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.

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**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 sensitizing effect was delivered according to the following scheme:
positive lymph nodes for metastasis (pN+) without ECS (−), 60 Gy in 30 fractions; pN+ with ECS (+) without macroscopic disease, 66 Gy in 30 fractions; pN+ ECS+ with macroscopic disease, 70 Gy in 35 fractions; pN− with risk level superior to 5%, 50 Gy in 25 fractions. All patients with positive surgical margins and ECS+ were proposed to Cisplatin based ChT, given every 3 weeks at 100 mg/m², 3 doses was the drug used as an irradiation sensitizing 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 peripheratively (one with an acute myocardial infarction and another with a massive hemorrhage 3 weeks after surgery) and 11 patients whose surgical margins interrupted 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.

### Table 1 Tumour Details Classified by Primary Site and T Stage.

<table>
<thead>
<tr>
<th>T Stage</th>
<th>Subglottis</th>
<th>Glottis</th>
<th>Supraglottis</th>
<th>Hypopharynx</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>0</td>
<td>2</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>T2</td>
<td>2</td>
<td>6</td>
<td>31</td>
<td>22</td>
</tr>
<tr>
<td>T3</td>
<td>5</td>
<td>17</td>
<td>11</td>
<td>33</td>
</tr>
<tr>
<td>T4</td>
<td>2</td>
<td>5</td>
<td>12</td>
<td>19</td>
</tr>
<tr>
<td>Total</td>
<td>15</td>
<td>58</td>
<td>47</td>
<td>120</td>
</tr>
<tr>
<td>Rate, %</td>
<td>12.5</td>
<td>48.3</td>
<td>39.2</td>
<td>100</td>
</tr>
</tbody>
</table>

### 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 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 (22.2%) tumours that had origin in the subglottis, in 23/59 (38.9%) that had origin in the glottis, in 13/33 (39.4%) that had origin in the supraglottis and in 9/19 (47.3%) 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 N0 group and 27/65 (41.54%) for group N+ (P<.001) (Figs. 1 and 2).

The disease-free and overall survival between N0, 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 N0 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.

<table>
<thead>
<tr>
<th>Site</th>
<th>cN</th>
<th>pN</th>
<th>cN</th>
<th>pN</th>
<th>cN</th>
<th>pN</th>
<th>cN</th>
<th>pN</th>
<th>cN</th>
<th>pN</th>
<th>No./Rate, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N0</td>
<td>N0</td>
<td>N1</td>
<td>N1</td>
<td>N2</td>
<td>N2</td>
<td>N3</td>
<td>N3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subglottis</td>
<td>6</td>
<td>6</td>
<td>3</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
<td>0 (0.00%)</td>
</tr>
<tr>
<td>Glottis</td>
<td>50</td>
<td>26</td>
<td>4</td>
<td>15</td>
<td>4</td>
<td>17</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
<td>24/50 (48.00%)</td>
</tr>
<tr>
<td>Supraglottis</td>
<td>23</td>
<td>14</td>
<td>5</td>
<td>8</td>
<td>4</td>
<td>11</td>
<td>1</td>
<td>0</td>
<td></td>
<td></td>
<td>9/23 (39.13%)</td>
</tr>
<tr>
<td>Hypopharynx</td>
<td>9</td>
<td>1</td>
<td>5</td>
<td>3</td>
<td>4</td>
<td>14</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
<td>8/9 (88.89%)</td>
</tr>
<tr>
<td>Total</td>
<td>88</td>
<td>47</td>
<td>17</td>
<td>29</td>
<td>12</td>
<td>42</td>
<td>3</td>
<td>2</td>
<td></td>
<td></td>
<td>41/88</td>
</tr>
<tr>
<td>Rate, %</td>
<td>73.3</td>
<td>39.2</td>
<td>14.2</td>
<td>24.2</td>
<td>35.0</td>
<td>26.0</td>
<td>21.4</td>
<td>17.4</td>
<td>24.9</td>
<td>15.0</td>
<td>46.59</td>
</tr>
</tbody>
</table>

pN+— 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 pN+ Disease

With regards to the patterns of treatment failure in patients and according to the pathologic findings, recurrence 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 perioperatively). 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 metastasis 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 NO 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 NO patients, in 10/26 (38.46%) of the N+ ECS−, in 7/13 (53.85%) of the N+ ECS+ (1 lymph node) and in 22/26 (84.62%) of the N+ ECS+ (more than one lymph node). Analysing locoregional recurrence vs distant metastasis, this happened respectively 2/42 (4.72%) vs 2/2 (4.72%) in the NO group, 8/26 (30.77%) vs 2/2 (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%) in 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 distant 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 number of patients with recurrence in some of the groups in analysis, these differences could not be statistically validated.

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 disease 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 node metastasis, and these findings are also recently corroborated 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 hypopharynx, we can consider this as an adequate sample to achieve the goals of this study, since all patients were submitted to bilateral ND concomitant with the removal of the primary tumour as a primary treatment.

Regarding the exclusion criteria, the authors considered 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 regimens (chemoradiotherapy) and patients with synchronous lesions.22 Patients presenting with distant metastasis were also excluded.

The prevalence of false negative cN0 is well recognized in literature. For SCC of larynx and hypopharynx, Carvalho found a rate of 22.8% of false-negative N0 necks,8 while Otzturkcan 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 imaging techniques, 20%–50% of clinically N0 patients had occult metastatic disease.10 Similarly, when analysing our clinical (cN) and our pathological (pN) staging, we verified that 41 out of 88 (46.6%) of our cN0 patients were false-negative (Table 2), in spite of that the preoperative staging was performed 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 presence of micrometastasis and is in line with Ferlito et al. that emphasize the actual virtual impossibility to detect microscopic 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 metastasis of head and neck SCC portends a poor prognosis.3,7,11–15 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 institution.

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.8,16–18

Concerning the prognostic relevance of the number of ECS+ nodes, Greenberg et al.17 found a statistically significant 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
disease-free survival were statistically significant for groups N0, N+ ECS−, N+ ECS+ (one lymph node) and N+ ECS+ (more than one lymph node): 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.5,12,14,17,18 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 the 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,19 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


