Occult lymph node metastasis in laryngeal squamous cell carcinoma: Therapeutic and prognostic impact

M. Mnejja, B. Hammami, L. Bougacha, A. Chakroun, I. Charfeddine, A. Khabir, T. Boudaour, A. Ghorbel

Service ORL et chirurgie cervicofaciale, CHU Habib Bourguiba, 3029 Sfax, Tunisia
Service d’anatomie pathologique, CHU Habib Bourguiba, 3029 Sfax, Tunisia

Summary

Objectives: To assess the incidence and impact on treatment and prognosis of occult lymph node metastasis in laryngeal cancer.

Patients and methods: A retrospective study was performed on 164 patients treated for laryngeal cancer, initially classified as N0, with cervical lymph node dissection.

Results: Occult metastases were found in 41 neck specimens (12.5%) from 32 patients (19.5%). Involvement per neck level was: 7% level IIa, 2.4% IIb, 4.2% III and 2.7% IV. Lymph node involvement was significantly increased in case of T3T4 tumor or invasion of the pre-epiglottic space or cartilage. Survival was significantly influenced by pN status (pN- = 12 years, vs pN+ = 9 years; P = 0.006).

Conclusion: Level IIb or IV involvement is rare. Superselective neck dissection (IIa, III) seems to be indicated in T1T2 N0 tumor. In case of advanced tumor or pre-epiglottic space or cartilage invasion, functional neck dissection is mandatory.

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Introduction

In laryngeal as in all upper aerodigestive tract cancer, lymph node metastasis is an important prognostic factor, and adapted treatment is critical to management and prognosis.

Achieving earlier diagnosis of the laryngeal tumor increases the frequency of patients presenting stage N0 lymph node involvement. Optimal management of N0 cases is controversial. Functional neck dissection entails a non-negligible risk of nervous and lymphatic morbidity, especially when applied to levels IIb and IV [1]. As these are the least frequently affected levels, the advisability of dissection is questionable, given advances in various diagnostic strategies.

The present retrospective study of 164 patients, operated on in first intention for stage-N0 laryngeal squamous cell cancer, assessed the incidence of occult lymph node metastasis, and sought to determine predictive factors and impact on treatment and prognosis.

Patients and methods

Patients who had undergone lymph node neck dissection for laryngeal squamous cell cancer, classified as stage N0 at
diagnosis, over an 18-year period (1990 through 2007) were retrospectively studied.

There were 164 patients: 5 female, 159 male; mean age, 62 years (range, 35–87 yrs).

All patients were pre-operatively classified as stage NO: i.e., absence of cervical adenopathy on physical examination and imaging. Patients classified as NO on clinical assessment and with radiology (CT or US) indicating benign lymph node status [2] were also counted as being at stage NO.

Tumors were T1 in 7.3% of cases (n = 12), T2 in 14.6% (n = 24) and T3T4 in 78% (n = 128). Table 1 presents tumor sublocations.

Systematic bilateral functional neck dissection was the favored attitude in all cases of laryngeal cancer except for T1 glottic lesions. All patients in the present series had undergone bilateral neck dissection, removing levels II, III and IV. Level VI dissection was performed in case of subglottic involvement (n = 34).

Dissection specimens, removed as a single piece, were located and sent for anatomopathology. All nodes were examined whole by series of 5μ cross-sections, without immunohistochemical analysis, to determine the presence/absence, number and location of metastases.

Postoperative radiotherapy was prescribed in 123 cases (75%). Mean follow-up was 36 months.

Certain tumor parameters were explored for predictive factors of occult lymph-node involvement: tumor class and site, pre-epiglottic space involvement, cartilage lysis, extralaryngeal extension, and histologic type.

Statistical analysis used SPSS 13.0 software, and comprised uni- and multi-variate analysis. In multivariate analysis, the Cox model specified parameters impacting overall survival. Overall survival was assessed by the Kaplan-Meier method, and survival curves were compared by log-rank test. The significance threshold was set at 5%.

## Results

All 164 patients underwent bilateral neck dissection removing levels II, III and IV. 328 specimens were thus analyzed.

Occult metastases were detected in 41 specimens (12.5%) from 32 patients (19.5%). Capsule rupture was found in 10 specimens (3%). Metastases were bilateral in 9 patients (5.5%) and otherwise ipsilateral to the tumor (23 patients, 14%).

The distribution of levels Ila, IIb, III and IV in the 328 specimens was respectively 7% (n = 23), 2.4% (n = 8), 4.2% (n = 14) and 2.7% (n = 9).

In the 32 patients with occult lymph node metastases, the tumor was systematically graded T3 or T4, and never T1 or T2. The tumor was transglottic in 15 cases (47%), supraglottic in 11 (34%) and glotto-subglottic in 6 (19%).

The rate of level IIb involvement in stage T3 and T4 tumor was respectively 2.7% (4/146) and 3.6% (4/110). Level IV showed invasion in 1.36% of T3 (2/146) and 6.3% of T4 tumors (7/110).

Statistical research for predictive factors showed that pre-epiglottic space and cartilage invasion correlated significantly with lymph node involvement in T3 and in T4 tumor (P = 1.5 × 10⁻⁷, 8 × 10⁻⁵ and 6 × 10⁻³, respectively). No such correlation emerged for supraglottic involvement (P = 0.07), extralaryngeal extension (P = 0.06) or histologic type (differentiation) (P = 1) (Table 2).

Complications secondary to dissection were: lymphorhea in 4 cases (1.2%) and spinal nerve damage in 13 (4%).

After treatment in case of occult lymph node metastasis, tumor recurrence was observed in 4 cases (12.5%), recurrence of lymph node involvement in 2 (6.25%) and remote metastasis in 4 (12.5%).

Comparison of tumor and lymph node recurrence and remote metastasis between patients with and without occult lymph node metastasis found no significant differences (Table 3).

Mean survival in pN- patients was 12 years, and 9 years in pN+ patients; this difference was significant (P = 0.006) (Fig. 1). Multivariate Cox analysis showed lymph node involvement to have a significant (P = 0.01) prognostic

### Table 1 Tumor sublocations (n = 164).

<table>
<thead>
<tr>
<th>Sublocation</th>
<th>Number</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supraglottic</td>
<td>7</td>
<td>4.2</td>
</tr>
<tr>
<td>Glottic</td>
<td>8</td>
<td>4.8</td>
</tr>
<tr>
<td>Subglottic</td>
<td>2</td>
<td>1.2</td>
</tr>
<tr>
<td>Glotto-supraglottic</td>
<td>55</td>
<td>33.5</td>
</tr>
<tr>
<td>Glotto-subglottic</td>
<td>8</td>
<td>4.8</td>
</tr>
<tr>
<td>Transglottic</td>
<td>84</td>
<td>51.2</td>
</tr>
<tr>
<td>Total</td>
<td>164</td>
<td>100</td>
</tr>
</tbody>
</table>

### Table 2 Prediction factors for lymph node involvement.

<table>
<thead>
<tr>
<th>Factors analyzed</th>
<th>pN negative (n = 132)</th>
<th>pN positive (n = 32)</th>
<th>Total (n = 164)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number</td>
<td>%</td>
<td>Number</td>
<td>%</td>
</tr>
<tr>
<td>Tumor class T3T4</td>
<td>96</td>
<td>72.7</td>
<td>32</td>
<td>100</td>
</tr>
<tr>
<td>Supraglottic invasion</td>
<td>114</td>
<td>86.3</td>
<td>32</td>
<td>100</td>
</tr>
<tr>
<td>Pre-epiglottic space involvement</td>
<td>20</td>
<td>15.1</td>
<td>15</td>
<td>46.8</td>
</tr>
<tr>
<td>Cartilage involvement</td>
<td>55</td>
<td>41.6</td>
<td>22</td>
<td>68.7</td>
</tr>
<tr>
<td>Extralaryngeal extension</td>
<td>22</td>
<td>16.6</td>
<td>10</td>
<td>31.2</td>
</tr>
<tr>
<td>Histologic type poorly or moderately differentiated</td>
<td>33</td>
<td>25</td>
<td>8</td>
<td>25</td>
</tr>
</tbody>
</table>
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Paleri et al. [1] concluded from a review of the literature systematically associated with involvement of another level. Rinaldo et al. [5] and Bolzoni et al. [6], analyzing data from several prospective multicenter studies of N0 laryngeal cancer, reported level IIb involvement in 1.4% of cases, systematically associated with level II involvement, and concluded that level IV dissection was not always required. Cagli et al. [11], in a series of 58 cases of supraglottic cancer, showed that level IV involvement was never isolated. Van der Brekel et al. [12] reported no cases of level IV involvement. According to Ferlito et al. [13], level IV dissection is not indicated in supraglottic or glottic cancer clinically graded as N0. In the present series, level IV involvement was found in 2.7% of cases (9/328), systematically associated with involvement of levels II and/or III. Certain authors [14] therefore recommend extemporaneous examination of levels Ila and III; like others, however, we consider extemporaneous examination insufficiently sensitive to detect micrometastases.

In subglottic cancer, metastasis is basically paratracheal, and requires level VI dissection; lateral dissection is unnecessary [13].

Routine anatomopathology fails to diagnose metastases smaller than 2 or even 5 mm [16]. Lymph node micrometastasis may thus be systematically underestimated. Burcia et al. recommended sentinel lymph node biopsy with immunohistochemistry as the technique of choice, detecting micrometastases with 100% sensitivity [16]. The interest of this technique in laryngeal cancer remains as yet to be demonstrated.

According to Rodrigo et al. [17] and Cagli et al. [18], routine bilateral functional dissection is inappropriate in N0 T1 and T2 supraglottic cancer, and should be reserved for bilateral and medial lesions.

In the present study, advanced tumor stage (T3T4) (P < 10⁻³) and pre-epiglottic invasion (P < 10⁻⁵) emerged as significant risk factors for lymph node metastasis, whereas occult metastasis did not correlate with cartilage involvement, extralaryngeal extension or histologic type. Most literature reports recommend limiting the number of levels removed, with superselective dissection to remove only levels Ila and III. The present study suggests that superselective dissection should be reserved for T1 and T2 glottic and/or supraglottic tumor without palpable cervical adenopathy.

In a prospective multicenter study, Brentani et al. [19] concluded that the type of dissection (selective vs. functional) did not correlate with the rates of ipsilateral, contralateral or bilateral recurrence in the lymph nodes.

### Table 3  Locoregional and remote evolution according to lymph node status.

<table>
<thead>
<tr>
<th></th>
<th>pN negative (n = 132)</th>
<th>pN positive (n = 32)</th>
<th>Total (n = 164)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number</td>
<td>%</td>
<td>Number</td>
<td>%</td>
</tr>
<tr>
<td>Tumor recurrence</td>
<td>7</td>
<td>5.3</td>
<td>4</td>
<td>12.5</td>
</tr>
<tr>
<td>Lymph node recurrence</td>
<td>2</td>
<td>1.5</td>
<td>2</td>
<td>6.25</td>
</tr>
<tr>
<td>Remote metastasis</td>
<td>8</td>
<td>6</td>
<td>4</td>
<td>12.5</td>
</tr>
</tbody>
</table>

**Figure 1**  Overall survival curve according to lymph node status (Kaplan Meier calculation and comparison of curves by log rank test).

**Discussion**

The role and type of neck dissection in clinically graded N0 laryngeal cancer remain controversial. The procedure of choice used to be complete functional neck dissection removing levels I through V, with associated morbidity mainly concerning spinal nerve, deep cervical plexus and thoracic canal damage. Dissection was later limited to levels II, III and IV (“selective neck dissection II-IV”, according to the Committee for Head and Neck Surgery and Oncology of the American Academy of Otolaryngology—Head and Neck Surgery [3]), given the rarity of level I or V involvement. More recently, certain authors argued against dissecting levels Iib and IV in N0 tumor, to reduce associated morbidity; others consider the occult lymph node metastasis rate to be non-negligible (37% in Shah’s series [4]), and that functional dissection is the appropriate attitude to prevent regional recurrence.

The question arises as to whether there exist any selection criteria for patients in whom levels Iib and IV can be conserved. This requires knowing the real distribution of occult lymph node metastases in the various levels of the neck. Rinaldo et al. [5] and Bolzoni et al. [6], analyzing data from several prospective multicenter studies of N0 laryngeal cancer, reported level Iib involvement in 1.4% of cases, systematically associated with involvement of another level. Paleri et al. [1] concluded from a review of the literature that level Iib was involved in only 0.4% of laryngeal squamous cell carcinomas radiologically and clinically graded as N0. All these studies agreed that level Iib dissection provided no benefit for patients free of palpable cervical adenopathy.

In the present series, Iib involvement was found in 2.4% of cases, systematically associated with Ila involvement.

Three prospective studies [7—9], including 175 patients with laryngeal cancer clinically graded as N0, reported level IV involvement in 6 patients: i.e., 3.4% of cases. Khalif et al. [10], in a retrospective study of 71 patients, reported a single case of level IV involvement, associated with level II involvement, and concluded that level IV dissection was not always required. Cagli et al. [11], in a series of 58 cases of supraglottic cancer, showed that level IV involvement was never isolated. Van der Brekel et al. [12] reported no cases of level IV involvement. According to Ferlito et al. [13], level IV dissection is not indicated in supraglottic or glottic cancer clinically graded as N0. In the present series, level IV involvement was found in 2.7% of cases (9/328), systematically associated with involvement of levels II and/or III. Certain authors [14] therefore recommend extemporaneous examination of levels Ila and III; like others, however, we consider extemporaneous examination insufficiently sensitive to detect micrometastases.
Leon et al. [20] reported no cases of failure of lymph node treatment with dissection of levels II and III.

In the present study, occult lymph node metastasis did not correlate with elevated risk of locoregional recurrence or remote metastasis. Regional evolution was observed in only 4 cases (2 pN- and 2 pN+; 2.4%), compared to 5.5% of cases reported by Lim et al. [21]. Regional recurrence often involves levels II and III [18]. In the present study, survival was significantly poorer in pN+ than pN- patients on multivariate analysis, pN stage having greater prognostic impact than tumor stage.

Conclusion

Level IIa and IV involvement in laryngeal cancer is rare and often associated with involvement of other levels. Superselective (IIa and III) neck dissection seems indicated in NO T1 and T2 glottic and/or supraglottic tumor, limiting morbidity without increasing risk of failure. In case of advanced tumor (T3 or T4) or pre-epiglottic space or cartilage involvement, occult lymph node invasion is more frequent and functional dissection is mandatory.

Conflict of interest

None.

References
