy, *0-E* observed minus expected

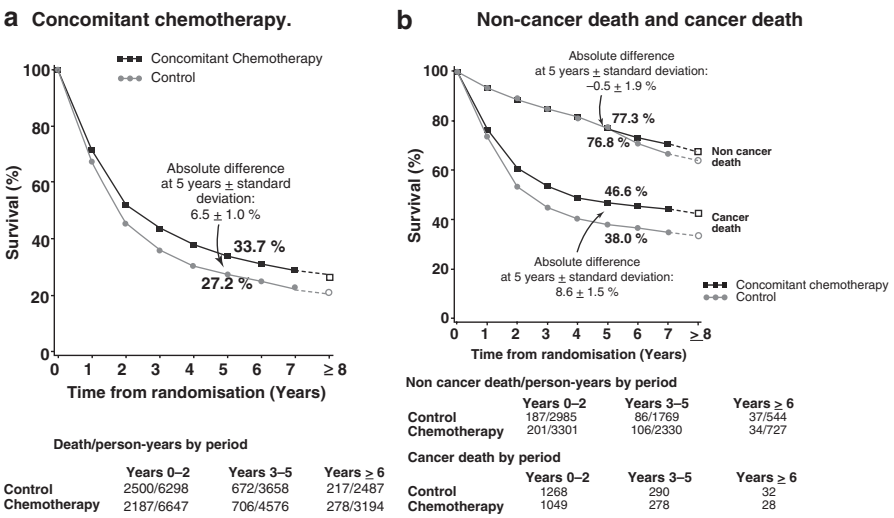
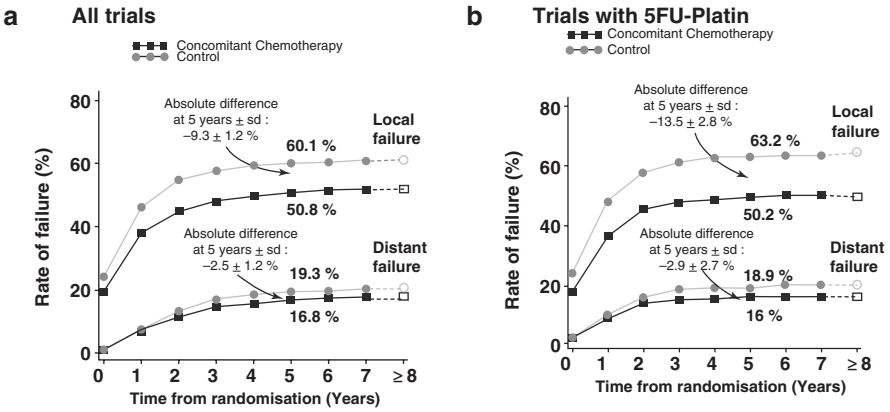


Fig. 9.4 (**a**) Survival curves for concomitant chemotherapy. Absolute differences are given with their standard error. (**b**) Non-cancer death and cancer death survival curves in the recent trials comparing loco-regional treatment plus concomitant chemotherapy with loco-regional treatment alone. Absolute differences are given with their standard error



Local failure and distant failure /person-years by period

	Years 0–2	Years 3–5	Years ≥ 6
Local failure			
Control	2509/8969	127/2812	18/2016
Chemotherapy	2045/9789	162/3881	21/2822
Distant failure			
Control	382/9817	82/3026	9/2195
Chemotherapy	370/10438	96/4010	10/2896

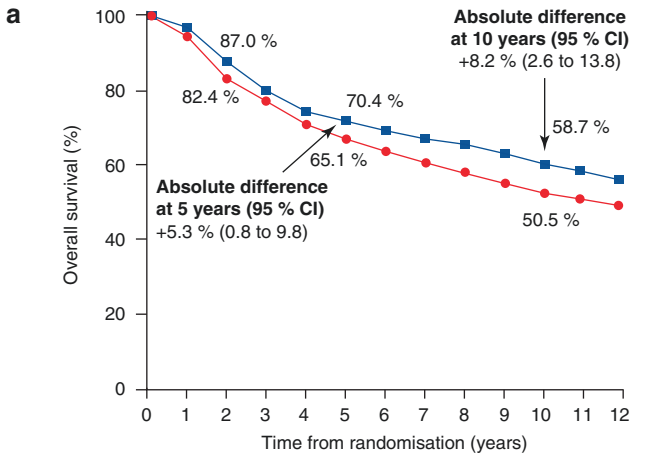
Local failure and distant failure /person-years by period

	Years 0–2	Years 3–5	Years ≥ 6
Local failure			
Control	493/1648	22/406	2/165
Chemotherapy	373/1837	20/603	1/240
Distant failure			
Control	82/1756	8/416	1/166
Chemotherapy	83/1915	6/616	0/241

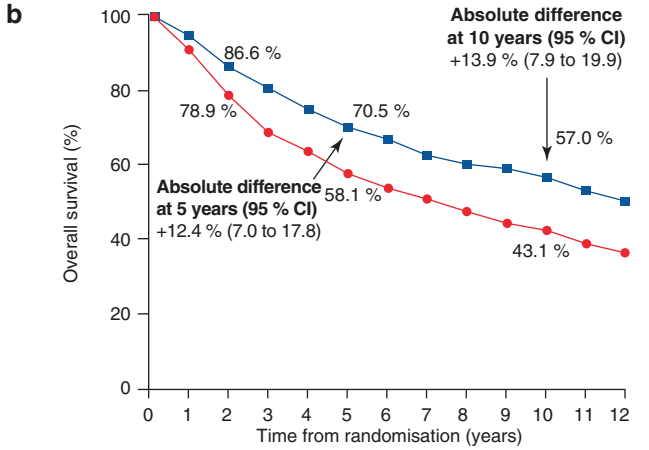
Fig. 9.5 (**a**) Cumulative loco-regional and distant failure rates comparing loco-regional plus concomitant treatment with loco-regional treatment alone. Absolute differences are given with their standard error. **(b)** Cumulative loco-regional and distant failure rates comparing loco-regional plus concomitant treatment with loco-regional treatment alone

FU combinations and of 26 % ($p = .006$) for platinum alone indicate the high efficacy of this combined treatment approach. The interaction test between CTX timing and treatment effect was only significant for OP ($p < .0001$) and laryngeal tumours ($p = .05$), not for OC or HP-tumours [52]. Independent of the different tumour locations, the HR reductions for death were in the range of 13 % ($p < .0001$) corresponding to an absolute OS-benefit of 5.1 %, 5.3 %, 4.5 % and 3.9 % for OC, OP, larynx and HP-tumours at 5 years, respectively. There was a clear age dependence for CRTX-regimes (MACH-NC) with no benefit for age class >70 years.

An update of the role of RTX and CTX for nasopharyngeal cancer (MAC-NPC meta-analysis) based on individual patients' data comprised 19 RCT with a total of 4806 patients [53]. For NPC, most of these patients had a positive Epstein-Barr viral load and >50 % of tumour progressions were observed at distant sites. A major target for adjuvant treatment is therefore a reduction of distant metastases, which has been shown to be dependent on the number of CTX-cycles applied [54]. The concentration of persistent circulating Epstein-Barr virus DNA after definitive cCRTX is the reason for a high risk of tumour failures and can be used as an appealing biomarker in selection of those patients, who qualify for adjuvant CTX [55]. Four different treatment groups were defined for the analysis: induction CTX, cCRTX ± adjuvant CTX and adjuvant CTX alone. The results showed an absolute survival benefit of 6.3 % (95%CI: 3.5–9.2 %) at 5 years corresponding to a HR reduction of death of 21 % (95%CI: 14–27 %; $p < .0001$) for the whole patient population. The benefit of the addition of CTX was present for all endpoints studied (LRC, DM, PFS and PFS). However, for OS the treatment effect and the timing of CTX was crucial for the



Number of deaths/ person-years	Years 0–2	Years 3–5	Years 6–10	Years > 10
Experimental	116/1714	144/1968	63/1790	27/662
Control	157/1654	145/1841	81/1592	20/513



Number of deaths/ person-years	Years 0–2	Years 3–5	Years 6–10	Years > 10
Experimental	84/1188	102/1460	67/1477	24/420
Control	135/1151	129/1226	72/1171	20/281

Fig. 9.6 Overall survival curves in trials with (**a**) concomitant and (**b**) concomitant plus adjuvant chemotherapy in NPC; *CI* confidence interval

results and favoured cCRTX plus adjuvant CTX with an absolute OS-benefit of 12.4 %/13.9 % at 5/10 year vs. cCRTX alone of 5.3 %/8.2 % at 5/10 year, respectively, corresponding to a HR reduction of 35 % and 20 % Fig. 9.6). After exclusion of the data for induction and adjuvant CTX, the OS-benefit from cCRTX increased up to 9.4 %/9.9 % at 5/10 year, respectively. Induction CTX and adjuvant CTX alone were not superior to RTX alone. This is the first meta-analysis who addressed the value of concurrent ± adjuvant CTX in NPC.

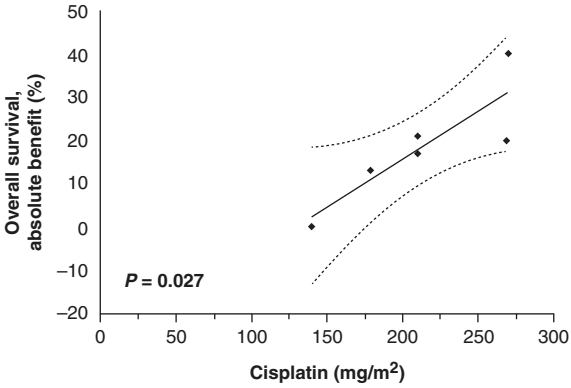


Fig. 9.7 Absolute overall survival benefit is strictly dependent on cumulative total platinum dose from prospective randomized trials on concurrent chemoradiation with single agent platinum

A recent systematic review addressed the issue of cumulative platinum dose in cCRTX-trials for HNSCC [56]. The optimal dose and the timing of platinum in various CRTX protocols for LAD HNSCC have not yet been determined. The OS-benefit at 5 years for 11 trials with 2.542 patients was 13 %. An unequivocal dose response relationship for higher cumulative platinum doses was established. Between 150 mg/m^2 taken as reference value and 300 mg/m^2 total dose the OS-benefit was in the range of 0 % up to 25 % at 5 years (Fig. 9.7).

Mixed treatment comparison meta-analyses of AF-RTX with cCRTX have been addressed by some authors [57]. AFX-RTX like HFX-regimens on the one hand and platinum-based concurrent SFX-CRTX on the other hand are highly effective treatment schemes for LAD HNSCC. In fact, there are so far no direct comparisons of AFX-RTX with SFX-CRTX or a combination of both. A network meta-analysis or indirect comparison is the only way to study this question at present time. Blanchard et al. 2011, pooled the data of both the MARCH and the MACH-NC meta-analyses resulting in a cohort of 103 trials with a total of 24.000 patients. When taking into account comparisons of the complete data set using the basic random-effects model, the best HR reduction of 31 % (95%CI: 19 %–42 %) was observed with platinum-based CRTX vs. loco-regional treatment alone. The estimation of a HR of about 0.9 from network meta-analysis for a comparison of SFX-CRTX vs. ACFX-CRTX would suggest a recruitment of more than 3.000 patients with a power of 90 % and type 1 error of 0.05. This kind of study is currently not conceivable in the framework of a classical pairwise RCT.

Summary

Altered fractionation and concurrent chemoradiation regimens for LAD HNSCC have been investigated by means of a large number of RCTs during the last decades. The single studies were sometimes contradictory and did not lead to conclusive

results. Meta-analyses based on individual patients' data piled up all these data sets and by means of the large numbers behind could generalize the results on a level IA evidence. The summary of these meta-analyses is as follows:

Take Home Message for Chemoradiation, Part 3

- Overall, chemoradiation (induction, concurrent and adjuvant) versus radiation alone led to an absolute overall survival benefit of 4.5 % corresponding to a HR reduction of death of 12 % ($p = .0001$) at 5 years.
- Concurrent chemoradiation versus radiation alone proved to be superior to induction or adjuvant chemotherapy. For 50 trials of concurrent chemoradiation, the absolute benefit was 6.5 % at 5 years with a corresponding HR reduction of death of 19 % ($p < 0.0001$).
- Platinum/5-FU-based chemoradiation versus radiation alone showed a reduction in local and distant failure rates of 13.5 % and 2.9 %, respectively, corresponding to HR reductions of about 25 % for death at 5 years.
- Mitomycin C-based chemoradiation is a reasonable alternative for elderly frail patients with large and hypoxic tumours, who are not candidates for platinum-based chemotherapy.
- Patients up to the age of 70 years benefit in terms of OS ($p = .003$).

Take Home Message for Chemoradiation, Part 4

- A pronounced benefit of concurrent chemoradiation regimens was only shown for OP and laryngeal tumours.
- The benefit of adding chemotherapy to loco-regional treatment is consistent in all tumour locations of HNSCC.
- NPC-patients often are Epstein-Barr virus positive. Concurrent chemoradiation with adjuvant chemotherapy showed an OS-benefit of 12.4 % vs. 13.9 % at 5 and 10 years, respectively.
- For NPC patients concurrent chemoradiation alone showed a OS-benefit of 9.4 % vs. 9.9 % at 5 and 10 years, respectively.
- For NPC, no OS-benefit was observed for adjuvant or induction chemotherapy alone. Circulating Epstein-Barr viral DNA load can be used as an attractive biomarker to select patients for adjuvant chemotherapy after concurrent chemoradiation.

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Chapter 10
Treatment of Viral-Associated HNC (OPC and NPC)

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Introduction

Epstein-barr virus (EBV) and human papillomavirus (HPV) are well-established viral tumourigenic agents of epithelial tumours in the pharyngeal mucosa. Although the predominant tumour types attributable to EBV and HPV are in the nasopharynx and oropharynx, respectively, emerging evidence proposes a subset of nasopharyngeal cancer (NPC) that is HPV-related, especially in non-endemic population [1]. HPV has also been detected in non-oropharyngeal/non-nasopharyngeal mucosa [2].

EBV-related (EBV+) NPC and HPV-related (HPV+) oropharyngeal cancer (OPC) share similarities in clinical behaviour [3]. Both often affect younger patients, although their ethnicity may differ: NPC patients are mostly Asian (e.g. from southern China) [1], while HPV+ OPC patients are mostly Caucasian [4]. A painless neck mass (classically at level 2) is the most frequent initial presentation. Retropharyngeal lymph nodal involvement is evident in both but is significantly more common in EBV+ NPC than in HPV+ OPC. A new TNM stage classification for HPV+ OPC was proposed recently with an N-classification similar to traditional NPC [5–7].

Both EBV+ NPC and HPV+ OPC are highly radiosensitive. Locoregional control (LRC) is rarely a major problem with contemporary treatment, while distant metastasis (DM) predominates and is the main cause of death [8, 9]. Risk-stratified management is applicable to both diseases.

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Treatment of Nasopharyngeal Cancer

Treatment of Non-metastatic Disease

Primary treatment of NPC is radiotherapy (RT). This relates to the need to eradicate gross or microscopic disease at the base of skull and retropharyngeal nodal regions which represent major challenges for surgery. Moreover, NPC is extremely radiosensitive.

Impact of Evolving RT Technology

The ability to avoid critical anatomy using precise techniques to plan, guide and deliver RT is paramount in the treatment of NPC. Intensity-modulated radiotherapy (IMRT) remains the most frequently used approach for precision RT. It offers conformal (concave) shaping of tumouricidal doses and steep dose fall-off gradients, thereby providing the opportunity for safe delivery of high doses targeted to the tumour. Specific to NPC, the dosimetric advantages of IMRT have resulted in improvement in locoregional control (LRC) and overall survival (OS), and substantial reduction in incidence of late toxicity, such as blindness and xerostomia.

The ascent of IMRT as the preferred RT technique for NPC had its background in early institutional reports [10] that demonstrated substantial improvements in tumour control with IMRT, relative to historical reports using conventional RT (4-year LRC 97 % and distant control [DC] 66 %). Subsequently, a single-arm phase II trial by the Radiation Therapy Oncology Group (RTOG) [11] demonstrated a reduction in the rates of xerostomia from salivary gland sparing-IMRT. Additional randomized phase II trials showed the effect of IMRT on normal tissue toxicities and quality of life in early stage disease [12, 13] but were underpowered to detect tumour control differences. The findings were corroborated in a large randomized phase III trial [14] that compared IMRT versus 2D-conformal RT in 616 NPC patients with an OS advantage (5-year 80 % vs. 67 %) and superior LRC, particularly among T4 tumours (81.5 % vs. 62.2 %) favouring IMRT. Late grade 2 xerostomia (9.5 % vs. 27.1 %) and auditory complications (47 % vs. 89 %) were also significantly lower with IMRT.

Improved imaging modalities (MRI and PET/CT) for diagnosis and RT planning have also led to increased accuracy in these domains, accounting in part for the substantial improvements in LRC. The implementation of volumetric image-guidance (IGRT) during RT further improves setup accuracy with an opportunity for monitoring tumour volume and normal tissue changes over the course of RT, with the eventual promise of ‘real-time’ dose-volume parameter adaption to anatomic structures when necessary. Recently, particle therapy, e.g. intensity-modulated proton therapy (IMPT), has emerged as an additional attractive option. Potentially IMPT may enhance normal tissue sparing over IMRT, as evidenced by early observations of reduced toxicity [15, 16]. However, long-term clinical benefits and cost-effectiveness remain to be determined.

Role and Sequence of Chemotherapy

Progress has also been realized by combining RT with systemic therapy, especially cisplatin. Generally, stage I and II NPC are treated with RT-alone. The role of concurrent chemo-RT (CCRT) in stage II NPC is uncertain, although results of a single randomized phase III trial support its use in this subgroup [17]. Some concerns about the study include the use of an unconventional staging system for patient selection [13 % of the trial cohort had UICC/AJCC stage III (N2) disease], and a higher proportion of patients had parapharyngeal involvement and N2 disease in the CCRT-arm. These factors confound the interpretation of the available results in limited stage II disease. In truth, aggressive disease may benefit from systemic treatment intensification and may be selected by circulating EBV DNA as a biomarker. Leung and colleagues previously identified an unfavourable stage II NPC subgroup at risk of DM according to EBV DNA titers of ≥4000 copies/ml [18].

There is universal consensus that locally advanced NPC (LA-NPC) should be treated with combined chemotherapy using CCRT followed by adjuvant chemotherapy (ACT), according to the Intergroup-0099 protocol [19]. The necessity of ACT remains uncertain due to lack of compliance to ACT in numerous CCRT trials (e.g. only 50–75 % completed at least two cycles of ACT). An individual patient data (IPD) meta-analysis in NPC (MAC-NPC) reported an 18 % mortality risk reduction, with the main contribution derived from concurrent chemotherapy (risk reduction of 40 %, with only modest contributions from induction [ICT] and/or ACT) [20]. Conversely, a more recent IPD network meta-analysis, updated with contemporary trials, suggested a superiority for CCRT + ACT over CCRT-alone across all end points [21]. The need for ACT in addition to CCRT in LA-NPC has been challenged by the negative findings of a randomized phase III trial comparing CCRT + ACT versus CCRT-alone in 508 patients [22]. It is likely that not all LA-NPC patients require ACT. A recent review of 547 N2-N3 NPCs reported that the addition of ACT appears to be beneficial in N3 (reduction of DM) but not in N2 disease [23]. Consequently, efforts are focusing on risk-stratified approaches using post-RT EBV DNA titers to select patients for ACT (NCI-2014-00635). Such approaches require robust characterization and harmonization of circulating EBV DNA titer quantitation across centres [24].

ICT is an alternative approach for systemic treatment intensification [25, 26], given the putative advantage of reducing tumour bulk to facilitate critical structure sparing in RT planning and the potential to eradicate occult DM in advanced disease. However, the caveat with ICT is the consequential reduction of cisplatin dose intensity during the concurrent phase of treatment. A literature-based non-IPD meta-analyses suggested enhanced OS and reduced DM [27], while ACT may be more beneficial for LRC. However, this disparity was not observed in the preliminary analyses of the NPC-0501 [28] trial, which compared the Intergroup-0099 regime of CCRT + ACT against a ‘reverse’ scheduling Intergroup-0099 regime. Moreover, the updated IPD MAC-NPC meta-analysis [21] (19 trials, 4806 patients) also reported that an OS advantage was restricted to CCRT + ACT (HR 0.65 [0.56–0.76]) and CCRT (HR 0.80 [0.70–0.93]), but not evident with ACT (HR 0.87 [0.68–1.12]) or ICT-alone (HR 0.96 [0.80–1.16]). Two other randomized studies of

ICT + CCRT against CCRT-alone did not reveal survival benefits with ICT [29, 30]. Based on current evidence, ICT in addition to CCRT remains investigational. Finally, we await mature data of a randomized trial of CCRT with or without TPF (docetaxel, cisplatin and 5-fluorouracil) (NCT01245959), as well as a Taiwanese companion study, albeit using MEPFL (mitomycin, epirubicin, cisplatin, 5-fluorouracil, leucovorin) as the induction regimen (NCT00201396).

Post-Treatment Surveillance

Radiological imaging and clinical examination remain the cornerstones of post-RT surveillance. Imaging of the head and neck region using conventional computed tomography (CT) or magnetic resonance imaging (MRI) is indicated for assessment of deep-seated skull base and intracranial tumours, as well as nodal disease in the retropharyngeal space and lower neck, while nasoendoscopy is best for surveying superficial mucosal lesion. Modern imaging techniques now offer improved accuracy in terms of differentiating between post-RT changes and recurrent/residual tumours, and these include [18] F-FDG-PET/CT and functional MRI [31, 32].

With the exception of whole body [18] F-FDG-PET/CT, all other imaging modalities are restricted to assessment of locoregional anatomy, and preclude early detection of DM, which may be heralded by the onset of detectable circulating cell-free EBV DNA [33, 34]. This phenomenon is widely interpreted to reflect the extreme sensitivity of EBV DNA as a measure of tumour burden, but it is plausible that tumour shedding of EBV DNA may closely relate to the biological activity of NPC cells. In support, early disappearance of this biomarker after treatment commencement appears to correspond with a favourable prognosis [35]. EBV DNA can thus be employed to complement radiological imaging for early detection of tumour recurrence [36] and seems most sensitive for DM detection compared to locoregional failure (LRF) [37, 38]. This provides potential opportunities for novel salvage strategies, such as EBV-vaccine therapy in low-burden disease (NCT01094405).

Management of Local and/or Regional Failure

Salvage options for local recurrences include surgery, external beam RT, brachytherapy, stereotactic radiosurgery (SRS), chemotherapy and photodynamic therapy. Often, the choice of treatment is determined by the tumour extent and location, along with the available local resources and expertise. The philosophy of these approaches is addressed in Chap. 13.

Management of Distant Metastasis

The management of metastatic NPC has evolved [39]. For a favourable subgroup of patients (lung only metastasis and/or oligo-bone metastasis), aggressive treatment in the form of CCRT and metastatectomy/ablative RT is progressively being considered, with the aim of achieving long-term survival [40–43]. Better clinical or molecular stratification tools are thus required in this unique subgroup. For patients with disseminated metastases, while platinum-doublet regimes remain the standard first-line treatment, immunotherapeutic strategies employing either tumour antigen-specific vaccines or immune-checkpoint inhibitors represent new frontiers of treatment [44–46].

Treatment of HPV-Related Oropharyngeal Cancer

HPV-related OPC is a rapidly emerging disease entity, and major treatment guidelines do not yet differ between HPV+ OPC and its less favourable smoking-related counterpart, despite exemplary outcomes for the former. Since more than 90% HPV+ OPC has lymph node involvement at presentation [3], it has traditionally been classified as 'advanced' stage according to 7th edition TNM, with a mandate for intensified treatment based on current treatment guidelines. However, evidence is emerging that most HPV+ OPC (except T4 or N2c-N3) can be cured even in many patients identified as having traditional 7th edition TNM stage IV disease using less intensified treatment, such as RT-alone [47, 48] or transoral robotic surgery (TORS) [49, 50]. A new stage classification has been recently proposed [7] based on a single institution data and has been modified and validated in a multi-institutional study [8]. This is needed to depict the character and prognosis of HPV+ disease and to guide clinical trial design in researching optimal treatments for HPV+ OPC.

Current research in HPV+ OPC is refining risk groups and exploring deintensification in low-risk groups while maintaining or augmenting intensification in the high-risk group. However, controversies exist regarding which subgroups are 'low risk' and which are 'high risk', what end point (risk of death or risk of DM) is optimal and what contemporary treatment options should be [51]. Several deintensification strategies are under evaluation.

Initial Treatment of Non-metastatic Disease

Risk Stratification

OS is a traditional outcome end point for clinical trial design. In the first publication of the RTOG 0129 trial, Ang and colleagues [52] constructed two mortality risk groups for HPV-related OPC based on 7th edition TNM and smoking pack-years. It

classified all HPV+ OPC patients, except >10 pack-year smokers with N2b-N3 disease, as the 'low-risk' group to be considered as deintensification trial candidates. All patients in this analysis received intensified treatment. Whether the excellent results from the intensified regimens used in the clinical trial setting would be reproducible when replaced by less intensified treatment and whether lower risk of death is a sufficient criterion for choice of deintensification remain uncertain. In addition, using smoking pack-year as the risk stratification for treatment decision-making remains problematic, since lower OS by heavy smokers may not necessarily reflect altered tumour biology and may also reflect competing mortality risk from smoking (comorbidities, second primary, severe late toxicity and social problems). It might also be due to impaired treatment tolerance due to comorbidities, as well as compromised radiotherapy efficacy (hypoxia) among current smokers. In addition, heavy smokers are less tolerant of more intensified treatment. Recently, smoking has been described as having almost no impact on disease recurrence in surgically treated patients [53].

LRC is no longer the overwhelming problem for many HPV+ OPC patients questioning the necessity for intensive local treatment in all patients since DM is the most common cause of death. Given the clinically unpredictable development of DM [54, 55], the medical community has understandably been fearful of omitting or reducing chemotherapy. O'Sullivan and colleagues performed a risk stratification analysis on an institutional cohort of prospectively compiled HPV+ OPC patients but addressed DM risk as the end point, and found that DM risk was significantly associated with T4 or N2c-N3 category diseases, while T1-3 N0-N2a and T1-3N2b<=10 pack-year smokers have minimal risk of DM and may achieve an excellent result with RT-alone. The DM risk for the T1-3N2b >20 pack-year smoker treated by RT-alone is uncertain although did suggest an adverse DM outcomes for heavy smokers. The finding of a subgroup with excellent LRC and DC finally permitted dislodgement of the deintensification impasse to commence for HPV+ OPC, directly leading to the design of the currently accruing NRG-HN002 deintensification trial (NCT02254278).

Deintensification and Intensification Strategies Under Testing

Currently several treatment deintensification trials are targeting the 'low-risk' HPV-related OPC cohort described above. Deintensification strategies under evaluation include substitution of cisplatin by EGFR inhibition (e.g. RTOG 1016, NCT01302834), reduction of RT dose or chemotherapy intensity [e.g. NRG-HN 002, NCT02254278, a institutional phase II trial (NCT01530997) [56]], induction chemotherapy followed by lower RT dose in good responders (e.g. ECOG 1308, NCT01084083) and TORS resection with or without adjuvant chemoradiotherapy (e.g. ECOG 3311, NCT01898494). For high-risk populations, induction chemotherapy and immunotherapy are under discussion. Potential opportunities may exist to mitigate the risk of DM through the use of TPF triplet induction regimens following evidence from an IPD meta-analysis reported by the MACH-NC group [57]. Such strategies will require HPV+ OPC specific clinical trials.

Role of Post-radiotherapy Neck Dissection

Role of post-radiotherapy neck dissection (PRND) is evolving for patient with N2-N3 diseases. A retrospective analysis of a prospective compiled study suggests that HPV+ OPC lymph node (LN) may involute more slowly and suggest that PRND may be withheld for selected cases with an incomplete radiological response with close imaging surveillance [58].

Post-treatment Surveillance

Surveillance strategies should consider both the duration and the surveillance tools. For HPV+ OPC, active surveillance should be longer than the traditional 2 year window due to possibility of late onset DM. In some series, DM may manifest up to 8 years after initial treatment [55, 59, 60]. CT thorax is still the routine screening and surveillance tool for DM since lung is the main site of HPV (+) DM [55, 59]. Liver ultrasound may add additional value because solitary liver DM is often asymptomatic. Clinicians should also be aware of the possibility of late onset and unusual site of DM [54, 55, 59]. Lung, bone and liver oligometastases have been reported to be salvageable by surgery, radiotherapy or chemotherapy. Active aggressive treatment may be considered as long-term survival or even cure is possible for a subset with an indolent DM phenotype [55, 59, 61].

Besides clinical (including imaging) evaluation, pre- and post-treatment HPV DNA in blood (serum or plasma) and saliva are currently under investigation for disease surveillance [62–69].

Management of Local and/or Regional Failure

As already noted, LRF is uncommon for this disease. In resectable LRF disease without DM, salvage surgery +/− post-operative re-irradiation is the treatment of choice [70, 71]; if unresectable, definitive re-irradiation (preferred small fraction size to minimize severe late toxicity) +/− systemic therapy may be considered. If surgery or re-irradiation is not possible, systemic therapy may be considered. The philosophy of these approaches is addressed in Chap. 13.

Management of Distant Metastasis

Two distinct types of DM appear to exist: disseminating versus indolent phenotypes [55, 60]. For HPV+ patient with limited DM, long-term survival may still be possible [55, 61] and an aggressive treatment for ablation of metastatic lesion may be

considered. For patient with the 'disseminating' phenotype and multiple organ metastases, supportive care and symptom management is important. For limited DM disease, salvage treatment, including surgical resection, radiotherapy or chemotherapy, should be considered; for patient with 'disseminating' DM, cure is unlikely with contemporary approaches, and the goal should focus on symptom control and supportive care.

The role of EGFR inhibition for recurrent/metastatic disease is uncertain. The EXTREME trial (NCT00122460) showed some effect of combining chemotherapy plus cetuximab [72]; however, the SPECTRUM trial (NCT00460265) did not show a survival benefit in HPV+ disease with the addition of panitumumab to chemotherapy [73]. Immunotherapy is now on the horizon with promising results. The preliminary encouraging results of a phase Ib multisite study (NCT01848834) evaluating the activity of pembrolizumab in patients with recurrent or metastatic HNSCC regardless of PD-L1 or HPV status were reported at the ASCO Annual Meeting in 2015 [74]. Recently, the CheckMate-141 phase III trial (NCT02105636) was stopped early after an independent monitoring panel determined the primary end point of improvement in OS was met with the anti-PD-1 agent versus the investigators' choice of cetuximab, methotrexate or docetaxel in patients with platinum-refractory recurrent or metastatic head and neck cancer. The result was presented at the 2016 AACR Annual Meeting and showed that nivolumab improved OS in both HPV+ and HPV– patients.

Conclusion

Optimal imaging and IMRT (Level 1 evidence) represents the locoregional 'gold standard' treatment for NPC. DM is the main form of failure. Chemotherapy is needed for LA-NPC, and CCRT is arguably the most important component while additional chemotherapy might enhance systemic control but sequence and precise systemic approach remains uncertain. Risk stratification using EBV DNA may be helpful in guiding adjuvant treatment (NRG HN01 trial).

HPV+ OPC has a remarkably good outcome/prognosis in low-risk group, and there is a strong likelihood that we are overtreating this subset (at least 50 % of OPC) using treatments designed for a different disease. There is scant evidence that this subset requires intensive treatment combining high-dose radiotherapy with high-dose cisplatin; abundant evidence is emerging that suggest that more conservative approaches may be sufficient. Higher risk groups need intensive/different approaches for LRC and DC. Serological assays of HPV DNA (potentially) copies may provide a valuable index of disease bulk and guide to recurrence in the future.

The viral-related oropharyngeal and nasopharyngeal cancers represent unique mucosal cancers with special characteristics including the possibility that 'cure' of metastasis may be possible.

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Chapter 11
Patient and Treatment Factors in Concurrent Chemoradiotherapy

Jan B. Vermorken

Concurrent Chemoradiotherapy

Standard treatment options for patients with locoregionally advanced squamous cell carcinoma of the head and neck (LA-SCCHN) are: (1) a surgical approach, including reconstructions plus postoperative radiotherapy or platinum-based concurrent chemoradiotherapy (CCRT) in those patients in whom high-risk features are found in the pathology specimen (positive margins and/or extracapsular extension) and (2) a nonsurgical approach when the anticipated functional outcome and/or prognosis is so poor that mutilating surgery is not justified. Platinum-based CCRT is also the standard approach in patients with nonresectable LA-SCCHN [1, 2]. Other nonsurgical approaches with level IA evidence include altered fractionation radiotherapy and hypoxic modification of radiotherapy [3, 4]. This latter approach is nowadays standard only in Denmark, but a confirmatory trial is ongoing outside Denmark within the framework of the European Organization on Research and Treatment of Cancer (EORTC) Radiation Oncology Group (ROG) and Head and Neck Cancer Group (HNCG).

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History of Platinum-Based Chemoradiotherapy

Already for several decades cisplatin is used for the treatment of patients with LA-SCCHN to enhance the effect of radiation [5]. The basis for this has been derived from four large randomized phase III studies that evaluated the role of cisplatin both in the definitive setting and the adjuvant, postoperative, setting [6–9]. Further support for this was obtained from the individual patient-based meta-analysis of chemotherapy in head and neck cancer (MACH-NC) reported by Pignon et al. [10, 11]. In the updated report published in 2009, with focus on CCRT, the hazard ratio (HR) of death was 0.81 (95 % confidence interval [CI], 0.78–0.86; $p < 0.0001$) in favor of using CCRT versus RT alone, showing an absolute survival benefit of 6.5 % (33.7 % vs. 27.2 %) at 5 years [11]. Subset analysis revealed that both single-agent cisplatin and combinations of either cisplatin or carboplatin with 5-fluorouracil (5-FU) induced beneficial effects of the same order of magnitude, i.e., a risk reductions of death of 26 and 25 %, respectively. Although the French regimen [12] of carboplatin 70 mg/m^2/d, day 1–4, and 5-FU 600 mg/m^2/d, day 1–4, three times during RT is being seen as a reasonable alternative for high-dose cisplatin, most randomized trials made use of single-agent cisplatin, given at a dose of 100 mg/m^2 three times during the course of radiotherapy (on days 1, 22, and 43) [11]. Therefore, this latter approach is still being recognized as the preferred CCRT regimen when treating patients with LA-SCCHN both in Europe and in the USA [1, 2]. The improvement in the meta-analysis was observed irrespective of type of radiation (conventional or altered fractionation), the setting (definitive or postoperative), and the site of the primary tumor. However, the MACH-NC did confirm that the magnitude of benefit of CCRT was less in older patients, i.e., those with a calendar age > 70.

Toxicity of Chemoradiotherapy Underreported?

The improved locoregional control rate and survival gain with the use of platinum-based CCRT has been reached at the cost of an increased amount of early and late toxicities. Early effects are expressed during or within a few weeks after the end of therapy and typically occur in highly proliferating tissues such as the hematopoietic system, the mucosal lining of the gastrointestinal tract, and the skin [13]. Late effects in patients become manifest after latent periods ranging from months to years and include radiation-induced fibrosis, atrophy, vascular damage, neural damage, and a range of endocrine and growth-related effects [13]. The early effects are typically transient, but for a number of tissues data have been presented supporting the concept that severe early effect may be causally related to the subsequent late effect [14]. The late toxicities in particular have major implications for the quality of life of the cancer survivors [15]. In Western societies, due to the decrease in smoking, the increase of oropharyngeal cancer (OPC), and the preponderance of

human papillomavirus (HPV)-associated OPC, showing better survival figures, late toxicity and quality of life are becoming more and more of an issue. Late toxicities have not always been analyzed adequately and reported consistently. In that respect the study reported by Machtay et al. is very informative, as it is specifically dealing with factors associated with severe late toxicity after CCRT [16]. An analysis was done on a subset of patients that participated in three previously reported Radiation Therapy Oncology Group (RTOG) trials of CCRT for LA-SCCHN (RTOG 91–11, 97–03, and 99–14), all being cisplatin-based. Severe late toxicity was defined as chronic grade 3–4 pharyngeal/laryngeal toxicity, using the RTOG/EORTC late toxicity scoring system, and/or requirement for a feeding tube ≥2 years after registration, and/or potential treatment-related death (e.g., pneumonia) within 3 years. The original, potential patient population from these three trials was 479. However, 130 patients were excluded from the late toxicity analysis because of locoregional failure or death due to the cancer, while 100 others were excluded because of severe pretreatment cancer-related laryngopharyngeal dysfunction; 13 patients were excluded because of missing data and six patients were excluded because of early death due to acute toxicity, leaving 230 assessable for the analysis. Of those 230 patients, 99 (43 %) experienced severe late toxicities, 27 % showing pharyngeal dysfunction, 13 % being feeding-tube dependent > 2 years post-RT, and 12 % showed laryngeal dysfunction. Extremely worrying was the fact that there were 10 % (unexplained?) deaths. The long-term analysis of RTOG 91–11 in particular is a clear example of how the use of chemotherapy concomitantly with radiation can lead to an increase in noncancer-related deaths compared to the sequential use of chemotherapy, i.e., given before the radiation [17]. Remarkably, the survival curves in RTOG 91–11 start to separate after 4.5 years of follow-up. When investigating the factors associated with the development of severe late toxicity, the RTOG analysis of the three studies showed that older age, advanced T stage, and larynx/hypopharynx primary disease site were strong and independent risk factors. Moreover, neck dissection after CCRT was associated with an increased risk of these complications [16]. In a later publication the same group reported that, after analyzing the detailed radiation therapy records, the radiation dose to the hypopharynx was also associated with the occurrence of late toxicity [18].

There have been different ways by which toxicities have been documented and reported, especially in patients with SCCHN [19, 20]. When methods and also the completeness of toxicity reporting differ in different studies, some researchers not only have expressed concerns about underreporting but also raised questions regarding the reliability of toxicity data and have cast doubt on the ability to compare morbidity between trials [13]. The RTOG recently examined formally an established method of summarizing adverse events (the max-grade method) in 2304 patients in five trials (13 treatment arms) that were executed between September,1991, and August, 2000, and showed that the maximum-grade summary method excluded 29–70 % of high-grade (grade 3–4) acute adverse events and 26–48 % of high-grade late adverse event. The authors also looked at the worst grade over time method (maximum-time) and concluded that both the maximum-grade and maximum-time summary methods make the more intensive treatment programs seem less toxic than

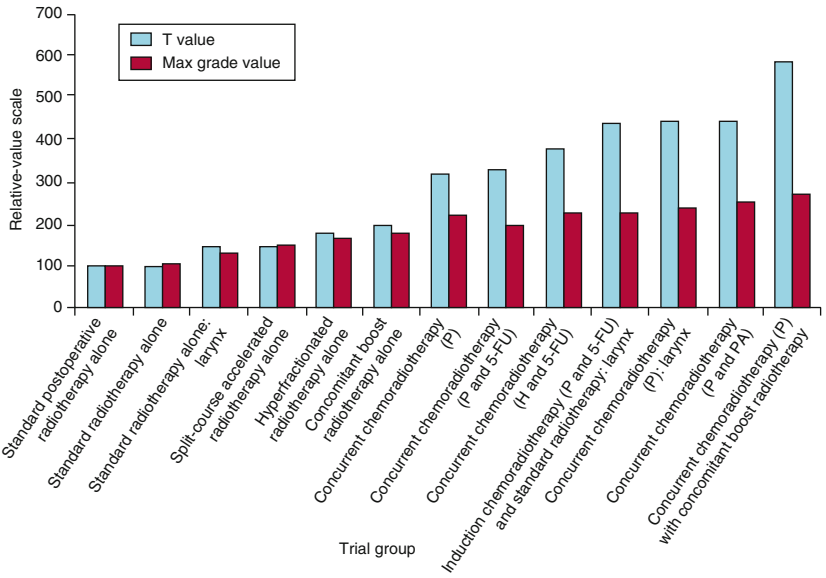

Fig. 11.1 Acute toxicity relative risk values (T_{RR}) and relative max-grade values for 13 head and neck treatment groups ranked by increasing relative risk. *P* platinum, *H* hydroxyurea, *5-FU* 5- fluorouracil, *PA* paclitaxel (From Trotti et al. [21], reproduced with permission)

they really are [13, 21]. For comparison a new investigational metric, the TAME reporting system, that includes time and multiplicity factors for summarizing the toxicity burden, was used in the same group of patients. TAME represents three well-recognized risk domains: short-term (acute) toxicity (T), adverse long-term (late) events (A), and treatment-related mortality (M), in an end-results (E) summary format [21]. Although TAME is meant as a supplement to the detailed adverse event information, and not as a substitute, the information with TAME was quite impressive (see Fig. 11.1). The relative T values in the 13 treatment programs showed an increase of almost 500 % in acute toxicity burden (100–590) between the treatment groups compared with a 170 % increase (100–270) between treatment groups when using the max-grade method. There was less variation noticed in the relative risk of late events (100–250) by the TAME method for late effects.

Patient Factors in Concurrent Chemoradiotherapy

As mentioned in Chap. 6 (Clinical decision making), there are several factors playing a role in decision making during multidisciplinary team meetings, i.e., disease factors, patients factors, treatment factors, and adequate communication with and information to the patient, giving sufficient support, taking into account the wish of the patient. With respect to patient factors, we mentioned that among others age, sex, performance status, nutritional status, comorbid chronic disease, oral health,

lifestyle habits, and socioeconomic status all play a role. Multiple studies have shown several demographic and health status characteristics to be associated with a higher chance of noncancer-related death [22–26]. Factors most commonly associated with increased noncancer-related mortality include increasing age, male sex, increasing comorbidity, decreasing body mass index (BMI), and an unmarried status. In a cohort study of 479 patients with stage III/IV carcinoma of the head and neck, all treated with CCRT, with or without induction chemotherapy, in a series of five successive multi-institutional protocols in the USA, the authors reported results of a multivariable analysis on predictors of competing mortality. The study showed that older patients with comorbidities were more likely to die of noncancer causes, while women and patients with a lower BMI (log BMI lower than 3) and traveling shorter distances to the treating center were at higher risk for treatment-related mortality [23]. Median distance traveled correlated with race (blacks 5 miles, nonblacks 27 miles, $p < 0.001$), nevertheless race was not considered to be a confounding factor. In the decision making on how and with what to treat the patients, his/her own wish is playing a crucial role. It is therefore important to be aware of the considerations and the prioritizations of the head and neck cancer patient. In that regard, the study reported by List et al. [27] is of interest. Two hundred forty-seven newly diagnosed head and neck cancer patients from nine institutions in the USA and 131 nonpatients were asked to rank a set of 12 potential treatment outcomes from highest [1] to lowest [12]. The top three items most frequently mentioned by both patients and nonpatients were "being cured of cancer," "living as long as possible," and "having no pain," in that order. In contrast, head and neck cancer patients ranked "cure" (90 % vs. 80 %) more frequently, while they ranked "no pain" less frequently (34 % vs. 52 %) in the top three. So, evidently for patients, survival seems to be of paramount importance, overshadowing associated toxicities and potential dysfunction. This means that unless there are unsurmountable objections we should choose for the best treatment approach. However, alternative options should be mentioned and discussed, balancing pros and cons of each treatment option within the context of that individual patient.

If indeed high-dose cisplatin-based CCRT is the preferred standard of care treatment option for patients with LA-SCCHN, one should be aware of the absolute and relative contraindications of that treatment. According to experienced radiation oncologists, there are no absolute contraindications for radiotherapy, although extreme caution should be given to considerations of radiotherapy for patients with scleroderma (especially those with CREST [Calcinosis, Raynaud phenomenon, Esophageal dysmotility, Sclerodactyly, and Teleangiectasia] syndrome) and ataxia telangiectasia. Moreover, caution is also generally advised in case of Fanconi's anemia, systemic lupus erythematosis, rheumatoid arthritis, dermato- and polymyositis, and other autoimmune and collagen vascular conditions (Brian O'Sullivan, personal communication). It goes without saying that re-irradiation is also a major concern in all patients, and is addressed more specifically elsewhere in this textbook. With respect to the use of cisplatin, absolute and relative contraindications for the use of cisplatin in general and high-dose cisplatin in particular were defined by a consensus panel in August 2014 [28]. Absolute contraindications for the use of (high-dose) cisplatin include an ECOG score ≥ 3, a creatinine clearance < 50 ml/

Table 11.1 Clinical criteria for patients at high risk for platinum toxicity. *ECOG* Eastern Oncology Cooperative Group, *NCI-CTC* National Cancer Institute - Common Toxicity Criteria, *HIV/AIDS* human immunodeficiency virus infection/acquired immune deficiency syndrome, *CD4* cluster of differentiation 4

ECOG performance status 2
Biological age (>70 years; geriatric assessment, cognitive function)
Creatinine clearance 50–60 ml/min (consider lower dose of cisplatin)
Borderline function (NCI-CTC grade 1) of target organs (oto/neuro)
Marrow, hepatic, and respiratory dysfunction ≥ grade 2 (Child-Pugh score B)
Comorbidities (cardiovascular, diabetes, recurrent pulmonary infections)
HIV/AIDS (CD4 count < 350/μl)/immune-compromised conditions
Previous cisplatin therapy, including induction chemotherapy (>200 mg/m^2)
Involuntary weight loss (≥20 %) and a low body mass index
Concomitant use of nephrotoxic drugs
Socioeconomic status; lack of social support, no support at home

Head and neck cancer Expert Panel meeting, Seoul, Korea, August 2014 [28]

min, preexisting hearing loss or tinnitus ≥ grade 2, neurologic disorders ≥ grade 2, known hypersensitivity to platinum-based therapy, pregnancy and lactation, and HIV/AIDS (with CD4 count < 200/μl). Relative contraindications for the use of cisplatin are summarized in Table 11.1.

Treatment Factors in Concurrent Chemoradiotherapy

Methods to reduce the toxicity of cisplatin-based CCRT include, among others, better radiation targeting, use of newer RT techniques, and alternatives to the use of high-dose cisplatin.

Better Targeting and New Radiotherapy Techniques

Better targeting can be obtained by computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET) scans and more accurate delivery using daily image-guided radiotherapy. More precise contouring reduces toxicity as it lowers the volume of unnecessary irradiated healthy tissue and increases tumor control by reducing the risk of geographical misses. New radiation techniques such as rotational intensity-modulated radiotherapy (IMRT) has gradually replaced the static beam IMRT, leading to a more conformal dose distribution

and better sparing of organs at risk [29]. IMRT became state of the art in head and neck cancer therapy based on level I evidence of static beam IMRT reducing xerostomia compared to conventional radiotherapy, while evidence of superiority of IMRT to conventional radiation both in terms of quality of life and survival is growing [30–37]. In a Dutch study, grade ≥2 swallowing dysfunction in head and neck cancer patients treated with (chemo) radiation was best predicted by the mean radiation dose to the superior pharyngeal constrictor muscle and to the supraglottic larynx and swallowing sparing IMRT therefore seems of interest for specific patient categories [38]. Parallel to IMRT, there has been the clinical implementation of stereotactic radiation (CyberKnife and linac-based stereotactic RT) and particle therapy (protons and carbon ions). Stereotactic radiotherapy or radiosurgery is a nonsurgical procedure that delivers targeted irradiation very precisely at much higher doses than conventional radiotherapy while sparing the nearby organs at risk. Stereotactic radiotherapy in head and neck cancer can be used as a boost after conventional radiation or for re-irradiation after relapse or second primary in previous irradiated areas. As it is felt by some that photon-based radiotherapy may have reached the limits of its possibilities, other particles gained interest. Most popular are protons and carbon ions. Both have dose distributions that are superior to any photon technique. This approach may be particularly interesting for children and when there are radiosensitive organs at risk nearby, such as spinal cord, brainstem, parotid, and submandibular glands. Carbon ions will mainly be used for radioresistant cancers because of its supplementary higher biologic effect (e.g., melanoma, adenoid cystic carcinoma, certain sarcoma subtypes).

Alternatives for High-Dose Cisplatin (in Combination with RT)

Several alternatives for the use of high-dose cisplatin can be considered, such as (1) other cisplatin doses or schedules, (2) other cytotoxics, e.g., carboplatin, taxanes, or low-dose gemcitabine, (3) targeted agents, e.g., cetuximab (the only approved targeted agent for head and neck cancer), or (4) hypoxic modification (an approach which is used in standard [chemo] radiation schedules in Denmark).

Many attempts have been made to reduce the toxicity of cisplatin-based CCRT while maintaining the antitumor effect. Parameters of cisplatin that theoretically can be modified are the cumulative dose, the dose intensity, the peak dose, and the administration schedule. In a recent systematic review, Strojan et al. [39] concluded, based on six definitive chemoradiation trials, that there is a statistically significant association between treatment outcome and the cumulative dose of cisplatin, independent from the schedule used, showing survival benefit for the higher doses. Although the critical cumulative dose is not exactly known, earlier publications suggested to use minimally a cumulative dose of 200 mg/m^2 [40–42]. That cut-off point was used in a retrospective study of 659 newly diagnosed patients with LA-SCCHN (404 HPV-positive/95 % OPC; 255 HPV-negative/38 % OPC) treated with cisplatin-based CCRT at the Princess Margaret Cancer Center in Toronto, Canada, and the

Istituto Nazionale dei Tumori in Milan, Italy, from 2000 till 2012. Overall survival was significantly less in patients treated with a cumulative dose below 200 mg/m^2 compared with those receiving higher cumulative doses. However, that only was the case in patients with HPV-negative tumors. No such difference in outcome was observed in patients with HPV-positive tumors [43]. This could be in agreement with the observed higher sensitivity of HPV-positive tumors to both radiation and chemotherapy and give support to the ongoing studies testing the concept of deintensification in HPV-positive OPC patients. Many cisplatin-induced toxicities are peak dose related; therefore administering the 100 mg/m^2 cisplatin dose over a longer period of time (e.g., 24 h) or giving the dose split over 5 days might be an option that could induce less toxicity. Although this has not been explored in head and neck cancer patients in a prospective randomized study, the toxicity data reported of the German ARO 96–3 trial, a study in which CCRT with cisplatin (20 mg/m^2/d × 5) plus 5-FU was compared to RT alone, do suggest that might be a reasonable option [44]. Although there is no evidence of its equivalence with the high-dose cisplatin regimen, there is a tendency to use a weekly low-dose cisplatin (40 mg/m^2) in several areas of the world. One may argue that more frequent cisplatin administrations during RT might lead to stronger radiosensitization and less chance of radioresistance. However, some caution is needed since recent data presented at ASCO 2015 showed that survival data might be less with that approach [45]. Comparative studies are therefore needed before the low-dose weekly regimen is to be adopted as the new standard approach of administering cisplatin in CCRT strategies.

The use of other cytotoxics has mainly been studied in patients that were not candidates for cisplatin or showed unacceptable toxicity when they started on cisplatin. Carboplatin has a more favorable toxicity profile with lower rates of otoxocity, nephrotoxicity, neurotoxicity, and emesis [46]. Carboplatin is primarily excreted with the urine and therefore can be better dosed based on the glomerular filtration rate [47]. There are no large randomized trials comparing carboplatin versus cisplatin in the CCRT setting, and the individual patient-based meta-analysis from Pignon et al. [11] suggested that monochemotherapy with drugs other than cisplatin led to inferior results and therefore should not be recommended in routine practice. Therefore, despite the fact that more contemporary studies suggest that it might be a reasonable option when cisplatin is contraindicated or not tolerated [48], adequate trials supporting this notion are needed. The same can be said about taxanes, although some data on CCRT in the postoperative setting suggested a beneficial effect of taxanes versus cisplatin. In RTOG 0234, 238 patients were randomized to receive 60 Gy radiation with cetuximab once weekly plus either cisplatin 30 mg/m^2 or docetaxel 15 mg/m^2 once weekly. The 2-year disease-free survival (66 % vs. 57 %) and 2-year overall survival (79 % vs. 69 %) were in favor of the taxane arm [49]. Further studies in that direction seem appropriate. A recent review highlighted the enormous radiosensitizing potential of gemcitabine and suggested that very low dosages (less than 50 mg/m^2 per week) provide a sufficient therapeutic ratio and therefore should be further investigated [50]. However, many of the reported studies lack sufficient data on late toxicity. For those without any experience with gemcitabine in this clinical setting, it is not advised to use it outside clinical trials.

The addition of cetuximab to irradiation improves locoregional control and prolongs progression-free survival and overall survival [51, 52]. Treatment adherence of >90 % of cetuximab plus RT seems better than what has been observed with cisplatin-based CCRT, and quality of life with cetuximab plus RT was not found inferior to that with RT alone [53]. Despite these promising data, many clinicians in Europe are still hesitant to use cetuximab plus RT routinely instead of platinum-based CCRT, because of lack of large prospective randomized phase III trials that compare efficacy and adverse events of RT plus cetuximab versus RT plus cisplatin (or RT plus carboplatin/infusional 5-FU for that matter, both considered standard of care CCRT regimens). Most clinicians see RT plus cetuximab as a treatment option for patients with absolute (or relative) contraindication for platinum-based therapy. A further trigger to this discussion was evoked by a recent small randomized phase II study with a rather negative outcome of the bioradiation arm [54]. For further reading on this topic, the reader is advised to read the two editorials that appeared in relation to this article [55, 56].

Hypoxic modification is another biological modification that has markedly improved outcome [4]. Nimorazole is the most studied hypoxic radiosensitizer. Previous studies in Denmark have shown that nimorazole improves outcome of radiation, whether given by conventional fractionation or accelerated fractionation, without an indication that the (late) complication rate of the radiotherapy thereby is increased. The positive effect on locoregional control and survival was particularly evident in the more strongly hypoxic tumors and less so in the less hypoxic tumors. HPV/p16 positive tumors did not seem to benefit from hypoxia modification, despite the fact that they may express hypoxic features. The feasibility and tolerance of the combined schedule of nimorazole, accelerated fractionation radiotherapy, and CCRT with weekly cisplatin (40 mg/m^2 weekly for at least 5 weeks) has been evaluated in the DAHANCA 18 study and since then has become standard in Denmark. These intriguing data ask for confirmation, and this will hopefully be done by protocol 1219 ROG-HNCG of the EORTC, comparing CCRT plus nimorazole versus CCRT plus placebo. This study will be executed outside Denmark. The two primary endpoints of the trial are: (1) to study whether locoregional control rate can be improved with this combined approach and (2) to test whether the benefit is restricted to patients whose tumors have a hypoxic gene profile. In case confirmation of the Danish study can be obtained, this will lead to new treatment possibilities and opportunities.

Conclusion

The preferred standard of care CCRT is high-dose cisplatin with 100 mg/m^2 on days 1, 22, and 43 during conventional fractionation-based RT. The long-term follow-up of protocol RTOG 0129 suggests that standard fractionation radiation with 3×100 mg/m^2 equals accelerated fractionation radiation with 2×100 mg/m^2 [57]. Irrespective of the type of radiation, and irrespective of whether it concerns a

HPV-positive or a HPV-negative tumor, a minimum cumulative dose of 200 mg/m^2 should be tried to reach an optimal outcome. Acute and late toxicities are a downside of this treatment, and specific demographic and health status characteristics are associated with higher chance to die from a noncancer-related cause or from treatment-related toxicity. It should be noted that better targeting of the radiation and newer radiotherapy techniques may lead to less toxicity and a better quality of life. Moreover, deintensification strategies in patients with HPV-positive OPC are getting attention. These studies might show the way how to optimally treat such patients other than with platinum-based CCRT. Unfortunately, that option might not be available for the many patients that smoke and/or have a HPV-negative tumor. Therefore, clinicians should be aware of the absolute and relative contraindications for the use of cisplatin and look for the most optimal way to administer it. Alternative options for high-dose cisplatin in case of contraindications or intolerance are the use of the French regimen of carboplatin/infusional 5-FU (preferred) or cetuximab. The less favorable results reported recently on bioradiation with cetuximab further stresses the need for a prospective randomized study that compares this approach versus platinum-based CCRT. Finally, hypoxic modification is an option that is going to be further explored and might open new areas of research in this still devastating disease.

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Part VI
Recurrent/Metastatic Head and Neck Cancer: How and When to Treat

Chapter 12
Salvage Surgery of Head and Neck Cancer

C. René Leemans

The role of the modern surgeon is evolving, with more emphasis on salvage surgery than before. Besides, surgery must treat complications and sequelae of chemotherapy and radiotherapy, such as edema, strictures, and radionecrosis. Surgery may also be an option for certain selected cases of distant metastases, but this will not be described herein.

Treatment guidelines, including the NCCN Guidelines for recurrent or persistent disease after prior radiation therapy advise surgery as first line treatment in tumor is resectable [1]. Depending on adverse features of histopathology, adjuvant (chemo) re-irradiation may in very selected case be indicated. Salvage surgery for (chemo) radiation failure is thus increasingly employed for cancers of the oropharynx, larynx, and hypopharynx and offers the best chance of survival for the patient.

However, not all recurrent disease is operable. The surgeon must ensure meticulous preoperative assessment and decision-making before embarking on this rescue modality. It is of great importance that the description of the original tumor is taken into account, as well as the extent at the time of recurrence. As a rule of thumb, an originally unresectable case will remain unresectable, even if the recurrence seems resectable. Also the tumor extent on imaging is vital and a careful discussion with the radiologist is mandatory. Limitations of surgery include resection of the common or internal carotid artery and prevertebral fascia. Involvement of these structures indicates a biologically highly aggressive tumor and although technically feasible, resection of these structures may bring more harm than benefit to the patient. It is here that the surgeon's experienced judgment becomes vital to balance these two extremes. Total glossectomy for salvage is feasible as a life-altering procedure. These patients may still have useful communication and a soft oral intake without aspiration. A laryngectomy in conjunction with a total glossectomy for recurrences at the interphase of these two major structures is also technically

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possible, but this may be a procedure that is just a bridge too far in view of the expected therapeutic ratio. Esophagectomy in order to achieve clear margins is technically possible, albeit (for head and neck cancer recurrence after chemoradiation) with only moderate help on the expense of severe complications and high morbidity. In general salvage surgery is only feasible in a minority (20–40 %) of patients, making initial multidisciplinary decision-making for the primary treatment even more important; the expression "we will start with non-surgical treatment, and in case of recurrence we can always operate" is not true.

Also, early detection or recurrence and subsequent salvage yields improved control and survival and therefore reliable diagnostics are essential. MRI and CT lack specificity due to edema, delayed volume reduction, and artifacts by dental filling. The negative predictive value of FDG-PET-CT at 3 months is in general very reliable; at earlier points in time, there is a high incidence of equivocal and inaccurate interpretation both at the local and regional level due to the inflammatory effect and inability to visualize small lesions (<0.5 cm). Ultrasound-guided fine needle aspiration of residual neck masses after chemoradiation has been investigated. While sensitivity and positive predictive value are reasonably high, specificity and negative predictive value lack accuracy.

Since salvage surgery after chemoradiation is possible only in a limited number of patients and has a high complication rate even when vascularized flaps are used liberally and high rate of further recurrences after salvage, the question is what is the outcome? Goodwin in 2000 described a clear influence of pretreatment stage on outcome [2]. Stage I and II have a 70 % outcome, with good quality of life in 60–85 % of patients and low surgical complication rate. In the more advanced stages, this picture deteriorates considerably. In stage III, patients have only 33 % 2-years survival with markedly less quality of life and 40 % complications. For stage IV, this is still worse, with less than 25 % 2-years survival and even lower quality of life. Swallowing and speech problems were very common after salvage surgery. Deaths related to surgery were extremely low in all stages.

Although salvage surgery also exists for oral cancer patients who recur after chemoradiotherapy, those who need salvage for laryngeal cancer benefit most, followed by hypopharynx and oropharynx cancer patients. Several reports have focused on these specific sites, as well as the neck only [3–11, 11a, 12–19]. Overall survival after total laryngectomy for salvage after chemoradiation is usually in the order of 40–50 % at 5 years [7–10]. It is notable that Forastiere et al. in their report on long-term results of RTOG 91–11, state that "integrating chemotherapy and conservation laryngeal surgery in selected patients with T3 disease warrants investigation. Our exploratory analysis of the outcome after salvage laryngectomy for patients receiving induction or concomitant chemotherapy suggests that early identification of patients who will eventually experience failure with nonsurgical therapy may be important for long-term survival" [11].

Probably because of higher attributable fractions to HPV, results of salvage for failure of chemoradiation for oropharyngeal cancers has improved over the last 15 years from 26 to 42 % at 5 years, with a complication rate of about 40 %. Remarkably, HPV-positive oropharyngeal cancers fare better when salvaged by

surgery than HPV-negative tumors [20]. In very selected cases, transoral robotic surgery for salvage of oropharyngeal cancers yields improved outcome, less morbidity, and improved quality of life [17].

In conclusion, salvage surgery is feasible and offers the best possibility for cure for the patient, provided that careful indication has taken place, flaps are used liberally and the team is vigilant as to immediate postoperative complications. The outcome is acceptable albeit moderate in terms of survival.

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Chapter 13
Recurrent/Metastatic Head and Neck Cancer: When and How to Irradiate

Shao Hui Huang, Nadeem Riaz, Nancy Lee, and Brian O'Sullivan

Introduction

The landscape of recurrent head and neck cancer (HNC) is evolving. On the one hand, emerging technologies (IMRT, IGRT, and IMPT) and new systemic agents (chemotherapy, biotherapy, and immunotherapy) provide potential new tools and opportunities to improve outcomes; on the other hand, the characteristics of recurrent tumors may be different in the contemporary era compared to what was typical historically. For example, there may be more radio-resistant clones in recurrences and more toxicity can be anticipated following initial more intensified treatment. Evidence suggests that survival is significantly reduced in patients who received previous concurrent chemoradiotherapy compared with patients who were CCRT-naïve (2-year overall survival [OS] rate, 10.8 % vs. 28.4 %; $p = 0.004$) [1]. In addition, emergence of HPV-positive oropharyngeal cancers is a confounder, since these tumors may have different outcomes after recurrence compared to traditional HNC [2–4] and treatment algorithms may require modification.

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General Considerations for Management of Recurrent/ Metastatic Head and Neck Cancer

Management of recurrent HNC is dictated by the initial treatment received, interval to recurrence, site (s) of recurrence (locoregional vs. distant), availability of salvage options in each institution, and patient performance status. For locoregional recurrences, radiotherapy can be given with curative or palliative intent, and in the definitive or adjuvant setting. The purpose of RT is to enhance tumor control, to palliate symptoms (e.g., bleeding, obstruction, and pain), and/or to prolong survival.

When making a salvage treatment decision, one needs to take into account factors from both the original treatment (s) and at the time of recurrence. Factors from initial treatment need to be carefully examined when planning salvage efforts, such as treatment modality, radiotherapy dose/volume, surgical technique and extent, and original anatomical disease extent. Factors at recurrence that need to be considered include: interval from initial treatment to recurrence, tumor location/size/volume/resectability, patient performance status and comorbidities, and local available resources, including expertise and supportive care. Treatment algorithms should aim at achieving a balance between treatment efficacy and normal tissue toxicities. The decision for salvage therapy must have a clear understanding of anticipated outcomes (overall prognosis) and must also involve and respect a well-informed patient's and family's decision and wishes.

Radiotherapy for Recurrence Arising from Radiation-Naive Field

Radiotherapy is an effective treatment if the recurrence is arising within a region without previous exposure to radiation. These scenarios include: recurrence after laser surgery alone for T1 glottic cancer or other ablative surgery alone for early stage oral cavity cancer, or out-of-field failure (e.g., failure in the contralateral neck lymph nodes following unilateral radiotherapy). RT is a plausible option for salvage and may be used as adjuvant (+/− systemic agent) treatment to facilitate the outcome of salvage surgery or as a primary salvage treatment, although published literature is limited in this setting.

Reirradiation for Recurrent Head and Neck Cancer

For cases with treatment failure within a previously irradiated volume, surgery is ordinarily the mainstay of salvage treatment and may require adjuvant reirradiation (reRT) with or without chemotherapy. Decisions regarding reRT should be made in a multidisciplinary setting with careful review of all clinical information, including

biopsy results, to rule out inflammation or fibrosis, imaging studies to assess disease extent, graphical representation of previous radiation volumes with dosimetry, and an appreciation of available treatment options in each institution. Caution must always be maintained in this setting since reRT may be associated with a high risk of egregious consequences [5–7] that may include carotid blowout, major pharyngeal and bone damage, or cartilage necrosis (a unique concern of reRT for recurrent laryngeal cancer).

The American College of Radiology Expert Panel on Head and Neck Cancer has emphasized the importance of patient selection and recommended evaluation and treatment at tertiary-care centers with a head-and-neck oncology team equipped with the resources and experience to manage the complexities and toxicities of re-treatment [8]. Optimizing the therapeutic ratio of reRT requires consideration of several strategies that may facilitate the goal of disease control with reduction of morbidity. One needs to review the prior management in detail and identify whether a patient would benefit from salvage treatment; the former should include RT specifics (dose, tissues treated previously, and the interval since prior treatment). The decision about proceeding must carefully address the present disease extent and will include the choice of treatment modality with specific details of the proposed reRT regimen including dose/fractionation, volume necessary to be irradiated, as well as the technique and accuracy of the proposed reRT delivery. Finally a decision is needed regarding appropriate use of combinations of systemic therapy including sequence, agents, and dosages.

Prognostic Factors with reRT

Re-treatment is associated with an increased risk of severe toxicity and impaired quality of life (QOL) with uncertain survival advantages [7, 9]. Both patient and tumor factors should be taken into account when considering reRT. Patients with higher performance status, younger age, and longer interval between initial treatment and progression represent the best candidates for reRT.

Studies on prognostic factors after reRT are often retrospective with limited sample size and selection bias, inclusion of various treatment regimens, and inadequate/inconsistent follow-up. Nonetheless, conclusions from such studies are informative though require careful evaluation and further validation. Tanvetyanon et al. [10] retrospectively reviewed 103 patients who had undergone reRT and identified that comorbidity and preexisting organ dysfunction were independent survival predictors after reRT (median survival was only 5.5 months for patients with both organ dysfunction and high comorbidity index vs. 59.6 months for neither). In addition, larger tumor bulk after salvage surgery and lower reRT dose (<=50 Gy) were adverse prognostic factors for survival. Hoebers et al. [7] reviewed 58 reRT patients and found that postoperative reRT (vs. primary reRT), treatment with RT only (vs. CRT), and longer interval (>3 years) from previous RT were positive prognostic factor for survival. Buglione et al. [11] reviewed 75 reRT patients and found that

KPS at reRT and reRT dose was an independent prognostic factor for OS. Oksuz et al. [12] reviewed outcome of 41 patients with recurrent nasopharyngeal cancer and found that total reRT dose, interval to recurrence ($p=0.03$), and T-category at recurrence were significant prognostic factor for survival. These results suggest that younger patient with higher performance status and earlier stage of recurrent tumor and longer interval between initial treatment and disease recurrence represents the best candidates for reRT.

To facilitate patient selection for reRT, several nomograms have been developed. Tanvetyanon et al. [10] developed a nomogram based on 103 reRT patients combining patient (comorbidity, organ dysfunction) and disease (isolated neck recurrence, tumor bulk, and time interval to recurrence) factors and showed a good concordance index (0.75) for predicting the probability of death within 24 months after reRT. Riaz et al. [13] reviewed 257 reRT (142 definitive and 115 adjuvant) for recurrent HNC patients and reported 2-year LRC 47 % and 2-year OS 43 %. A nomogram was developed to predict locoregional failure (LRF) at 2 years combining recurrent tumor stage, disease site, organ dysfunction, surgery, and RT dose; the concordance index was 0.68.

Strategies for Optimizing reRT

Optimizing therapeutic ratio needs to carefully balance tumor control and toxicities. If the goal of reRT is for disease control, a sufficient tumoricidal dose (e.g., total dose ≥50 Gy), preferably delivered in a continuous course to avoid tumor repopulation, should be considered. If the goal of reRT is for palliation of symptoms, larger fraction/shorter course with or without planned treatment break may be more appropriate. Generally, if a patient has distant failure at the time of reRT, the goal of reRT is typically palliative. However, for EBV-related nasopharyngeal cancer or HPV-related oropharyngeal cancer with limited distant metastatic disease, an aggressive reRT regimen might still be considered as a subset of such patients might achieve long-term survival or even cure [14–18].

Regardless of the goal of treatment, a major challenge is normal tissue tolerance. Several strategies might be considered to minimize late toxicities, such as smaller fraction size (e.g., twice daily [BID], 6 h apart), limited target volumes (e.g., treating recurrent volume with tighter margin without prophylactic volume), and employment of advanced reRT techniques (IMRT, IGRT, SBRT, IMPT).

Consideration of reRT Dose, Fraction, and Volume

Several randomized trials investigated the efficacy of reRT (Table 13.1) either in the adjuvant setting or in definitive settings and showed unsatisfactory outcomes. For resectable patients, salvage surgery is the treatment of choice. The question remains whether and when to give postoperative reRT. The GETTEC-GORTEC phase III

Table 13.1 Outcomes of Selected reRT trials with curative intent

	Setting	Outcomes
Janot et al. [19] GETTEC-GORTEC phase III trial (NCT00180934)	$n=130$ (65 each arm) Resectable recurrent HNC Sx + postoperative reRT (vs. Sx alone) Total 60 Gy: 2 Gy/fraction, 5 days/week for 5 days, six cycles after 9 days rest Conventional RT	Minimal FU: 2 years PO reRT arm had a higher LRC but similar OS (8 % tx-related deaths) Significantly more grade 3–4 late toxicity (39 % vs. 11 % at 2 years) Five treatment-related deaths
Spencer et al. [21] RTOG 9610 phase II trial	$n=79$ Unresectable recurrent HNC Definitive reRT (1.5 Gy per fraction bid x 5 days every 2 weeks x 4) + 5-FU/hydroxyurea Conventional RT	Minimal FU: 5 years 2-year OS: 16.9 % Late toxicity: grade 3: 19.4 %; grade 4: 3.0 %; grade 5: 0
Langer et al. [22] RTOG 9911 phase II trial (NCT00005087)	$n=105$ Unresectable recurrent HNC Definitive reRT (1.5 Gy per fraction bid x 5 days every 2 weeks x 4) + CDDP/paclitaxel/G-CSF Conventional RT	Median FU: 23.6 months 2-year OS: 25.9 % Late toxicities: grade 3: 16.9 %; grade 4: 16.9 %; grade 5: 3.6 %
Chen et al. [28] Prospective trial	$n=21$ Resectable or unresectable recurrent HNC or second primary IMRT with daily IGRT (MV CT) 66 Gy (range, 60–70 Gy) Postoperative RT: 11; definitive RT: 10	Median FU: 20 months 2-year OS: 40 % 2-year in-field control: 65 % 57 % had G-tube dependency at last FU
Cohen et al. [36] Phase I trial	$n=25$ Unresectable recurrent HNC Conventional RT 72 Gy/42f (1.8 Gy/f for the first 54 Gy; 1.5 Gy/day boost after 32.4 Gy) + tirapazamine and cisplatin	2-year OS 27 % One with grade 3 trismus and one with grade 3 otitis; one patient from each cohort experienced a fatal carotid hemorrhage.
Vargo et al. [37] Phase II trial	$n=48$ Unresectable recurrent HNC or in-field second primary SBRT (40–44 Gy/5f/1–2 weeks) plus cetuximab	Median FU: 18 months 1-year OS: 40 %; 1-year LRC: 37 % Grade 3 late toxicity: 6 %; no ≥ grade 4 toxicity

randomized trial (NCT00180934) [19] comparing postoperative reRT combined with chemotherapy after salvage surgery versus salvage surgery alone in 130 resectable recurrent HNC patients. The study found that full-dose reRT combined with chemotherapy after salvage surgery significantly improved locoregional control (LRC) (55 % vs. 20 % at 2 year), but had no significant impact on OS (around 40 % for both arms at 2 years). An increase in both acute and late toxicity was observed in the postoperative reRT arm. The severe late toxicity rate at 3 years was much higher in the postoperative reRT arm compared to surgery alone (39 % vs. 16 %). For the

surgery alone arm, 50 % of patients experienced subsequent LRF and 50 % were salvaged with reRT raising the possibility of close observation with delayed reRT (to delay reRT toxicity) as a reasonable alternative for such patients [20]. For unresectable LRF, reRT as definitive treatment combined with different chemotherapy regimens was investigated in RTOG 9610 [21] and RTOG 9911 (NCT00005087) [22] multi-institutional phase II trials. The 2-year OS was 17 % vs. 26 %, respectively. Although RTOG 9911 trial had a better OS versus RTOG 9610, the severe late toxicity was also higher (grade 4: 16.9 % vs. 3.0 %, grade 5: 3.6 % vs. none).

All three trials above reported significant late toxicities (Table 13.1). However, these trials all used conventional RT technique which may have contributed to inability to spare normal tissue. As well, reRT protocols in all three trials implemented planned treatment breaks between cycles which might have allowed tumor repopulation, thereby affecting treatment efficacy.

When selecting RT dose/fractionation, balancing the inconvenience of RT protraction versus the risk of late toxicity with short hypo-fractionation courses (e.g., stereotactic) needs to be considered. Although stereotactic radiosurgery (SRS) or stereotactic body irradiation (SBRT) is attractive option for reRT, the large fraction sizes employed are a concern for severe late toxicity. Owen et al. [23] reported long-term follow-up of stereotactic radiosurgery in 184 HNC patients, of whom 120 (65 %) were treated for recurrent HNC and detected late effects in 59 patients, the most common being temporal lobe necrosis (15 patients). From the radiobiology point of view, smaller fraction sizes are beneficial for protecting normal tissue from late toxicity [24]. Cvej et al. [25] reported relatively hyper-fractionated SBRT (48 Gy in 16 fractions, twice daily, 6 h apart) for 40 recurrent HNC patients treating recurrent gross tumor (GTV) with only a 3 mm margin for RT coverage without any prophylactic nodal volume. One-year OS and LC were 33 % and 44 %, respectively. Mandibular osteoradionecrosis occurred in four cases (10 %); however, neither carotid blowout syndrome nor other grade 4 late toxicity occurred. This supports a benefit for smaller fraction size in reducing late toxicities.

Consideration of reRT Technique

IMRT has shown promising possibilities in improving therapeutic ratio on the reRT setting. The potential advantages of IMRT include more conformal dose distribution to an irregularly shaped tumor resulting in less tumor under-dose, higher tumoricidal doses can be given due to normal tissue sparing, and more accurate RT delivery under daily image guidance. Target delineation is an important aspect in IMRT. reRT target volume definition has varied among institutions. Lee et al. [26] analyzed 105 recurrent HNC patients who underwent reRT, of whom 74 (70 %) were treated with IMRT. IMRT targets included GTV with 1.0–2.0 cm expansion for RT coverage without treating any subclinical volume. The 2-year LRC was 52 % for the IMRT cohort compared to 20 % in the non-IMRT cohort, a result confirmed in multivariable analysis for LRF (IMRT vs. non-IMRT HR 0.37, $p = 0.006$). Grade 3 or 4 late toxicities occurred in 12 (11 %) patients. Sher et al. [9] reported efficacy and toxicities of

35 recurrent HNC treated with IMRT with concurrent chemotherapy. The median RT dose was 67.5 Gy. The clinical target volume (CTV) included 1.0–1.5 cm expansion from GTV for RT tumor coverage and another 0.5 cm expansion for PTV. The 2-year OS and LRC rates were 48 % and 67 %, respectively, an improvement from historical data. However, approximately 46 % of patients developed at least one late grade 3 toxicity, and four (11 %) late deaths occurred in patients without evidence of disease (two aspiration events, one oropharyngeal hemorrhage, and one infectious death). The potential reason for the late toxicity might be the large RT margin used for CTV and PTV. Popovtzer et al. [27] reported patterns of failure of 66 patients (44 definitive reRT and 22 adjuvant reRT) after either 3D conformal or IMRT with recurrent GTV (rGTV) plus a 0.5 cm margin for RT coverage without an additional prophylactive nodal volume or coverage for subclinical disease in the vicinity of the rGTVs and found 45/47 LRF were in-field and only two (4 %) LRF were out-of-field. The 2-year OS was 45 %, suggesting that tighter margins without a prophylactive volume seem reasonable. Chen et al. [28] conducted an institutional prospective trial of 21 patients for IMRT with daily IGRT (MV CT) using tight CTV and PTV margin design. The CTV was a 0.5 cm expansion from GTV, and the PTV was a 0.3 cm expansion from CTV. The 2-year OS was 40 %, and the 2-year in-field control was 65 %. Toxicity seemed acceptable. There were no treatment-related fatalities or hospitalizations. Curtis et al. [29] reported the reRT outcome of 81 patients treated at the Mayo clinic, of whom 77 (95 %) received IMRT but the margin of the target volume was not described. Two-year LRC was 60 %, and 2-year OS was 53 % for adjuvant reRT and 48 % for definitive reRT. Late serious toxicity was uncommon but included osteoradionecrosis (two patients) and carotid artery bleeding (one patient, nonfatal).

Proton therapy offers theoretical advantages for normal tissue protection for reRT owing to its sharper dose falloff characterized by the Bragg peak. The clinical evidence for its role is emerging. Romesser et al. [30] reported early promising result of proton reRT for 85 oropharyngeal cancer patients (39 % postoperative reRT and 61 % definitive reRT). With a median follow-up of 13 months, the 1-year LRC was 75 % and 1-year OS was 65 %. Grade 3 or greater late skin and dysphagia toxicities were noted in six patients (8.7 %) and four patients (7.1 %), respectively. Two patients had grade 5 toxicity due to treatment-related bleeding. However, longer follow-up is needed to make any final deductions.

Brachytherapy, essentially the most sparing and traditional form of local RT delivery process available, is a plausible modality for use in reRT protocols. It delivers radiotherapy by positioning radioactive sources in direct proximity to the tumor target area. The advantage of brachytherapy is its highly conformal dose distribution to a small target area by virtue of a rapid “falloff” within surrounding normal tissues. It can be used alone or after surgery and as a local boost in combination with external-beam radiation therapy for salvage of small recurrences. No randomized trials have been performed comparing brachytherapy versus other conventional treatment in HNC. The 2-year OS rates for reRT with brachytherapy approaches from retrospective series vary from 17 to 71 % [31]. The large variation in results is potentially a consequence of cohort heterogeneity and case selection in reported series.

Table 13.2 Outcome of intraoperative reirradiation for recurrent HNC

	Techie et al. [34] (MSKCC, New York)	Scala et al. [33] (Beth Israel)	Chen et al. [35] UCSF
Cohort	*N* = 57, 1998–2011 IORT 15 Gy (12–20)	*N* = 76, 2001–2010 IORT: 12 Gy for margin (−); 15–17.5 Gy for margin (+)	*N* = 137, 1991–2007 IORT: 15 Gy (10–18)
Median FU	16 m (1.3 years)	11 m (0.9 years)	41 m (3.4 years)
OS	1 year 75 %	1 year 64 %	3 years 36 %
In-field PFS	1 year 67 %	1 year 66 %	3 years 67 %
LRC	1 year 63 %	1 year 88 %	3 years 51 % **Margin +ve predict local failure*
DC	1 year 74 %	1 year 32 %	3 years 46 %
Toxicity	No G4 or G5 late tox G3 late tox: 16 % Dysphagia: 6 Nerve injury: 2 Fistula: 1	No perioperative deaths Nonfatal carotid hemorrhage: 1 Vagal neuropathy: 1	No perioperative deaths Wound infection: 4 Orocutaneous fistula: 2 Flap necrosis: 1 Trismus: 1 Neuropathy: 1

An exploratory brachytherapy approach for recurrence is intraoperative radiotherapy (IORT). IORT delivers radiation directly to the tumor bed immediately following surgical resection. The hypothetical advantages of IORT are its capability to deliver high single fraction doses to a specific target with high precision, thus protect surrounding normal tissue and faster treatment times between surgery and adjuvant reirradiation. The latter may combat the deleterious influence of tumor cell proliferation during the overall management duration and potentially make the best use of the residual vascularized condition of tissues immediately following surgery to maximize tumor control [32]. It is often combined selectively with external-beam RT and concurrent or induction systemic approaches. Several institutions have reported institutional experience in highly selected cases [33–35] (Table 13.2). However, this approach requires local expertise and very close cooperation between surgical and radiation teams, in addition to significant functional and rehabilitation support. Currently it remains investigational within centers with expertise in these approaches.

Conclusion

Treatment for recurrent HNC is determined by the original treatment administered, tumor and patient factors at recurrence, in addition to the infrastructure, skill, and resources available. For RT-naïve recurrences, RT is a potentially valid option. For previously irradiated cases, reirradiation is a valid option for salvage either as an

adjuvant to enhance the result of salvage surgery or as a definitive treatment but must balance efficacy versus toxicity. The major challenge of reRT is to mitigate severe late toxicity. Evidence regarding efficacy and clinical benefit is sparse with very few prospective trials, and most reports are retrospective and characterized by small sample size. reRT regimens (dose/fractionation, volumes) vary among institutions which make comparison and recommendations difficult. Several strategies may be useful and are derived from low-level clinical evidence. Generally adequate doses are needed using total doses ≥50 Gy for tumor control with conventional fractionation as continuous courses to enhance LRC by avoiding tumor repopulation or using short course high dose per fraction regimens precisely delivered stereotactically to small volumes, but recognizing the potential adverse normal tissue effects of higher than normal dose fractions. More traditionally, sparing of normal tissue may be enhanced by using smaller than normal fraction sizes administered more than once daily which might provide a chance to reduce late toxicity in addition to limited target volumes delivered by brachytherapy (conventionally or with IORT) or with newly emerging RT technologies (e.g., IMRT, IGRT, and IMPT). Novel approaches, such as combinations with new systemic agents, and/or immunotherapy, need to be explored. Higher levels of evidence are needed to further improve treatment outcomes for these patients.

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Chapter 14
Systemic Treatments: Chemotherapy and Targeted Therapies

Jean-Pascal Machiels and Sandra Schmitz

Introduction

Squamous cell carcinoma of the head and neck (SCCHN) afflicts an estimated 600,000 patients annually worldwide and is the seventh most common cancer. Less than 50 % of the patients with locoregional advanced disease (American Joint Committee on Cancer (AJCC) stages III, IV) remain free of disease at 3 years despite aggressive multimodal local therapy with surgery and/or chemoradiation [1–3].

Cancer that recurs after multimodal local treatment and not amenable to salvage surgery (Chap. 12) or radiation (Chap. 13) is considered incurable (median survival around 10 months) [4, 5]. Different prognosis factors for patients with palliative SCCHN have been identified. In two phase III trials from the Eastern Oncology Cooperative Group (E1393 and E1395) that investigated platinum-based chemotherapy, the following parameters were associated with a poor survival in the multivariate analysis: weight loss more than 5 %, Eastern Oncology Cooperative Group performance status (ECOG PS) >0, well and moderate differentiated tumor, primary tumor localized in the oropharynx and oral cavity, and prior radiation therapy [6]. Patients with ≥3 of these parameters had a median survival of 6 months compared with patients with ≤2 of these parameters who had a median overall survival of 2 years. Alcohol and tobacco are still responsible for the majority of SCCHN. Another cause of oropharyngeal cancer that increases in incidence is the human papillomavirus (HPV). HPV-positive and negative tumors are different entities based on differences in their clinical and molecular behaviors [7]. The prognosis of HPV-positive SCCHN is better than HPV-negative tumor even in case of relapsing disease [8].

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Argiris and colleagues analyzed 64 patients for HPV (hybridization in situ) and 65 for p16 (immunochemistry). The objective response rate was 55 % for HPV-positive versus 19 % for HPV-negative ($P=0.022$), and 50 % for p16-positive versus 19 % for p16-negative ($P=0.057$) [9].

In this chapter, we review the systemic treatment available to treat these patients including chemotherapy and targeted therapies. We will not discuss the novel immunotherapies that are the topic of Chap. 15.

What Evidence Supports That Palliative Chemotherapy Improves Overall Survival?

Platinum-based chemotherapy is the backbone of systemic treatment in SCCHN. Platinum-based chemotherapy in the palliative setting gives objective response rate (ORR) in around 30 % [4, 10–12].

Palliative SCCHN cancer has a median OS ranging between 6 and 10 months and only 20–40 % of the patients are still alive at 1 year [4, 10, 11]. Although cetuximab improves overall survival when associated with chemotherapy, it is still debatable if chemotherapy without a targeted agent increases survival versus best supportive care (BSC) [4, 5].

Morton and colleagues conducted two phase III trials [13–15]. The first compared BSC ($n=26$) versus bleomycin alone ($n=22$) versus cisplatin alone ($n=38$) versus cisplatin plus bleomycin ($n=30$). The second compared methotrexate alone ($n=30$) versus cisplatin alone ($n=32$) versus cisplatin plus methotrexate ($n=32$) versus cisplatin plus 5-fluorouracil (5-FU) ($n=30$). The conclusions from these trials were that cisplatin significantly improved overall survival compared with BSC by 10 weeks, that cisplatin was better than bleomycin or methotrexate when these latter two drugs are used as a single agent, and that cisplatin monotherapy (median survival: 160 days) was at least as effective as the platinum-based combinations. Even if it seemed that some patients could derive individual benefit from chemotherapy, these two trials, with less than 40 patients in each group, were clearly underpowered to definitively answer the question regarding a potential increase in OS due to chemotherapy. No other trials comparing chemotherapy with BSC have been performed subsequent to these studies, and therefore this question remains definitively unanswered.

Single-Agent Activity

The most frequently used agents are platinum compounds, methotrexate and taxanes. Cisplatin monotherapy reported ORR ranging between 14 and 41 % [16, 17]. Although no randomized trials have demonstrated that methotrexate can increase overall survival (OS) compared with BSC, this drug is still frequently used in the clinic as first-line palliative treatment in patients judged unfit for cisplatin-based chemotherapy or as second line when the disease progresses after platinum-based

therapy. The ORR varied between 1.3 and 77 % depending on the dose used and the treatment lines [5, 16–20].

Taxanes have promising activity in SCCHN with ORR between 13 and 42 %. In the palliative setting, however, no studies to date have been able to demonstrate that paclitaxel or docetaxel are better than BSC or the older cytotoxics (cisplatin or methotrexate) [21–24].

Some activity has been also detected with other cytotoxics and this has been reviewed elsewhere [16].

Combination Therapy

The most frequent studied combination is cisplatin (100 mg/m^2 day 1, every 3 weeks) and 5-FU (1000 mg/m^2/day, days 1–4 over 96 h). A meta-analysis performed in the pre-taxane era suggested that the combination of cisplatin plus 5-FU was better than other combinations and therefore many considered this regimen to be the standard of care [12].

Randomized trials compared monotherapy versus polychemotherapy regimens (Table 14.1) [11, 25–27]. All of these trials included an arm in which patients were treated with the combination of cisplatin and 5-FU. The key messages from these studies include the following: polychemotherapy produces a significantly higher

Table 14.1 Selected studies investigating polychemotherapy versus monochemotherapy

Regimens	*N*	ORR (%)	Median survival (months)	Reference
Cisplatin/5-FU	249	32 %	5.5 months	[26]
vs.				
Cisplatin		17 %	5 months	
vs.				
5-FU		13 %	6.1 months	
Cisplatin/methotrexate/bleomycin/vincristine	382	34 %	8.2 months	[25]
vs.				
Cisplatin/5-FU		31 %	6.2 months	
vs.				
Cisplatin		15 %	5.3 months	
Cisplatin/5-FU	277	32 %	6.6 months	[11]
vs.				
Carboplatin/5-FU		21 %	5 months	
vs.				
Methotrexate		10 %	5.6 months	
Cisplatin/pemetrexed	795	12.1 %	7.3 months	[27]
vs.				
Cisplatin		8 %	6.3 months	

ORR objective response rate

ORR than monotherapy, 21–34 % versus 10–17 %. Overall survival is not improved by polychemotherapy and is low ranging between 5 and 8.2 months. Carboplatin may be less effective than cisplatin in SCCHN, based on the results of Forastiere and colleagues, who compared the combination of cisplatin plus 5-FU to that of carboplatin plus 5-FU with an ORR of 32 % and 21 %, respectively. A four-drug regimen is not superior to a two-drug regimen in terms of ORR or OS. Finally, an improvement in ORR is possible but at the cost of higher toxicity in the combination arms. Altogether, these data suggest that monotherapy with cisplatin or methotrexate is still a valid option for patients with poor performance status or low disease burden or those who are frail or altered.

The cisplatin plus paclitaxel combination was also compared with cisplatin plus 5-FU in a randomized phase III trial, but this trial showed no significant difference in OS or response rate (ORR: 22 and 29 %; median OS: 9 and 8 months, respectively) [10].

Epidermal Growth Factor Receptor (EGFR) Inhibition

The epidermal growth factor receptor (EGFR) is a member of the HER tyrosine kinase growth factor receptor family. Its expression is frequently dysregulated in SCCHN and leads to a poorer prognosis [28].

The most studied EGFR inhibitor in SCCHN is cetuximab [29]. Cetuximab is a chimeric IgG1 monoclonal antibody that specifically binds to the EGFR with high affinity. Cetuximab has been studied in phase III trials in combination with chemotherapy and significantly improves survival when added to the combination of cisplatin and 5-FU or carboplatin and 5-FU [4]. In this study, the ORR was 20 % in the chemotherapy arm alone and 36 % in the chemotherapy plus cetuximab group with a median survival of 7.4 and 10.1 months, respectively (Table 14.2).

Interestingly, cetuximab has been investigated in combination with paclitaxel (80 mg/m^2) in the first-line treatment of recurrent and/or metastatic SCCHN [30]. Overall response rate was 54 % with 22 % complete responses and a disease control rate of 80 %. Median progression-free and overall survival times were 4.2 and 8.1 months, respectively. Cetuximab was also investigated in three phase II trials in patients who progressed on cisplatin or carboplatin-based chemotherapy [29]. The median time to disease progression ranged between 2.2 and 2.8 months, and the median overall survival ranged between 5.2 and 6.1 months. No patients who progressed on cetuximab alone responded to additional platinum. These survival data compared favorably with those from a retrospective study that investigated best supportive care or chemotherapy in this setting (median survival, 3.4–3.6 months).

Panitumumab and Zalutumumab are two other monoclonal antibodies that target the EGFR [5, 31]. A phase III trial compared cisplatin plus 5-FU with or without panitumumab [31] (Table 14.2). Panitumumab did not significantly improve the OS (median: 11.1 months versus 9.0 months, $p=0.14$), the primary endpoint, but did yield significantly higher ORR (36 % versus 25 %; $p=0.007$) and PFS (5.8 months vs. 4.6 months; $p=0.004$). An unplanned analysis of the results stratified by tumor p16 status suggested that panitumumab improved OS and PFS in patients with p16-negative tumors but not

Table 14.2 Selected phase III trials investigating EGFR or pan-HER inhibitors

Regimens	N	Median PFS (months)	Median survival (months)	Reference
[a]Platin/5-FU	442	3.3 months	7.4 months	[4]
versus				
Platin/5-FU/cetuximab		5.6 months	10.1 months	
[a]Cisplatin/5-FU	667	4.6 months	9 months	[31]
versus				
Cisplatin/5-FU/panitumumab		5.8 months	11.1 months	
[b]Methotrexate	483	1.7 months	6 months	[18]
versus				
Afatinib		2.6 months	6.8 months	

PFS progression-free survival
[a]First treatment line
[b]Second treatment line

in those with p16-positive. Zalutumumab did not improve overall survival versus BSC or methotrexate (6.7 versus 5.2 months, $p=0.06$) in palliative SCCHN that progressed after platinum therapy but significantly prolonged PFS ($p=0.001$) [5].

EGFR tyrosine kinase inhibitors are orally available small molecules. The two main compounds are erlotinib and gefitinib. Gefitinib has been investigated in two phase III trials in palliative patients but did not show any survival benefit. The first trial compared gefitinib to methotrexate and the second investigated docetaxel plus gefitinib versus docetaxel plus placebo [20, 32].

Human Epidermal Receptors (HER) Inhibition

A minority of patients will benefit from anti-HER or anti-EGFR therapy. Blocking the other receptors of the HER family is one approach to try to overcome anti-EGFR therapy resistance.

A second generation of HER inhibitors, the irreversible small molecule pan-HER inhibitors including afatinib and dacomitinib, has been developed [18, 33]. By covalently binding and irreversibly blocking all kinase receptors from the ErbB family, a prolonged inhibition is obtained with the aim of improving clinical activity. The phase III trial LUX-Head and Neck 1 randomized 483 patients with recurrent and/or metastatic SCCHN progressing after first-line platinum regimens to oral afatinib (40 mg/day) or intravenous methotrexate (40 mg/m^2/week) [18]. Afatinib significantly improved PFS versus methotrexate (median 2.6 vs. 1.7 months; $p=0.030$), without significant improvement in OS (Table 14.2).

The IgG1 antibody MEHD7945A blocks EGFR- and HER3-mediated signaling and mediates ADCC [34]. A phase I study of 36 patients showed promising safety profile and evidence of antitumor activity [35]. Best response included two partial responses in SCCHN and six stable diseases lasting more than 8 weeks (two non small-cell lung cancer and four colorectal cancer). Seven out of eight patients were

previously treated with EGFR inhibitors. A randomized phase II trial compared MEHD7945A to cetuximab in patients with recurrent/metastatic SCCHN that progressed during or shortly after platinum-based chemotherapy. No difference between the two arms could be detected in this trial [36].

Predictive Biomarkers for Therapies Targeting the HER Family

In SCCHN, we are lacking predictive biomarkers to predict treatment activity or resistance. Hypotheses to explain anti-EGFR resistance include the acquisition of oncogene activating mutations, activation of alternative signaling growth pathways, or modifications in tumor composition.

The majority of the trials support the hypothesis that anti-EGFR or anti-HER therapies are more active in p16-negative and HPV-negative SCCHN [18, 31, 36] (Table 14.3). Only the EXTREME trial suggested that the survival benefit of chemotherapy plus cetuximab over chemotherapy could be independent of tumor p16 and HPV status [37]. However, all these analyses are impaired by the low number of patients in the subgroups investigated, the different cutoff used among the studies to assess p16 positivity, and the fact that the significance of p16 positivity is probably different in oropharynx cancer compared with the other SCCHN subsites.

Table 14.3 p16 as a predictive biomarker of EGFR or HER inhibitors

Regimens	*N*	Population	Benefit	Reference
Platin/5-FU	p16+=18 p16−=178	Recurrent/metastatic: first line	p16−: HR: 0.82 (OS)	[37]
versus				
Platin/5-FU/ cetuximab	p16+=23 p16−=162		p16+: HR: 0.63 (OS)	
Cisplatin/5-FU	p16+=57 p16−=179	Recurrent/metastatic: first line	p16−: HR: 0.73 (0S)	[31]
versus				
Cisplatin/5-FU/ panitumumab	p16+=42 p16−=165		p16+: HR: 1 (OS)	
Methotrexate	p16+=31 p16−=141	Recurrent/metastatic: second line	p16−: HR: 0.69 (PFS)	[18]
versus				
Afatinib	p16+=11 p16−=42		p16+: HR: 0.95 (PFS)	

PFS progression-free survival, *OS* overall survival, *HR* hazard ratio

Recently, the biomarker analysis of the LUX-Head and Neck 1 has been presented [38]. A more pronounced progression-free survival benefit with afatinib versus methotrexate was observed in p16-negative versus p16-positive, PTEN-high versus PTEN-low, and HER3-low versus HER3-high disease. A trend towards prolonged progression-free survival was also observed with afatinib in EGFR-amplified tumors. These data need further validation in prospective trials.

Novel Targets and Biomarker-Driven Clinical Trials

Recently the Cancer Genome Atlas project has given new insights about the molecular aberrations of SCCHN [39]. Several genetic alterations are actionable in HPV-negative tumor: *EGFR* amplification (15%), *CCDN1* amplification (20–30%), *PI3KCA* amplifications or mutations (34%), activations of one of the *FGFR* genes (10%), *HRAS* mutations (4%), etc. In HPV-negative tumor, SCCHN tumor cells also harbor alterations (p16 loss and cyclin D1 overexpression) that enable them to circumvent the mitotic checkpoints through impaired cyclin-dependent kinase (CDK) activities, supporting the investigation of CDK4/6 inhibitors. In contrast, the most frequent targetable genetic alteration in HPV-positive tumor is the presence of hotspot *PI3KCA* mutations.

Different targeted therapies have been investigated in SCCHN. Even if some patients experience durable and meaningful clinical response, the activity of these compounds remains low in a large unselected SCCHN population [40]. Identification of predictive biomarkers able to identify the subgroups of patients that are the most likely to respond to all these novel therapies will help to tailor treatment and will avoid to expose some patients to noneffective and expensive compounds.

To address these issues, several new designs for clinical trials are currently proposed with the aim being to use more precise genetic diagnostics to allow a better selection of patients. Among them, « umbrella trials » are trials that, within the same protocol, divide the patients in multiple biomarker subgroups based on the genetic alterations identified in their own tumor. The activity of a drug targeting a specific biomarker is investigated in each subgroup. These approaches have been successfully implemented in some cancers (I-SPY and SAFIR-01 in breast cancer, Master Protocol and ALCHEMIST in lung cancer, and FOCUS4 in colorectal cancer) but still need to be implemented in SCCHN [41]. One of the drawbacks of this last approach is the spatial and temporal heterogeneity of the tumor.

Conclusions

Patients with relapsing SCCHN should be first evaluated for potentially curative treatment options such as re-irradiation, surgery or, in selected cases, metastasectomy. However, despite these approaches, the prognosis remains poor.

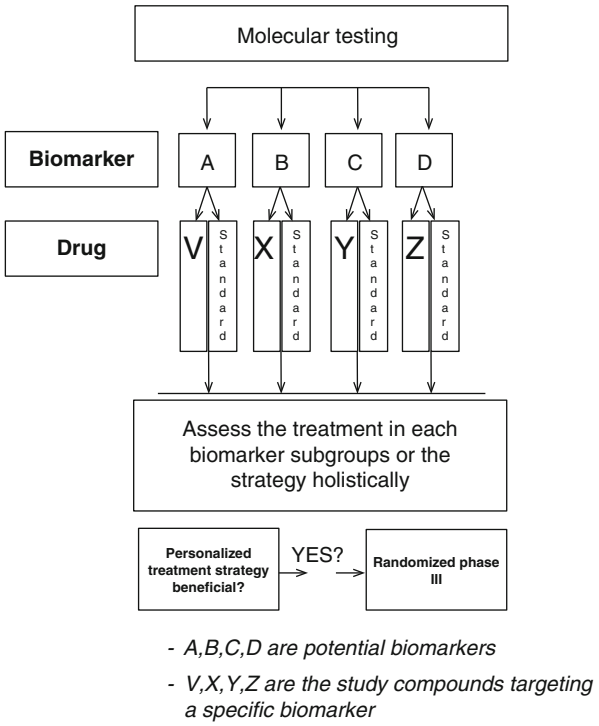

Fig. 14.1 Example of the design of an umbrella trial

Patients with SCCHN not amenable to curative treatment have a dismal prognosis with a median survival of between 6 and 10 months. Cetuximab in combination with platinum improves overall survival but all the patients develop rapidly treatment resistance. Immunotherapy with PD-1/PD-L1 pathway inhibitors has shown promising activity in early clinical trials and will probably become a standard treatment for recurrent SCCHN (Chap. 15).

Some patients are also subject to many local problems that interfere with swallowing, breathing, and speaking, and these have a significant impact on quality of life. Therefore, it is of utmost importance that the multidisciplinary team maintains regular follow-up of these patients to adequately evaluate the consequences of disease recurrence and provide the best supportive care.

A better understanding of the molecular mechanisms involved in treatment resistance and identification of predictive biomarkers are crucial to improve treatment outcome (Fig. 14.1).

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Chapter 15
Immunotherapeutic Approaches

Petr Szturz and Jan B. Vermorken

One Hundred Fifty Years of Progress

Not many fields in medicine have seen so sharp fluctuations in attitude of healthcare professionals as cancer immunotherapy. Since the second half of the nineteenth century, there have been several fundamental discoveries leading to either an increase or decrease in its popularity [1, 2]. The first report to document the intriguing involvement of the immune system in cancer development was published more than 150 years ago. In 1863, Rudolf Virchow described immune infiltrates in neoplastic tissues. This finding gave at the same time early evidence for the origin of cancer at sites of chronic inflammation [3]. However, it was not until 1890s that a serious attempt at cancer immunotherapy was made. In 1893, based on a series of ten cases, William B. Coley confirmed that the phenomenon of cancer remission, occasionally occurring in patients with feverish infections, could be reproduced by injecting streptococcal cultures in and around tumours [4]. Subsequently, about 900 patients, mostly diagnosed with inoperable sarcomas, received the "Coley's toxin", but due to severe accompanying fevers and the low perceived cure rates, this approach remained purely experimental [5]. Thus, despite initial high hopes, the following five decades were marked by growing scepticism and even the prophetic hypothesis about tumour recognition by the immune system conceptualized by Paul Ehrlich in 1909 did not receive much attention [6].

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A major turning point came in the late 1950s. Based on tumour transplantation models, Thomas and Burnet resurrected the Ehrlich's theory by postulating the existence of tumour-associated antigens as a mechanism of the so-called immunosurveillance recognizing and eliminating malignant cells [7, 8]. Nevertheless, this promising era ended soon after it began, in the early 1970s. Owing to the lack of strong experimental evidence in favour of the hypothesized immunosurveillance, the prevailing notion questioned the role of the immune system in cancer prevention, which was also supported by observations of athymic nude mice exhibiting a normal incidence of tumours [1]. Gradually, with advances in medicine, several multifunctional cytokines entered clinical testing as anticancer drugs such as interleukin-2 in 1983, interferon-α in 1985 and tumour necrosis factor-α in 1992 [9–11]. During that period, emerging data on tumour-associated antigens ushered immunotherapy to the forefront of cancer research once again [1]. In 1985, adoptive cell transfer was used for the first time and further developed thereafter [2, 12]. Twenty years later, vulvar intraepithelial neoplasia was successfully treated with the topical immune-response modulator imiquimod and by vaccination against human papillomavirus (HPV)-16 oncoproteins, followed by the approval of sipuleucel-T vaccine for prostate cancer therapy [13–15]. However, the real breakthrough in cancer immunotherapy took place with the introduction of immune checkpoint inhibitors in metastatic melanoma. In 2010, a phase III trial demonstrated an improvement of overall survival by 3.5 months achieved by ipilimumab, an anti-cytotoxic T-lymphocyte antigen-4 (CTLA-4) monoclonal antibody, compared with a glycoprotein 100 (gp100) peptide vaccine [16]. This was for the first time in history that a randomized trial proved a significant survival benefit in these patients. Moreover, it opened up new avenues for anticancer research in various other malignancies including head and neck cancer.

This chapter focuses on the applicability of immunotherapy for recurrent and/or metastatic squamous cell carcinoma of the head and neck (R/M-SCCHN), highlights the recent progress made in just a few years and outlines some of the associated challenges and hurdles to overcome.

Cancer-Immunity Cycle and Immunoediting

Throughout the multistep evolution of cancer, accumulating genomic instability leads to the acquisition of sustained proliferative signalling, evasion of growth suppressors, resistance to cell death, replicative immortality, angiogenesis, invasion and metastasis. Recently, two additional hallmarks have been suggested. According to the first one, cancer cells can reprogram cellular metabolism to gain energy for proliferation. The second enables them to avoid immune destruction, particularly by T and B lymphocytes, macrophages and natural killer cells [17]. Consequently, to prevent such immune evasion, a series of stepwise events, referred to as the cancer-immunity cycle, must be accomplished. Initially, dendritic cells capture and process neoantigens released by cancer cells. The captured antigens are presented on major

histocompatibility class I and II (MHC I and MHC II) molecules to T lymphocytes. In the next step, priming and activation of effector T-cell responses against cancer-specific antigens takes place in the lymph nodes. This represents a critical point for the final immune response, controlled by the balance between effector and regulatory T lymphocytes. Afterwards, the activated effector T cells infiltrate the tumour bed and kill cancer cells through the interaction of the T-cell receptor with the cognate antigen bound to MHC I on the neoplastic elements. As a result, additional tumour-associated antigens are released, amplifying and propagating the cancer-immunity cycle. Altogether, this process represents the executive arm of the immunosurveillance system. At each step, it is controlled by multiple regulatory feedback loops to ensure efficacy and protect from autoimmune reactivity [18, 19].

However, with the beginning of the new millennium, it became clear that the concept of immunosurveillance does not fully explain the complex interplay between cancer and immunity. In 2001, the seminal work of Shankaran et al. showed that the immune system can promote the development of tumours with reduced immunogenicity allowing them to escape immune recognition [20]. Thus, immunosurveillance represents just a part of a broader, dynamic process known as cancer immunoediting that is capable not only of preventing but also of sculpting/promoting the formation and growth of neoplastic tissue. These dual opposing functions cross at a point of balance, so that three phases of immunoediting can be recognized. The first, elimination phase corresponds to immunosurveillance, when transformed cells are eradicated by the innate and adaptive immune responses. The second, equilibrium phase is at the balance point. The tumour persists in a subclinical stage, restricted from expansion. Finally, when immune exhaustion or inhibition occurs or when there is an outgrowth of aggressive tumour cell variants evading immune pressure, the third phase begins leading to clinically overt disease. Importantly, non-immunogenic malignant cells enter directly this escape phase [21]. The mechanisms of immune evasion are summarized in Table 15.1 [22, 23].

Table 15.1 Mechanisms of immune escape in cancer [22, 23]

Mechanism	Specification
1. Reduced antigen processing and presentation	Downregulation or mutation of HLA class molecules
2. Tumour-permissive cytokine profile	Increase of immunosuppressive cytokines: TGF-β, IL-6 Decrease of stimulatory cytokines: IL-2, IFN-γ
3. Immunosuppressive microenvironment	Production of IDO
4. Cellular immune escape	Tregs, M2 macrophages, MDSCs
5. Anergic T cells 5a. by increase of co-inhibitory receptors 5b. by decrease of co-stimulatory receptors	 CTLA-4, PD-1, TIM-3, LAG-3 CD137, OX40

HLA human leukocyte antigen, *TGF-β* transforming growth factor-beta, *IL* interleukin, *IFN-γ* interferon-gamma, *IDO* indoleamine 2,3-dioxygenase, *Tregs* regulatory T cells, *MDSC* myeloid-derived suppressor cells, *CTLA-4* cytotoxic T-lymphocyte antigen-4, *PD-1* programmed death-1, *TIM-3* T-cell immunoglobulin mucin protein-3, *LAG-3* lymphocyte-activation gene-3

Immune Checkpoint Inhibitors

Cancer immunotherapy is based on functional restoration of certain signalling pathways of the host immune system that help counteract immune escape of neoplastic tissue. After being recognized as foreign, the tumour can be eliminated. In broad terms, immunotherapy encompasses a variety of diverse treatment approaches like tumour-specific monoclonal antibodies (e.g. cetuximab, bevacizumab), cancer vaccines (e.g. peptide vaccine against HPV, sipuleucel-T), adoptive cell transfer (e.g. autologous tumour-infiltrating lymphocytes, chimeric antigen receptors) and immune-modulating antibodies (e.g. immune checkpoint inhibitors) [24]. The current chapter details the last group, immune checkpoint inhibitors. These drugs, blocking the inhibitory signalling, have brought a fundamental shift in the field of precision medicine, mainly due to their potential to induce durable responses even in patients with refractory disease and cause relatively low incidence of serious adverse events. Tumour-specific antibodies are traditionally excluded from chapters on immunotherapy and are being covered elsewhere, and the remaining two categories are in early phases of clinical testing in head and neck cancer.

By means of receptor-ligand interactions, immune checkpoint pathways regulate the duration and extent of immune system activity to prevent autoimmune reactions. CTLA-4, a receptor expressed on CD4+, CD8+ and regulatory T cells, competitively disrupts the axis between tumour-specific T lymphocytes bearing CD28 receptor and stimulatory ligands CD80 (B7) and CD86 (B70) on antigen-presenting cells. Programmed death-1 (PD-1) is a receptor exposed on the surface of activated T and B lymphocytes and myeloid elements. Programmed death ligand-1 (PD-L1/CD274/B7-H1) and programmed death ligand-2 (PD-L2/CD273/B7-DC) are transmembrane proteins found on a wide variety of cells transmitting a negative signal down-regulating T-lymphocyte activation. An impaired immune recognition may thus occur in case of a high fraction of CTLA-4 or PD-1 positive T cells in the tumour microenvironment or an increased expression of PD-L1 or PD-L2 by the tumour itself. Importantly, while PD-1 is a receptor for both PD-L1 and PD-L2 ligands, PD-L1 binds also to B7-1 receptor located on T cells. Consequently, although PD-1 blockage interferes with interactions between PD-1 and its two ligands, PD-L1 can still activate B7-1 receptor [23, 25].

During the application of immune checkpoint inhibitors, practitioners may encounter two specific situations concerning the distinctive kinetics of antitumour response and the characteristic, immune-related side effects. First, pseudoprogression, rare in SCCHN patients, describes a transient clinical phenomenon detectable early after treatment onset. Although resembling true neoplastic growth, it merely reflects inflammatory changes generated by immune cell infiltration. In addition, compared to classic cytotoxic agents, immunotherapy often elicits delayed responses as it may take some time to unlock the natural anticancer potential of the immune system. Consequently, this modality may not be appropriate for patients with rapidly progressive, symptomatic disease, who require prompt relief. Moreover, such a unique behaviour of cancer upon exposure to immunotherapy warrants specific

immune-related response criteria, since traditional measurement guidelines do not allow for treatment beyond initial progression [26, 27]. Based on survival analysis of 592 melanoma patients treated with pembrolizumab, Hodi et al. showed that conventional Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST v1.1) might underestimate the benefit of pembrolizumab in about 15 % of cases [28].

Secondly, autoimmune reactions affect a significant proportion of patients and appear usually 6–12 weeks following therapy initiation. The most frequent are endocrinopathies (hypophysitis, thyroiditis, adrenal insufficiency), diarrhoea, colitis and maculopapular rash, but they also include general symptoms like fevers, chills, and lethargy, hepatotoxic side effects, neuropathies and less commonly pneumonitis [29]. In a phase II trial exploring ipilimumab among 155 subjects with pretreated melanoma, immune-related adverse events were reported in 70 % of study population with grade 3–4 toxicities observed in 34 (22 %) patients [30]. To prevent unnecessary treatment discontinuation or enable an early re-initiation, timely diagnosis and appropriate management are warranted. Glucocorticoids can reverse nearly all immune-related adverse reactions but should be employed only for grade 3–4 or prolonged grade 2 toxicities [29].

There are several immune checkpoint inhibitors undergoing clinical evaluation in head and neck cancer. Two monoclonal antibodies of the immunoglobulin (Ig) G4 type with a high affinity for PD-1, pembrolizumab (MK-3475) and nivolumab (ONO-4538), have already been approved for treatment of advanced melanoma and lung cancer. Durvalumab (MEDI4736), atezolizumab (MPDL3280A) and avelumab (MSB0010718C) belong to an evolving category of monoclonal antibodies against PD-L1. As indicated above, ipilimumab (MDX-010) entered the market as a practice-changing drug for melanoma patients. A phase Ib study exploring ipilimumab with cetuximab and irradiation is ongoing in patients with locally advanced head and neck cancer (NCT01860430), whereas tremelimumab, another CTLA-4-directed antibody, is being studied in the recurrent/metastatic setting (see below).

Immunotherapy in R/M-SCCHN

SCCHN is a suitable candidate for the immunotherapeutic approach. As an immunosuppressive disease, SCCHN utilizes several mechanisms to evade immunosurveillance. It manipulates its own immunogenicity, produces immunosuppressive mediators (e.g., transforming growth factor-beta, interleukins 6 and 10) and promotes immunomodulatory cell types (myeloid-derived suppressor cells, suppressive regulatory T cells, tumour-associated macrophages) [23]. Immune dysfunction has been implicated in carcinogenesis of HPV-related oropharyngeal cancer as well as the majority of remaining SCCHN cases which are linked to smoking and alcohol. Oncogenic types of HPV, such as 16 and 18, encode E6 and E7 proteins which, together with host and environmental factors, contribute to the ability of the virus to persist in the infected organism for long periods of time. Tobacco-driven tumours harbour chronic inflammation and a high mutational load leading to increased

immunogenicity. In this regard, establishment of T-cell tolerance to chronic HPV infection and overexpressed or mutated antigens poses one of the key mechanisms of immune escape [23, 31]. Recently, using gene expression-based consensus clustering, copy number profiling and HPV status, five new subtypes of SCCHN were identified to overcome some of the limitations associated with traditional classification based on anatomic site and stage. Two of these subtypes, one HPV-positive and one negative, demonstrated a prominent immune and mesenchymal phenotype with marked CD8+ lymphocyte infiltration. Such a strong activation of the immune system provides a further rationale for immunotherapy and may become a predictive biomarker for this therapeutic approach [32].

As outlined above, head and neck cancer ranks among cancers with higher somatic mutation rates. In lung cancer, a high mutation frequency was attributed to smoking and implicates increased immunogenicity due to an increment in tumour neoantigens [33]. Interestingly, the efficacy of anti-PD-1 and anti-PD-L1 antibodies seems to correlate with tobacco exposure [34–36]. This finding is intriguing within the context of head and neck cancer considering its close etiological relationship to tobacco abuse. Moreover, a subset analysis of 42 patients with melanoma, non-small-cell lung, colorectal, renal-cell and prostate cancers treated with an anti-PD-1 antibody indicated an association between PD-L1 expression on tumour cells and objective response [37]. In head and neck cancer including nasopharyngeal carcinoma, several reports confirmed that PD-L1 expression is a common event found in 46–100 % of tumour samples [38, 39]. However, these data should be used with caution because of variable quality of archival tissue specimens and differences in the used assays and scoring methods. Nonetheless, they add further evidence to the prominent immune phenotype of head and neck cancer.

The majority of R/M-SCCHN patients qualify for palliative measures with an expected survival of 6–10 months. At present, according to the pivotal EXTREME (Erbitux in first-line treatment of recurrent or metastatic head and neck cancer) trial, the platinum/5-fluorouracil/cetuximab regimen is the approved first-line systemic treatment for fit patients [40]. Unfortunately, the long-term follow-up data are far from being satisfactory underscoring the burning need for further improvement [41]. The following part of this chapter describes the preliminary results from two early clinical trials exploring pembrolizumab and durvalumab as well as the recently presented, possibly practice-changing phase III data of nivolumab.

Pembrolizumab

KEYNOTE-012 is an ongoing non-randomized, multi-cohort phase Ib trial (NCT01848834), which recruited participants with a diagnosis of SCCHN, bladder, triple-negative breast and gastric cancers. At the 2014 American Society of Clinical Oncology (ASCO) annual meeting, the first results of cohort B from the KEYNOTE-012 study were made public [42]. Cohort B consisted of 56 PD-L1

positive R/M-SCCHN cases with or without previous systemic therapy. Pembrolizumab at a dose of 10 mg/kg intravenously every 2 weeks yielded a 20 % overall response rate. Subgroup analysis based on HPV status found comparable overall response rates, while median progression-free and overall survivals were longer in HPV-positive than negative patients (17.2 vs. 8.1 weeks and median overall survival not reached vs. 9.5 months, respectively). The most frequently observed toxicities were fatigue (18 %), pruritus (10 %) and nausea (8 %) [42, 43].

At ASCO 2015, results from cohort B2 of this study were released. Patients with R/M-SCCHN, regardless of PD-L1 expression, HPV status or prior systemic therapy, were eligible for inclusion if they had measurable disease based on RECIST v1.1 and Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Pembrolizumab was given at a fixed dose of 200 mg intravenously every 3 weeks until either progression, intolerable toxicity, or a 24-month treatment limit was reached. The investigators permitted treatment beyond progression as well as pembrolizumab rechallenge. Tumour assessments were performed at baseline and every 8 weeks with radiographic imaging. Primary objectives of this trial are overall response rate (ORR) per investigator evaluation (RECIST v1.1) and adverse events determined according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Secondary end points include progression-free survival, overall survival and duration of response.

As of March 2015, 132 predominantly male patients with a median age of 60 years (range, 25–84) were enrolled. Twenty-two percent had received one and almost 60 % two or more prior lines of therapy for R/M disease. Overall, pembrolizumab was well tolerated; no treatment-related deaths occurred. Drug-related adverse events of any grade were reported in 79 subjects (60 %) with the most frequent one being fatigue (15 %) followed by hypothyroidism (9 %). Other side effects developing at a rate of at least 5 % comprised decreased appetite (8 %), rash (8 %), dry skin (7 %), pyrexia (7 %), arthralgia (5 %), nausea (5 %) and weight loss (5 %). Thirteen patients (10 %) experienced severe acute toxicity (grade 3–4), most commonly swelling of the face and pneumonitis observed in two cases each. Concerning adverse events of special interest, which are those potentially associated with the investigational compound, they included the following toxicity, apart from the already mentioned hypothyroidism and pneumonitis: grade 1–2 thyroiditis (2 %), grade 3 colitis (1 %), grade 1–2 interstitial lung disease (1 %), grade 1–2 acquired epidermolysis bullosa (1 %), grade 3 drug-induced liver injury (1 %), grade 1–2 epidermolysis (1 %) and grade 4 diabetic ketoacidosis (1 %). Patients with pneumonitis, colitis, interstitial lung disease and drug-induced liver injury required treatment discontinuation.

Efficacy analyses were performed in 117 subjects who received one or more doses of pembrolizumab, had measurable disease at baseline and at least one post-baseline scan or discontinued therapy due to progressive disease or drug-related adverse events. Pembrolizumab produced overall response, complete response, partial response and disease control rates of 25 %, 1 %, 24 %, and 50 %, respectively. More than half of the study group (56 %) experienced tumour shrinkage of any

degree. Both HPV-positive and negative cases benefited from the drug with a slightly higher response rate in the latter group (21 % versus 27 %). Interesting results were found in the exposure-response analysis. Responses occurred largely at 8 or 16 weeks corresponding with the time of imaging; median time to response was 9 weeks. Two patients had a late response at about 25 weeks. Median time of follow-up was 6 months, but it was not reached for the duration of response. Importantly, 40 patients including many of those with stable disease continued receiving pembrolizumab. Moreover, at the time of data cut-off, 86 % (25/29) of the responding patients had an ongoing response [27].

Subsequently, a pooled analysis of the two R/M-SCCHN cohorts from the KEYNOTE-012 trial (a total of 173 patients, 56 from cohort B and 117 from cohort B2) were reported. The aim of this post hoc analysis was to identify R/M-SCCHN subgroups that may derive the greatest clinical benefit from pembrolizumab. The anti-PD-1 antibody achieved an overall response rate of 24 % with two cases of complete remission. The response rate was higher in patients who received two or less previous treatment lines versus those with more prior therapies (32 % versus 14 %). Also, response rates were higher in patients with smaller tumour sizes: 36 % in those in whom the tumour size was ≤ median value versus 15 % in those with larger tumours. In this respect, HPV status did not confer any advantage. Median progression-free and overall survival for the whole population ($n = 173$) were 2.2 (95 % confidence interval [CI], 2.0–3.6) and 9.6 months (95 % CI, 6.6-not reached), respectively. Median follow-up time was 13.7 and 5.7 months in cohorts B and B2, respectively [44]. When compared with results achieved by various epidermal growth factor receptor (EGFR) inhibitors in second-line therapy, progression-free survival appears not to be much different as opposed to response rate and overall survival clearly favouring pembrolizumab [44–50] (Table 15.2). Even more convincing data are available for the randomized trial with nivolumab as described below.

An exploratory biomarker analysis confirmed that PD-L1 expression by immunohistochemistry correlates with response. However, pembrolizumab exhibits activity also in PD-L1 negative cases. Using a preliminary PD-L1 cut-point derived from the Youden index, it could be demonstrated that tumours with a value above this cut-point responded better (46 %, 5/11) than those underneath (11 %, 5/44) [42]. Very recently, Yearley et al. shed more light on this issue introducing a novel immunohistochemistry assay for PD-L2, which was verified also on head and neck cancer samples. As a result, the authors stated that PD-L2 expression may be present even in the absence of PD-L1, which partly explains the phenomenon of PD-L1 negative patients responding to PD-1-directed agents. In this regard, patients resistant to anti-PD-L1 antibodies might still have benefit from anti-PD-1 drugs blocking both PD-L1 and PD-L2 signal transduction pathways [51]. Another area of biomarker research concerns gene-expression signatures. Using NanoString technology, Seiwert and colleagues tested 43 PD-L1 positive patients enrolled in the KEYNOTE-012 trial. The investigators proved a statistically significant correlation between progression-free survival and inflamed phenotype consisting of four

Table 15.2 Trials with PD-1-directed agents and randomized studies of EGFR inhibitors in second-line treatment of R/M-SCCHN

Study, author (year)	*N*	Regimen (treatment arms A, B, C)	Response rate (%)	Median PFS (months)	Median OS (months)
KEYNOTE-012 (cohort B and B2) Chow (2015) [44]	173[a]	Pembrolizumab	23.7	2.2	9.6
CHECKMATE-141 Gillison (2016), Ferris (2016) [45, 46]	361	A: Nivolumab B: MTX or D or cetuximab	22.2[b, c] 2.3[b]	3.2[b, c] 2.0[b]	7.5[c] 5.1
IMEX Stewart (2009) [47]	486	A: Gefitinib (250 mg) B: Gefitinib (500 mg) C: MTX	2.7 7.6 3.9	ND ND ND	5.6 6.0 6.7
ECOG 1302 Argiris (2013) [48]	270	A: D + Gefitinib B: D + placebo	12.5 6.2	3.5 (TTP) 2.1 (TTP)	7.3 6.0
ZALUTE Machiels (2011) [49]	286	A: Z + BSC B: BSC (optional MTX)	6.3 1.1	2.3[c] 1.9	6.7 5.2
LUX-Head & Neck 1 Machiels (2015) [50]	483	A: Afatinib B: MTX	10.2 5.6	2.6[c] 1.7	6.8 6.0

PD-1 programmed death-1, *EGFR* epidermal growth factor receptor, *N* number of randomized patients, *MTX* methotrexate, *D* docetaxel, *Z* zalutumumab, *BSC* best supportive care, *PFS* progression-free survival, *ND* no data, *TTP* time to progression, *OS* overall survival

[a]Evaluable patients

[b]For programmed death ligand-1 (PD-L1) expression ≥5 %

[c]Significant differences

previously established multigene expression signatures (interferon-γ, T-cell-receptor signalling, expanded-immune, and de novo). Furthermore, interferon-γ signature was significantly associated with best overall response and, interestingly, it has been linked to the independently discovered inflamed/mesenchymal SCCHN subtype alluded to above [52].

Nivolumab

Another PD-1-directed agent, nivolumab, has recently been brought to the spotlight of healthcare professionals as the first drug ever to show a survival benefit in patients with platinum-refractory R/M-SCCHN. At American Association for Cancer Research (AACR) annual meeting in New Orleans in April 2016, the investigators of the randomized, global CHECKMATE-141 phase III trial (NCT02105636) announced that the study was stopped early, after a planned interim analysis performed by an Independent Data Monitoring Committee, because the statistical

boundary for overall survival was crossed. The trial evaluated the efficacy and safety of nivolumab at a dose of 3 mg/kg intravenously every two weeks versus weekly intravenous single-agent chemotherapy (methotrexate 40 mg/m^2, docetaxel 30 mg/m^2) or cetuximab (400 mg/m^2 once, then 250 mg/m^2) in a 2:1 ratio. Key eligibility criteria were as follows: R/M-SCCHN of the oral cavity, pharynx or larynx not amenable to curative therapy, progression on or within 6 months of platinum-based chemotherapy, good ECOG performance status (0 or 1), no active brain metastases and p16 immunohistochemistry to determine HPV status. Prior cetuximab treatment served as a stratification factor. Primary endpoint was overall survival and secondary endpoints included progression-free survival, overall response rate, safety, duration of response, biomarkers and quality of life.

Of the 361 mostly male patients enrolled in the trial, 236 (of 240 assigned) received nivolumab and 111 (of 121 assigned) investigator's choice (46 methotrexate, 52 docetaxel and 13 cetuximab). In the overall population, median age was 60 years with 113 (31 %) patients being older than 64. A substantial proportion of patients (55 %) had two or more prior lines of systemic therapy. Median time on therapy was 1.9 months in both cohorts and median duration of follow-up 5.3 and 4.6 months in the experimental and control arms, respectively. At data cut-off, 41 patients (17 %) continued treatment with nivolumab as opposed to 3 (3 %) receiving single-agent chemotherapy or cetuximab. Treatment-related adverse events occurred at a rate of 59 % (139/236) and 78 % (86/111) in the nivolumab and control arms, respectively. Correspondingly, grade 3–4 toxicities were less frequent with the experimental drug (14 %) than investigator's choice (35 %). In the nivolumab-treated group, skin toxicity (16 %) and fatigue of any grade (14 %) were the most common side effect, while other toxicities did not exceed 10 %. Apart from the skin reactions, adverse events with a potential immunologic aetiology comprised endocrine (8 %), gastrointestinal (7 %), hepatic (2 %), pulmonary (2 %), infusion-related (1 %) and renal toxicities (0.4 %).

At interim analysis, conducted after 218 events, subjects assigned to nivolumab were found to have a 30 % reduction in risk of death compared to the control arm regardless of the p16 status or PD-L1 expression (hazard ratio [HR], 0.70; 97.73 % confidence interval [CI], 0.51–0.96; $p = 0.0101$). Median overall survival was 7.5 months versus 5.1 months in favour of nivolumab. At 12 months, 36 % of patients on nivolumab versus 17 % of those assigned to therapy of choice were still alive. An exploratory analysis suggested that the benefit was greater for patients treated with nivolumab whose tumours had PD-L1 expression (≥5 %: median 8.8 versus 4.6 months in PD-L1 negative cases) or were p16 positive (median 9.1 versus 4.4 months in p16-negative cases) [45, 46].

Durvalumab

This novel, PD-L1-blocking anticancer drug has several advantages over other immune checkpoint inhibitors. While PD-1 inhibition disrupts both PD-L1 and PD-L2 pathways, durvalumab does not bind to PD-L2, which might avoid PD-L2-mediated toxicities, as observed in animal models [53]. In addition, its Fc domain was engineered in order to reduce IgG-mediated side effects by removing

antibody-dependent cell-mediated cytotoxicity and complement-dependent cytotoxicity [54]. Finally, electrochemiluminescence assays in human serum detected only low incidence (2 %) of anti-drug antibodies [55].

An ongoing global, multicenter, open-label phase I/II trial (NCT01693562) evaluates safety and efficacy of durvalumab administered intravenously at 10 mg/kg every 2 weeks in patients with various solid malignancies (SCCHN, melanoma, non-small-cell lung, pancreatic, gastroesophageal, triple-negative breast and liver cancers, and eight additional tumour types). The study design consists of a conventional 3 + 3 dose-escalation phase followed by a cohort expansion. Patients with PD-L1 positive and negative SCCHN met the inclusion criteria if they had R/M disease incurable with local approach, ECOG performance status of 0 or 1 and adequate organ functions. Prior anti-CTLA-4 but not anti-PD-1 or anti-PD-L1 therapies were permitted. The investigators planned durvalumab administration for 1 year even in case of progressive disease if there was no clinical deterioration and the patient continued to derive benefit. Primary endpoints consisted of safety and tolerability, while radiologic assessment of response (computed tomography or magnetic resonance imaging, using RECIST v1.1) was a secondary endpoint.

As of April 2015, 62 R/M-SCCHN cases received a median of six doses of durvalumab in the dose-expansion phase. Similarly to the KEYNOTE-012 trial, the mean age of study population was 58 years (range, 24–96) with male preponderance. Thirty-six percent of patients were PD-L1 positive, 60 % negative. HPV status was positive in 40 % of subjects, negative also in 40 % and unknown in the remainder. Drug-related adverse events of any grade occurred in 61 % of participants, mostly fatigue (11 %), diarrhoea, (8 %), nausea (7 %) and skin toxicity. Serious side effects were observed at a rate of 10 % with no cases of colitis, pneumonitis, toxic death or discontinuation due to drug-related toxicity.

Among 62 evaluable patients with a minimum of 24 weeks of follow-up, overall response and disease control rates were 11 % and 15 %, respectively, favouring the PD-L1 positive cases (18 % and 18 %, respectively) over the negative ones (8 % and 11 %, respectively). Noteworthy, antitumour responses were obtained also in heavily pretreated patients who received up to 5 prior systemic treatment lines. At the time of the study presentation, 71 % (5/7) of these responses were ongoing with a minimum duration of 16-week duration (range, 16–55) and lasting beyond 1 year in three cases. Despite the lower response rate in PD-L1 negative subjects, all the responses were ongoing at the time of analysis (3/3). Another subgroup analysis revealed that the antitumour activity appears to be more pronounced in HPV-negative disease with overall response and disease control rates of 16 % and 20 %, respectively, versus HPV-positive SCCHN, where these parameters reached 4 % each [56].

Nasopharyngeal Carcinoma

The non-randomized, multi-cohort, phase Ib trial KEYNOTE-028 (NCT02054806) recruited participants with PD-L1 positive unresectable or metastatic nasopharyngeal carcinoma failing prior therapy. Treatment consisted of pembrolizumab at a dose of 10 mg/kg administered every 2 weeks until disease

progression, unacceptable toxicity or 2 years elapsed. Using RECIST v1.1, the investigators assessed responses every 8 weeks for the first 6 months, increasing the interval to 12 weeks afterwards. Primary objectives included safety, tolerability and efficacy.

Among 27 patients, primarily of Asian ancestry, median age was 52 years (range, 18–68). The majority (93 %) received at least one prior therapy and one third more than four prior therapies for R/M disease. Peaking at 74 %, the incidence of drug-related toxicity was higher than in the aforementioned studies on immune checkpoint inhibitors in R/M-SCCHN. The following adverse events exceeded the threshold of 10 %: pruritus (26 %), fatigue (19 %), hypothyroidism (19 %), rash (11 %), maculopapular rash (11 %), pneumonitis (11 %), herpes zoster infection (11 %) and hepatitis (11 %). Severe toxicity was noted in 30 % of study population. With seven patients achieving a partial response and no observed complete remissions, the overall response rate was 26 %. Tumour shrinkage and disease control rates were 67 % and 78 %, respectively [57].

Conclusions

It is for the first time that a randomized trial has clearly demonstrated an improved overall survival in patients with platinum-refractory recurrent and/or metastatic squamous cell carcinoma of the head and neck. The data observed in the CHECKMATE-141 trial and reported in 2016 more or less confirmed what could already be deduced from the extensive experience with pembrolizumab reported in 2014 and 2015. Responses, although still limited in number, are long-lasting, progression-free survival is not much different from what is known from standard-of-care treatment, but overall survival figures are improved. Longer follow-up is needed in order to judge whether survival curves will show a horizontal ending. An important observation is that most patients seem to tolerate the treatment reasonably well and can be treated for a longer period of time. Long-term follow-up will also tell us what the ultimate consequences are of such immunotherapeutic interventions.

Despite these reservations, it can only be hoped for the benefit of the head and neck cancer patients that immune checkpoint inhibitors will become available as a new option for such patients in this unfavourable setting. Further studies in the first-line R/M disease setting are ongoing and studies in the primary disease setting in combination with radiation have started. It is too early to conclude whether one drug is more favourable over the other, and that also holds for anti-PD-1 versus anti-PD-L1 monoclonal antibodies. A summary of ongoing immunotherapy trials is given in Table 15.3. Two trials explore the efficacy of a toll-like receptor 8 agonist (motolimod) and a vaccine against HPV-16 oncoprotein E7 (ADXS11-001), both of which are not classified as immune checkpoint inhibitors. In addition, there are other promising inhibitory (lymphocyte-activation gene-3 [LAG-3]) or activating T-cell receptors (OX40, CD137, glucocorticoid-induced tumour necrosis factor-receptor-

Table 15.3 Ongoing randomized immunotherapy trials in R/M-SCCHN

Trial	Phase, line	Estimated enrolment	Target	Regimen (treatment arms A, B, C)	Estimated completion date
NCT02252042 (KEYNOTE-040)	III, 2nd line	600	Anti-PD-1	A: Pembrolizumab B: Cetuximab or MTX or docetaxel	4/2017
NCT02358031 (KEYNOTE-048)	III, 1st line	780	Anti-PD-1	A: Pembrolizumab B: Pembrolizumab + PF C: PFE	11/2017
NCT01836029 (ACTIVE8)	IIR, 1st line	175	TLR8 agonist	A: PFE + motolimod B: PFE	9/2016
NCT02291055	I/IIR, 2nd line	66	Vaccine Anti-PD-L1	A: ADXS11-001 B: Durvalumab C: ADXS11-001 + durvalumab	7/2019
NCT02319044 (CONDOR)[a]	IIR, 2nd line	240	Anti-PD-L1 Anti-CTLA-4	A: Durvalumab B: Tremelimumab C: Durvalumab + tremelimumab	12/2017
NCT02369874 (EAGLE)	III, 2nd line	720	Anti-PD-L1 Anti-CTLA-4	A: Durvalumab B: Durvalumab + tremelimumab C: Standard of care	9/2018
NCT02551159 (KESTREL)	III, 1st line	628	Anti-PD-L1 Anti-CTLA-4	A: Durvalumab B: Durvalumab + tremelimumab C: PFE	11/2017

PD-1 programmed death-1, *TLR8* toll-like receptor 8, *PD-L1* ligand for PD-1, *CTLA-4* cytotoxic T-lymphocyte antigen-4, *MTX* methotrexate, *PFE* platinum/5-fluorouracil/cetuximab according to the EXTREME trial

[a]In patients with PD-L1 negative tumours

related protein [GITR]) that could serve as targets for the next generation of T-cell immunomodulators [58].

Undoubtedly, the present promising data with checkpoint inhibitors in the clinic have led to a renewed interest in this treatment modality and hopefully will lead to further exploration of immunotherapeutic approaches for the benefit of patients with head and neck cancer. The next step will be to tailor treatment protocols to those who reach long-term disease control (response or stable disease) and to find adequate biomarkers in order to select those who might benefit. At the same time, due to its mechanism of action, immunotherapy may not be recommended for patients with comorbid autoimmune disorders and those requiring prompt symptom relief. Therefore, unfortunately, there will remain a large proportion of patients that will not benefit from these approaches or for whom such treatment is contraindicated, underlining the huge unmet need in this population.

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Chapter 16
Treatment in the Elderly

Petr Szturz and Jan B. Vermorken

Cancer and Ageing

As documented in many epidemiological studies, there is a marked association between tumour development and ageing. Advanced age is indeed the major risk factor for cancer, which in turn represents the second most common cause of death for persons over 65 years in Europe [1, 2]. In accordance with demographic projections clearly showing the steadily growing number of the elderly people, the global cancer burden will nearly double in the near future. By 2030, up to 22 million new cases (12 million in those 65 years or older) and 13 million cancer deaths (8.4 million in those 65 years or older) are to be expected worldwide each year. Of note, these figures exclude non-melanoma skin cancers, which are frequent and generally well curable [3]. However, the biological landscape of malignant transformation in older adults is far from being straightforward. Besides the dominant role of somatic mutations accumulating over lifetime, other age-related processes promote but also hinder tumourigenesis. Vascular ageing and a decline in circulating levels of various hormones probably counteract neoplastic progression, while it may be fostered by chronic low-grade inflammation and an increased fraction of senescent cells [1]. Interestingly, cancer incidence and mortality were reported to decrease or plateau in the oldest population (over 90 years) owing partly to the selection of less vulnerable individuals [4].

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But how to define old age? This is one of the key questions; unfortunately, no universally accepted criteria that would facilitate clinical decision-making exist. The elderly are usually classified into young old (65–75 years), old old (76–85) and oldest old (>85) [5]. This categorization has been adopted by the National Institute on Aging and the National Institutes of Health, whereas most clinical studies use the age of 70 (or even 75) as a cut-off defining the elderly [6]. However, chronological age is not a reliable predictor of life expectancy, functional reserve or the risk of treatment side effects. Ageing is associated with a progressive loss of functional reserve of multiple organ systems, increased prevalence of chronic diseases and enhanced susceptibility to stress. These age-related changes occur at different rates in different individuals. Moreover, they are usually accompanied by fluctuations in social support and economic resources. Hence, chronological age provides limited information for individual patient management, since it does not always correlate with biological parameters [5, 7].

Notwithstanding the general importance of addressing geriatric oncology issues, older patients have been underrepresented in clinical trials mainly due to disqualifying medical conditions. This remains to be a continuing problem despite the fact that their willingness to participate does not seem to pose a barrier [8]. The resulting lack of evidence-based data hampers effective implementation of novel drugs and development of clinical practice guidelines in the older patient population. This chapter details cancer care in elderly patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck (R/M-SCCHN). It sets out to briefly review the answers to the following two fundamental questions: “How to select an appropriate approach to an elderly person?” and “What is the current state of evidence on systemic treatment in these patients?”

Elderly Head and Neck Cancer Patients

SCCHN follows the same epidemiologic trends as outlined above. According to the 2010 cancer incidence projections for the United States, 54 % of malignant head and neck cancer cases occurred in patients older than 65 years of age. By 2030, the proportion is expected to rise to 66 % [9]. Although major risk factors for SCCHN in the elderly are still tobacco and alcohol consumption, their prevalence is lower than in an unselected population (40 % versus 70 %) underscoring age alone as an important risk factor. Compared to younger patients, older age groups have a higher ratio of female cases and are more likely to have primary tumours located in the oral cavity and larynx but less in the hypopharynx. Metastatic spread to the regional lymph nodes and human papillomavirus-associated oropharyngeal cancer also appear to be less frequent in the elderly [10].

At first glance, results from clinical trials may be interpreted as ambiguous. On the one hand, geriatric SCCHN patients experienced similar outcomes when treated similarly as the younger cohort, but on the other hand, worse survival was noted due to higher comorbidity status and competing causes of mortality. To resolve this

discrepancy, we have to take into account the heterogeneity of the elderly population represented by functional and not chronologic age. In this respect, several studies have demonstrated that radical surgical interventions and radiotherapy with curative intent can be delivered safely to older adults without significant comorbid conditions. Such patients can employ effective coping strategies and maintain quality of life comparable to their younger counterparts [11–13]. Despite these arguments, many physicians concerned about excessive toxicity still tend to use chronological age a sole discriminator and opt for non-standard or less aggressive therapies in otherwise fit elderly persons [11]. Retrospective data indicate that only half of these patients are managed according to institutional policies [14]. The resulting suboptimal treatment has been hypothesized as one of the reasons for shorter survival. In oral cavity and pharynx cancers, Surveillance, Epidemiology, and End Results (SEER) database from 2003 to 2009 revealed 5-year overall survival of 67 and 54 % for patients younger and older than 65 years, respectively [15]. Other factors that may have contributed to such difference in outcomes include serious age-related comorbidities and individual decisions to avoid receiving full-dose regimens [16]. This is in line with the results of a long-term prospective observational study of 266 subjects showing that chronological age has no independent prognostic value as opposed to comorbidities and non-standard treatment [17]. In this regard, judging only by age may also have a detrimental impact on younger persons, which could subsequently be overtreated.

One possible solution of how to address the complexity in delivering patient care at an individual level is a team approach in treatment planning represented by multidisciplinary tumour boards. These meetings should offer a collaborative review of each case with a special attention to disease factors (site, stage, biology, risk factors for locoregional or distant relapse), patient factors (age, sex, performance and nutritional status, comorbid conditions, oral health, life-style habits, socio-economic background), treatment options and patient preferences. A geriatrician is not always available and practicing oncologists should therefore familiarize themselves with some of the assessment tools described below.

Geriatric Evaluation in Oncology

Although often used as traditional oncology measures, performance status scores alone (e.g. Karnofsky or Eastern Cooperative Oncology Group [ECOG]) do not convey sufficiently accurate information about functional status, comorbidities and physiological reserves. However, these characteristics are one of the key components essential for differentiating between a fit and a frail person of the same age. Functional status evaluated by a geriatrician comprises an assessment of the patient's ability to complete activities of daily living (ADLs) such as the ability to bathe, dress, feed oneself, maintain continence and transfer from a bed or chair without assistance, and instrumental activities of daily living (IADLs) like doing housework, using transportation, shopping and taking medications. Both ECOG and

functional status assessed by IADL predict postoperative morbidity, toxicity to chemotherapy and survival [18]. In a study of 203 elderly cancer patients, the association of ECOG performance status with ADL/IADL was moderate, but it was low or absent when compared to comorbidity scales. Similarly, low or absent correlation was found in a comparison of ADL/IADL with comorbidities [19].

Comorbidities are defined as additional concurrent diseases unrelated to cancer. Due to worsening pulmonary functions with reduced vital capacities and gas exchange, weaker cardiac output, decreasing renal blood flow and changes in hepatic metabolism, the prevalence of comorbid conditions increases with growing age [14]. About 60 % of SCCHN patients suffer from at least one coexisting illness and this number is estimated to approach 75 % in the population over 70 years old [20, 21]. Among various comorbidity scores, the Charlson Comorbidity Scale and the Adult Comorbidity Evaluation 27 (ACE-27) were shown to have independent prognostic value for overall survival in a retrospective analysis of 103 SCCHN cases with primary or recurrent disease [22]. In oropharyngeal squamous cell carcinoma, the inclusion of a comorbidity score measured by the ACE-27 led to a further refinement of a prognostic model containing also human papillomavirus status and nodal stage [23].

In addition to functional status and comorbidities, further factors linked to survival include cognition, nutritional status, social support and psychological state (depressions) [18]. About half of patients over 70 years of age can be treated with a standard oncologic approach, while the other half will require more extensive care [24]. In an outpatient oncology clinic setting, the following issues and their prevalence were reported in older cancer patients: comorbidity (>90 %, severe in 30–40 %), IADL dependence (50–60 %), nutritional compromise (30–50 %), depression (20–40 %), cognitive impairment (25–35 %), ADL dependence (about 20 %) and ECOG $\geq$2 (about 20 %) [25]. To address the complexity of geriatric assessment, certain scales and tools were developed for use in clinical practice.

Comprehensive Geriatric Assessment (CGA)

GCA was introduced by geriatricians to estimate overall health status of an individual, detect unknown deficits, predict survival, and anticipate on adverse effects of chemotherapy. It includes validated tests for evaluation of functional status, comorbid conditions, cognition, nutritional status, social support, psychological state and polypharmacy [10, 22, 24, 26] (Table 16.1). Information about life expectancy may help guide treatment decisions. A CGA can predict morbidity and mortality not only in the general geriatric population but also in elderly patients with cancer, where it was shown to modify the initially proposed treatment plan in about 40–50 % of patients [18, 27, 28]. This multidimensional interdisciplinary diagnostic process is thus both a diagnostic and therapeutic tool aiming at improving quality of life, compliance to therapy and overall survival. With a notable remark that results from randomized trials are available mostly for non-malignant diseases, a CGA has

Table 16.1 Components of comprehensive geriatric assessment and how to measure them

Assessment of functioning	**Social assessment**
Definition: ability to live independently at home and in the community, physical performance (mobility, balance, fall risk)	Definition: adequate social support to undergo treatment
Measurement: ADLs, IADLs, history of falls, Timed Up and Go, Short Physical Performance Battery, handgrip testing	Measurement: needs assessment of financial capabilities, transportation, and caregiver status; Medical Outcomes Survey Social Support
Medical assessment	**Psychological assessment**
Comorbidity and medication	*Cognition*
Measurement: Charlson Comorbidity Scale, Adult Comorbidity Evaluation 27, Cumulative Illness Rating Scale-Geriatrics, comorbidity count and severity, medication count, Beers Criteria[a]	Measurement: Mini-Mental Status Examination, Blessed Orientation Memory Scale, Short Portable Mental Status Questionnaire, Montreal Cognitive Assessment
Nutritional status	*Depression and anxiety*
Measurement: Mini-Nutritional Assessment, weight loss, body mass index	Measurement: Geriatric Depression Scale, Hospital Anxiety and Depression Scale

Adapted from [10, 22, 24]
ADLs Activities of Daily Living, *IADLs* Instrumental Activities of Daily Living
[a]Beers Criteria for Potentially Inappropriate Medication Use in Older Adults

been recommended by the National Comprehensive Cancer Network, the European Organisation for Research and Treatment of Cancer and the International Society of Geriatric Oncology (SIOG) [16, 26]. One of the first randomized controlled studies of a CGA in elderly cancer patients is the EGeSOR trial currently recruiting participants with SCCHN in France. Both control and experimental cohorts receive standard-of-care management, while in the latter group, GCAs are performed by geriatricians at predefined time points. The primary endpoint is a composite of death, ADL, and weight loss $\geq$10%. The investigators expect at least a 10% decrease in the primary endpoint to be achieved by the intervention [16].

However, owing to the fact that a CGA is time-consuming and not necessary for all patients, it is rarely performed in oncology practices. Consequently, a two-step approach has been developed furnishing clinicians with geriatric screening tools to decide: (1) which patients will need a full assessment, (2) who will benefit from a specific examination and (3) in which cases no further testing is required.

Geriatric Screening Tools

Several geriatric screening tests have been used in oncology including the G8, the Flemish version of the Triage Risk Screening Tool (fTRST), the Groningen Frailty Indicator, the Vulnerable Elders Survey-13 (VES-13) and an abbreviated CGA. The G8 and the fTRST were prospectively validated in a non-interventional, multicentre

study. Both instruments demonstrated high sensitivity and moderate negative predictive value to identify patients with a geriatric risk profile. Moreover, they were prognostic for overall survival, especially the G8 [26]. In a recent update on SIOG recommendations, a systematic review of 44 studies on the use of 17 different screening tools was reported. The G8 proved to be more or equally sensitive than other tests. The authors concluded that the screening tools should not replace a full assessment. However, a busy practice setting entitles the physicians to use them for triage decisions prior to a CGA [29].

Stratifying elderly head and neck cancer patients according to the VES-13 test into frail, vulnerable and fit cohorts, Perri et al. proposed possible approaches for their management. Frail (VES-13 score = 3) and vulnerable (score = 1–2) groups should undergo a CGA, while standard therapy is advised for the rest. Importantly, physicians should respect physiological changes in the elderly concerning drug metabolism as well as limited bone marrow reserve reflected in guidelines for growth factor prophylaxis. Where indicated, a CGA tailors planned interventions, so that frail persons receive best supportive care only, whereas patients designated as vulnerable are treated with anticancer modalities. However, in the latter category, doses are often reduced, drugs substituted and regimens switched in order to prevent excessive toxicity [30].

Treatment of Elderly People with Recurrent/Metastatic Head and Neck Cancer

R/M-SCCHN is a devastating disease qualifying most of the patients for palliative measures with an expected overall survival usually not exceeding 1 year. As outlined above, evidence from the literature is insufficient to draw firm conclusions regarding the management of the elderly population. Generally, eligibility for and tolerance to a locoregional approach (surgery and radiation) is better than in the case of systemic therapy [10]. However, just a minority of locoregional recurrences can be successfully salvaged by complete resection or irradiation [31]. Similarly, only carefully selected cases with metachronous pulmonary metastases may be considered for surgical intervention [32]. In the remainder, irrespective of age, treatment goals focus primarily on symptom control and improvement of quality of life. A single-drug regimen or best supportive care is offered to fragile patients with poor performance status and comorbidities. Fit individuals may benefit from multidrug chemotherapy with or without the targeted agent cetuximab (epidermal growth factor receptor [EGFR] inhibitor) [31]. The landmark EXTREME (Erbitux in first-line treatment of recurrent or metastatic head and neck cancer) trial found significant overall survival improvement with platinum (cisplatin or carboplatin)/5-fluorouracil/cetuximab combination over the chemotherapy doublet alone and therefore is the only approved new standard first-line systemic treatment today [33].

As a result of age-related changes in pharmacokinetics and pharmacodynamics, chemotherapy administration carries safety concerns in the elderly. The physiologi-

cal decline in glomerular filtration rate, caused by reduced renal blood flow, necessitates dose adjustments or even omission of some chemotherapeutics (e.g. cisplatin, carboplatin, methotrexate). In this respect, cisplatin may be replaced with carboplatin. Importantly, serum creatinine level is not a sensitive indicator of renal functions in the elderly. Effects on the gastrointestinal tract involve a decrease in splanchnic blood blow, production of hydrochloric acid and gastric enzymes, interfering with the rate of absorption of many oral drugs, but also reduced liver mass and activity of the cytochrome P450 enzymes, which should be kept in mind when prescribing medication with exclusive liver metabolism (e.g. opioids). Another consideration relates to the higher incidence of preexisting neuropathy and the resulting drug restrictions (cisplatin, vinca alkaloids, taxanes). In addition, older adults are more susceptible to dehydration and this can be precipitated by 5-fluorouracil and other fluoropyrimidines as these agents are associated with an increased risk of diarrhoea and mucositis. The potential danger of 5-fluorouracil is further accentuated by the fact that the elderly have a physiologic decline in intracellular levels of dihydropyrimidine dehydrogenase, the rate-limiting enzyme in the catabolism of fluoropyrimidines. Finally, age over 65 years is an important predisposition for chemotherapy-induced myelosuppression and febrile neutropenia. In this setting, myelopoietic growth factor support has proved beneficial [30].

In a combined analysis of two phase III trials conducted by ECOG (1393 and 1395), Argiris et al. compared the toxicity, response rates and survival of elderly R/M-SCCHN patients (70 years or older) with their younger counterparts. The ECOG 1393 trial randomized participants to receive a cisplatin/paclitaxel doublet at two dose levels, while treatment arms in the ECOG 1395 trial comprised cisplatin plus either 5-fluorouracil or paclitaxel. Altogether, 53 older patients were compared to 346 younger ones. No statistical difference was observed in terms of objective response rate (28 % versus 33 %), median time to progression (5.25 versus 4.8 months), median overall survival (5.3 versus 8 months) or 1-year survival (26 % versus 33 %) between these two subgroups, respectively. However, the authors noted a significantly higher incidence of severe nephrotoxicity, diarrhoea and thrombocytopenia in the elderly population, which was paralleled by a trend towards a higher toxic death rate (13 % versus 8 %). In conclusion, cisplatin-based doublets yielded comparable survival outcomes among fit elderly and younger patients, yet at the cost of increased side effects in the former group [6].

Population aged 65 or more made up 17 % of the total number of patients (77/442) enrolled in the EXTREME trial and was equally distributed between both treatment arms. Subgroup analysis of this cohort revealed that the survival benefit conferred by adding cetuximab to platinum/5-fluorouracil chemotherapy fell short of statistical significance, in contrast to younger adults and the whole intention-to-treat population. Median progression-free survival was 4.2 and 3.2 months (hazard ratio [HR], 0.65; 95 % confidence interval [CI], 0.38–1.12) and median overall survival 9.1 and 7.8 months (HR, 1.07; 95 % CI, 0.65–1.77) in the cetuximab and control arms of the elderly subpopulation, respectively [33]. Analogous data are available in the second-line setting, where currently no evidence-based standard-of-care exists. The LUX-Head & Neck 1 trial evaluated the clinical efficacy of afatinib, an

irreversible human epidermal growth factor family receptor (ERBB) blocker, matched up to methotrexate in a 2:1 ratio among 483 eligible subjects (128 [27 %] aged 65 or more). Although the study was sufficiently powered, no improvement in overall survival was achieved by the ERBB antagonist. However, afatinib induced a marginal but significant improvement in median progression-free survival versus methotrexate in the overall population (2.6 versus 1.7 months; HR, 0.80; 95 % CI, 0.65–0.98, $p = 0.030$) [34]. Moreover, similar progression-free survival benefit with afatinib versus methotrexate was observed in patients 65 years or older (2.8 versus 2.3 months; HR, 0.68; 95 % CI, 0.45–1.03, $p = 0.061$) and younger patients (2.6 versus 1.6 months; HR, 0.79; 95 % CI, 0.62–1.01, $p = 0.052$). Also objective response rates with afatinib versus methotrexate were 10.8 % versus 6.7 % and 10.0 % versus 5.2 % and disease control rates were 53.0 % versus 37.8 % and 47.7 % versus 38.8 % in older and younger patients, respectively, without an indication of excessive toxicity in the older population [35]. Taken together, these results suggest that benefit of systemic treatment also exists in the elderly, but that newer forms of systemic therapy need to be studied prospectively and separately in the elderly population with R/M-SCCHN.

Broadly addressing the issue of SCCHN unsuitable for surgery, the ELAN-ONCOVAL study was designed to establish a standard treatment for individuals aged 70 or over. It is currently recruiting patients who undergo a geriatric evaluation upon enrolment and then enter one of the following three distinct trials. In the curative setting, unfit patients are offered radiotherapy (standard versus hypofractionated split course schedule) within the randomized non-inferiority ELAN-RT phase III trial (NCT01864850). In the recurrent and/or metastatic setting, unfit patients are proposed to be enrolled in the ELAN-UNFIT phase III trial (NCT01884623) comparing single-agent cetuximab versus methotrexate monotherapy, whereas the fit ones may participate in the ELAN-FIT phase II trial (NCT01864772) evaluating the carboplatin/5-fluororuracil/cetuximab (EXTREME) regimen. The ELAN-ONCOVAL is planned to enrol 448 patients with an estimated completion date between 2017 and 2018 [36].

In summary, to better understand the behaviour of cancer in patients at an advanced age and the possibilities of its management we advocate supporting the development and implementation of elderly specific prospective trials instead of settling for stratifications based on age. Integration of formal geriatric assessment with comorbidity scores should take into account a direct applicability to the daily clinical practice. Institution of predictive models for chemotherapy toxicity and outcome, examination of tumour genetics and comparative molecular genomic analysis of elderly patients versus their younger counterparts may further assist us in defining new standards-of-care in this population [37].

Conclusions

In 2011, the first wave of the baby boom generation, born after the Second World War between 1946 and 1964, reached retirement age. Unlike their parents' generation, the elderly Boomers are different. They demand more involvement and

competence in their health care, pursue social engagement and healthy lifestyle, continue to have physical and intellectual activity, use the Internet and modern information technologies [38]. It is thus to expect that in this patient population, the gap between chronological and biological age will continue to grow together with an increasing need for improved implementation of geriatric assessment tools in routine practice.

Oncologists must be careful in generalizing results from clinical research to the geriatric population, since these patients have often been underrepresented in prospective studies. However, at the same time they have been highly selected according to strict inclusion criteria tailored for younger individuals in better overall condition. This observation further supports the importance of determining biological age rather than promptly resolving the situation just by asking for the birth date in a busy practice setting. Consequently, popularization of geriatric screening tools and their integration in treatment protocols along with the development of elderly specific prospective trials are urgently needed.

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Chapter 17
Palliative Care in Patients with Head and Neck Cancer

Dirk Schrijvers

Introduction

Head and neck cancer is the sixth common cancer worldwide and is increasing in incidence. In Europe, yearly around 143,000 patients are diagnosed with this disease, and more than 68,000 die yearly from head and neck cancer [1].

Around 40 % of patients with head and neck cancer present with metastatic disease (e.g., lung, mediastinal lymph nodes, liver, or bone metastases) [2].

After primary treatment, around 30–40 % will develop recurrent loco-regional disease and 20–30 % develop recurrent metastatic disease, indicating the bad prognosis of this disease [3]. Factors that are prognostic of disease recurrence are related to the patient (e.g., comorbidity, tobacco and alcohol abuse, viral infections (e.g., human papillomavirus (HPV) infections)) or to the disease itself (e.g., tumor type, tumor grade, location of disease, extent of disease (stage), extracapsular tumor spread) [4]. Also pain has been identified as a factor for disease recurrence: persistent pain after primary treatment with radiotherapy is an indicator of worse survival [5], while disease-specific survival is better in patient with no or low levels of pain compared to patients with intermediate and high levels of pain after primary treatment [6].

In patients with recurrent loco-regional head and neck cancer, prognosis is determined by patient-related factors such as performance status, comorbidity, weight loss, tobacco and alcohol abuse, and viral infections (e.g., HPV infections) or disease-related factors such as HPV-associated oropharyngeal cancers, poorly differentiated histology, previous response to chemotherapy, prior radiotherapy and the possibility of loco-regional rescue treatment [7].

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In patients with metastatic head and neck cancer, a worse prognosis is observed in patients aged between 65 and 79 years, with a higher Charlson's comorbidity score, a lower insurance status, a treatment at nonacademic/research program, or the combination loco-regional and systemic therapy versus systemic treatment alone [8].

Problems Observed in Patients with Recurrent/Metastatic Head and Neck Cancer

Problems that are observed in patients with recurrent and/or metastatic head and neck cancer (RMHNC) are related to different factors such as societal factors (e.g., limited social network, judgment, blame, isolation, financial problems) or patient-related factors in different fields such as the physical field (e.g., comorbidity, dependency, nutritional problems with weight loss, dysphagia), the psychological field (e.g., depression, anxiety), the spiritual field (e.g., meaning of life; meaning of suffering), and the social field (e.g., role in family, work, loss of work).

They may also be related to side effects of previous treatments (e.g., difficulties in communication, disfigurement, xerostomia, siallorhea, trismus, loss of taste, loss of smell, dysphagia, tube feeding, neurotoxicity, fibrosis) or due to the disease recurrence (e.g., pain, dysphagia).

Most reported symptoms in patients with RMHNC during their last 6 months of life are pain (62 %), anorexia and weight loss (45 %), fatigue and weakness (43 %), dyspnea (39 %), cognitive changes (26 %), hoarseness and dysphonia (14 %), neuropathic pain (11 %), anxiety (10 %), and depression (5 %) [9].

Problems in patients with RMHNC have been studied with different evaluations instruments (e.g., EORTC-QOL-Head and Neck 35, EORTC-Core 30, EORTC QLQ-C15-PAL [10], Functional Assessment of Cancer Therapy (FACT)-H&N, FACIT-Pal: Functional Assessment of Chronic Illness Therapy – Palliative Care, FACIT-Pal-14: Functional Assessment of Chronic Illness Therapy – Palliative Care 14-item version).

Recently a questionnaire specifically for patients with RMHNC has been developed, that focuses on 35 physical symptoms including 12 physical symptoms specifically for head and neck cancer including diet change, tongue movement affecting speech/swallowing, face/neck swelling, neck/jaw cramping, bad breath, drooling, wound drainage/pain/odor, nasal congestion/drainage, eyes watering, face/tongue/ear/scalp numbness, headaches, confusion, and 12 psychosocial issues including seven psychosocial issues specifically for head and neck cancer such as burden to family/friends, lost independence, fear, embarrassment, mood swings, stress, and boredom [11].

By applying this questionnaire to patients at diagnosis of RMHNC, it was shown that around one third of patients suffered from difficulties in swallowing solid foods and had problems in the speech and the communication domain, swelling of the face/neck and a decreased movement of the neck and shoulder

regions as well as problems with movement of the jaw, increased saliva production or xerostomia, pain, and severe generalized weakness [11]. In the psychosocial field, around one fifth of the patients complained of severe feelings of being a burden to family and friends, loss of independency, mood swings, stress, and boredom [11].

Effect of Anticancer Treatment in Patients with RMHNC

Several treatment modalities have been tested in patients with RMHNC. They should be carefully evaluated depending on the status of the patient, the type of recurrence, and the aim of the treatment.

Loco-Regional Recurrence Treated with Curative Intent

Surgery applied to patients with an operable loco-regional recurrence can result in a durable disease control in around 15 % of highly selected patients [1].

Reirradiation in this patient population can control loco-regional recurrent disease in 20 % of patients after resected disease or 10 % in patients with unresectable loco-regional disease. The results depend on the comorbidity, the radiation dose, organ function, the recurrent tumor stage, the tumor bulk at reirradiation, and the time interval between previous radiation and reirradiation. The median overall survival is 5.5 months when both organ dysfunction and a higher comorbidity (Charlson's comorbidity index) are present, but in patients without organ dysfunction or comorbidity a median survival of 59.6 months has been reported [1].

RMHNC Treated with Palliative Intent

The majority of patients with recurrent and/or metastatic cannot be cured by a loco-regional treatment, and these patients are candidates for systemic anticancer treatment. Different chemotherapeutic agents given as first-line treatment, either as single agents or in combinations, resulted in an overall survival of 6–10 months (Table 17.1) [12–18], although some of them induce higher response rates in combinations compared with single agent.

Many combinations of chemotherapeutic agents and targeted drugs (e.g., interferon, cetuximab, panitumumab) are not superior in terms of overall survival compared to chemotherapy alone [19–21]. Only in one study, the combination of chemotherapy with cetuximab resulted in an improved overall survival (overall survival 7.4 versus 10.1 months, hazard ratio (HR) for death, 0.80; 95 % confidence interval (CI), 0.64–0.99; $P = 0.04$) compared to chemotherapy alone [22].

Table 17.1 Effect of first- and second-line systemic treatment in patients with recurrent/metastatic head and neck cancer

Author	No. of Pts	Treatment	Response rate (%)	Median survival (months)
First-line treatment chemotherapeutic agents				
Jacobs	245	PF P F	32[a] 17 13	5.5 5.0 6.1
Forastiere	277	PF CF M	32[a] 21 10	6.6 5.0 5.6
Clavel	382	PMBV PF P	34[a] 31[a] 15	7.0 7.0 7.0
Gibson	218	PF PPac	27 26	8.7 8.1
Forastiere	210	PacP HDPacP	36 35	7.0 7.0
Urba	397	PPlac PPem	8.1 12.1	6.3 7.3
Fountzilas	166	PacGem Pac-LD	20 29	8.6 11.05
First-line treatment with targeted agents				
Schrijvers	240	PF PF+ INF	47.1 37.4	6.3 6.0
Burtness	117	P+ Plac P+ C	10 26[a]	8.0 9.2
Vermorken	657	PF PF+Pan		9.0 11.1
Vermorken	442	PF PF+C	20 36[a]	7.4 10.1[a]
Second-line treatment				
Stewart	486	G250 G500 M	2.7 7.6 3.9	5.6 6.0 6.7
Argiris	270	DocPlac Doc+G	6.2 12.5	6.0 7.3
Machiels	483	M Afatinib	5.6 10.2	1.7 2.6[b]

No number, *Pts* patients, *P* cisplatin, *F* 5-fluorouracil, *C* carboplatin, *M* methotrexate, *B* bleomycin, *V* vincristine, *Pem* pemetrexed, *Plac* placebo, *Gem* gemcitabine, *Pac* paclitaxel, *LD* liposomal doxorubicin, *HD* high dose+G-CSF, *C* cetuximab, *INF* interferon, *G* gefitinib, *Pan* panitumumab, *Doc* docetaxel, ° cisplatin-resistant or unsuitable for cisplatin,

[a]<0.05, *Pem*

[b]Progression-free survival <0.05

After progression on first-line treatment, some patients are still fit enough to receive second-line treatment. However, none of the newer drugs (e.g., gefitinib, axitinib) were able to improve overall survival compared to chemotherapy (e.g., methotrexate, docetaxel), although axitinib induced a slightly higher progression-

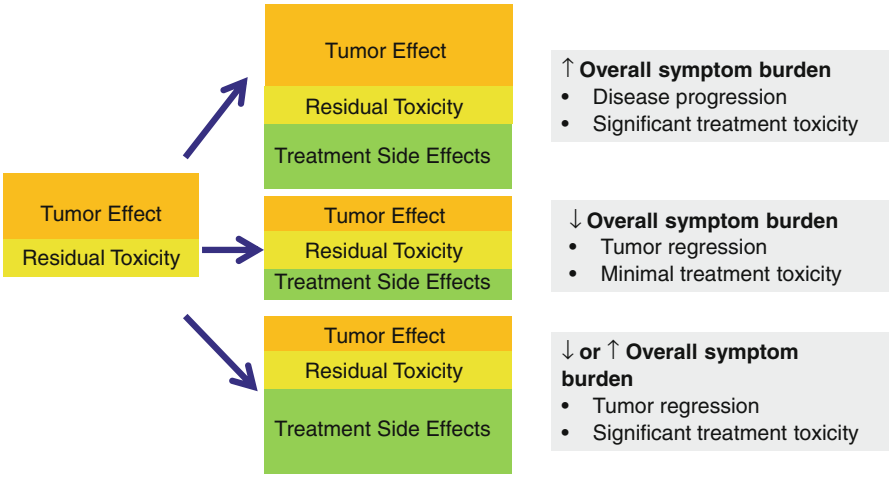

Fig. 17.1 Symptom burden according to disease control and treatment toxicity (Based on Jackson et al. [11])

free survival (median progression-free survival 2.6 months versus 1.7 months; HR 0.80; 95 % CI 0.65–0.98; $P = 0 \cdot 030$) [23–25].

Since overall survival is not influenced by most of the treatments, improving quality of life (QoL) is one of the most important aims of chemotherapeutic treatment in this patient population. However, studies looking at QoL were not able to demonstrate an important improvement in QoL [23, 26], and even the influence on pain was not significantly better by giving the newer drug combinations compared with the older ones [26].

These data show that the impact of anticancer treatment in patients with RMHNC is limited in terms of survival and even on QoL. Therefore, patients should be carefully selected for anticancer treatments, and the treatment regimen should be individualized based on comorbidity and treatment aim.

A conceptual framework may be used to select anticancer treatment (Fig. 17.1). Patients with RMHNC have a certain symptom burden due to disease recurrence but also due to the residual toxicity of previous treatments. The optimal treatment approach should decrease the total disease burden compared to the initial status by combining an important disease regression and minimal toxicity. However, if the treatment does not lead to a tumor control and induces a significant toxicity, it increases the symptom burden and such treatments should not be offered since they only decrease QoL.

Palliative Care in Patients with RMHNC

Palliative care is an approach that improves the QoL of patients and their families facing the problem associated with life-threatening illness. This aim is realized through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of physical, social psychosocial, and spiritual

problems [27]. Palliative care should be given by a multidisciplinary team that addresses all these problems.

Physical problems can be addressed by a palliative treatment, directed towards the cancer itself (e.g., palliative chemotherapy, palliative radiotherapy), with the aim to control or decrease the disease hereby improving QoL. In this setting, cure is not an aim (≠ treatment with curative intent).

At the same time, symptomatic treatment approaches (e.g., analgesics) that address only the problem without doing something against the cancer itself should be initiated to control symptoms.

Studies have shown that including palliative care in patients with cancer improves their QoL and sometimes their survival [28] and all patients with RMHNC should be offered palliative care.

Pain in Patients with RMHNC

Pain is an important symptom in patients with RMHNC: the prevalence of pain at diagnosis of recurrent disease is 30 % [11], while 70 % are suffering from pain during the period of advanced disease [29]. Patients with RMHNC are mainly suffering from chronic pain that can be classified as nociceptive pain, which is linked to the activation of receptors, or neuropathic pain, which is caused by nerve damage [30].

Management of pain should be by a multidisciplinary team to cover all aspects of pain experience, such as physical aspects (e.g., cause of cancer pain, other somatic symptoms (e.g., cough, nausea, dysphagia)), psychological aspects (e.g., frustrations, depression, anxiety), social aspects (e.g., financial problems, place in family, job loss), and spiritual aspects (e.g., meaning of disease, life, end-of-life decisions).

The medical treatment of pain should be by the guidelines proposed by the World Health Organization [30].

For the treatment of nociceptive pain, analgesics (e.g., paracetamol, nonsteroidal antiinflammatory drugs, weak and strong opioids) should be given by the clock (e.g., analgesics on regular basis, escape medication for breakthrough pain, easy accessibility), by the easiest way (e.g., analgesics by the mouth), by the ladder (e.g., analgesics according to pain intensity/severity), and adapted to the individual patient (e.g., organ function, comorbidity, age). The effect of analgesic treatment should be monitored carefully and regularly. Also medication to cope with side effects of analgesic should be provided.

Neuropathic pain is more difficult to control, and analgesics should be combined with systemic tricyclic antidepressants (e.g., amitriptyline) and antiepileptics (e.g., gabapentin, pregabalin) and local drugs such as local anesthetics (e.g., lidocaine) or capsaicin.

In case of uncontrolled pain, neurolytic or neurostimulatory interventions should be combined with medical treatments.

In patients with RMHNC, 97 % are receiving analgesics and 100 % drugs directed against neuropathic pain indicating the importance of pain in this patient popula-

tion. By adhering to the guidelines of the WHO, pain can be controlled in the majority of patients and only 5% of patients are still suffering from severe pain not controlled by these measures [31].

Conclusion

Patients with RMHNC experience different problems related to disease recurrence or metastatic disease but also related to the toxicity of previous treatments.

Treatment choice should be weight against the beneficial effect on tumor control and QoL versus the toxicity of the proposed treatment. There is a need for better selection criteria to identify these patients who will benefit of a specific treatment. Palliative care should be provided to all patients with RMHNC.

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Part VII
Quality of Life and End of Life Issues

Chapter 18
Quality of Life Issues

Susanne Singer

Typical Quality of Life Concerns in Head and Neck Cancer Patients

Keeping quality of life (QoL) as good as possible is very important for patients being treated for cancer. Head and neck cancer patients suffer frequently from problems with swallowing, a changed ability to smell and taste something, from sticky saliva, dry mouth, coughing, problems with teeth, inability to open the mouth wide, or difficulties speaking [1–7].

It depends on the individual patient what QoL issues are most important to him. This should be elucidated during the patient-doctor consultation. However, for developing treatments and supportive care measures, it is helpful to find out what QoL issues are of importance to many patients. In a recent international study [8], the majority of head and neck cancer patients rated the following QoL issues as most relevant for them: swallowing, anxiety, eating, talking, dry mouth, pain and skin problems.

Mental Health as a Predictor of Quality of Life

Psychological morbidity is an important associate of poor quality of life [9–11]. It is important to note that head and neck cancer patients suffer more frequently than other cancer patients from psychosocial problems, especially some time after their diagnosis [12]. This fact goes often unnoticed by the doctors and nurses in charge for the patients:

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Only about half of the patients with severe emotional problems such as a clinical depression are identified as emotionally distressed by the medical team [13, 14].

Reasons for this underdiagnosis are manifold. One is that doctors have usually little time for conversations with their patients. Talking with patients is unfortunately paid worse than prescribing medicines. Another reason is that some colleagues may feel poorly trained in how to talk to patients and, probably more important, how to deal with their emotional concerns. A third reason is that some patients tend to conceal their emotional concerns. This happens, inter alia, because they do not want to bother their oncologists or surgeons with their problems, realising that the doctors have already very little time and so much work to do, and they do not want to disturb them with their – as they may feel it – minor or ridiculous problems. Some patients may find it easier to open up to their general practitioner than to their surgeon.

Head and neck cancer occurs more often in men than in women, and men find it, on average, harder to talk about their emotional problems, simply because they were brought up with the slogan "boys don't cry," and hence, they feel as a looser or "sissy" when they do. It takes patience and an active approach from the doctor to learn from the patients where he is suffering from. Men may find it difficult to be in need for help in the first place, and needing help for emotional problems may be even harder.

In an Australian study [15], about 1,100 general practitioners were interviewed about their experience with men talking about their emotional concerns. The doctors said, for example: "*Men find it hard to open up*, *you have to be very alert to notice warning signs. Often first impressions. A good history usually makes diagnosis relatively easy*, *but men don't generally volunteer as much information …. Reluctant to come to the doctor in the first place and when they do*, *they focus on physical symptoms rather than their state of mind*."

Even relatives may underestimate the patients' emotional problems because the patients feel unable to confide in them. An illustrative example was published by Gibson and McCombe [9]. They interviewed patients who had been treated with total laryngectomy along with their partners after discharge from the hospital. The following passage illustrates the despair of the patients and their inability to open up even to their partners: "*The patient's partner felt that the patient's mood was unchanged following the operation. The only difference she felt was that he was more willing to walk the dog. When interviewing the patient later that afternoon he graphically explained how when walking the dog he would stand for hours by the railway line*, *staring at the track*, *trying to build up the courage to jump in front of the speeding trains*." (p. 351).

Stigma and Social Withdrawal

A specific problem in head and neck cancer is that the consequences of the disease and its treatment can not be concealed – other people can see, hear and sometimes even smell that these patients had cancer. This may result in stigmatisation [16]. In

general, a stigma is an unwanted individual characteristic that differentiates one person from the others and that leads to social withdrawal of these "others" [17]. The extent of withdrawal depends on the type of the stigma: A disease that is visible and severe evokes more social distance than a disease that is visible but not serious. The withdrawal is lowest if the disease is invisible [18]. Research into stigmatisation has shown that the reasons for such a social withdrawal are insecurity in social interactions, fear that the own wellbeing may suffer, assuming moral weakness in the stigmatised person, feeling guilty to be healthy, and disgust [18].

However, not only the others may withdraw from the patient. Head and neck cancer patients also withdraw from their social environment [19–22]. Why do they do this? It can again be explained by stigmatisation which is a two-sided process. If people are stigmatised by others, they receive negative reactions more frequently. This can result in a negative self-concept, especially when the stigma is accepted as being a part of the self. Avoiding contact with other people alleviates negative feelings (of being unwanted, ugly, disabled, etc.) and makes the patient feel more in control. On the downside, it prevents him from making positive experiences in the social contact with other people which can result in a vicious circle [21].

How to Measure Distress and Quality of Life

Distress and quality of life issues can be identified in the doctor-patient consultation simply by asking "How do you feel?" if this is accompanied with showing the patient that we have the time and willingness to listen to him.

Another option, optimally in addition to the individual consultation, is to use validated questionnaires. They provide reliable data and are easy to use in the daily routine and in clinical studies. Frequently used tools to screen for distress are the Hospital Anxiety and Depression Scale (HADS) [23], the Patient-Health-Questionnaire Short Form (PHQ-9) [24], and the Distress Thermometer (DT) [25]. All of them are reliable, validated for cancer patients, translated into several languages and brief [26–28].

Good instruments to measure quality of life in cancer patients are the Functional Assessment of Cancer Therapy (FACT-G) [29] and the European Organisation for Research and Treatment of Cancer Quality of Life Core Questionnaire (EORTC QLQ-C30) [30]. For patients in palliative care, the shortened version EORTC QLQ-C15 can be recommended.

Specific for head and neck cancer are, for example, the Functional Assessment of Cancer Therapy, Head and Neck Module (FACT-HN) [31], the University of Washington Quality-of-Life Instrument (UW-QOL-R) [32], the MD Anderson Symptom Inventory – Head and Neck Module (MDASI-HN) [33], and the head and neck module of the EORTC (QLQ-H&N35) [4]. The latter is currently being revised and updated to cover side effects of modern treatment schemes [8]. All these instruments are well accepted by patients [34–36].

How to Talk About Emotional Distress and Quality of Life

As outlined above, head and neck cancer patients might find it difficult to approach the doctor actively and talk about their emotional concerns. This is not only related to the fact that they are frequently men who are socialised not to show weakness or despair, they also often had less education than the doctor whom they are speaking to which may make them feel intimidated and shy. The best way to cope with this situation is to actively and repeatedly ask the patient about his quality of life, with interest and concern. When patients realise their doctor really cares, they open up more freely. This is not only in the interest of the patient but also helpful for tailoring supportive care and increasing adherence to treatment [37].

The following advices can guide doctor-patient consultations:

- Don‘t wait until your patient says something.
- Ask actively how he/she feels.
- Ask repeatedly.
- You do not need a lot of time for this, just be present in the moment and show that you really care.
- If professional psychological help is needed, offer it as something normal. Make it a “prescription” that the patient should use.
- Provide addresses of social workers, psychologists, self-help groups, etc.
- Patients want to talk to you in the first place. Do not simply send them away to the psychosocial experts. Instead, offer your time and *additionally* the help of the experts.

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Chapter 19
Symptoms at End-of-Life of Head and Neck Cancer Patients

Dirk Schrijvers

Introduction

Patients with recurrent/metastatic head and neck cancer will eventually develop a disease stage that is not amendable anymore for cancer-directed treatment with surgery, anticancer medication, and/or radiotherapy. These patients should receive optimal symptom control by means of palliative care.

Palliative care is an approach that improves the quality of life (QoL) of patients and their families facing the problem associated with a life-threatening illness. This aim is realized through the prevention and relief of suffering by means of early identification, assessment, and treatment of physical, psychological, social, and spiritual problems [1]. Palliative care should be given by a multidisciplinary team that addresses all these problems.

Epidemiology of Symptoms at the End-of-Life

During the last weeks of the life, head and neck cancer patients experience problems at many levels.

- Severe *physical problems*, defined as a score >4 on the Edmonton Symptom Assessment Scale (ESAS), which are most commonly experienced during this phase are weight loss, pain (±30–85 %), dyspnea (±20), nausea (±15 %), lack of appetite (±37 %), asthenia (±58 %), drowsiness (±30 %), dysphagia, feeding problems (62 %), respiratory (43 %), and communication difficulties [2–4].

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- *Emotional problems*, such as anxiety (±30 %) and depression (±25 %), are also commonly observed in head and neck cancer patient at the end-of-life [3].
- *Social problems* are prevalent. The stress level of the nonprofessional caregiver determines if a patient can stay at home during the last phase of his/her life. This depends on the support, that is provided to help the caregiver to perform his/her tasks at home. In case of insufficient support, the patient will be institutionalized because of burn-out or unbearable stress of the caregiver [5].
- *Spiritual problems* at the end-of-life have not well been studied in patients with head and neck cancer [6], but in cancer patients at the end-of-life, it seems that they are discussed in only around 20 % of patients [7].

All these problems should be addressed, and by using of a standardized approach they may be adequately discussed and handled, resulting in a better QoL [3].

Treatment of Selected Physical Problems

Physical problems should be addressed, but the situation of the patient should be taken into account before deciding on the adequate approach. Several problems (e.g., nutrition issues) may be important in the perception of the patient and the family, but may be not considered to be essential by the professional caregiver. However, the perception of these problems by the patient and the family should be addressed adequately by the professional caregiver to avoid miscommunication and inadequate behavior by both parties.

Problems should only be addressed by an aggressive treatment approach if it will improve/stabilize the QoL of the patient. Otherwhile, the professional caregiver should explain the benefits and harms of any intervention, in order not to persist or start with a meaningless treatment and adhere to therapeutic obstinacy.

Gastro-Intestinal Problems

Many patients with head and neck cancer experience gastro-intestinal problems at the end-of-life such as foul breath, trismus, xerostomia, sticky saliva, swallowing difficulties, dysphagia, or insufficient calorie intake, partly due to the disease but also due to previously administered treatments.

Some of these symptoms cannot be alleviated (e.g., trismus, dysphagia), while others can be improved by care measures (e.g., treatment of yeast mucositis, mouth hygiene, antibiotics against anaerobic bacteria, adequate hydration of the mouth mucosa or artificial saliva) or the use of artificial feeding measures such as the use of an available percutaneous gastrostomy or a nasogastric tube.

Nutrition by mouth should be used very carefully in patients with dysphagia or swallowing difficulties at the end-of-life because they can give rise to an aspiration pneumonia.

Constipation may develop in patients with inadequate fluid and food intake and should be addressed by laxatives, either orally or by rectal administration to avoid gastrointestinal obstructive due to fecal impaction.

Respiratory Problems

Respiratory problems may be a consequence of loco-regional recurrent disease resulting in an airway obstruction. The placement of a tracheotomy may be considered, but this treatment option should be discussed in advance with the patient, since a tracheotomy needs adequate care and may result in additional problems.

Dermatological Problems

Loco-regional recurrences or metastases may give rise to ulcerations of the skin. In case of ulcerations that result in excessive exudation, specific dressings may be used to absorb exudations; in case of foul odor, due to sur-infection by anaerobic bacteria, topical metronidazole, or specific antibacterial dressings may control the smell.

Pain

Patients with head and neck cancer may experience pain at the end of their lives. Pain can adequately controlled in around 80 % of patients by using the guidelines of the World Health Organization [8]. At the end of life, many patients are not able to swallow pain medication. They can be administered by other means taking into account that for chronic pain control, transdermal or subcutaneous opioids have a different absorption in cachectic patients and the interval of administration should be decreased (e.g., every 48 h instead of 72 h for fentanyl) or the dose should be increased.

In case of problems of administration, opioids, paracetamol, and nonsteroidal anti-inflammatory drugs may be administered intravenously in order to improve the delivery of these drugs.

Treatment of Psychological Problems

At the end-of-life, many patients with head and neck cancer experience anxiety for their future or of specific symptoms (e.g., suffocation).

Anxiety should be addressed by psychological support, but medication (e.g., benzodiazepines such as midazolam) may be used in selected patients.

Treatment of Uncontrollable Symptoms

At the end-of-life, patients with head and neck cancer may experience symptoms that cannot be controlled by standard symptomatic treatment. They may occur in every field (e.g., physical problems of dyspnea, pain, delirium; psychological problems such as anxiety, depression; spiritual problems such as existential issues).

If these symptoms cannot be controlled by interventions of experts in the field of the problem, a palliative sedation may be used to control these treatment-refractory complaints. By reducing the level of consciousness with sedative drugs such as benzodiazepines or anesthetics, refractory symptoms may be controlled [9].

Discussing End-of-Life Issues

Patients with head and neck cancer at the end of their lives have gone through a long disease trajectory, and at each moment of a change in the disease status (e.g., recurrent disease, first-, second-, and third-line treatment, palliative care), the opportunity of discussing advanced care planning may be explored in order not to be in a position that the family or the professional caregiver have to decide on further treatment (e.g., reanimation), palliative sedation, or other life decisions. Therefore, end-of-life issues should be discussed and registered in the patient file [10].

Conclusions

Patients with head and neck cancer suffer from different problems at the end of their lives. These problems should be evaluated in a standardized manner and adequately addressed to maintain or improve QoL.

Patients should be informed of the different issues that may arise in the future and discussions on end-of-life issues should be integrated in patient care.

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Chapter 20
Issues at End of Life

Rodger Charlton

This chapter focuses on the issues at the end-of-life from a GP/family physician perspective for patients dying from head and neck cancer. It is rare for a GP to encounter such patients, but I can vividly recall those who have died, and similar to other cancer patients, there are many individual challenges posed by the area of the body that the cancer affects.

In my experience, particular issues of and concerns for patients with head and neck cancer are:

- Change in body image
- A disease which is often very slow and distressing to watch
- Pain which is difficult to treat
- Feeding which is a huge issue
- Protecting the airway
- Difficulties with speech and mouth care
- Input from a specialist is always helpful and appreciated
- To have regular medical and nursing contact and availability

The greatest issue of all dying patients is maintaining quality of life and ensuring a 'good death' for people whom we have cared for, often for many years. I will now discuss the issues at the end of life that influence quality of life and so end of life care.

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Why Talking About Dying Is So Difficult

Freud in 1915 reflects and tells us why this whole subject is so difficult [1];

> Our own death is indeed unimaginable and whenever we make the attempt to imagine it we can perceive that we really survive as spectators … at bottom no one believes in his own death, or to put the same thing in another way, in the unconscious every one of us is convinced of his own immortality.

When talking to a patient about dying, it reminds us of our own mortality and patient and doctor alike; it makes us perhaps ask two searching questions;

- Is it death we are frightened of or not being here and being a part of everything?
- Is it the anxiety and fear through the anticipation of dying?

These are questions that we rarely consider when we are well and 'healthy', but changes when we are ill and could be viewed as spiritual anxiety or pain which often has nothing to do with religious faith. We know when we are successfully communicating with a dying patient when they ask, "What will dying be like?" We cannot know and it is an unnerving question.

It is important to talk to the patient, gain their trust and keep talking. Successful palliative care is about two things:

- Good communication
- Adequate symptom control

'Total Pain' and Spiritual Pain

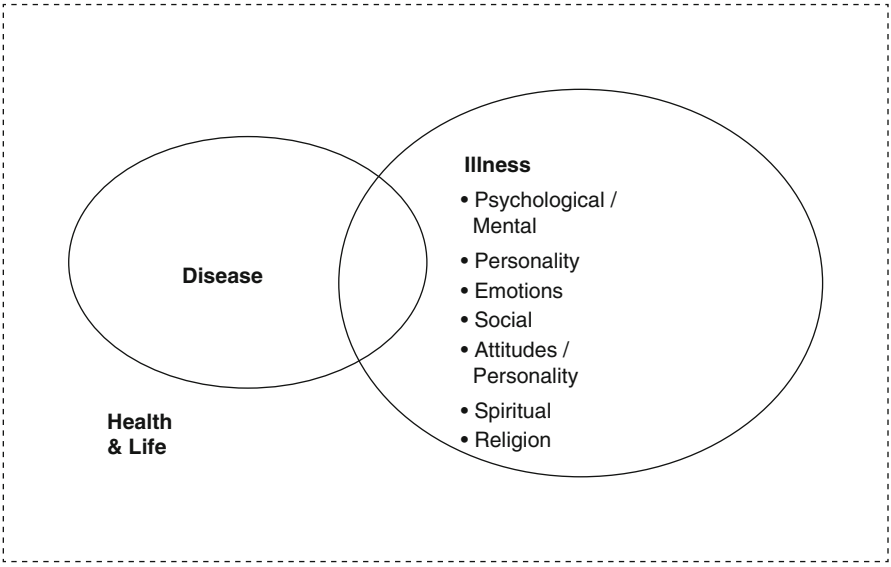
This thinking is not new, but is rarely discussed and yet is something all doctors encounter. The late Dame Cicely Saunders who is attributed as the founder of the modern hospice movement coined the phrase 'total pain' in the 1960s which she referred to as the physical, psychological, mental, emotional, social, as well as spiritual [2]. Consideration of this helps to adopt a more holistic and patient-centred approach to the care of a dying patient. In a personal communication by someone who met Dame Cicely Saunders as a student (Prof Patrick Pietroni) when she informed him that 'feelings are facts', a phrase that he has not forgotten.

The concept of spiritual is included in the European Association of Palliative Care (EAPC) definition of palliative care as follows:

> Palliative care is the active, total care of the patients whose disease is not responsive to curative treatment. Control of pain, of other symptoms, and of social, psychological and spiritual problems is paramount [3].

The concept of spiritual pain or spirituality is not necessarily related to a religious faith. It may overlap but in the dying patient is often totally separate from it.

It is possible to try and illustrate spirituality in a Venn Diagram [4] as follows, which has been annotated from the late Prof Cecil Helman [5], GP and an anthropologist;



The broken line or box is meant to signify the existential element to health and illness. One should consider the total needs of the patient and not just their pain and symptoms. Where symptoms cannot be controlled, it is because all aspects of a person have not been considered, for example, unresolved personal conflicts.

The Transition from 'Being' to 'Un-being'

To understand spirituality and spiritual pain, it can be considered by reflecting on the author of the novel 'Ring of Bright Water' by Gavin Maxwell which was set in rural Scotland. He is reported to have recalled the great pain of the solitary moment of moving from 'being to un-being' when he was dying of cancer.

Doctors are rarely present at the moment when patients die and tend not to have or avoid conversations about dying. However, it could be argued that reducing spiritual pain is facilitating a person to the transition from 'being' to 'un-being' [6].

Another author [7] wrote in a similar vein describing who illness is a threat to our very being:

> As soon as we are ill we fear that our illness is unique. We argue with ourselves and rationalise, but a ghost of the fear remains. And it remains for a very good reason. The illness, as an undefined force, is a potential threat to our very being.

Subjectivity and Objectivity

It is challenging to provide objectivity when we reflect on how we might talk to dying patients as it is an area of subjectivity. In relation to the term spirituality and spiritual pain, there are several possible definitions. For example, spirituality as a mechanism which allows a person to experience transcendent meaning in life or it could be as is often the case something which is frequently expressed as a relationship with God. Spirituality can also be about nature, art, music, family or community and so whatever beliefs and values give a person a sense of meaning and purpose [8].

In order to try and be objective about what is important to patients rather than us considering what might be important, a USA paper considered the factors important at the EOL by patients, family, physicians and other care providers [9]. A random national survey was conducted in 1999 of seriously ill patients ($n=340$), bereaved ($n=332$), physicians ($n=361$), other carers (nurses, social workers, chaplains, hospice volunteers; $n=429$). The paper found 44 attributes of quality at EOL as important. The key findings of this paper were the following issues which were important to patients and others but not so important to physicians ($p<0.001$):

1. Be mentally aware
2. Be at peace with God
3. Not be a burden to family
4. Being able to help others
5. Prayer
6. Have funeral arrangements planned
7. Not be a burden to society
8. Feel one's life is complete

Doctors might have thought that the following would be of the upmost importance:

- Pain control
- Symptom control
- Depression
- Cure

However, overall "Freedom from pain" and "Being at peace with God" were ranked as most important (and were statistically equivalent) by patients and doctors. It is important never to make assumptions caring for a dying patient, but to ask them what worries them the most.

Patients Reaching Acceptance That They Are Dying

For most people, death is almost a taboo subject, where a taboo is literally a social prohibition to talk about the subject. In the 1960s, Elizabeth Kubler Ross, a Swiss born psychiatrist working in the United States, was someone who also had a

considerable influence on the modern hospice movement. She is perhaps best known for her proposed five stages of anticipatory grief of which the last stage is when the patient moves from depression to acceptance of their illness [10]. As part of the taboo, it could be argued that it is rare to experience a patient who is dying that reaches the stage of acceptance, but rather more appropriately they are resigned to their fate and so in a state of resignation, thus adding a sixth stage to the original proposal.

It is vital that doctors talking to dying patients do not view these view these five stages as written in tablets of stone and that in reality few patients reach a stage of acceptance and it is important to recognise this. Despite what anyone tells you, remember that most patients are not in acceptance of their fate but rather resigned to it.

As Doctors, We Have Medicalised Death

When we communicate with dying patients, we should bear in mind that as well as ameliorating physical pain and symptoms, for example, a cancer patient, our greatest role, although we least appreciate it, is facilitating the transition to ideally acceptance of dying. This is difficult as for the public [11].

- It is rare for the majority of the public to see a dead body.
- Dying has been 'medicalised' in UK institutions where more than 70 % of people die.
- Death has been transformed from being an accepted everyday occurrence and natural part of the life cycle, into a 'taboo subject'.
- Dying has been medicalised, professionalised and sanitised to such an extent that it is now alien to many people's daily lives ('The lost art of Dying').

As we attempt to communicate with our patients who are dying, in order to help them accept their fate, we need to take into account the personal conflicts with family members or friends that are so important in enabling a person to re-order their priorities and let go. Getting involved in these conversations and circumstances is something that doctors tend not to do as they do not appreciate that although they are not medical their influence on the patient's state of mind are paramount. During our conversations with the dying, it is difficult for both us and our patients to come to terms with death as a 'rite of passage' in which we will all participate as family member, provider or, eventually, patient.

All, whether doctor or patient contradict all that we know and so what was written as long ago as 1612 Sir Francis Bacon that death is part of the natural life cycle [12]; '*To die is as natural as to be born'*. Very poignant, as now you have to have a form signed which allows you to die, the DNAR (Do Not Attempt Resuscitation form) and inevitably end up with a syringe driver in case of pain or perceived distress where the 'doctrine of the double effect comes into place' where the intention is to relieve symptoms but unintentionally the use of opiates may hasten death.

Patients, particularly dying patients, do not fit guidelines and so the advocated palliative care pathways. Talk to the patient, find out what they want and overcome the taboo. Make sure they are aware and have consented to a DNAR form which again means good communication and a difficult conversation and similar conversations over the use of a syringe driver and that it is for the patient's symptoms and not treating observed distress of the carers.

'Conspiracy of Silence'

In relation to communicating with dying patients, Elizabeth Kubler Ross was also remembered for coining the phrase 'conspiracy of silence' [13] when thinking of a patient with a terminal illness where nobody is talking to each other or the patient, but everybody's talking about their terminal illness. So often is the case that a patient has a very good idea what is happening to them when they are dying, but no one is talking to them about it directly. Furthermore, the influence of the family is strong who can sometimes request doctors not to disclose details of the terminal illness to the patient. Relatives may be well intentioned by not wanting their loved one to suffer through such information.

However, the spiritual pain the patient will experience is the fact that information is being kept from them to which they are entitled and so they perhaps cannot make the preparations they would wish and address any unresolved conflicts. Ideally, patients should always be assured of their autonomy and confidentiality. A review of one of Kubler-Ross's books states [14];

> [Kubler-Ross's] work has vanquished the conspiracy of silence that once shrouded the hospital's terminal wards....In so doing, it has shown how, and with what quiet grace, the human spirit composes itself for extinction.

It is important not to exclude the patient from conversations that affect them, matter how well-intentioned. If necessary, talk with everyone present, including any close relatives / carers. Always remember the needs of the informal carer as the workload can takes its toll on them often looking after a person 24 h a day and it is important to check that they are coping and well.

Enabling a 'Good Death'

Bevins and Cole describe how technology and modern medicine at the EOL may be at odds with the concept of enabling a 'good death' and overcoming spiritual pain [15];

> Death is the edge of a mystery, and turning our faces toward the problematic, through the persistent use of technology, at the hour of death keeps us from having to face this mystery. Death is no problem to be solved; it resists any such formulation…by keeping our attention on end-of-life problems, we ignore the mystery of the end of life.

It is important to treat every patient as an individual.

When a Patient Dies and the Bereavement That Follows

Communication does not finish with the death of the patient

It could be disputed whether or not bereavement is a medical problem [16], but in terms of the lay person,

> Grief is like a raging river [17]

It is a significant life event and it is inevitable that all medical practitioners regardless of speciality will encounter patients who have or are presently experiencing bereavement.

Shakespeare in his play, Much ado about nothing [18], states,

> Everyone can master a grief but he that has it.

Palliative care does not stop with the death of a patient, but continues with the needs and care of the bereaved. It is greatly valued by those who are left.

Important Considerations

Achieving a 'Good Death' means having choice and control over;

1. Where death occurs (at home or elsewhere)
2. Who is present and shares the end
3. Adequate resources of staff / appropriate bed
4. Availability community staff to anticipate crises at home
5. Good symptom control

Despite best attempts, inappropriate admissions to hospital are common. However, it should be recognised that more than 90 % of patients spend the majority of their last year of life and receive palliative care at home, despite a significant proportion of patients dying in hospital. This places GPs at the heart of palliative care provision.

Careful Planning is required for the last 7 days of life, and where it can be predicted, the last 24 hours. Continuity and availability for this period from dedicated staff to anticipate crises and prevent inappropriate hospital admission are essential.

Feelings of Gilt and Personal Bereavement

Caring for the dying, if done well is exhausting. To provide the best level of care to our dying patients, we have to get to know them well to understand their concerns and fears fully. This requires an emotional investment by doctors that can result in a more significant emotional cost when their patient inevitably dies. We are not immune to the emotional effects of death, and we will sometimes need to express our own emotion and grief.

At this stage, it is likely that the specialist may not be involved, and after a very long relationship with a patient, there are feelings of guilt and a personal bereavement. It is vital therefore to be aware of this, and it is important therefore to look after our own wellbeing whilst helping our dying patients, but without losing sight of their needs.

Ideally, you follow up and care for a patient from the time of diagnosis, through to death. This is not realistic for a specialist as many patients die in their own homes. However, if you wish and are able practically to stay in contact, then do so and it will be greatly appreciated by the patient and their family.

If this is not possible, when informed of a patient's death it may be helpful to reflect on their death with colleagues which will help with your care of future patients. Consider recording the anniversary of their death to make contact with the relatives as a part of a good bereavement protocol.

Where treatment is not possible it is important to emphasise that death is not a failure of medicine but is the inevitable result of life. As medicine has advanced, we have put more and more effort into delaying death. Atul Gawande in his essay entitled 'Letting Go', the priority should be a move away from fighting death to a focus on building a healthcare system that will help dying patients achieve what is important to them [19].

Place of Death

Although research has suggests that majority of patients would wish to die at home, it should not be assumed that everyone wishes to die at home [20]. Some people may wish to die in hospital as they wish not to be a burden and to have a pain-free death under the specialist as dying in pain can be a huge anxiety. Interestingly, caregivers show a greater preference for institutional death [21].

Typically for me as a UK GP if a diagnosis, for example, of terminal cancer is made, I attempt to follow that person up in clinic and have a coding system on the computer to remind me. The patient is given an 'open door' policy giving the security of knowing there is someone there for them is vital and to have the all important conversation avoiding the 'conspiracy of silence'.

For all doctors, to keep in touch when they are no longer able to get to the clinic, the GP should engage community services, for example, the community nurse and palliative care nurse specialist. A point will come when the patient cannot get to your clinic, and there is a need to visit where possible. A considerable challenge is being available in-hours and out-of-hours to prevent crisis hospital admissions and although ideal, like anything altruistic, is very difficult to achieve.

The GP should do their best to support the carers/family and be available at the time of death and afterwards. The challenge to all of us whether specialist or GP, working together, is how to influence change to achieve these ideals, see what hurdles can be overcome and where possible work towards a death at home, remembering a good death is possible in hospital. But the key for the patient is staying in touch with these patients as long as you can which will be mutually helpful.

Conclusion

When one of our long standing patients can no longer be cured,

- It may come as a shock, to both patient and doctor
- The science of symptom control is the easy bit, or at least it can be learnt and there is a huge resource of knowledge and expertise.
- Consulting and talking to dying patients is difficult.
- It is an area of medical training which is deficient and yet needed by doctors in all specialties.
- Death has been medicalised and the general population has little contact with it.
- It is difficult as it questions our mortality and like patients results in 'spiritual pain' often in the absence of a religious faith.
- The final and often most difficult part of palliative care, which is often unintentionally neglected, is bereavement and so what happens afterwards.

To best help a dying patient with head and neck cancer, their expectations of a doctor whether a specialist or GP have not changed and are:

- To be their doctor
- Accompany them on the journey
- To follow them up, even when cure is not possible
- Availability
- Be there for them
- Communication, communication, communication
- Not sympathy or empathy but compassion

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