Is elective neck dissection necessary in cases of laryngeal recurrence after previous radiotherapy for early glottic cancer?

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Abstract

Objectives: To assess the clinical utility of elective neck dissection in node-negative recurrent laryngeal carcinoma after curative radiotherapy for initial early glottic cancer.

Methods: A retrospective review was undertaken of 110 consecutive early glottic cancer patients who developed laryngeal recurrence after radiotherapy (34 recurrent T_1, 36 recurrent T_2, 29 recurrent T_3 and 11 recurrent T_{4a}) and received salvage laryngeal surgery between 1995 and 2005.

Results: Six patients presented with laryngeal and neck recurrence and underwent salvage laryngectomy with therapeutic neck dissection, 97 patients with recurrent node-negative tumours underwent salvage laryngeal surgery without neck dissection and only 7 underwent elective neck dissection. No occult positive lymph nodes were documented in neck dissection specimens. During follow up, only three patients with neck failure were recorded, all in the group without neck dissection. There was no significant association between the irradiation field (larynx plus neck *vs* larynx) and the development of regional failure. A higher rate of post-operative pharyngocutaneous fistula development occurred in the neck dissection group than in the group without neck dissection (57.2 per cent *vs* 13.4 per cent, *p* = 0.01). Multivariate logistic regression analysis showed that early (recurrent tumour-positive, node-positive) or delayed (recurrent tumour-positive, node-negative) neck relapse was not significantly related to the stage of the initial tumour or the recurrent tumour. An age of less than 60 years was significantly associated with early neck failure (recurrent tumour-positive, node-positive).

Conclusion: Owing to the low occult neck disease rate and high post-operative fistula rate, elective neck dissection is not recommended for recurrent node-negative laryngeal tumours after radiation therapy if the initial tumour was an early glottic cancer.

Key words: Laryngeal Cancer; Vocal Cords; Laryngectomy; Neck Dissection; Salvage Therapy; Radiotherapy

Introduction

Early glottic cancer can be treated with surgery or radiotherapy (RT), with no significant difference in oncological outcome. However, RT appears to ensure better voice and swallowing results.[1] Nevertheless, the recurrence rate after primary RT is 5–13 per cent for tumour–node–metastasis (TNM) stage T_1 and 25–30 per cent for T_2 carcinomas.[2,3] Surgery is the mainstay of salvage treatment in patients with recurrence after RT failure,[4,5] but management of recurrent clinically diagnosed node-negative (N_0) neck tumours remains controversial and, at the time of salvage laryngeal surgery, surgeons must decide whether or not to perform elective neck dissection. Previous reports indicate an incidence of 10–28 per cent occult neck metastasis in persistent and recurrent laryngeal disease after

primary RT.[6–9] Accurate restaging with scrupulous reassessment of the nodal status cannot completely rule out the presence of occult neck disease.[10–12] Small nodal metastases are still a diagnostic challenge despite continuing improvements in imaging techniques. Computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography and ultrasound-guided fine needle aspiration cytology are all generally used in clinical practice to stage head and neck cancers, and can be useful for detecting cervical lymph node metastases. However, their diagnostic accuracy for sub-centimetre metastases and micrometastases is limited. Positron emission tomography has a low specificity and sensitivity for nodal metastases of diameter less than 6 mm.[13,14] Recently, CT perfusion scans have been shown to depict nodal

metastases of less than 1 cm in diameter.[15] In untreated patients, cervical lymphatic tumour spread follows a predictable path;[10] this knowledge has led to improvements in the surgical management of clinically staged N_0 laryngeal cancer.[11,12] Nowadays, it is widely accepted that the incidence and location of occult metastases are related to tumour stage and site. Selective neck dissection of levels II–IV (formerly known as 'jugular node dissection'[10]) is considered adequate in patients with clinically staged N_0 laryngeal cancer, while modified radical neck dissection is now considered obsolete.[11,12] Furthermore, to minimise post-operative morbidity, super-selective dissection of sublevels IIa–III has recently been proposed because of the rare involvement of sublevel IIb and level IV in clinically staged N_0 laryngeal carcinomas.[16,17] In a previously irradiated neck, however, the usual regional lymphatic pathway for both the larynx and neck may have been extensively modified by radiation-induced sclerosis of the lymphatic vessels. Hence, a post-RT recurrent laryngeal tumour could spread to lymph nodes beyond the original predicted pathway. To date, there are no consistent data describing the prevalence of neck metastases and the incidence and location of occult neck metastases following RT failure for initial early glottic cancer.

This study aimed to investigate the appropriateness of elective neck dissection during salvage laryngeal surgery in patients with recurrent clinically staged N_0 tumours following RT failure for initial early glottic cancer. We also aimed to identify the subpopulation at the highest risk of occult neck disease and the neck levels at the highest risk of regional tumour spread.

Materials and methods

We assessed all patients from 1995 to 2005 with local recurrence of early laryngeal cancers ($T_{1-2}N_0$) following elective RT, who had undergone salvage surgery.

Inclusion criteria were no previous treatment, primary curative RT for early glottic carcinoma ($T_{1-2}N_0$), biopsy-proven laryngeal carcinoma after radiation, and salvage surgery. Our case series comprised 107 male patients and 3 female patients, with a median age of 63.2 years (range 47–83 years). Tumours had been initially staged as T_1N_0 in 75 patients and as T_2N_0 in 35 patients. The total dose varied from 60 to 70 Gy: 69 patients (62.7 per cent) received a mean dose of 65.0 ± 3.0 Gy to the larynx alone, while 41 patients (37.3 per cent) were irradiated with a mean dose of 64.3 ± 2.3 Gy to the larynx and a mean dose of 52.8 ± 5.0 Gy to the neck. Follow-up time was calculated from the date of salvage surgery to the date of the last follow up or death. Follow up ranged from 1 to 200 months, with a mean of 45.42 ± 44.36 months. Head and neck examinations were scheduled every month for the first year, every two months for the second year, every three months for the third year, and every six months thereafter until the fifth year. Magnetic resonance imaging and/or CT scans of the head and neck were performed twice a year for the first three years, and then annually. Patients with suspicious lesions underwent panendoscopy with biopsy and imaging. Persistent and recurrent laryngeal cancers were originally classified according to the current TNM Classification of Malignant Tumours; for this study, each tumour was re-evaluated and restaged according to the seventh edition of the TNM staging system, using information in the clinical records.[18] Radiological criteria to define a N_0 neck tumour were based on the characterisation of lymph nodes detected by a contrast-enhanced CT scan: diameter less than 10 mm, no central necrosis and no contrast enhancement of the lymph node capsule.[11] No specific indications for elective neck dissection were used in this study. Therefore, elective neck procedures were performed according to the surgeon's preference. The extent of neck dissection ranged from selective neck dissection of levels II–IV to comprehensive modified radical neck dissection. Modified radical neck dissection was performed in the earlier cases prior to implementation of an institute policy recommending selective neck dissection (levels II–IV).[10]

Descriptive statistics were compared using Student's *t*-test for continuous variables and Fisher's exact test for categorical variables. The Kaplan–Meier method was used for survival analysis. All analyses were performed using STATA version 10.0 software (StataCorp, College Station, Texas, USA). A *p* value of less than 0.05 was considered statistically significant.

Results

After RT, the median time to local recurrence was 23.5 ± 33.2 months (range 1–216 months, 95 per cent confidence interval (CI) 17.25 to 29.8). The most common salvage procedure was total laryngectomy (90 patients, 81.8 per cent), while only 20 patients (18.2 per cent) underwent salvage partial laryngectomy without elective or therapeutic neck dissection. Restaging showed 34 recurrent T_1, 36 recurrent T_2, 29 recurrent T_3 and 11 recurrent T_{4a} tumours; 6 patients also had clinically staged neck metastases (1 recurrent $T_{4a}N_1$, 2 recurrent T_2N_1, 1 recurrent T_3N_1, 1 recurrent T_2N_{2b} and 1 T_2N_{2c}). Neck level II was involved in four cases (three with N_1 and one with N_{2b} tumours), and neck levels III and IV were involved in only two cases; all of these patients underwent radical neck dissection or modified radical neck dissection. Of the remaining 104 patients, 97 were managed using a 'wait-and-see' protocol for neck relapse and 7 patients with recurrent N_0 tumours underwent elective neck dissection: 2 with ipsilateral selective neck dissection (levels II–IV), 2 with bilateral selective neck dissection (levels II–IV) and 3 with ipsilateral modified radical neck dissection. The characteristics of both groups at original diagnosis are shown in Table I; tumour stages were similar in both patient groups. No occult lymph node metastases were documented in the seven cases of elective neck dissection.

TABLE I
PATIENT CHARACTERISTICS

Characteristic	Elective neck dissection group ($n = 7$)	'Wait-and-see' group ($n = 97$)	p value
Median age (years)	60.9 ± 6.3	67 ± 9.6	0.10
Sex			
– Male	6 (85.7%)	95 (98%)	0.19
– Female	1 (14.3%)	2 (2%)	
Field of radiation therapy			
– Larynx	5	63	1.00
– Larynx & neck	2	34	
Initial staging			
– T_1	7 (100%)	63 (65%)	0.09
– T_2	0	34 (35%)	
Recurrence			
– T_1	1 (14.3%)	33 (34%)	0.70
– T_2	3 (42.9%)	29 (30%)	
– T_3	3 (42.9%)	25 (26%)	
– T_4	0	10 (10%)	
Follow-up (months: range, mean $\pm$ SD)	1–103, 29.3 $\pm$ 43.0	1–199, 48.7 $\pm$ 44.9	0.27

Post-operative medical and surgical complications are summarised in Table II. There was a higher rate of post-operative complications in the elective neck dissection group than in the 'wait-and-see' group (71.4 per cent *vs* 26.8 per cent, respectively, $p = 0.02$, Fisher exact test), resulting from a higher rate of pharyngocutaneous fistula development (57.2 per cent *vs* 13.4 per cent, respectively). Furthermore, 2 (2.1 per cent) patients in the 'wait-and-see' group died as a result of peri-operative myocardial stroke. The median follow up after salvage surgery was 45.4 ± 44.4 months (range 1–200 months, 95 per cent CI 37.04 to 53.8), while the median time to a second local or locoregional relapse was 36.5 ± 36.3 months (range 1–200 months, 95 per cent CI 29.6 to 43.4). The incidence of local, regional and distant failure is shown in Table III. In the 'wait-and-see' group, three patients (one with a recurrent T_3 tumour and two with recurrent T_2 tumours) developed pathologically staged N_1 or N_{2b} neck metastasis without local recurrence; in all cases, level II was the only level involved. Of note, post-operative local recurrences were significantly higher in the neck dissection group ($n = 5$, 71.5 per cent) than in the 'wait-and-see' group ($n = 27$, 27.8 per cent, $p = 0.028$). Distant metastases were detected in two patients in the 'wait-and-see' group (2.1 per cent). At the end of the study, the overall survival rate was 42.9 per cent in neck dissection patients, and 62.0 per cent in the 'wait-and-see' group (shown in Figure 1). No significant differences in overall survival were observed between patients with recurrent node-positive (N+) tumours receiving therapeutic neck dissection at the time of salvage laryngectomy and those with recurrent N_0 tumours receiving elective neck dissection or salvage laryngectomy alone ($p = 0.071$; Figure 2).

Multivariate regression analysis demonstrated that an initial T_1 stage tumour and age less than 60 years correlate with a higher risk of neck failure after curative RT (Table IV; $p = 0.04$ and $p = 0.038$, respectively). Indeed, Fisher's exact test confirmed that a younger age was significantly associated with a risk of neck metastasis following local recurrence ($p < 0.001$).

TABLE II
POST-OPERATIVE COMPLICATIONS FOR PATIENTS UNDERGOING SALVAGE SURGERY

Complication	Elective neck dissection group (n (%))[*]	'Wait-and-see' group (n (%))[†]	p value
None	2 (28.6)	71 (73.2)	0.02
Surgical			
– Salivary fistula	4 (57.2)	13 (13.4)	0.01
– Wound infection	0 (0.0)	1 (1.0)	1.0
– Wound dehiscence	0 (0.0)	1 (1.0)	1.0
– Bleeding	0 (0.0)	1 (1.0)	1.0
– Flap failure	0 (0.0)	1 (1.0)	1.0
– Revision procedure	0 (0.0)	1 (1.0)	1.0
– Pneumonia	1 (14.3)	3 (3.1)	0.24
Medical			
– Cardiovascular	0 (0.0)	2 (2.1)	1.0
– Death	0 (0.0)	3 (3.1)	1.0

[*]$n = 7$. [†]$n = 97$.

TABLE III
SITES OF RECURRENCE AFTER SALVAGE SURGERY IN PATIENTS WHO DIED FROM THE DISEASE

Recurrence site	Elective neck dissection group (n (%))	'Wait-and-see' group[*] (n (%))	p value
None[†]	2 (28.5)	66 (68.0)	0.047
Local[†]	5 (71.5)	27 (27.8)	0.028
– Peristomal[‡]	2 (40.0)	19 (70.4)	0.08
– Hypopharynx[‡]	2 (40.0)	5 (18.5)	0.61
– Larynx (for partial salvage laryngectomy)[‡]	1 (20.0)	3 (11.1)	
Regional (neck)[†]	0 (0.0)	3 (3.1)	1.0
Distant[†]	0 (0.0)	2 (2.1)	0.0

[*]One patient had multiple metastatic sites (neck + hypopharynx); [†]percentage of total group; [‡]percentage of patients with local tumours.
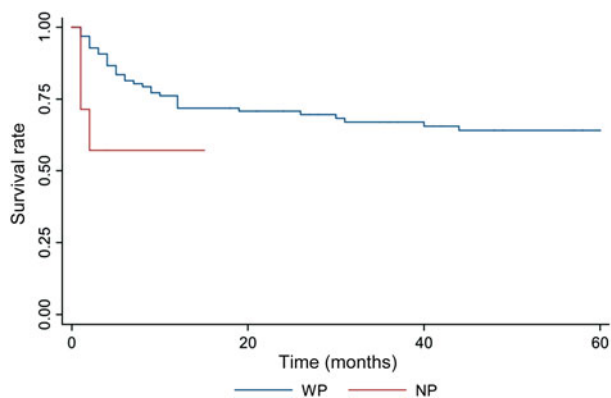
FIG. 1

Kaplan–Meier curve showing overall survival of patients who underwent simultaneous elective neck dissection and salvage laryngeal surgery (NP) and those who underwent only salvage laryngeal surgery (WP) for recurrent early glottic cancer. ($p = 0.7$)
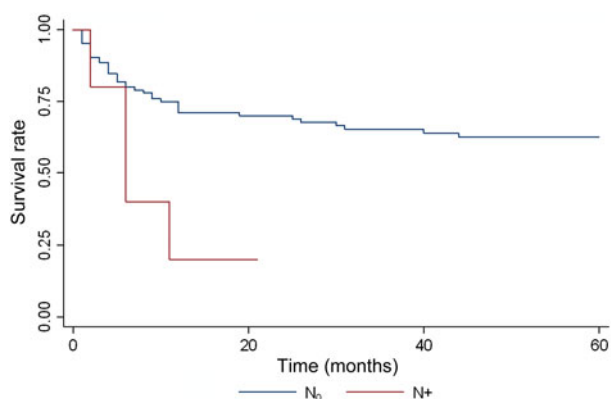

FIG. 2

Kaplan–Meier curve showing overall survival after curative radiation therapy for node-negative (N_0) *vs* node-positive (N+) tumours. ($p = 0.071$)

Discussion

Radiotherapy (RT) is often indicated for early glottic cancers to preserve organ function and post-treatment voice quality compared with surgery. Unfortunately, RT may be unsuccessful and some patients will experience recurrence or persistent laryngeal cancer. The Union for International Cancer Control and American Joint Committee on Cancer staging criteria for laryngeal recurrences are identical to those for untreated primary tumours, except for addition of the prefix 'recurrent' applied to the TNM categories. Regional

recurrence after curative RT correlates with poor prognosis, independent of the initial tumour stage.[19,20] Our data confirmed this finding: we showed that prognosis after salvage laryngectomy was more strongly associated with TNM restaging than with initial staging.

Previous studies reported a rate of occult neck metastases of 4–28 per cent in supraglottic and glottic cancer patients treated with RT alone.[6,7,21] This is especially true for advanced laryngeal carcinomas after failure of chemoradiation protocols; however, there are few data for early glottic cancers that recur after RT. In fact, at the time of first diagnosis, these patients have a very low risk of occult neck disease. After RT failure, both the risk of cancer spreading to other laryngeal sites and frequent progression or upstaging of persistent or recurrent lesions may lead to a higher rate of occult neck disease. We analysed only cases of persistent or recurrent cancers after primary RT that initially presented as early glottic laryngeal carcinomas. To the best of our knowledge, no other studies have considered this specific patient cohort. Thus, there is very little information on the correct management of recurrent N_0 neck tumours when salvage laryngectomy is indicated.

In our case series, 6 patients who underwent therapeutic neck dissection after primary RT had recurrent N+ tumours (5.5 per cent; 4 with N_1 and 2 with N_2 tumours) and 3 out of 97 patients in the 'wait-and-see' group had neck recurrence at follow up after salvage laryngeal surgery. Pathological examination showed that no neck dissection patient had occult neck disease and none experienced neck treatment failure during follow up. Thus, in our series, neck disease was detected in only nine patients (8.7 per cent; six with recurrent N+ tumours at the end of primary RT and three with recurrent N+ tumours within the 'wait-and-see' group at follow up). There was a higher rate of neck metastasis development in patients aged less than 60 years ($p < 0.001$), and an increased risk in those who originally presented with a T_2 glottic carcinoma or at a younger age ($p = 0.04$ and $p = 0.038$, respectively). Furthermore, the overall neck recurrence rate was 2.9 per cent after salvage laryngeal surgery. This low incidence of neck disease may be related to radiation-induced neck sclerosis sealing lymphatic vessels and thus hampering cancer lymphatic embolisation. Nevertheless, extension of the irradiation field to include the neck (larynx plus

Parameter	Correlation coefficient	SEM	z-score	p value	95% CI
Sex	−0.048	0.14	−0.33	0.74	−0.34, 0.24
Age	−0.14	0.067	−2.11	0.038	−0.27, 0.08
Radiation field (larynx *vs* larynx + neck)	0.055	0.068	0.81	0.419	−0.08, 0.19
T_1	−0.14	0.69	−2.09	0.04	−0.28, 0.06

TABLE IV

MULTIVARIATE ANALYSIS OF NECK FAILURE RISK AFTER CURATIVE RADIATION THERAPY

SEM = standard error of the mean; CI = confidence interval; T_1 = tumour–node–metastasis stage T_1

neck levels II–IV) did not completely protect from regional failure development, although it seemed to delay it. In fact, all six patients with recurrent N+ tumours received RT to the larynx alone, while the radiation field was extended to the neck in all three recurrent N_0 patients.

> - **Surgery is the main salvage treatment for laryngeal cancer patients with recurrence after radiotherapy**
> - **The management of clinically negative cervical lymph nodes in persistent or recurrent laryngeal cancers after primary radiotherapy is controversial**
> - **For initial early glottic cancer recurring after radiotherapy without clinical or radiological lymph node involvement, salvage laryngeal surgery alone may be appropriate regardless of restaging**
> - **Elective neck dissection is not recommended because of the increased risk of post-operative complication with no survival advantage**

The five-year survival rate was 57.14 per cent in the small group of neck dissection patients and 64.6 per cent in the 'wait-and-see' group; however, the difference was not statistically significant ($p = 0.7$). Nevertheless, this result is consistent with the demonstrated impact of lymph node metastases on head and neck cancer prognosis. Several recent studies concluded that neck dissection is indicated for recurrent advanced stage laryngeal cancer.[7,22] However, these studies failed to demonstrate a survival advantage in patients who underwent neck dissection. Some authors have advocated bilateral neck dissection for all advanced stage (T_3 and T_4) glottic recurrences and for all supraglottic recurrences regardless of stage.[22] In our series, there were 38 recurrent T_{3-4} cancers, and 8 of these had supraglottic involvement in the recurrence. Furthermore, we documented involvement of the supraglottic larynx in 12 T_2 recurrences. Among these 50 patients, 4 underwent elective neck dissection with no evidence of lymph node metastasis at pathological examination; in the remaining 46 patients, only 1 showed neck relapse at follow up. Furthermore, neck dissection did not lead to an overall survival benefit in our case series, and neck dissection did not provide additional protection from local recurrence (71.5 per cent vs 27.8 per cent, $p = 0.028$). Nevertheless, no regional failure was recorded in neck dissection patients, while only three patients in the 'wait-and-see' group experienced neck failure (0.0 per cent vs 3.1 per cent, $p = 1.0$). However, these data are not consistent with other reports.[21,22] Conversely, neck dissection during salvage laryngeal cancer was associated with an increased rate of post-operative complications (71.4 per cent in the neck dissection group vs 26.8 per cent in the 'wait-and-see' group, $p = 0.02$), especially pharyngocutaneous fistulas (Table II; 57.2 per cent), as previously reported.[22–24] These discrepancies suggest a selection bias toward treating RT-recurrent laryngeal carcinoma patients with salvage laryngeal surgery and concomitant neck dissection, and a possible negative impact of uni- or bilateral neck procedures on devascularised irradiated soft neck tissue, associated with a higher risk of locoregional complications, especially pharyngocutaneous fistulas.

Conclusion

Patients who experience recurrent or persistent laryngeal cancer after primary RT for early glottic cancer without clinical and radiological involvement of cervical lymph nodes benefit from exclusive salvage laryngeal surgery. The prevalence of neck disease in these patients is less than 10 per cent, and the incidence of occult neck disease is less than 5 per cent. This is also true for recurrent T_{3-4} lesions and for extension to the supraglottic or hypoglottic areas. Moreover, elective neck dissection is not recommended in these cases because it exposes patients to an increased risk of post-operative complications without a definite survival advantage.

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