Letter to the editor

Can the lymph node ratio predict outcome in head and neck cancer with single metastasis positive-node?*

Introduction

People with head and neck cancer (HNC) and a single histologically positive-node (PN1+), account for 12–34% of cases in reported studies [1–6]. The risk classification of patients with HNC–PN1+, is not clear perhaps because these individuals generally have a loco-regional recurrent disease risk of less than 18% [5,7–9] and 5-year survival rates ranging from 70% to 81% [10,11]. Accurate risk stratification of patients with HNC–PN1+, is not possible at present, but may be influenced by the presence of other adverse histopathological features [12].

The lymph node ratio (LNR), ratio of the number of metastasis positive nodes to the total count of excised lymph nodes, has been proposed to circumvent the apparent inadequacy of a limited neck dissection and its consequent understaging effect. Recently, the LNR has been evaluated mostly for its prognostic relevance in oral carcinomas [4,6,13–16]. Our objective was to determine whether the LNR is useful in predicting locoregional recurrence (LRR) and prognosis in individuals with HNC–PN1+.

Patients and methods

This retrospective study was approved by the institutional review board. Thirty-four patients treated between 1976 and 2000, were selected for this clinical investigation because they met the following inclusion criteria: had a diagnosis of HNC–PN1+, underwent definitive surgery; had a minimum of 10 resected cervical lymph nodes and available post-treatment follow-up information. (Neck dissection has been considered adequate when ≥10 cervical lymph nodes are excised [6]). Exclusion criteria included people with ≥2 histologically positive nodes; fewer than 10 excised neck nodes or in whom the total number of resected lymph nodes was not known, or who were lost to follow-up.

All patients (eight women and 26 men with a median age of 56 years; age range, 38–85 years; seven (21%) were 65 years of age or older) were staged by clinical examination, imaging studies and histological confirmation according to the American Joint Committee on Cancer system. The total number of excised and examined nodes ranged from 10 to 75 nodes (median 22 nodes; mean 24 nodes). With a median LNR value of 5%, 16 people with a LNR finding of <5% were compared to 18 individuals with a LNR value of ≥5%.

Treatment

Depending on the primary tumor site, definitive surgery consisted of composite resection for oral cavity (10 patients) or oropharyngeal cancers (7 patients) or total laryngectomy for larynx (15 patients) with thyroid lobectomy in four patients or hypopharynx (1 patient) cancers; one individual underwent salvage neck dissection for regional recurrent disease after prior primary surgery for a T3N0M0 oral tongue cancer. Neck dissection was unilateral in extent in 27 patients; bilateral neck dissection was performed for supraglottic laryngeal neoplasms or midline located tumors of the soft palate or floor of mouth in the remaining seven subjects. Following primary surgery, conventional fractionated external beam megavoltage irradiation was administered using a cobalt-60 or 6 MV linear accelerator treatment unit. The mean total dose to the primary tumor bed/upper neck was 59.4 Gy (range 50–70 Gy) and to the lower neck was 50.9 Gy (range 45–60 Gy). During the years of the study, the decision to administer postoperative radiotherapy (PORT) was highly individualized and made at the discretion of the radiation oncologist considering the absence of a formal institutional policy. PORT was applied based on the presence of additional adverse histopathological findings such as insecure/positive surgical margins (4 patients), poorly differentiated tumor (3 patients), perineural invasion (1 patient), nodal recurrent disease (1 patient), T3/4 primary neoplasms (11 patients) and on personal preference (4 patients). Ten people did not receive PORT due to the radiation oncologist’s judgment.

Statistical analysis

Cohort outcomes were in terms of locoregional recurrence, overall and disease-free survival rates. Survival rates were estimated using the Kaplan–Meier method and compared by the log-rank test. Cox proportional hazards regression analysis was used to examine independent significant factors that impact on overall and disease-free survival. Variables included in the model were age, primary tumor site and stage, the presence of other risk features, and the application of PORT. The LNR was analyzed as a continuous variable in the Cox model. All analyses were performed using the SAS software for statistical computing (SAS version 9.3, SAS Institute Inc., Cary, NC, USA).

Results

The subsites for the 10 individuals with oral cavity cancers were the oral tongue (4 patients), gingiva (3 patients), floor of mouth (2 patients), and lip (1 patient). In the seven people with oropharyngeal neoplasms, the subsite locations of the tumor were the soft palate (1 patient), tonsil (3 patients), and base of tongue...
patients might indicate a dire outcome. In the present disease [4,6,13].

Other studies examining the lymph node ratio (LNR) in head and neck cancer, T3/T4 tumors, regional recurrence.

Figure 1. Disease-free survival with <5% and ≥5% lymph node ratios in head and neck cancer with single metastasis positive-node.

Table 1
Patient and treatment characteristics.

<table>
<thead>
<tr>
<th>Feature</th>
<th>Lymph node ratio</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age in years</td>
<td>≤5% (n = 16)</td>
<td>&lt;5% (n = 18)</td>
</tr>
<tr>
<td>Range</td>
<td>56</td>
<td>55</td>
</tr>
<tr>
<td>≥65 years</td>
<td>38–70</td>
<td>46–85</td>
</tr>
<tr>
<td>Risk factors present</td>
<td>(3) 19%</td>
<td>(4) 22%</td>
</tr>
<tr>
<td>Unilateral neck dissection</td>
<td>(10) 63%</td>
<td>(10) 56%</td>
</tr>
<tr>
<td>Tumor stage</td>
<td>(12) 75%</td>
<td>(15) 83%</td>
</tr>
<tr>
<td>T1–T2</td>
<td>(9) 56%</td>
<td>(11) 65%</td>
</tr>
<tr>
<td>T3–T4</td>
<td>(7) 44%</td>
<td>(6) 35%</td>
</tr>
<tr>
<td>Tumor site</td>
<td>≤5% OC–OPX</td>
<td>≤5% LYX–HPX</td>
</tr>
<tr>
<td>Postoperative radiotherapy use</td>
<td>(8) 50%</td>
<td>(8) 44%</td>
</tr>
</tbody>
</table>

* Insecure/positive surgical margin, perineural invasion or poorly differentiated cancer, T3/T4 tumors, regional recurrence.

Figure 3: Three-Year Disease-free Survival by LNR

Discussion

The answer to our initial question is this: a low LNR value in HNC–PN1 patients might indicate a dire outcome. In the present study, the observed median/mean number representing the total resected/examined cervical nodal count appears in line with that accepted minimum amount of >18 excised lymph nodes from the neck. An increase in nodal yield from the neck dissection has been associated with a greater chance of detecting nodal neoplastic invasion [17]. Moreover, the more metastases are found, so does the risk of recurrent disease rise [2,3,18] and the prognosis worsen [10,11]. The published literature (Table 2 [4,6,13,14]) has consistently demonstrated that a larger LNR value is associated with an adverse outcome. Although these retrospective studies were essentially not aimed at addressing the prognosis predictive value of the LNR specifically in HNC–PN1 people, subgroup analysis revealed that the LNR could prove useful in determining the risk of failure [13], regional relapse [4] or survival [4,6,14] in individuals with HNC including those patients with PN1 disease [4,6,13]. In contrast, the lower LNR value (one positive node/>22 nodes) in this cohort study was linked to a poorer patient outcome and difficult to explain adequately. The large variance in nodal yield from standard or modified neck dissection has undefined effects on the quality of life, cure rate, and survival. The number of lymph nodes in a person is not fixed and reflects, in part, the interaction between the tumor and host. It has been speculated that tumor necrosis usually connoting neoplasm aggressiveness, when sometimes observed, is a potent stimulator of lymph node hyperplasia leading to a detected rise in lymph node count.

The constraints of this analysis are its retrospective design, the small number and mix of the studied population including the absence of a standard adjuvant treatment policy. We decided to

Table 2
Other studies examining the lymph node ratio (LNR) in head and neck cancer.

<table>
<thead>
<tr>
<th>Author</th>
<th>No. of patients</th>
<th>Compared LNR values</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gil et al. [13]</td>
<td>386</td>
<td>≤0.06 vs &gt;0.06</td>
<td>Poorer 5-year disease-specific survival for patients with LNR &gt; 0.06 vs LNR ≤ 0.06 (34% and 65% respectively)</td>
</tr>
<tr>
<td>Kim et al. [14]</td>
<td>211</td>
<td>≤0.06 vs &gt;0.06</td>
<td>Poorer 5-year survival for patients with LNR &gt; 0.06 vs LNR ≤ 0.06 (47% and 80% respectively)</td>
</tr>
<tr>
<td>Sayed et al. [4]</td>
<td>1408</td>
<td>≤0.09 vs &gt;0.09</td>
<td>Poorer 5-year survival for patients with LNR &gt; 0.09 vs LNR ≤ 0.09 (19% and 70% respectively)</td>
</tr>
<tr>
<td>Urban et al. [6]</td>
<td>3091</td>
<td>&lt;0.06 vs.0.06–0.13 vs &gt;0.13</td>
<td>Median survival shortest for LNR &gt; 0.13 vs LNR &lt; 0.06 and LNR 0.06–0.13 (16 mos vs 32 mos and 25 mos respectively)</td>
</tr>
</tbody>
</table>

* Median total number of positive nodes (2–3 nodes)/median total number of resected nodes (23–27 nodes) [4,6,14].
report our finding of LRR (36%) and 3-year disease-free survival (56%) rates associated with a lower LNR value because on this basis, there could be a case for recommending PORT. Conventional wisdom advocates the use of adjuvant therapy when the relapse risk is >20% [19]. While the value of the LNR can only be suggested by our review of cases, the uncertain prognostic significance in HNC–PN1+ patients would seem underscored in this selected series.

Conclusion

It is important to ensure that staging is accurate so that locoregional tumor control and prognosis are not jeopardized by inadequate surgery or by the omission of adjuvant therapy based on misleading pathology.

A useful application of the LNR is to improve upon the risk stratification of patients in whom this consideration is not clear. In this limited experience, the LNR was found to have an outcome predictive potential in patients with HNC–PN1+. A randomized study is required to resolve our posed question and establish best practice regarding the option of postoperative radiotherapy for this especial cohort of people.

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Conflict of interest statement

None of the authors of this study has financial or other relationships that may cause a conflict of interest.

References


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