

HEAD AND NECK

Elective neck dissection during salvage surgery after radiotherapy in patients with head and neck squamous cell carcinoma

Svuotamento linfonodale cervicale elettivo nella chirurgia di salvataggio dopo radioterapia in pazienti con carcinoma a cellule squamose del distretto testa-collo

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SUMMARY

Elective neck dissection in patients with recurrent head and neck squamous cell carcinoma (HNSCC) without evidence of neck disease (crN0) is poorly defined. A retrospective review was carried out on 165 crN0 patients treated with salvage surgery and elective neck dissection. Multivariate Cox analysis and recursive partitioning analysis were used to evaluate prognostic factors. The frequency of occult neck node metastases in the neck dissection (rpN+) was 16.4%. The risk of occult metastases for glottic rpT1-T2 recurrences was 5.9%, for glottic rpT3-T4 recurrences 13.2%, for non-glottic rpT1-T2 recurrences 16.1% and for locally advanced (rpT3-T4) non-glottic recurrences 31.1%. Patients with occult neck node metastases (rpN+) had a 5-year adjusted survival rate of 38.1%, while patients without nodal disease (rpN0) had a 5-year adjusted survival rate of 71.1% ($p = 0.0001$). Elective neck dissection can be omitted in crN0 patients with rT1-T2 glottic recurrence. We consider it advisable to perform elective neck dissection in all other situations.

KEY WORDS: Salvage surgery • Elective neck dissection • Occult neck node metastases • Head and neck cancer

RIASSUNTO

Lo svuotamento linfonodale cervicale elettivo in pazienti con recidiva di carcinoma a cellule squamose del distretto testa-collo, senza evidenza clinico-radiologica di metastasi linfonodale (crN0), è scarsamente descritto in letteratura. Per questa ragione è stata condotta una revisione retrospettiva di una coorte di 165 pazienti crN0, sottoposti a chirurgia di salvataggio e svuotamento cervicale elettivo. Per la valutazione dei fattori prognostici sono state utilizzate l'analisi multivariata di Cox e l'analisi di partizione ricorsiva. Successivamente allo svuotamento cervicale, la frequenza di metastasi linfonodali occulte (rpN+) è stata del 16,4%. Il rischio di metastasi occulte, in caso di tumori glottici recidivanti, è stato del 5,9% per le categorie rpT1-T2, e del 13,2% per le categorie rpT3-T4. Per quanto riguarda i tumori non-glottici recidivanti, il rischio di metastasi occulte è stato del 16,1% per le categorie rpT1-T2, mentre in caso di neoplasie localmente avanzate (rpT3-T4) è stato del 31,1%. La sopravvivenza a 5 anni dei pazienti con metastasi linfonodali occulte (rpN+) è stata del 38,1%, mentre la sopravvivenza a 5 anni dei pazienti che non hanno presentato invasione linfonodale (rpN0) è stata del 71,1% (con una differenza statisticamente significativa, $p = 0,0001$). Lo svuotamento cervicale potrebbe essere omesso in pazienti con neoplasia glottica recidiva crN0 rT1-T2. Al contrario, alla luce di questi risultati, riteniamo che sia consigliabile eseguire questa tecnica in tutte le altre situazioni.

PAROLE CHIAVE: Chirurgia di salvataggio • Svuoamento laterocervicale • Metastasi cervicali occulte • Tumore del distretto testa-collo

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Introduction

There is no doubt about the benefits of performing therapeutic neck dissection during salvage surgery in patients

with local recurrence of head and neck squamous cell carcinoma (HNSCC) after radiotherapy or chemoradiotherapy and evidence of cervical metastases (crN+). However,

the convenience of elective neck dissection in patients with local recurrence of HNSCC and no evidence of regional disease (crN0) remains unclear.

Some authors recommend performing elective neck dissection on crN0 patients during salvage surgery¹⁻⁴. Others consider it appropriate to carry out elective neck dissection only in patients with locally advanced recurrence or clinically positive nodes at the time of initial diagnosis of the tumour^{5,6}. On the other hand, a group of authors do not consider it necessary to systematically perform neck dissection in crN0 patients with HNSCC local recurrence during salvage surgery due to: (i) low percentage of occult neck node metastases in these patients; (ii) good regional control achieved in patients kept under observation; (iii) increase in postoperative complications related to performing neck dissection⁷⁻¹⁴.

The goal of our study was to determine the risk of occult nodal metastases in HNSCC patients with local recurrence without evidence of neck disease (crN0), and to define the utility of performing elective neck dissection during salvage surgery in this group of patients.

Materials and methods

We conducted a retrospective study using a database that has prospectively collected data on epidemiology, treatment and follow-up of all patients with HNSCC treated at our centre since 1985¹⁵. Eligible patients met the following criteria: (1) pathological diagnosis of HNSCC of the oral cavity, oropharynx, hypopharynx, or larynx treated with radical intention between 1992 and 2012; (2) primary tumour treated with radiotherapy or chemoradiotherapy; (3) not having undergone a neck dissection during primary treatment of the tumour; (4) pathologically confirmed recurrence of the tumour at the primary site; (5) clinical and radiological N0 at the time of salvage surgery; (6) salvage surgery of the local recurrence with an elective neck dissection; (7) minimum follow-up of 2 years after salvage surgery unless recurrence or death. Patients were staged using the 7th edition of the TNM classification at the time of initial treatment and at the time of salvage surgery¹⁶. An oncology panel evaluated all patients and recommended salvage surgery and neck dissection. All procedures were reviewed by the Institutional Review Board of our centre. The study conforms to the principles outlined in the Declaration of Helsinki.

All patients included had a radiologic screening of the N0 neck. A CT scan was routinely used for patients with a laryngeal or hypopharyngeal tumour, while for patients with an oral cavity or an oropharyngeal tumour MRI was used preferentially. In all cases, the radiologic report ex-

cluded the presence of positive or suspicious neck nodes. None of our patients was studied with PET-CT.

In our centre, elective neck dissection was performed systematically in patients with local recurrence when salvage surgery was carried out using an open cervical approach. One hundred and sixty-five patients who met the inclusion criteria were included in the study. Table I shows location of the primary tumour, local and regional extension of the primary tumour, local and regional management during primary treatment, local extension of the recurrence and salvage surgery. For early glottic carcinomas, the field of radiotherapy was limited to the central neck, avoiding prophylactic irradiation of the cervical neck nodes. One hundred and three patients received radiotherapy over the neck nodes during the treatment of the primary head and neck tumour. Patients with N0 primary tumour (n = 69) received 50 to 55 Gy as a total dose of radiotherapy over the neck. The group of N+ patients (n = 34) received 65 to 72 Gy. Local recurrences were diagnosed during the first 2 years of follow-up after treatment of the primary tumour in 83.8% of cases.

Table I. Characteristics of patients included in the study.

		N	(%)
Sex	Men	157	(95.2%)
	Women	8	(4.8%)
Age: mean / standard deviation	58.9 / 10.1 years		
Primary tumour location	Oral cavity	14	(8.5%)
	Oropharynx	18	(10.9%)
	Hypopharynx	7	(4.2%)
	Supraglottis	36	(21.8%)
	Glottis	90	(54.5%)
Primary tumour local extension	T1-2	112	(67.9%)
	T3-4	53	(32.1%)
Primary tumour regional extension	N0	131	(79.4%)
	N+	34	(20.6%)
Primary tumour treatment	RT	145	(87.9%)
	CT-RT	20	(12.1%)
Primary tumour neck management	Observation	62	(37.6%)
	Radiotherapy	103	(62.4%)
Recurrence local extension	rT1-2	82	(49.7%)
	rT3-4	83	(50.3%)
Salvage surgery	Total laryngectomy	88	(53.3%)
	Laryngopharyngectomy	20	(12.1%)
	Partial laryngectomy	29	(17.6%)
	Pelviglossectomy	19	(11.7%)
	Bucopharyngectomy	9	(5.5%)

All patients underwent an elective neck dissection during salvage surgery. A total of 221 selective neck dissections at levels II-IV, 26 of levels I-III and 13 of levels II-III were carried out. For patients with a glottic tumour with subglottic extension ($n = 13$) a dissection of the paratracheal nodes (level VI) was also included. Bilateral neck dissection was performed in 57.6% of patients.

We used the Chi-square or Fisher's exact test in univariate analysis, and a logistic regression model in the multivariate analysis. Patients were classified according to a recursive partitioning analysis with a classification and regression tree (CRT) method, considering the appearance of occult neck node metastases in the neck dissection (rpN+) as the dependent variable. Location of the primary tumour, local and regional extension of the primary tumour, local extension of the recurrence, and initial management of the neck were considered as independent variables. We reviewed the pathologic reports of neck dissections of the rpN+ patients, collecting data about the size of the positive neck nodes. Micrometastases were defined as microscopic deposits of malignant cells smaller than 2-3 mm in diameter.

Survival curves were calculated using the Kaplan-Meier technique. Differences in survival were compared using the log-rank test.

Results

Occult neck node metastases were found during neck dissection (crN0/rpN+) in 27 patients (16.4%). Of the 27 patients with positive neck dissection, 14 (51.9%) were found to have only one pathological neck node (rpN1), 10 (37.0%) had 2 or more ipsilateral metastatic neck nodes (rpN2b) and 3 (11.1%) showed bilateral nodal involvement (rpN2c). Six of the rpN+ patients (22.2%) had pathological evidence of nodes with extracapsular tumour spread.

Eleven patients had micrometastases, 14 had metastatic neck nodes up to 1 cm and only 2 had neck node metastases larger than 1 cm. In both cases of neck node metastases greater than 1 cm, the pathologic report pointed out that the size of the neck nodes was about 2 cm, and in one case it had necrosis. We reviewed the images of these two patients (a CT and a MRI corresponding to one patient with a hypopharyngeal crT4N0 tumour and one patient with an oropharyngeal crT2N0 tumour, respectively), and did not find any radiological evidence of neck disease.

Table II shows the percentage of patients with occult neck node metastases depending on the location of the primary tumour, local and regional extension of the primary tumour, neck management during the initial treatment and local extension of the recurrence. According to the results of uni-

variate analysis, the only variable significantly associated with the appearance of occult neck node metastases was the local extension of the tumour at the time of recurrence. None of the variables had significant prognostic influence when included in the multivariate analysis. Nevertheless, a higher frequency of occult neck node metastases was found in patients with locally advanced recurrences (rT3-4), and a lower frequency was found in those with glottic tumours. Information regarding HPV status was available for 17 of the 18 patients with oropharyngeal carcinoma. Only one patient was HPV positive, without showing evidence of occult metastasis in the neck dissection. The frequency of occult neck node metastasis in patients with HPV negative tumours was 18.8% (3/16).

Considering the appearance of occult neck node metastases as the dependent variable, the CRT method classified patients according to the initial tumour location and the extension of the recurrence. A total of four terminal nodes were obtained using this classification method (Fig 1). Due to the similar risk of occult neck node metastases between nodes 2 (rT3-4 glottic carcinoma) and 3 (rT1-2 non-glottic carcinoma), both nodes were grouped in one category. Table III shows the categories according to the risk of appearance of occult neck node metastases as defined by the CRT classification system.

The three patients with early glottic recurrences (rT1-2) who had occult neck node metastases were specifically reviewed. All three patients had recurrences with subglottic extension of the tumour (rT2). In two cases, the neck node metastases appeared in the anterior neck dissection, and not in the lateral neck dissection. In the third case, the occult neck node metastases appeared in the lateral selective neck dissection.

Survival was analysed according to the risk of having occult neck node metastases at neck dissection. Figure 2 shows adjusted survival curves after salvage surgery for patients without occult neck node metastases (rpN0, $n = 138$), and for patients with occult neck node metastases (rpN+ $n = 27$). Five-year adjusted survival was 71.1% (CI 95%: 62.9-79.3%) for rpN0 patients, and 38.1% (CI 95%: 18.4-57.8%) for rpN+ patients. Significant differences in survival were found according to the pathological state of the neck dissection ($P = 0.0001$).

Discussion

The management of nodal areas in patients without clinical or radiological evidence of cervical disease (crN0) treated with salvage surgery after local failure of the previous treatment with radiotherapy or chemoradiotherapy is a controversial topic. The incidence of occult neck node

Table II. Risk of occult neck node metastases in elective neck dissection according to different clinical variables.

		Univariate analysis		Multivariate analysis		
		rpN+	P	HR	CI 95%	P
Primary tumour location	Oral cavity (n = 14)	3 (21.4%)	0.088	1		
	Oropharynx (n = 18)	4 (22.2%)		0.94	0.16-5.41	0.946
	Hypopharynx (n = 7)	2 (28.6%)		1.16	0.13-10.12	0.891
	Supraglottis (n = 37)	10 (27.0%)		0.89	0.18-4.33	0.892
	Glottis (n = 89)	8 (9.0%)		0.23	0.04-1.28	0.095
Primary tumour local extension	T1-2 (n = 112)	14 (12.5%)	0.051	1		
	T3-4 (n = 53)	13 (24.5%)		1.23	0.40-3.82	0.711
Primary tumour regional extension	N0 (n = 131)	20 (15.3%)	0.455	1		
	N+ (n = 34)	7 (20.6%)		0.55	0.17-1.78	0.324
Recurrence local extension	rT1-2 (n = 82)	8 (9.8%)	0.023	1		
	rT3-4 (n = 83)	19 (22.9%)		2.47	0.90-6.80	0.079
Primary tumour neck management	Observation (n = 62)	6 (9.7%)	0.072	1		
	Radiotherapy (n = 103)	21 (20.4%)		0.78	0.18-3.78	0.739

metastases in elective neck dissection performed in these patients ranges between 0% and 25% in the different published series (Table IV). Variability in the percentage of occult neck node metastases may be attributed to the different types of patients included in each study. Some series evaluated patients with laryngeal tumours^{12 4 5 8 11-14 17}, including different proportions of patients with glottic

tumours, while in other series several head and neck locations were involved^{3 7 9 10 18 19}. Moreover, some series included patients with locally advanced tumours or recurrences^{4 10-12}, while others preferentially evaluated patients with more limited tumours^{5 7 8 18}.

As a result, conclusions by different authors are highly variable. A number of authors recommend performing elective neck dissection in crN0 patients when salvage surgery is carried out. Others only consider performing neck dissection in patients with locally advanced recurrent tumours, in patients with tumours localised in the supraglottis, or in patients with initial nodal involvement. Finally, based on the low incidence of occult neck node metastases and the acceptable results achieved with the policy of neck observation, a group of authors do not consider it necessary to perform elective neck dissection at the time of salvage surgery (Table IV).

One of the reasons to perform elective neck dissection in crN0 patients during salvage surgery after treatment with radiotherapy or chemoradiotherapy would be that the more aggressive biological behavior of the tumour involved in the recurrence is associated with an increased risk of occult neck node metastases. Additionally, as initial treatment with radiotherapy or chemoradiotherapy failed to eradicate the primary tumour, the persistence of subclinical disease at the cervical level could be possible. Moreover, in case of nodal recurrence, control options with a second salvage surgery at the cervical level are very limited^{20 21}.

The authors who advocate for a “wait and see” policy argue that due to the low incidence of occult neck node

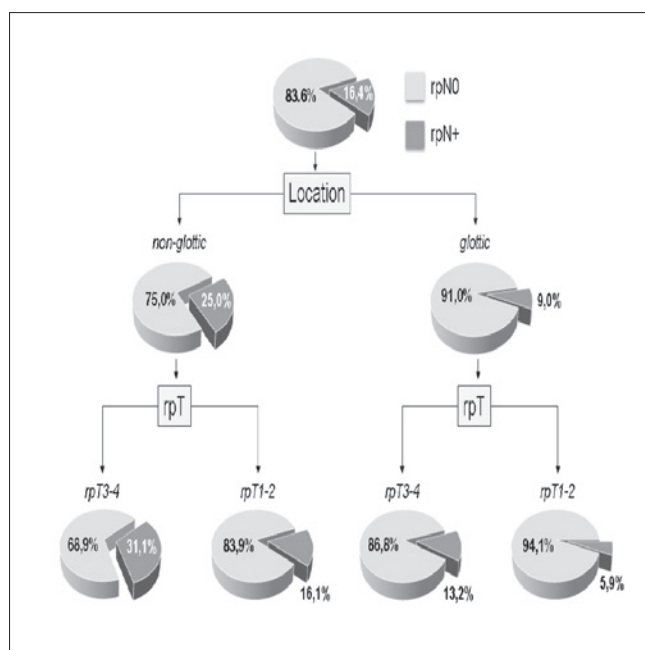
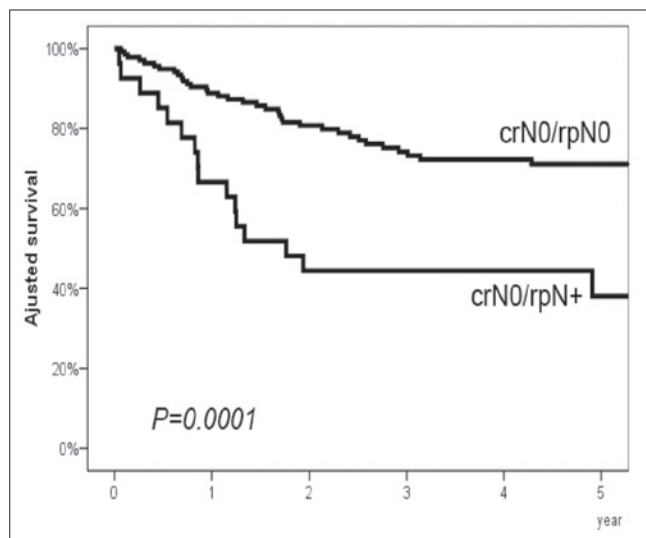
**Fig. 1.** Classification obtained with the classification and regression tree method.

Table III. Classification of patients according to the risk of occult neck node metastases in elective neck dissections.

Category		Number of patients	% Occult metastases
Low risk	Glottic tumours rT1-2	51	5.9%
Intermediate risk	Glottic tumours rT3-4 Non-glottic tumours rT1-2	69	14.5%
High risk	Non-glottic tumours rT3-4	45	31.1%

**Fig. 2.** Adjusted survival of patients with HNSCC local recurrence according to the presence of occult neck node metastases.

metastases, there is no evidence that the systematic addition of elective neck dissection increases regional control of the tumour or improves prognosis. In addition, some authors found that performing elective neck dissection involved an increase in postoperative complications^{8,9,12-14}. Sanabria et al.²² reviewed the results reported in the literature and concluded that the observation policy would be justified for patients with glottic tumours classified originally as early tumours (T1-T2), and also in recurrent early tumours (rT1-2). For patients with advanced laryngeal recurrences (rT3-4) and non-glottic tumours, an elective neck dissection should be considered.

Our study analysed a wide range of patients with head and neck tumours of different locations. They were treated with a protocol that included the systematic performance of elective neck dissection in crN0 patients who are candidates for open salvage surgery. We reached conclusions similar to those of Sanabria et al.²². The recursive

partitioning analysis classified patients according to the risk of having neck node metastases, and three categories were defined. Patients with limited glottic recurrences (rT1-2) showed a relatively low risk of subclinical nodal involvement (5.9%), so that the observation policy for the neck would be justified. In case of recurrence with subglottic involvement, performing dissection of lymph nodes along the recurrent laryngeal nerves would be indicated. Patients with advanced glottic recurrences (rT3-4) or limited tumour recurrences located outside the glottis (rT1-2) showed an intermediate risk of nodal involvement (14.5%). Finally, in patients with advanced tumour recurrence with non-glottic location (rT3-4), the risk of occult neck node metastases was high (31.1%). Based on our results, we consider it justified to systematically perform elective neck dissection in patients whose risk of having lymph node involvement is intermediate or high.

In the majority of rpN+ cases, the tumour burden was low. Eleven patients had micrometastases, and 14 patients had metastatic nodes up to 1 cm. However, 2 patients had 2 cm neck nodes. We reviewed the radiological images carried out prior to the salvage surgery, and did not find any evidence of nodal neck disease. A progression of the tumour in the period between the radiologic study and the salvage surgery could justify the inconsistency between the image study and the pathologic report in those two patients.

One aspect to consider is the influence of radiation fields in the appearance of neck node metastases in case of recurrence. Radiotherapy causes loss of lymphoid tissue and its replacement by fibrous tissue^{23,24}. These changes may serve as a barrier for lymphatic dissemination in case of local recurrence in patients who were previously treated with radiotherapy. However, in a study performed by Soares et al.³ where the incidence of occult neck node metastases was assessed in patients who were treated with primary radiotherapy or chemoradiotherapy and had a local recurrence or a second primary tumour, the incidence and anatomic distribution of subclinical neck node metastases was comparable to what was reported in untreated N0 necks. The authors concluded that previous treatment with radiotherapy did not change the anticipated pattern of neck node metastases in patients with local recurrence after primary treatment with radiotherapy. Similarly, Deganello et al.¹³ did not find significant differences between previous treatment with neck radiotherapy and the risk of occult neck node metastases in crN0 patients treated with salvage surgery.

According to our results, the appearance of occult neck node metastases in neck dissection during salvage surgery was significantly associated with lower survival, as in patients with HNSCC and neck node metastases at initial treatment²⁵.

Table IV. Percentage of occult neck node metastases in crN0 patients and suggestions for performing elective neck dissection obtained from published studies.

Author (year)	Location	N	Treatment	% Occult metastases (rpN+/neck dissections)	Elective neck dissection
Wax (1999) ²	Larynx	34	RT	17% (6/34)	Yes
Solares (2005) ³	H&N	69	RT	25% (17/69)	Yes
Yao (2005) ⁵	Larynx	63	RT	12% (5/41)	Only rT3/4 and supraglottis
Temam (2005) ¹⁰	H&N	30	RT	3% (1/30)	Not necessary
Farrag (2006) ¹¹	Larynx	51	RT	12% (4/34)	Not necessary
Dagan (2010) ⁷	H&N	57	RT	10% (4/40)	Not necessary
Bohannon (2010) ¹²	Larynx	71	RT	8% (3/38)	Not necessary
Amit (2013) ⁴	Larynx	42	RT	19% (8/42)	Yes
Yirmibesoglu (2013) ⁹	H&N	44	RT	10% (3/30)	Not necessary
Lee (2013) ¹⁷	H&N	149	RT/Sur	8% (6/80)	Only initial N+ and early recurrence
Basheeth (2013) ⁸	Larynx	45	RT	8% (3/38)	Not necessary
Prendes (2014) ¹⁸	H&N (N+)	16	RT	40% (4/10)	Yes
Hilly (2013) ⁶	Larynx	87	RT	13% (6/48)	rT3-4
Deganello (2014) ¹³	Larynx	110	RT	0% (0/7)	Not necessary
Pezier (2014) ¹⁴	Larynx	28	RT	7% (2/28)	Not necessary
Koss (2014) ¹⁶	Larynx	68	RT	28% (19/68)	Yes

H&N: Head and neck; RT: Radiotherapy; Sur: Surgery

Only one of our patients with an oropharyngeal carcinoma treated with salvage surgery was HPV positive. We think that the low proportion of HPV positive oropharyngeal tumours in our study is a consequence of the low percentage of HPV positive patients in our geographical setting^{26,27}, coupled with the high control of the disease achieved with treatment in those HPV positive tumours. It would be interesting to investigate the frequency of occult neck node metastases in elective neck dissections in oropharyngeal patients in function of HPV status of the tumour.

The main limitation of our study is its retrospective nature and the wide period of time it covers. Although cervical management of patients with salvage therapy has not been substantially modified, progressive improvement of CT and MRI over the study period may have changed the classification of crN0 patients. We do not have experience about the efficiency of PET-CT in the assessment of crN0 patients who are candidates for salvage surgery. Currently¹⁸, F-FDG PET-CT has a fundamental role in the evaluation during follow-up of patients with a HNSCC, with a higher degree of accuracy in detecting recurrences of the disease than other imaging modalities^{28,29}. The results of a systematic review and a meta-analysis carried out by Gupta et al.³⁰ including 30 studies (1,525 patients) assessing the diagnostic performance of ¹⁸F-FDG PET and PET-CT in the assessment of response and surveillance for neck nodes in HNSCC patients, reported a high negative predictive value (94.5%) and a suboptimal positive

predictive value (52.1%). Most studies evaluating the predictive capacity of PET/PET-CT in the neck analyse the outcome obtained after completion of radical treatment. PET-CT has been shown to be an effective diagnostic tool for detecting occult cervical metastatic nodes in patients with negative neck palpation findings in the context of the initial assessment of patients with HNSCC^{31,32}. However, there are practically no data on the prognostic capacity in the detection of occult neck node metastasis of PET-CT in patients with local recurrence of the disease. Gilbert et al.³³ carried out a study examining the sensitivity and specificity of PET-CT in patients with a laryngeal carcinoma recurrence after radiotherapy treated with a total laryngectomy and neck dissections. The authors evaluated 8 patients crN0 who had PET-CT reads that were negative, three of whom had positive nodal disease in the elective neck dissection, giving a negative predictive value of the PET-CT of 62.5%. Larger studies are necessary to evaluate the efficiency of PET-CT in the detection of hidden cervical metastatic deposits in crN0 patients who are candidates for salvage surgery.

Conclusions

Based on our results, in patients without clinical or radiological evidence of lymph node involvement (crN0) we suggest to perform an elective neck dissection during salvage surgery in non-glottic rT1-T2 recurrences, and

in locally advanced glottic and non-glottic recurrences (rT3-T4). Due to the low incidence of occult neck node metastases in crN0 patients with early glottic recurrences (rT1-T2), elective neck dissection could be omitted in these cases.

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