Inclusion of Extracapsular Spread in the pTNM Classification System
A Proposal for Patients With Head and Neck Carcinoma

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Importance: The inclusion of data about the presence of metastatic neck nodes with extracapsular spread (ECS) in the neck dissection improves the prognostic classification of patients with head and neck squamous cell carcinoma (HNSCC).

Objective: To evaluate the prognostic capacity of ECS in patients with HNSCC, and to analyze the usefulness of including this information in the pathological classification of patients treated with a neck dissection.

Design: Retrospective unicenter study performed from 1985 through 2007.

Setting: Tertiary referral center.

Participants: A total of 1190 patients with HNSCC treated with a neck dissection.

Intervention: Unilateral or bilateral neck dissection.

Main Outcomes and Measures: Adjusted survival and local, regional, and distant metastases-free survival. Patients were classified according to a recursive partitioning analysis (RPA) method, considering pN category and number of neck nodes with ECS as the independent variables.

Results: Five-year adjusted survival for patients without metastatic nodes in the neck dissection (pN0) was 85.5%, for patients with neck node metastases without ECS (pN+/ECS−) it was 62.5%, and for patients with neck node metastases with ECS (pN+/ECS+) it was 29.9%. There were significant differences in survival between patients with pN0 lesions and pN+/ECS− (P < .001), and between patients with pN+/ECS− and those with pN+/ECS+ (P < .001). According to the RPA method, we propose classifying patients according to 4 categories: category I, pN0 lesions; category II, pN1/ECS+ or pN+/ECS−; category III, pN2/3/1 node and ECS+; and category IV, pN2/3/2 or more nodes and ECS+. The RPA-derived classification achieved a better prognostic discrimination than the pTNM classification.

Conclusions and Relevance: The inclusion of information about ECS in the neck dissection improved the prognostic classification of patients with HNSCC in relation to the pTNM classification.

and included in a database since 1985. A total of 1230 patients collected information of patients with HNSCC treated in our center. We performed a retrospective study based on prospectively collected results of the neck dissection.

The pathological report of the neck dissections did not include appropriate information about the microscopic or macroscopic character of the ECS. An ECS was defined as a breach in the nodal capsule by tumor. The pathological report of the neck dissections in our center did not include information about the microscopic or macroscopic character of the ECS.

A total of 1741 neck dissections were performed in the patients included in the study. Information was available for all patients concerning the type of neck dissection (unilateral or bilateral), the number of nodes dissected, the number of positive nodes, and the number of nodes with ECS. An ECS was defined as a breach in the nodal capsule by tumor. The pathological report of the neck dissections in our center did not include information about the microscopic or macroscopic character of the ECS.

A total of 1741 neck dissections were performed in the patients included in the study. A total of 639 patients (53.7%) had a unilateral neck dissection, and 531 patients (46.3%) had bilateral neck dissections. In patients treated with bilateral neck dissections, results were analyzed adding the neck nodes dissected on both sides of the neck. The mean (SD) number of nodes studied per patient was 31.6 (18.6) (range, 7-118).

A total of 706 patients (59.3%) had postoperative adjuvant treatment with radiotherapy (n = 674) or chemoradiotherapy (n = 32). The indications for adjuvant treatment were maintained throughout the study period. Patients considered candidates to adjuvant treatment were those with a local (pT3-T4) or regional (pN2-N3) advanced tumor, microscopically involved surgical margins, or nodes with ECS. Postoperative radiotherapy was delivered in 2 Gy fractions to a total of 50 Gy in 5 weeks directed to both the primary site and the neck. In cases with ECS, a boost of up to 60 to 65 Gy was administered over the compromised areas. After 2000, patients with an ECS received 2 or 3 cycles of cisplatin at a dose of 80 to 100 mg/m2 concomitantly with the radiotherapy.

In 163 cases (14%) the neck dissections were performed after a previous treatment with radiotherapy (n = 114) or chemoradiotherapy (n = 49). The neck dissections were performed 6 to 10 weeks after treatment with radiotherapy or chemoradiotherapy (median, 8.5 weeks). There were significant differences in regional extension of the disease in the function of the treatment. The percentage of patients with advanced neck disease (N2-N3) treated only with a neck dissection was 14.0% (321), for patients treated with neck dissection and postoperative radiotherapy the percentage was 47.3% (706), and for patients in whom neck dissection was performed after a previous treatment with radiotherapy or chemoradiotherapy it was 71.1% (16) (P < .001).

Patients were classified according to a recursive partitioning analysis (RPA) method, considering death as a consequence of the HNSCC tumor as the dependent variable and pN category, and presence and number of neck nodes with ECS as the independent variables. The RPA splits data into segments that are as homogeneous as possible with respect to the dependent variable.

We used the Kaplan-Meier method to calculate the adjusted survival and the local, regional, and distant metastases-free survival according to the pN category and the RPA classification. Differences in survival were compared using the log-rank test. The hazard ratio considering the adjusted survival as the dependent variable was calculated using the Cox proportional hazards model.

To compare pTNM and RPA classification methods, we used the measures of hazard discrimination and balance following the criteria as defined by Groome et al.9 Hazard discrimination measures how evenly the survival curves are spaced for each of the classification categories and how large the difference in survival is between the best and the worst categories. The hazard discrimination ranges from 0 to 1, where 1 represents an ideal classification with a full coverage of the survival area by evenly spaced curves. Balance quantifies the distribution of the number of patients for the classification scheme in each category. The higher the balance, the better the classification system.

RESULTS

Five-year adjusted survival for all the patients was 63.8% (95% CI, 60.3%-67.8%). Figure 1 shows the adjusted survival according to the neck pathological status.
survival in relation to neck disease. Five-year adjusted survival for patients without metastatic nodes in the neck dissection (pN0) was 85.5% (95% CI, 82.4%-88.8%), for patients with neck node metastases without ECS (pN+/ECS−) it was 62.5% (95% CI, 56.6%-68.4%), and for patients with neck node metastases with ECS (pN+/ECS+) it was 29.9% (95% CI, 24.2%-35.6%). There were significant differences in survival between patients with pN0 lesions and those with pN+/ECS− lesions (P < .001), and between patients with pN+/ECS− lesions and those with pN+/ECS+ lesions (P < .001).

Table 2 shows 5-year adjusted survival according to the status of the neck in function of the treatment. The differences were significant irrespective of the type of treatment provided.

Considering death as a consequence of the HNSCC tumor as the dependent variable, the classification tree obtained with the RPA method identified the number of nodes with ECS as the first splitting variable and the pN category as the second. A total of 5 terminal nodes were obtained using this classification method (Figure 2). Owing to the similar prognosis between node 2 (patients with pN+/ECS−) and node 3 (patients with pN1/ECS+), both nodes were grouped into 1 category. Table 3 shows the categories defined with the RPA-derived classification system.

Table 4 shows the 5-year adjusted survival and the values of the corresponding hazard ratio as a function of the pTNM- or RPA-derived classification systems. Figure 3 shows the adjusted survival as a function of the pN- and RPA-derived classification systems. The RPA-derived classification had a better prognostic capacity than the pTNM classification. According to the pTNM classification, the adjusted survival for patients with pN2 lesions was very similar to that for patients with pN3 lesions, and the difference in survival between the best (pN0) and the worst categories (pN3) was 56.6%. The RPA-derived classification achieved a more even distribution of the survival curves, and a larger difference in survival between the best (category I) and worst categories (category IV), reaching 69.3%.

Table 5 shows the results of the objective comparison of both classification systems. In accordance with the results, the RPA method achieved the best values regarding both the heterogeneity in survival between categories (hazard discrimination), and distribution of cases between categories (balance).

Table 6 shows the 5-year survival free of local, regional, and distant disease as a function of the pTNM- and RPA-derived classification. We found a more even distribution of the survival rates and a greater difference between the best and worst categories with the RPA-derived system than with the pTNM classification.

The results obtained in the present study showed that information about the presence of neck nodes with ECS in the neck dissection improved the prognostic classification of patients with HNSCC in relation to the pathological pTNM classification. We propose a new pathological classification that incorporates information about
the presence and number of metastatic nodes with ECS (Table 3).

According to the seventh edition of the TNM Classification of Malignant Tumours,7 the objectives of a staging system are to aid in the planning of treatment, to give prognostic information, to assist in the evaluation of the results of treatment, to facilitate the exchange of information, and to contribute to the investigation. Including variables with a high prognostic capacity in the classification system should contribute to the attainment of these objectives.

The presence of metastatic neck nodes with ECS in the neck dissection implies a more aggressive biological behavior of the tumor.10 In multivariate analyses performed in large series of patients, the presence of nodes with ECS was an important prognostic factor in relation to regional failure, appearance of distant metastases, and adjusted survival.11-15 Table 7 shows the results obtained by several authors comparing the survival of patients with pN+ lesions in the function of the presence of nodes with ECS in the neck dissection. Most authors found that the appearance of nodes with ECS significantly worsened prognosis in relation to patients with metastatic neck nodes but without ECS. In only 2 series were there no significant differences in survival in relation to the presence of ECS in the neck dissection. One of these studies evaluated patients with a clinically negative neck that had occult metastases in the neck dissection (cN0/pN+).22 It is possible that the low tumor volume in these patients could explain the lack of prognostic capacity of the ECS. In another study, the survival rates for the group of patients with pN+/ECS+ lesions were lower than for those with pN+/ECS− lesions, but the difference was not statistically significant.23 The authors justified the absence of significant differences in survival by the systematic use of a boost with electrons given to the neck areas with ECS.

Despite the prognostic value of the ECS, to date it has not been incorporated into the pathological classification criteria of the pTNM.7 According to our results using the RPA-derived classification, the variable with the most prognostic value was the number of metastatic nodes with ECS. This finding agrees with results found by several other authors regarding a significant relationship between the number of nodes with ECS and prognosis.5,31,32

In the group of patients without ECS, the RPA model found significant differences in survival in relation to the presence of metastatic nodes (pN0 vs pN+). In patients with 1 metastatic node with ECS, the model found significant differences related to the size and number of positive nodes (pN1 vs pN2-3). Because the adjusted survival for patients with pN+/ECS− lesions and those with pN1/ECS+ lesions was very similar, these patients were grouped in the same category. Finally, patients with more than 1 metastatic node with ECS had the worst prognosis, and they were grouped in another category.

In an objective comparison between classifications, both the heterogeneity in survival rates between categories (hazard discrimination), and the distribution of cases between categories (balance) were better with the RPA-derived system than with the pTNM classification system.

One of the drawbacks of the proposed RPA-derived system is that it requires an accurate description of ECS, if present. Given the prognostic significance of the ECS, we consider that the pathological report concerning surgical neck dissections must include this information. In our opinion, the increased complexity of the proposed system would be outweighed by the benefits in the prognostic capacity.

From the results obtained in clinical trials,31,34 both patients with advanced regional disease (N2-N3) and patients with metastatic nodes with ECS are candidates for adjuvant treatment with concomitant chemoradiotherapy. Clinical guidelines consider the convenience of adjuvant treatment with chemoradiotherapy for patients with more than 1 positive neck node, irrespective of the size or presence of ECS, or for patients with only 1 posi-

![Figure 3. Adjusted survival. A, As a function of the pN classification system. B, As a function of the recursive partitioning analysis–derived classification system.](http://archotol.jamanetwork.com/pdfaccess.ashx?url=/data/journals/otol/926966/)
tive neck node smaller than 3 cm (pT1) but with ECS. According to our results, these patients had only a moderate risk of failure in comparison with patients with more advanced regional disease (Figure 2). For those patients with more than 1 metastatic neck node but without ECS (pN2–ECS/H11002) or with only a small positive node with ECS (pN1/ECS/H11001), it would be reasonable to consider only an adjuvant treatment with postoperative radiotherapy. Postoperative chemoradiotherapy could be reserved for patients with more advanced regional disease.

Using the proposed RPA-derived classification system would allow more accurate postoperative treatment than with pTNM classification, thereby decreasing morbidity and economic costs in a determined group of patients.

Gospodarowicz et al established that any changes to the TNM classification must have clinical relevance in terms of assessment, treatment, and outcome and must improve the prognostic capacity of the classification system. According to our results, the inclusion of the information given by the presence of metastatic nodes with ECS in patients treated with a neck dissection improves the prognostic capacity of the pTNM classification and is worthy of consideration in future reviews of the TNM classification.

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Table 6. Five-Year Survival Free of Local, Regional, and Distant Disease as a Function of the pTNM Category and Recursive Partitioning Analysis (RPA)-Derived Classification

<table>
<thead>
<tr>
<th>Category or Classification</th>
<th>5-Year Actuarial Control, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Local</td>
</tr>
<tr>
<td>pTNM</td>
<td></td>
</tr>
<tr>
<td>pN0</td>
<td>89.8 (87.1-92.5)</td>
</tr>
<tr>
<td>pN1</td>
<td>77.6 (71.4-83.8)</td>
</tr>
<tr>
<td>pN2</td>
<td>61.3 (54.9-67.7)</td>
</tr>
<tr>
<td>pN3</td>
<td>75.7 (66.6-87.8)</td>
</tr>
<tr>
<td>RPA</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>89.9 (87.2-92.6)</td>
</tr>
<tr>
<td>II</td>
<td>73.5 (68.4-78.6)</td>
</tr>
<tr>
<td>III</td>
<td>67.7 (57.8-77.6)</td>
</tr>
<tr>
<td>IV</td>
<td>51.4 (38.5-64.7)</td>
</tr>
</tbody>
</table>

Table 7. Five-Year Survival Obtained in Several Studies Analyzing Survival in Patients With an HNSCC Treated With Neck Dissection in Function of the Pathological Status of the Neck

<table>
<thead>
<tr>
<th>Source</th>
<th>Patients, No.</th>
<th>Location</th>
<th>pN0</th>
<th>pN+/ECS</th>
<th>pN+ECS</th>
<th>P Value&lt;sup&gt;a&lt;/sup&gt;</th>
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<tbody>
<tr>
<td>Noone et al,16 1974</td>
<td>132</td>
<td>Oral cavity</td>
<td>70</td>
<td>48</td>
<td>27</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Snyderman et al,1985&lt;sup&gt;b&lt;/sup&gt;</td>
<td>96</td>
<td>Larynx</td>
<td>71</td>
<td>79</td>
<td>45</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Johnson et al,1985&lt;sup&gt;b&lt;/sup&gt;</td>
<td>161</td>
<td>Head and neck</td>
<td>62</td>
<td>52</td>
<td>28</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Richard et al,1987&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1713</td>
<td>Head and neck</td>
<td>43</td>
<td>25</td>
<td>13</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Hirabayashi et al,1991</td>
<td>52</td>
<td>Larynx (pN+)</td>
<td>81</td>
<td>76</td>
<td>17</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Marmelle et al,1994</td>
<td>914</td>
<td>Head and neck</td>
<td>71</td>
<td>47</td>
<td>27</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Steinhardt et al,1994</td>
<td>522</td>
<td>Head and neck</td>
<td>77</td>
<td>54</td>
<td>28</td>
<td>&lt;.05</td>
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<tr>
<td>Alvi and Johnson,1996</td>
<td>109</td>
<td>Head and neck (cn0)</td>
<td>82</td>
<td>47</td>
<td>31</td>
<td>&gt;.05</td>
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<tr>
<td>Pinsolle et al,1997</td>
<td>337</td>
<td>Head and neck</td>
<td>62</td>
<td>45</td>
<td>36</td>
<td>.45</td>
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<tr>
<td>Brasilino de Carvalho et al,1998</td>
<td>170</td>
<td>Larynx, hypopharynx</td>
<td>57</td>
<td>50</td>
<td>18</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Woolgar et al,1999</td>
<td>200</td>
<td>Oral cavity, oropharynx</td>
<td>81</td>
<td>64</td>
<td>21</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Shingali et al,1999</td>
<td>61</td>
<td>Oral cavity, oropharynx</td>
<td>NA</td>
<td>72</td>
<td>40</td>
<td>.008</td>
</tr>
<tr>
<td>Prim et al,1999</td>
<td>128</td>
<td>Larynx (pN+)</td>
<td>NA</td>
<td>73</td>
<td>29</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Myers et al,2001</td>
<td>266</td>
<td>Oral cavity</td>
<td>88</td>
<td>66</td>
<td>48</td>
<td>.02</td>
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<td>Andersen et al,2002</td>
<td>106</td>
<td>Head and neck</td>
<td>NA</td>
<td>75</td>
<td>56</td>
<td>.02</td>
</tr>
<tr>
<td>Suoglu et al,2002&lt;sup&gt;b&lt;/sup&gt;</td>
<td>67</td>
<td>Larynx (pN+)</td>
<td>NA</td>
<td>81</td>
<td>43</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Woolgar et al,2003</td>
<td>173</td>
<td>Oral cavity (pN+)</td>
<td>NA</td>
<td>70</td>
<td>35</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Jose et al,2003</td>
<td>155</td>
<td>Head and neck</td>
<td>69</td>
<td>62</td>
<td>29</td>
<td>.002</td>
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<tr>
<td>Wenzel et al,2004</td>
<td>115</td>
<td>Oral cavity, oropharynx</td>
<td>67</td>
<td>59</td>
<td>31</td>
<td>.005</td>
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<tr>
<td>Shaw et al,2010</td>
<td>400</td>
<td>Oral cavity</td>
<td>65</td>
<td>52</td>
<td>23</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Present study</td>
<td>1190</td>
<td>Head and neck</td>
<td>86</td>
<td>63</td>
<td>30</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Abbreviations: ECS, extracapsular spread; HNSCC, head and neck squamous cell carcinoma; NA, not applicable.

<sup>a</sup>P value, statistical differences in survival between pN+/ECS− and pN+/ECS+.

<sup>b</sup>Three-year survival.
REFERENCES


