Received: 11 April 2019 | Revised: 5 July 2019 | Accepted: 11 July 2019

DOI: 10.1002/hed.25890

ORIGINAL ARTICLE

WILEY

Long-term outcome of re-irradiation for recurrent or second primary head and neck cancer: A multi-institutional study of AIRO—Head and Neck working group

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Abstract

Background: To report the long-term outcome of patients undergoing re-irradiation (re-RT) for a recurrent or second primary head and neck cancer (RSPHNCs) in seven Italian tertiary centers, while testing the Multi-Institution Reirradation (MIRI) recursive partitioning analysis (RPA) recently published.

Methods: We retrospectively analyzed 159 patients. Prognostic factors for overall survival (OS) selected by a random forest model were included in a multivariable Cox analysis. To externally validate MIRI RPA, we estimated the Kaplan-Meier group-stratified OS curves for the whole population.

Results: Five-year OS was 43.5% (median follow-up: 49.9 months). Nasopharyngeal site, no organ dysfunction, and re-RT volume <36 cm^3 were independent factors for

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better OS. By applying the MIRI RPA to our cohort, a Harrell C-Index of 0.526 was found indicating poor discriminative ability.

Conclusion: Our data reinforce the survival benefit of Re-RT for selected patients with RSPHNC. MIRI RPA was not validated in our population.

KEYWORDS

head and neck cancers, modern RT techniques, overall survival, re-irradiation, toxicity

1 | INTRODUCTION

Although surgery represents the mainstay[1] of treatment for recurrent or second primary head and neck cancers (RSPHNC), only few selected patients with resectable tumors are eligible for salvage surgery.[2] In this scenario, and more significantly in case of intrinsically inoperable diseases, re-irradiation (re-RT) can play a relevant role, provided that the benefits of this approach on patients' outcome do not outweigh its potentially severe and life-threatening sequelae.[3,4] Thus, an appropriate patients selection for re-RT is crucial to improve the therapeutic ratio. Even in the presence of inherent shortcomings resulting from the heterogeneous sample of population included in retrospective and randomized prospective studies, several prognostic factors can be taken as relevant, such as the burden of comorbidities,[5,6] preexisting organ dysfunctions,[7] the volume of recurrence and its histology,[8] re-RT total dose and disease-free interval (DFI) between the two RT courses.[9,10] However, the best re-RT approach in terms of techniques and fractionation is still far from being defined.[11] Recently, the pivotal American multi-institution reirradiation (MIRI) consortium experience provided a toolkit to identify prognostic categories for overall survival (OS) for patients receiving re-RT with both stereotactic body radiotherapy (SBRT) and intensity modulated radiotherapy (IMRT).[8,12,13] In brief, a recursive partitioning analysis (RPA) identified three prognostic subgroups with distinct and homogenous OS ($P < .001$): class I included patients >2 years from their initial course of RT with resected tumors (2-year OS, 61.9%); class II included patients >2 years with unresected tumors or those ≤2 years and without organ dysfunctions (2-year OS, 40.0%), and the remaining patients formed class III (2-year OS, 16.8%).[8]

Taking into account the intrinsic uncertainty regarding the decision-making for re-RT, it would be worthwhile to assess if the MIRI data can be extrapolated to non-U.S. practice.

The aim of our study was to investigate the impact of re-RT on OS in a large multi-institutional cohort of patients with RSPHNC, with a special emphasis placed on the association with clinical, disease, and treatment-related factors. In addition, we sought to evaluate whether the MIRI RPA model could be transposed to our patients' population or not.

2 | MATERIAL AND METHODS

2.1 | Study population

On behalf of the Italian Association of Radiation Oncology (AIRO)—Head and Neck working group, a retrospective study was performed on patients who underwent re-RT for RSPHNC at seven tertiary cancer centers. This study was approved by each institutional ethical committee.

The study period was extended between 2002 and 2016. Inclusion criteria were the following: (a) initial and subsequent diagnosis (recurrent or second primary tumor) of squamous cell carcinoma (SCC), undifferentiated carcinoma of the nasopharynx (UNPC), or salivary gland carcinoma (sarcoma and melanoma were excluded) without metastatic disease at the time of re-RT; (b) histologically confirmed RSPHNC after physical examination, computed tomography (CT), magnetic resonance imaging (MRI), and/or positron emission tomography with 2-deoxy-2-[fluorine-18]fluoro-D-glucose/CT (18F-FDG PET/CT); (c) previous curative RT with a total dose of at least 50 Gy with conventional fractionation; (d) postoperative or definitive re-RT given with conformal three dimensional RT (3D-CRT), IMRT techniques or SBRT, with or without induction or concomitant chemotherapy (CHT); (e) DFI of at least 6 months between the two courses of radiation; (f) recurrent or second primary tumor with a ≥50% overlap with a previously irradiated area; (g) minimum follow-up after re-RT of at least 6 months; (h) re-RT given with conventional fractionation (CF) or hypofractionation with a total biological effective dose (BED) of at least 45 Gy ($\alpha/\beta = 10$ Gy, BED_{10}).

In all oncological centers, the indication for re-RT was considered by the multidisciplinary team in case of unresectable recurrence (definitive setting) or when high-risk pathologic features were found after salvage surgery, such as extranodal extension or close/positive margins (postoperative setting).

The addition of chemotherapy in both settings was prescribed based on a case-by-case decision.

In terms of re-RT technique, 3DCRT was given with 3-5 fields with CF (single daily fractionation of 1.8-2 Gy), whereas IMRT could be administered through step and shoot or sliding window techniques, volumetric modulated arc therapy (VMAT), or tomotherapy with CF (up to 2.2 Gy per

fraction, fr) or moderately accelerated RT (dose per fraction from 2.2 to 3 Gy/fr) up to a total dose of 45-70 Gy.

SBRT was delivered with CyberKnife or VMAT with high-precision imaged-guided systems or tomotherapy with hypofractionated regimens in 5 frs to a total dose of 29-30 Gy (5.8-6 Gy per fr).

Regarding re-RT target volumes, a clinical target volume (CTV) margin of 5-10 mm was usually added to the recurrent tumor, according to the treating center policy. Of note, no CTV margins were applied for SBRT. In adjuvant re-RT, a tumor bed CTV was defined based on presurgical clinical and imaging data, pathologic report, and postoperative imaging. Elective nodal irradiation was not performed in any case. Depending on the treatment facility and re-RT modality, a CTV to planning target volume (PTV) margin ranged between 3 and 5 mm.

TNM staging system, VII edition, was used to stage RSPHNC from 2009. All cases diagnosed before were restaged accordingly. Patients were defined to have organ(s) dysfunction in presence of at least one of the following conditions: feeding tube or tracheostomy dependence, fistula, osteonecrosis, open wound of skin, and/or mucosa. True cancer recurrence and second primary tumors were classified according to criteria by Warren and Gatesas modified by the National Cancer Institute.[14] In addition, from a radiobiological perspective, an α/β value of 10 Gy was assumed for all re-irradiated tumors. Toxicity profiles were evaluated according to Common Terminology Criteria for Adverse Events (CTCAE) criteria.[15] Acute toxicity was considered to occur within 90 days from re-RT completion. Late toxicity was considered an event occurring >90 days beyond the end of RT.

2.2 | Statistical methods

The main study end point was OS, defined as the time interval between the re-RT starting date and death from any cause, with censoring for patients alive at the date of the last follow-up. The putative prognostic factors for OS were analyzed by estimating the survival curves using the Kaplan-Meier method and by fitting univariable Cox models. In the latter, continuous variables were modeled using three-knots restricted cubic splines.[16] This analysis was performed in the whole patient population and then in the subgroup of patients with SCC. We also performed a multivariable Cox analysis to test the variables selected beforehand for inclusion in the multivariable model according to their significance in a random forest (RF) model for survival data.[17,18] In particular, the RF model allows to quantify the relative importance (RI) of each variable, whereby higher figures indicate stronger association with OS. Variable selection was based on RI empirical *P* values calculated according to a permutation test.[19] Optimal re-RT volume (VRec) and BED_{10} cutoffs to classify patients as high vs low risk for OS were determined according to Mandrekar et al.[20]

With the purpose of externally validating the MIRI RPA model,[8] we estimated the Kaplan-Meier group-stratified OS curves for both the whole population and the subgroup of patients with SCC. As a measure of the between-curves separation, we used the Harrell C-index,[21] which may vary between 0.5 and 1.0, indicating lack of or perfect discriminative ability, respectively.

We also estimated the Kaplan-Meier progression-free survival (PFS) curves, where time was the interval between the re-RT starting date and disease progression or death from any cause.

All tests were performed two-sided at a significance level of 5%. The binary association between continuous and categorical variables was assessed using the Mann-Whitney-Wilcoxon test. The comparison between the Kaplan-Meier curves was carried out using the log-rank test. The analyses were carried out using the SAS (version 9.1) and R software.

3 | RESULTS

One-hundred fifty-nine patients were eligible for this analysis. Patients' characteristics and re-RT treatment details are shown in Tables 1 and 2, respectively.

Most patients with a non-SCC RSPHNC had UNPC (45/71, 63.4%) followed by adenoid cystic carcinoma (ACC) (25/71, 35.2%) of major salivary glands and paranasal sinuses. Thirty percent of patients received concurrent CHT of whom 67% with platinum-based regimens. Induction CHT was given in 12% of cases.

At a median follow-up of 49.9 months (interquartile range, 28.9-86.3), the 2- and 5-year OS were 75.7% (95% confidence interval [CI], 69.0%-83.0%) and 43.5% (95% CI, 34.6%-54.8%) and the 2- and 5-year PFS were 49.5% (95% CI, 42.1%-58.1%) and 20.9% (95% CI, 14.7%-29.6%), respectively. In the subgroup of patients with SCC, the 2- and 5-year OS were 62.0% (95% CI, 52.2%-73.6%) and 30.2% (95% CI, 19.9%-45.8%), and the 2- and 5-year PFS were 37.2% (95% CI, 28.2%-49.1%) and 11.9% (95% CI, 6.2%-22.8%), respectively. At univariable Cox analysis (Table S1), younger age, nasopharyngeal site, Karnofsky Performance status (KPS) >80, absence of organ dysfunction, Charlson Comorbidity Index 0-1, histology other than SCC, recurrence N classification 0-1, IMRT, and lower re-RT volume were related to significantly better OS. As regard RT, SBRT resulted to have worse prognosis with respect to IMRT. OS according to RT technique is shown in Figure 1:2- and 5 -year OS estimates were 83.5% (95% CI, 74.6%-93.4%) and 64.3% (95% CI, 51.8%-80.0%) in patients treated with IMRT, and 64.1% (95% CI, 49.6%-82.9%) and 23.3% (95% CI, 10.8%-50.2%) in patients treated with SBRT, respectively.

TABLE 1 Patient characteristics

	No. of patients (%)
Age (y), median (first-third quartiles)	61 (52-72)
Institution	
a	48 (30)
b	32 (20)
c	28 (17)
d	20 (13)
e	19 (12)
f	9 (6)
g	3 (2)
Sex	
Male	106 (67)
Female	53 (33)
Site	
Nasopharynx	47 (30)
Oropharynx	32 (20)
Hypopharynx	10 (6)
Oral cavity	19 (12)
Larynx	25 (16)
Salivary glands	8 (5)
Paranasal sinus	18 (11)
Histology	
SCC	88 (55)
Other than SCC	71 (45)
Recurrent T classification	
rT0	31 (19)
rT1	24 (15)
rT2	27 (17)
rT3	26 (16)
rT4	51 (32)
Recurrent N classification	
rN0	103 (65)
rN1	23 (14)
rN2	31 (20)
rN3	2 (1)
KPS	
<80	23 (14)
≥80	136 (86)
Charlson comorbidity index	
0	16 (10)
1	14 (9)
≥2	129 (81)
Organ dysfunction	
None	140 (88)
Feeding tube dependency	5 (3)
Functional tracheostomy	7 (5)
Fistula	2 (1)
Osteonecrosis	1 (1)
Open wound of skin/mucosa	2 (1)
Tracheostomy and feeding tube	2 (1)
Disease status	
Recurrent	112 (70)
Second primary	47 (30)
Site of recurrence/second primary	
T	112 (70)
N	33 (21)
T+N	14 (9)
DFI (months), median (first-third quartiles)	40.3 (18-106)

(Continues)

TABLE 1 (Continued)

Abbreviations: DFI, disease-free interval; KPS, Karnofsky performance status; SCC, squamous cell carcinoma.

TABLE 2 Re-irradiation characteristics

Radiation therapy parameters	No. of patients (%)
Re-treatment setting	
Definitive	99 (62)
Adjuvant	60 (38)
Re-irradiation dose (Gy), median (first-third quartiles)	66 (60-70)
BED_{10} (Gy)*, median (first-third quartiles)	58.6 (48.0-66.0)
Cumulative dose (Gy), median (first-third quartiles)	120.0 (110.7-130.0)
Re-irradiation volume (cm^3), median (first-third quartiles)	32.1 (15.6-69.0)
Re-RT technique	
3D-CRT	21 (13)
IMRT	100 (63)
SBRT	38 (24)
Fractionation	
Conventional	121 (76)
Hypofractionation	38 (24)

Abbreviations:3D-CRT, three-dimensional conformal radiotherapy; IMRT, intensity modulated radiotherapy; SBRT, stereotactic body radiotherapy.
*Biological equivalent dose assuming an α/β value of 10 Gy: Biologically effective dose.

Re-RT volume was significant both when analyzed as a continuous and as a categorical (binary) variable using a statistically derived optimal cutoff value of 36 cm^3 (Table S1); 2- and 5-year OS estimates were 82.5% (95% CI, 74.5%-91.3%), 48.8% (95% CI, 35.9%-66.5%) in patients with ≤36 cm^3, and 67.8% (95% CI, 57.5%-79.9%) and 37.8% (95% CI, 26.8%-53.2%) >36 cm^3, respectively (Figure 2). On the other hand, as regards re-RT BED_{10}, which was not significant when analyzed as a continuous variable, it was not possible to derive a cutoff for discriminating two groups with significantly different OS.

After RF selection of prognostic variables, nasopharyngeal site, no organ dysfunction, histology other than SCC, and VRec ≤36cm^3 were significantly associated with better OS. Multivariable Cox model results are shown in Table 3, and the corresponding OS curves are shown in Figures S1-S4 and Figure 2.

In the subset of 88 patients with SCC, we separately investigated re-RT technique (SBRT vs others), cumulative dose, VRec, and re-RT setting (definitive vs postoperative) at univariable Cox analysis, and none was significantly associated with OS (P = .54, .70, .14, and .10, respectively).

Figure 3 shows the Kaplan-Meier OS curves of the entire population and of the subgroup of patients with SCC according to the MIRI RPA classes.[7] In our population, classes I and III were poorly represented. Considering all patients, most of them were categorized as intermediate risk (group 2; n = 123), followed by low (group 1; n = 25) and high risk (group 3; n = 11). A similar proportion among the three categories was found for patients with SCC (groups 1, 2, and 3 with 10, 16, and 62 cases each). The 2- and 5-year OS estimates for the whole series were 78.3% (95% CI, 63.2%-97.1%) and 55.5% (95% CI, 37.1%-83.2%) in group 1, 77.5% (95% CI, 70.2%-85.5%) and 43% (95% CI, 32.7%-56.7%) in group 2, and 45% (95% CI, 21.8%-92.7%) and 15% (95% CI, 2,6%-86.8%) in group 3, respectively (P = .27). For the SCC population, the 2- and 5-year OS for each class were as follows: 78.1% (95% CI, 53.5%-.99.7.1%) and 38.4% (95% CI, 16.8%-87.3%) in group 1, 62.4% (95% CI, 51%-76.3%) and 29.8% (95% CI, 18.1%-49.1%) in group 2, and 38.1% (95% CI, 36.8%-98.7%) and 19% (95% CI, 15.7-92.4%) in group 3 (P = 0.916). Harrell C-Index values of 0.526 and 0.521 were found by applying the MIRI RPA to the whole cohort and to the SCC population, respectively, indicating poor discriminative ability of such prognostic classification on our series.

With regard to toxicity, 28 patients (17.6%) developed ≥G3 late toxicity, in particular dysphagia with percutaneous endoscopic gastrostomy dependence (10 patients, 35.7%), esophageal stricture (5 patients, 17.9%), and osteoradionecrosis of the

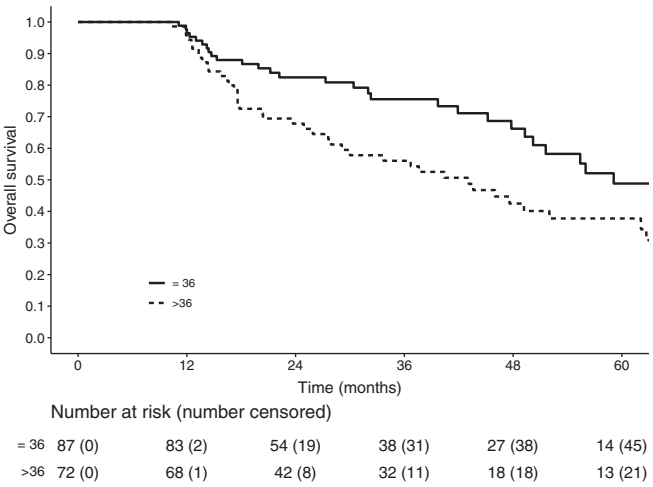

FIGURE 2 Kaplan-Meier overall survival curves in the two groups of patients with re-irradiation volume ≤36 cc and >36 cm^3

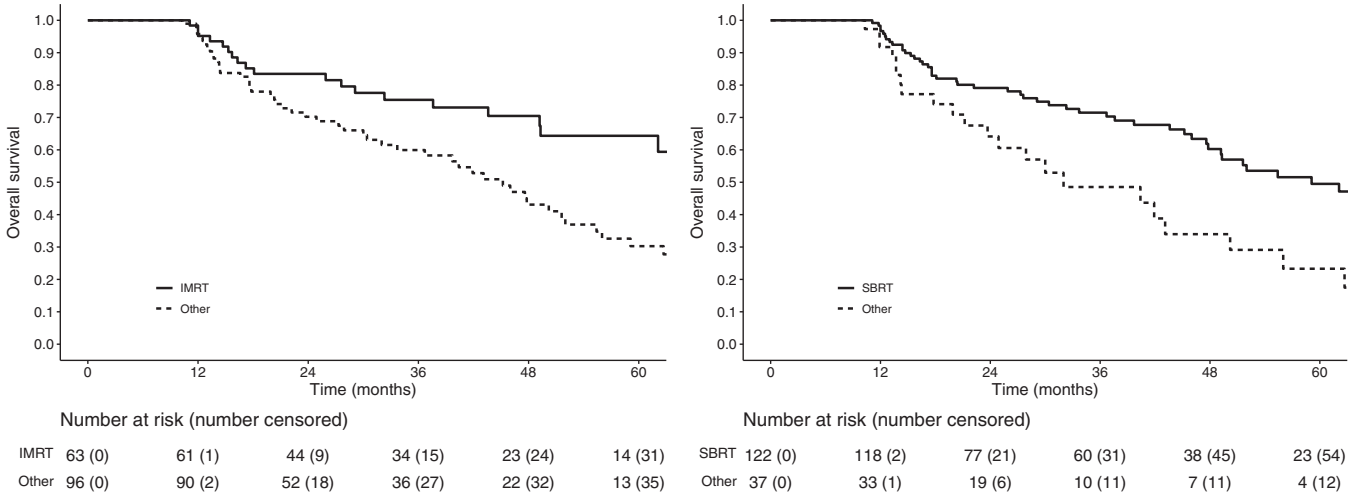

FIGURE 1 Kaplan-Meier overall survival curves according to RT technique: IMRT vs other (left) and SBRT vs other (right). IMRT, intensity modulated radiotherapy; RT, irradiation; SBRT, stereotactic body radiotherapy

mandible (2 patients, 7.1%) and necrosis of the temporal lobe (2 patients, 7.1%). One case of fatal carotid bleeding occurred, although it was impossible to clearly establish if the cause of this event was locoregional progression or re-RT-induced late toxicity.

The median (first-third quartiles) cumulative dose (Gy) for patients who did and did not develop ≥G3 late toxicity was 119 (108-130) and 120 (111-130), respectively ($P = .65$).

No significant association was found between the development of severe late toxicity and worse OS ($P = .19$). The 2- and 5-year OS estimates were 66.5% (95% CI, 50.7%-87.2%) and 43.2% (95% CI, 25.4%-73.4%) in ≥G3 subgroup, and 77.8% (95% CI, 70.7%-85.6%) and 43.8% (95% CI, 33.9%-56.5%) in the complementary subgroup, respectively.

TABLE 3 Results of the multivariable Cox model for overall survival including the variables selected according to the random forest model

Variables	Comparison	HR	95% CI	P[a]
Tumor site	Other sites vs nasopharynx	2.33	1.13-4.82	.04
	Oral cavity vs nasopharynx	3.05	1.28-7.31	
KPS	<80 vs ≥80	1.29	0.71-2.35	.41
Organ dysfunction	Some vs none	1.91	1.04-3.52	.04
Recurrence histology	SCC vs other	1.91	1.11-3.27	.02
Reirradiation volume[b] (cm^3)	>36 vs ≤36	1.91	1.18-3.08	.008

Abbreviations: 95% CI, 95% confidence interval of HR; HR, hazard ratio; KPS, Karnofsky performance status.

[a]Wald test *P* value.

[b]The cutoff was determined according to Mandrekar et al.[19]

4 | DISCUSSION

We analyzed the largest retrospective multicenter Italian series of patients with RSPHNC arisen in a previously irradiated field, treated with modern RT techniques. Due to the difficulties in designing and completing the accrual of randomized trials in this clinical scenario,[22,23] findings from a high-level multi-institutional collaboration, although retrospective, add important insights on the best clinical practice to select patients and re-RT approaches. We found that patients with at least one organ dysfunction or other than a nasopharyngeal RSPHNC had significantly worse prognosis than their counterparts, as already reported in other series. In particular, as for organ dysfunction, our data are aligned with the available literature.[5,7] Our data compare favorably with those from the multi-institutional MIRI collaborative study of 412 patients, where nasopharynx/base skull tumors, improved KPS, and the lack of organ dysfunction were independently associated with improved OS.[8]

Still, we came up with the independent role of histology with an unfavorable OS for patients with SCC. Despite a hazard ratio of 1.18 for patients with SCC, the prognosis was not significantly different between subjects with SCC and non-SCC histology in the Riaz et al series.[7] However, in that study, more than 85% of patients had SCC RSPHNC differently from the 55% mark represented in our study.

Interestingly, taking our series as a whole, about 30% and 16% of patients had UNPC and ACC, whereas in the MIRI database, only 10% and 8.7% had an RSPHNC of nasopharyngeal origin or rare histology, respectively.[8]

Recurrent ACC of the head and neck usually has a less aggressive biological behavior compared to recurrent SCC.[24,25] In addition, nasopharyngeal tumors are considered particularly favorable for re-RT although complications from

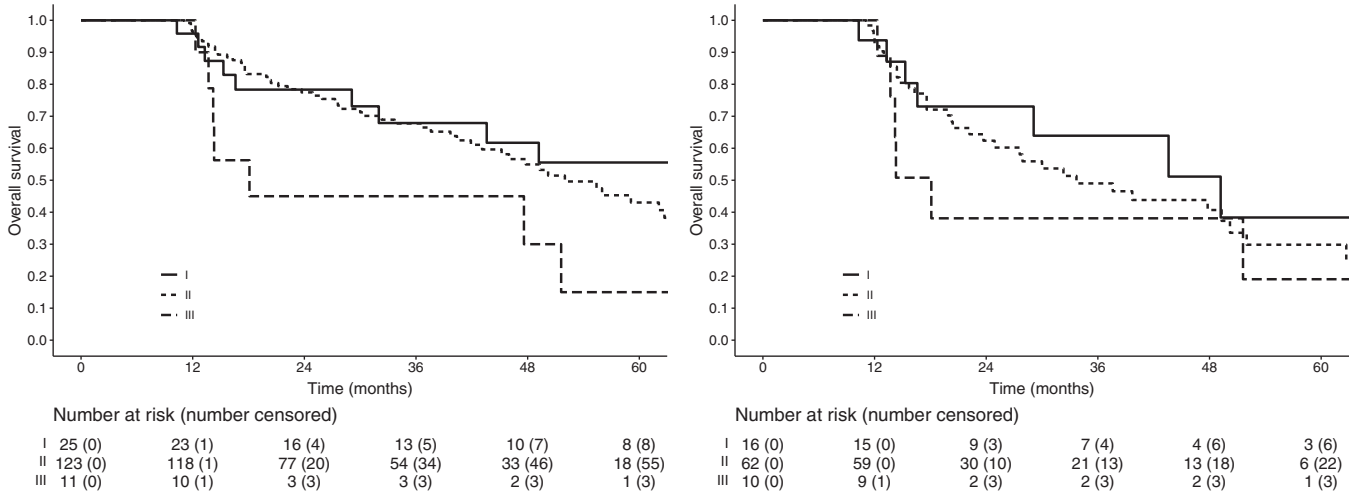

FIGURE 3 Kaplan-Meier overall survival curves according to MIRI RPA classes in the whole population (left) and in the subgroup of patients with SCC (right). MIRI RPA, Multi-Institution Reirradation (MIRI) recursive partitioning analysis; SCC, squamous cell carcinoma

retreatment can be life-threatening for this anatomical region.[10,26,27] We did not find a role for the treatment setting (definitive vs adjuvant) unlike other authors did.[8,28] In particular, Ward et al analysis[8] supported surgery as the standard salvage modality for RSPHNC because their results showed a better prognosis for surgical candidates compared to patients with unresectable diseases. However, the prognostic value of surgery could be a result of an intrinsic bias of the retrospective nature of the study, because surgical candidates are usually patients with smaller tumor volumes and higher KPS, as declared by the authors themselves. Our different result could be explained by the smaller number of patients included in the surgery group than the definitive one (25% and 75% of patients, respectively) in our series compared to the American ones (47.3% and 52,7% of patients, respectively) and by our higher frequency of UNPC and T3-T4 tumors. In our study, DFI was not related to OS. The median DFI was of 40.5 months, longer than in the MIRI experience (28 months). However, considering only the group of patients with SCC, the median DFI was 31 months, so similar to the American one. In general, it has been suggested that the longer the interval between radiotherapy courses is, the greater the likelihood of local control will be, and the lower the probability of developing severe secondary effects will be as well.[10,29]

Our survival outcome for the group of patients with SCC was unusually better than that of the American series (2-year OS 62% vs 40%). This could be related, in our cohort, to a higher number of patients without organ dysfunction and a slightly higher percentage of patients with second tumors compared to primary recurrences.

We were not able to validate MIRI RPA classification both for the whole patients' population and the SCC subgroup. This was probably due to the lack of significance of DFI and surgery in our multivariable model and a scarce number of patients. In particular, RPA classification did not differentiate between I and II classes with a greater distance of the high-risk survival curve compared to the counterparts. This is particularly evident considering our patients' population as a whole, suggesting that the proposed model could be hardly applicable for all histologies with RSPHNC.

Our results also consolidated the prognostic role of the recurrence volume reported in other series. Several studies considered surrogate parameters, such as T classification and PTV size, to express tumor volume demonstrating its relation with survival outcomes.[3,7,8]

Conversely, Tanveyanon and collegues[5] found tumor bulk at reirradiation, considered as a bidimensional continuous variable, to be one of the independent prognostic factors, whereas Vargo et al[30,31] found a volumetric cutoff of 25 cm^3 to be prognostic of inferior survival for patients treated with SBRT. In our study, a recurrence volume cutoff of 36 cm^3 was found, allowing the identification of two patient subgroups with different OS. As regards RT technique, IMRT showed better OS than SBRT only in univariable analysis. Similarly, no difference was observed between the two techniques in multivariable analyses in other studies.[7,13] However, after adjusting by RPA classes, IMRT remained superior to SBRT in class II patients (unresected patients with DFI >2 years or DFI <2 years and without organ dysfunction).[13] In addition, the authors demonstrated that SBRT with doses >35 Gy could be a treatment option as effective as IMRT for patients with small tumor volumes. In support to this, the same authors suggested the existence of dose-response relationship with superior local control and possibly improved OS for doses of 35 to 45 Gy (in 5 frs) compared with <30 Gy.[31] Of note, in our cohort, no patient received an SBRT dose higher than 30 Gy, partially justifying the lack of such clinical benefit with this approach at univariable Cox analysis. Again, we failed to establish a relationship between re-RT dose and survival. With the majority of patients receiving IMRT in definitive setting, we found at univariate analysis, only a trend of better survival when doses >48 Gy (BED_{10}) were given (Table S1). Our finding seems to be coherent with Riaz's work[7] reporting a cutoff dose of 50 Gy. Other investigators reported higher IMRT cutoff doses.[32] In particular, data from MIRI analysis confirmed that doses ≥66 Gy were associated with improvements in both LRF and OS in the definitive IMRT setting.[12]

Of note, we included in our study 30% of patients with recurrent NPC. In a review about long-term outcomes of re-RT with IMRT for locally recurrent NPC, a mean dose to the GTV ≥70 Gy was not associated with improved OS, potentially suggesting a higher radiosensitivity of recurrent tumor clonogens.[33] Finally, we found no prognostic significance of systemic therapy added to re-RT. In addition, the optimal scheme of CHT in re-RT setting is controversial. In patients receiving re-RT for RSPHNC, both cisplatin and single-agent cetuximab have been used with modest benefit,[4,34-36] potentially worsening the toxicity until unacceptable levels. However, recently published results of a phase II trial examining the combination of cisplatin, cetuximab, and involved field re-IMRT in 46 patients found that this treatment regimen is feasible and provided good survival outcomes in high-risk patients.[36]

This study has many weaknesses. The first one lies in its retrospective nature. Secondly, this multicenter population is heterogenous in terms of patients and treatment characteristics. As regards treatment dose, we decided to assume an α/β value of 10 Gy for all tumors, regardless of histology, based on the intrinsic uncertainties to establish this parameter for salivary gland tumors. Few data are reported about late toxicities Finally, in our series, we did not investigate the prognostic role of Epstein-Barr virus DNA (EBV-DNA) and the human papillomavirus in

patients undergoing re-RT. Indeed, only six patients among SCC had p16 positivity and no separate analysis was allowed. Despite these limitations, to our knowledge, this multi-institutional study from high-volume Italian centers has the longest median follow-up among the published papers on re-RT.

5 | CONCLUSION

Our data strengthen the prognostic value of clinical and patient-related factors reported in literature, underscoring that patients with better clinical conditions (no organ dysfunctions), nasopharynx site, and recurrence volume $<36\ cm^3$ could benefit the most from reirradiation. These factors with prognostic significance could potentially allow for a more refined patients' selection to reirradiation.

Finally, in the presence of a relevant proportion of non-squamous RSPHNC, the MIRI RPA classification failed to retain its prognostic validity, as well as for the SCC subgroup.

CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

How to cite this article: Orlandi E, Bonomo P, Ferella L, et al. Long-term outcome of re-irradiation for recurrent or second primary head and neck cancer: A multi-institutional study of AIRO—Head and Neck working group. *Head & Neck*. 2019;41:3684–3692. https://doi.org/10.1002/hed.25890