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# Validation of the pathological classification of lymph node metastasis for head and neck tumors according to the 8th edition of the TNM Classification of Malignant Tumors

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ABSTRACT

*Objectives:* One of the main changes in the 8th edition of the TNM Classification for head and neck tumors is the inclusion of extracapsular spread (ECS) as a criterion for evaluating the regional extension, both clinical (cN) and pathological (pN). The objective of our study is to evaluate the prognostic capacity derived from the inclusion of the ECS in the pathological classification of head and neck squamous cell carcinoma (HNSCC) patients treated with a neck dissection, as established by the 8th edition TNM Classification.

*Materials and methods:* Retrospective study of 1188 patients with HNSCC treated with a neck dissection between1990 and 2013.

*Results:* There were lymph node metastasis in 50.1% of the neck dissections. The pathological record revealed ECS in 50.5% of the positive neck dissections. The implementation of the changes of the 8th edition TNM classification produced the upstaging of 20.9% of the patients classified as pN1 with the 7th edition TNM classification to pN2a, and the upstaging of 58.4% of the patients classified as pN2 with the 7th edition TNM classification to pN3b. We conducted an objective comparison of the quality of both classifications. The 8th TNM classification edition achieved better results regarding both the discrimination in cause-specific survival between pN categories and in the distribution in the number of cases between categories than the 7th edition TNM classification.

*Conclusion:* The inclusion of ECS in the pathological classification (pN) of the neck nodes improves the prognostic capacity of the 8th TNM Classification edition.



## Introduction

One of the main objectives of a staging system, as stated in the introduction of the 8th edition of the *TNM Classification of Malignant Tumours* [1] (8th ed. TNM), is to provide prognostic information. With this aim, every new edition of the TNM incorporates modifications that improve the prognostic capacities of the classification.

Gospodarowicz et al. [2] 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.

The main changes for head and neck squamous cell carcinomas (HNSCC) in the 8th ed. TNM are the creation of a specific staging system for p16-positive oropharyngeal carcinomas and the inclusion of extracapsular spread (ECS) as a criterion for evaluating the regional extension, both clinical (cN) and pathological (pN).

As a general rule, patients with lymph node metastasis with ECS are upstaged as compared to similar cases without ECS. In the clinical classification (cN), all patients with lymph node metastases with clinical signs of ECS are classified as cN3b, irrespective of the size or laterality of the metastatic neck node.

In the pathological classification (pN), unilateral single positive lymph nodes less than 3 cm with ECS are classified as pN2a instead of pN1. All other cases with ECS are classified as pN3b irrespective

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of the size and laterality of the lymph node. Table 1 shows the new classification criteria for pathological regional extension for p16-negative patients. Patients with oropharyngeal p16-positive tumors have a specific classification.

ECS is defined as extension of the tumor outside the lymph node capsule. There is a wide consensus in the literature about the impact of ECS in the survival of the patients with HNSCC. The results of a meta-analysis by Dünne et al. [3] showed that the presence of ECS in neck dissections had a negative impact on survival, with a summarized odds ratio of 2.7 (95% CI, 2.2–3.4). Additionally, a recent systematic review of the literature and meta-analysis carried out by Mermod et al. [4] confirms the impact of ECS on locoregional recurrence and distant metastasis in HPV-negative HNSCC patients. Interestingly, the presence of ECS in patients with HPV-positive oropharyngeal tumors did not affect prognosis.

In a previous study performed in our center [5], we showed how the information about the number of nodes with ECS in the neck dissection improved the prognostic capacity as compared to the pN classification of the 7th ed. TNM, and advocate for the inclusion of ECS in new editions of the pTNM classification [6]. The 8th ed. TNM does not include the number of nodes with extracapsular spread, but the presence of any node with extracapsular spread as criterion in the pathologic classification.

The aim of our study is to evaluate the improvement in prognostic capacity derived from the inclusion of the ECS in the pathological classification of HNSCC patients treated with a neck dissection, as established by the 8th edition of the TNM Classification.

## Material and methods

We performed a retrospective study based on prospectively collected information of patients with HNSCC treated in our center [7]. A total of 1188 patients who had an HNSCC located in the oral cavity, oropharynx, hypopharynx, or larynx diagnosed from 1990 through 2013, and treated with a unilateral or bilateral neck dissection were initially included in the study. HPV status in oropharyngeal tumors was analyzed retrospectively by HPV-DNA detection with SPF-10 real time PCR assay in combination with LiPA genotyping [8]. We excluded 21 patients with HPV-positive oropharyngeal carcinomas, 4 patients who lacked appropriate information about the pathological results of the neck dissection, and 26 patients who did not have a minimum follow-up of 2 years.

**Table 1**
Classification criteria for pathological regional extension of head and neck carcinomas (excluding nasopharynx and p16-positive oropharynx) according to the 8th edition of the TNM Classification.

| | |
|---|---|
| pNX | Regional lymph nodes cannot be assessed |
| pN0 | No regional nodes metastasis |
| pN1 | Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension, without extranodal extension |
| pN2a | Metastasis in a single ipsilateral lymph node less than 3 cm in greatest dimension with extranodal extension or more than 3 cm but not more than 6 cm in greatest dimension, without extranodal extension |
| pN2b | Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension, without extranodal extension |
| pN2c | Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension, without extranodal extension |
| pN3a | Metastasis in a lymph node more than 6 cm in greatest dimension without extranodal extension |
| pN3b | Metastasis in a lymph node more than 3 cm in greatest dimension with extranodal extension or, multiple ipsilateral, or any contralateral or bilateral node(s) with extranodal extension |

**Table 2**
Characteristics of the patients included in the study.

| | | | |
|---|---|---|---|
| Age (years) | Median 60.8/Standard deviation 11.1 | | |
| Sex | Men | 1023 | 90.0% |
| | Women | 114 | 10.0% |
| Tobacco | No | 96 | 8.4% |
| | <50 pack-years | 148 | 13.0% |
| | ≥50 pack-years | 893 | 78.6% |
| Alcohol | No | 193 | 17.0% |
| | <80 g/day | 461 | 40.5% |
| | ≥80 g/day | 483 | 42.5% |
| Location | Oral cavity | 270 | 23.8% |
| | Oropharynx | 213 | 18.7% |
| | Hypopharynx | 179 | 15.7% |
| | Larynx | 475 | 41.8% |
| Local extension[a] | T1 | 143 | 12.5% |
| | T2 | 333 | 29.3% |
| | T3 | 427 | 37.6% |
| | T4 | 234 | 20.6% |
| Regional extension[a] | N0 | 567 | 49.9% |
| | N1 | 158 | 13.9% |
| | N2 | 377 | 33.1% |
| | N3 | 35 | 3.1% |

[a] According 7th ed. TNM.

Table 2 shows the characteristics of the 1137 patients included in the study.

We retrieved information 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 for all patients. ECS was defined as any breach in the lymph node capsule by tumor cells. The pathological report of the neck dissections in our center did not include information about the microscopic or macroscopic character of the ECS.

We performed 1820 neck dissections (410 radical neck dissections and 1410 selective neck dissections) on the patients included in the study. A total of 683 patients (60.1%) had bilateral neck dissections. In patients treated with a bilateral neck dissection, results were analyzed adding the neck nodes dissected on both sites of the neck. The mean number of lymph nodes studied per patient was 32.6 (standard deviation 19.9, range 7–118).

In 157 cases (13.8%) we performed the neck dissections after a previous treatment with radiotherapy (n = 71) or chemoradiotherapy (n = 86). The interval between the radiotherapy or chemoradiotherapy and the neck dissection was 6 to 10 weeks (median, 8.5 weeks).

A total of 596 patients (52.4%) had postoperative adjuvant treatment with radiotherapy (n = 525) or chemoradiotherapy (n = 71). The indications for adjuvant treatment were maintained throughout the study period. Patients with advanced tumor, either locally (pT3-T4) or regionally (pN2-N3), microscopically involved surgical margins, or ECS were considered candidates to adjuvant treatment. 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 60–65 Gy was administered over the compromised areas. Concomitant chemotherapy, consisting in 3 cycles of cisplatin at a dose of 80–100 mg/m$^2$ was offered in selected cases with indication of postoperative radiotherapy from 2000 to present.

The mean follow-up time was 5.6 years (standard deviation 4.9 years). During the follow-up period, 213 patients (18.7%) had local failure, 158 (13.9%) had regional failure, and 172 (15.14%) presented distant metastases.

We used the Kaplan-Meier method to calculate survival times. We calculated the cause-specific survival according to the 7th ed.