ORIGINAL ARTICLE

Prognostic Significance of Nodal Metastasis in Advanced Tumours of the Larynx and Hypopharynx

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KEYWORDS
Extracapsular spread; Squamous cell carcinoma of the larynx and hypopharynx; Survival; Lymph node metastasis

Abstract
Objectives: To estimate the relevance of post-surgical neck nodal classification (pN) on the global survival of patients with advanced tumours of the larynx and hypopharynx, primarily treated with surgery including neck dissection (ND). To understand the prognostic significance of metastatic lymph nodes’ extracapsular spread (ECS) and its impact on survival.

Materials and methods: A retrospective review of patients primarily submitted for total laryngectomy (TL) with either elective or therapeutic bilateral ND. Overall and disease-free survival was analysed according to post-operative histopathological ND results, concerning the presence or absence of nodal involvement, number of affected nodes and the existence of ECS.

Results: One hundred and twenty patients met the inclusion criteria of this study. Concerning nodal involvement, the histopathological evaluation demonstrated positive lymph nodes in 46.6% of the cN0 patients.

The rate of patients alive after 2 years of follow-up, based on pN analysis, was 88.1% for the pN0 group, 65.4% for the group N+ without ECS, 46.2% for the N+ ECS+ (1 node) and 15.4% for the N+ ECS+ (more than 1 node) group (P<.001).

Conclusions: This study demonstrates a high prevalence of occult neck disease in tumours of the larynx and hypopharynx. The involvement of metastatic cervical lymph nodes has a negative impact on survival. Patients with multinodal ECS have a poorer survival, reflected by a higher rate of loco-regional and distant metastases, when compared to ECS in one single lymph node.
Introduction

Squamous cell carcinoma (SCC) is the most frequent malignancy of the head and neck region. Several aspects affect the outcome of patients with this kind of tumour. It is generally accepted that these aspects are related to the tumour itself (e.g. anatomical localization, extent of disease), the patient’s general condition and co-morbidities, and treatment approach (treatment options and expertise). However, an accurate and precise staging of head and neck cancer is recognized as having a paramount importance, expressing the severity or extent of disease, thus facilitating estimation of prognosis and providing useful information for the choice of the best therapeutic options. At the time of diagnosis, 50% of the patients with head and neck SCC present either clinical or subclinical regional lymph node metastasis. Several surveys report an incidence of subclinical metastasis varying between 20% and 50%. Furthermore, metastasis in the lymph nodes seems to be the most important prognostic factor in these patients and the presence of ECS has been proven to be a reliable prognostic indicator.

Based on this observation, some efforts have been made to deepen the knowledge of the ECS process and its relationship with worst outcomes, namely studies about the importance of different degrees of capsular involvement, the extent of extracapsular measured in millimetres or the microscopic vs macroscopic extracapsular involvement. The aim of our study is to understand the relationship between the number of ECS metastatic cervical lymph nodes and survival, according to post-operative findings in NDs, in a Portuguese population of patients with advanced tumours of the larynx and hypopharynx undergoing TL and ND as primary treatment.

Materials and Methods

The charts of all patients with SCC submitted to TL associated with bilateral either elective or therapeutic ND, in a Portuguese Oncology Hospital, between January 2003 and December 2008, were reviewed. All treatments were defined in a multidisciplinary oncologic group decision taking into account the pre-therapeutic staging, performed according to procedures enunciated in the sixth AJCC/UICC classification of Tumours. Concerning ND, a selective ND of levels II–IV was the minimum applied, performing a radical ND when complete metastatic disease removal was unattainable without sacrificing either the cranial nerves, the internal jugular vein or the sternocleidomastoid muscle, involving levels I–V. Paratracheal nodes (level VI) were also dissected in glottic advanced tumours and in all subglottic tumours.

Adjuvant therapy was applied according to the following post-operative histopathological findings: size and grade of the tumour, depth of invasion, nerve or vascular invasion, status of surgical margins, status of cervical lymph nodes, ECS. Consequently, adjuvant radiotherapy (RT) alone or with chemotherapy (CHT) as an irradiation sensibilizing effect was delivered according to the following scheme:
preservation, specific age, the patients. Second, whose evaluation, synchronous ing, given every 3 weeks at 100 mg/m², 3 doses was the drug used as an irradiation sensibilizing effect since mid 2006. Up to that time they would follow adjuvant RT protocols. Patients with other adverse features as: pT4 primary, N2 or N3 nodal, disease perineural invasion or vascular embolism were also proposed for ChT and RT or RT alone, according to multidisciplinary group decisions at that time always depending on patients’ general condition and comorbidities.

For the present analysis only patients who underwent TL as primary treatment were considered. Patients treated with RT as primary treatment for head and neck SCC, patients submitted previously to partial laryngectomies, patients who had as first treatment organ preservation regimens (chemoradiotherapy), patients with synchronous lesions or presenting with distant metastasis were excluded.

In what concerns pre- and post-surgical ND evaluation, the histological results of 120 patients were analysed.

For survival analysis a minimum of 2 years follow-up was considered, having been calculated from the day of surgery until the time of last contact or death. To access the impact of pN+ disease on overall survival and disease-free survival, we excluded two patients who died perioperatively (one with an acute myocardial infarction and another with a massive hemorrhage 3 weeks after surgery) and 11 patients whose surgical margins intercepted the tumour (less than 2 mm free tumour surgical margins). Patients who died of second primary tumour, not belonging to the head and neck, were considered primary disease-free. Therefore, for global and free-disease survival rates, patterns of failure and second primary tumours analysis, our final sample was 107 patients.

The Kaplan–Meier method was used to create disease-specific and global survival curves. Differences between the actuarial curves were tested by log-rank test. Differences in the proportions of patients who survived and who were disease-free at 24 months were tested by the Pearson Chi-square test. Statistical analysis was performed in SPSS Statistics 19.0® for Macintosh®. Probability values less than 0.05 were considered statistically significant.

## Results

### Demographic Data

According to criteria for inclusion (TL as first therapeutic option), 120 out of 173 patients were considered the final sample for statistical analysis. One hundred and eighteen (98.3%) were male and 2 (1.7%) were female. The mean age at the time of surgery was 59.7 years (standard deviation=10.6), ranging from 32.0 to 89.9 years old.

| Tumour Details Classified by Primary Site and T Stage. |
|---------------------------------|------|------|------|------|------|------|
| Subglottis                      | 0    | 2    | 5    | 2    | 9    | 7.5 |
| Glottis                         | 0    | 6    | 31   | 22   | 59   | 49.2|
| Supraglottis                    | 0    | 5    | 17   | 11   | 33   | 27.5|
| Hypopharynx                     | 0    | 2    | 5    | 12   | 19   | 15.8|
| Total                           | 0    | 15   | 58   | 47   | 120  | 100 |
| Rate, %                         | 0    | 12.5 | 48.3 | 39.2 | 100  |     |

### Pre- and Post-surgical Staging

Regarding the distribution of patients by site of primary tumour, in 101 (84.2%) it was located in the larynx and the remaining 19 (15.8%) had origin in the hypopharynx. When analysing the extent and size of the primary tumour, a predominance of advanced tumours of the larynx and hypopharynx was evident, as T3 and T4 tumours were present in 105 (87.5%) patients (Table 1).

Concerning the histopathological evaluation of tumour surgical margins, 109 (90.8%) patients were found to be tumour free, while 11 (9.2%) demonstrated a distance between the tumour and the surgical margin less than 2 mm and were thus excluded from subsequent survival analysis.

With reference to the regional lymph node status only 47 out of 88 cN0 were confirmed in post-ND histological evaluation. So, the 88 cN0 and 32 cN+ turned out to be 47 pN0 and 73 pN+, respectively. The patients where the tumour was initially localized at the hypopharynx had a higher rate of occult metastatic neck disease cN+ pN+, compared to the tumours that had origin in the larynx (Table 2). None of the cN+ patients revealed to be cN−, after histological analysis.

In what concerns ECS, this was found in 47 out of 73 patients positive for cervical lymph node metastasis. When considering the number of nodes positive for ECS, 16 patients presented ECS in only one ganglion while the remaining 31 had more than one node with ECS. When accessing ECS by primary site this was present in 2/9 (22.22%) tumours that had origin in the subglottis, in 23/59 (38.98%) that had origin in the glottis, in 13/33 (39.34%) that had origin in the supraglottis and in 9/19 (47.37%) that had origin in the hypopharynx.

### Impact of Histological Nodal Status on Survival

For survival analysis, applying the exclusion criteria explained before, our final sample was 107 patients. In what concerns the overall survival at 2 years, it was 37/42 (88.01%) for the NO group and 27/65 (41.54%) for group N+ (P<.001) (Figs. 1 and 2). The disease-free and overall survival between NO, N+ ECS+−, N+ ECS+ (1 lymph node) and N+ ECS+ (more than 1 lymph node) was also compared. These differences revealed as statistically significant for the four groups (P<.001) (Figs. 3 and 4). The 2-year overall survival rates were 37/42 (88.01%) for the NO group, 17/26 (65.38%) for the N+ ECS− group, 6/13 (46.15%) for the N+ ECS+ (1 lymph node) and
Table 2  Clinical N (cN) Staging vs Pathologic N (pN) Staging, Classified by Primary Site.

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<tr>
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<tr>
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<td>1</td>
<td>5</td>
<td>3</td>
<td>4</td>
<td>14</td>
<td>1</td>
<td>1</td>
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<td>26</td>
<td>24</td>
<td>35</td>
<td>17</td>
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<td>88.89%</td>
</tr>
<tr>
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<td>73.3</td>
<td>39.2</td>
<td>50</td>
<td>41/88</td>
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<td>35.0</td>
<td>2.5</td>
<td>1.7</td>
<td>46.59</td>
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pN+: false negative cervical nodes for tumour.

Figure 1  Impact of pathologically positive lymph nodes on disease-free survival of patients with squamous cell carcinoma of the larynx and hypopharynx (P < .0001). pN0: node negative; pN+: node positive.

Figure 2  Impact of pathologically positive lymph nodes on overall survival of patients with squamous cell carcinoma of the larynx and hypopharynx (P < .0001). pN0: node negative; pN+: node positive.

Figure 3  Impact of extracapsular spread on disease-free survival of patients with squamous cell carcinoma of the larynx and hypopharynx (P < .0001). N0: node negative; N+ ECS+: node positive without extracapsular spread; N+ ECS+ 1: one positive node with extracapsular spread; N+ ECS+ more than 1 node: more than one positive node with extracapsular spread.

Figure 4  Impact of extracapsular spread on overall survival of patients with squamous cell carcinoma of the larynx and hypopharynx (P < .0001). N0: node negative; N+ ECS+: node positive without extracapsular spread; N+ ECS+ 1: one positive node with extracapsular spread; N+ ECS+ more than 1 node: more than one positive node with extracapsular spread.
4/26 (15.38%) for the N- ECS+ (more than 1 lymph node) 
(P<.001).

Patterns of Failure and Second Primary Tumours vs 
PnN+ Disease

With regards to the patterns of treatment failure in 
patients and according to the pathologic findings, recur-
rence occurred in 43 of the 107 patients (40.20%) when all 
recurrence types were taken together (excluding 11 patients 
with positive surgical margins and 2 who died perioper- 
atively). It was locoregional in 28 patients (26.17%) and 15 
patients presented with distant metastasis: bone marrow, 
6 patients (5.61%); lungs, 6 patients (5.61%); and skin, 3 
patients (2.80%). It must be remembered that these 
distant metastases were diagnosed during the follow-up period, 
since patients who had distant metastasis at presentation, 
were excluded from the initial analysis.

When evaluating the overall recurrence in N0 patients 
vs N+, a rate of 9.5% vs 60.0% was found. When assessing 
global recurrence by extracapsular rupture, it was present in 
4/42 (9.52%) of the N0 patients, in 10/26 (38.46%) of the 
N+ ECS−, in 7/13 (53.85%) of the N+ ECS+ (1 lymph 
ode) and in 22/26 (84.62%) of the N+ ECS+ (more than 
one lymph node). Analysing locoregional recurrence vs dis-
tance metastasis, this happened respectively 2/42 (4.72%) vs 
2/42 (4.72%) in the N0 group, 8/26 (30.77%) vs 2/26 (7.69%) 
in the N+ ECS− group, 4/13 (30.76%) vs 3/13 (23.08%) in 
the N+ ECS+ (1 lymph node) and 13/26 (50.00%) vs 9/26 
(34.61%) n the N+ ECS+ (more than one lymph node) group. 
Evaluating patterns of failure according to pN classification 
we found locoregional recurrence in 9/28 (32.14%) vs dis-
tance metastasis in 4/28 (14.29%) of the pN1 patients, 15/35 
(42.86%) vs 9/35 (25.71%) of the pN2 patients and 1/2 (50%) 
vs 1/2 (50%) for the N3 group. Because of the few num-
ber of patients with recurrence in some of the groups in 
analysis, these differences could not be statistically vali-
dated.

Second primary tumours occurred in 9 patients (8.41%), 
7 in the lung and 2 in the oesophagus, 6 of these patients 
being pN0, 2 pN+ ECS− and 1 N+ ECS+ (more than one lymph 
node).

Discussion

According to Gil et al.,3 there are many aspects that affect 
the outcome of patients with a malignant head and neck 
tumour. These relate to the tumour (the anatomical site 
and the clinical and pathological extent of the disease), the 
host (age, general condition and any intercurrent dis-
bale of the patient) and management (treatment options, 
expertise available, patient preference). By the time of 
diagnosis, according to Lindberg et al.,6 about half of the 
patients with head and neck SCC present with regional lymph 
ode metastasis, and these findings are also recently cor-
roborated by Zanaret et al.10 Nevertheless, the presence or 
absence of metastatic lymph node is accepted to be of the 
major important prognostic factors for survival in head and 
neck SCC.21,22

As far as we know and after searching in medline, neck 
metastatic lymph nodes and its prognostic meaning is being 
studied for the first time in the Portuguese population. 
Accordingly, in the present study, the pN+ patients had a 
worst prognosis than the pN0 (Figs. 1 and 2).

Notwithstanding the relative heterogeneity of this group 
of patients, presenting cancers of the larynx and hipophary-
ynx, we can consider this as an adequate sample to achieve 
the goals of this study, since all patients were submitted to 
biateral ND concomitant with the removal of the primary 
tumour as a primary treatment.

Regarding the exclusion criteria, the authors consid-
ered previous treatments that may have altered the 
normal pattern of cervical drainage or could contribute 
for a less accurate histological analysis: patients treated 
with RT as primary treatment for head and neck SCC; 
patients submitted previously to partial laryngectomies; 
patients who had as first treatment organ preservation reg-
imens (chemoradiotherapy) and patients with synchronous 
lesions.23 Patients presenting with distant metastasis were 
also excluded.

The prevalence of false negative cN0 is well recognized 
in literature. For SCC of larynx and hipopharynx, Carvalho 
found a rate of 22.8% of false-negative N0 necks,8 while 
Ozturkcan et al.9 and Snyderman et al.7 had a rate of 
32.2% and 20.0%, respectively, false-negative N0 patients for 
supraglottic SCC. Khaff et al. reported that, despite imag-
ing techniques, 20%–50% of clinically N0 patients had occult 
metastatic disease.10 Similarly, when analysing our clinical 
c(N) and our pathological (pN) staging, we verified that 41 
of 88 (46.6%) of our cN0 patients were false-negative 
(Table 2), in spite of that the preoperative staging was per-
formed according to AJCC/UICC guidelines,19 meaning they 
had occult metastatic neck disease. This stresses the need 
for complementary diagnostic exams for ruling out the pres-
ence of micrometastasis and is in line with Ferlito et al. that 
emphasize the actual virtual impossibility to detect micro-
scopic metastasis deposits prior to surgical and pathologic 
examination of the neck.5,24

Furthermore, a pN accurate staging is crucial in planning 
the following adjuvant treatment after primary surgery. So 
the role of cervical ND is not only as treatment, but also as 
a way to get a reliable tumour staging.24

Since the first description by Bennett et al.,22 several 
studies have concluded that extranodal extension of metas-
tasis of head and neck SCC portends a poor prognosis.1,7,11–15 
Our overall survival rates between pN+ ECS− and pN+ ECS+ 
were 17/26 (65.38%) vs 10/39 (25.64%) (P<.0001). So our 
study findings corroborate the literature data backing it up 
with information from patients who underwent the same 
type of surgery as initial treatment in a single institu-
tion.

Some efforts have been made in order to explain the 
concept of the ECS, namely analysing the microscopic extent 
in millimetres beyond the capsule and the presence or 
absence of tumour deposits in soft tissues, so far with no 
unanimous conclusions regarding the importance of these 
parameters.5,16–18

Concerning the prognostic relevance of the number of 
ECS+ nodes, Greenberg et al.17 found a statistically signifi-
cant poorer outcome in patients with multiple ECS+ nodes vs 
a single ECS+ node, in tongue SCC. In our analysis we found 
that this relationship is also observed for SCC of the larynx 
and hypopharynx, and the differences in overall survival and
The prognostic of about have hypopharynx. The 2-year overall survival rates were 37/42 (88.01%) for the N0 group, 17/26 (65.38%) for the N+ ECS− group, 6/13 (46.15%) for the N+ ECS+ (1 lymph node) and 4/26 (15.38%) for the N+ ECS+ (more than 1 lymph node) (P<.001) (Fig. 4).

Other studies also analysed the patterns of recurrence vs nodal status. The present study also aimed to analyse the relationship between recurrence and nodal status, considering pN0, pN+ ECS−, pN+ ECS+ (1 lymph node) and pN ECS+ (more than 1 lymph node), and was found that ECS was associated with a higher locoregional recurrence rate and with the presence of distant metastasis, in line with the previously cited bibliography. Analysing the pN status according to AJCC/UICC guidelines, the higher the pN status, the higher the presence of locoregional recurrence and distant metastasis. Though these results are indicative, because of the small number patients in some of the recurrence groups, statistical analysis could not be performed.

Conclusions
Metastatic lymph node is a major prognostic factor for survival in head and neck SCC and this fact stresses the need for an accurate staging. Nevertheless, in this study we found a very relevant rate (46.6%) of subclinical cervical metastasis, notwithstanding accurate staging procedures. Thereby we reinforce the importance of either elective or therapeutic bilateral ND in advanced tumours of the larynx and hypopharynx.

A poor prognosis associated to ECS+ involvement of cervical lymph nodes is well established in the literature. A striking finding of this study is the significantly poorer outcomes of patients with multiple ECS+ nodes. Our results about survival vs number of N+ lymph nodes with ECS have concluded that for SCC of the larynx and hypopharynx, the presence of more than one lymph node with extracapsular extension is reflected in poorer overall and disease-free survival, reflected in turn by a higher rate of locoregional recurrence and distant metastasis. Therefore, not only the presence or absence of ECS but also the number of lymph nodes with ECS must be considered when analysing prognosis of tumours of the larynx and hypopharynx.

Conflict of Interests
The authors declare that they have no conflict of interest.

References