Prognostic implications of node metastatic features in OSCC: A retrospective study on 121 neck dissections

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Abstract. Lymph node metastases are responsible for shorter survival in oral squamous cell carcinoma (OSCC). The aim of the present study was to assess the node metastasis frequency and survival according to the node metastasis features in 121 neck dissections (NDs) performed for OSCC, identifying evidence-based correlations and contrasts with previous literature. The retrospective study involved 121 patients affected by OSCC who had undergone modified radical ND (MRND) for therapeutic, elective reasons or after intraoperative positivity to metastasis of sentinel lymph nodes (SLN+). Node metastasis frequency and behaviour (typical vs. atypical) and their number and distribution according to pre-surgical cTNM cancer staging were considered and overall survival Kaplan-Meier curves were calculated for each group in order to compare mortality according to ND type (elective, therapeutic, after SLN+), lymph node metastatic pattern (typical or atypical), size (micrometastasis vs. macrometastasis) and number. Results showed statistically significant different overall survival according to pre-surgical staging, number of lymph nodes harvested and intent to surgery. Sentinel lymph node resulted in the sole positive node affected by metastasis in small cT1- cT2/cN0 OSCC and an ND subsequent to its positivity during intraoperative assessment may be considered an overtreatment.

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Introduction

Oral squamous cell carcinoma (OSCC) is the sixth most common cancer internationally, accounting for ~5% of all malignant tumours worldwide (1). OSCCs commonly metastasize to cervical lymph nodes. Each tumour generally metastasizes in a particular group of cervical lymph nodes and the principles and criteria governing neck dissection (ND) are based on the primary tumour characteristics, according to the cTNM staging and its primary site (2,3).

Cervical lymph node metastases (LNMs) are key malignancy criteria in OSCC (4). Their presence influences the therapeutic plan and prognosis, since it is associated with a 50% decrease in survival (5,6).

The selection of OSCC cases requiring ND depends mainly on the clinical TNM staging (cTNM). cTNM provides a stage

grouping based on the extent of the primary tumour (T score), the involvement of the regional, cervical, lymph nodes (N score) and the detection of distant metastases (M score) (2,3,7). These parameters are accurately quantified after performing a series of clinical-instrumental examinations such as PET, total body CT scan, neck echo-color Doppler, fibrolaryngoscopy, esophageal-gastric-duodenoscopy, bronchoscopy and, if any doubts persist, fine needle aspiration biopsy (FNAB) and biopsy must be also performed.

Once clinical T, N and M parameters have been defined, an ND is mandatory for the OSCCs showing cervical LNMs (any cT/N+) and for locally advanced primary tumours (cT3 or cT4) with clinically undetectable LNMs (cN0).

Based on the intent or purpose, NDs have been also classified into therapeutic and elective. Therapeutic NDs are performed in OSCCs with cervical metastases detected in clinical preoperative setting (any T/N+). Elective NDs are selected for locally advanced primary tumours (T3 or T4) with clinically undetectable LNMs (cN0) (8). NDs are also performed in the cases of small primary tumours clinically negative to node involvement (cT1-T2/N0) that during intraoperative assessment of their sentinel lymph node reveal positivity to metastasis (9).

Both ND anatomical extent and involvement of surrounding structures are related to the node levels involved in the dissection and they are planned on the basis of the OSCC primary site; correlations between primary site of the cancer and level of metastasis have been demonstrated and, to date, they aid the surgeon in the surgical ND management (10).

Currently, NDs are classified into four basic procedures according to the extent of different cervical lymph node groups and surrounding structures: radical ND, modified radical ND, (MRND) extended ND and selective ND (8,11).

Following histopathological assessment of the tumour margins of excision and after the evaluation of the involvement of the surrounding structures, adjuvant therapy may also be performed: radiotherapy for T4 tumours with free surgical margins and/or ≥N2; and both radiotherapy and chemotherapy for tumours with any N+ plus extracapsular spread (ECS) and ones with any T and positive or close margins or perineural invasion and/or neoplastic vascular embolization. T1-3 tumours with free margins and pN0/pN1 do not require adjuvant treatment (12,13).

Despite the progress in pre-surgical instrumental examinations (head and neck CT scan, neck echo-color Doppler, fibrolaryngoscopy, esophageal-gastric-duodenoscopy, bronchoscopy and PET), clinical lymph node staging is not completely error-free due to false positivity in the presence of reactive lymph nodes, non metastatic lymph node enlargement and false negativity for small- or micrometastases clinically undetectable (14,15). Finally, the controversial role of sentinel lymph node positivity and the surgical morbidity after ND have led to the evaluation of alternative and super-selective surgeries in order to reduce the overtreatments (15,16-18).

For these reasons, further in-depth studies regarding the behaviour of lymph node cervical metastases may be useful to refine therapeutic management, thereby decreasing the overtreatment-related morbidity and mortality.

The aim of the present study was to define LNM frequency, topographic distribution, size (micrometastases vs. macrometastases) and histological pattern correlating them with the clinical features of primary tumour in 121 OSCC patients who had undergone ND, considering the survivals related to their presence/absence and the morbidity related to the negative ND and due to the neck surgery, comparing our results with the literature and suggesting an evidence-based re-evaluation of the therapeutic approach to ND.

Materials and methods

Study population and clinical pathological data. Resection specimens from 121 patients who had undergone ND surgery for OSCC at the National Cancer Institute of Naples, 'G. Pascale', Italy, between the years 1993-2004, formed the basis of the present retrospective analysis. All patients underwent MRND for OSCC (11,19). Patients who had had previous surgery (other than diagnostic biopsy) were excluded. Throughout the time period of the study, the resection specimens were performed by the same surgical team and were assessed by the same pathological team. Pathological report and topography of the extent and location of the metastatic disease for each patient were reviewed and number, size and histological patterns of LNM-positive cases (pN+) were re-evaluated according to previous literature (14,15,20,21) in order to calculate frequency, distribution and other significant statistical correlations existing between primary tumour features and pN+.

The series comprised 80 males (mean age of 63.10±10.79 years; range, 30-83 years, median 63 years) and 41 females (mean age, 63.12 ±15.19 years; range, 25-86 years, median, 65 years). The cTNM staging was assessed according to the 6th edition AJCC (2) since data refer to the period between 1999-2004. Patient demographic and clinical characteristics of the 121 cases are summarized in Table I.

Pre-operative, operative and post-operative protocols. At the National Cancer Institute of Naples 'G. Pascale', Italy, the selection of OSCC cases requiring ND depends on the cTNM (2). cTNM parameters are accurately quantified after performing a series of clinical-instrumental examinations such as PET, total body CT scan, neck echo-color Doppler, fibrolaryngoscopy, esophageal-gastric-duodenoscopy, bronchoscopy and, if any doubts persist, fine needle aspiration biopsy (FNAB) and biopsy.

According to the literature, MRNDs are considered mandatory for the OSCCs clinically showing cervical LNMs (any cT/N+ and therapeutic ND), for locally advanced primary tumours with clinically undetectable LNMS (cT3/N0 and cT4/cN0, elective ND) and in the cases of small primary tumours clinically negative to node involvement (cT1-T2/N0) that during intraoperative assessment of their sentinel lymph node reveal a positivity to metastasis (SLN+) (8,9).

For the ND surgical approach, we adopted MRND (10), thus involving levels I-IV for all oral sub-sites, except for trigone, posterior tongue and anterior pillar where ND extended until level V; level IIB was always comprised.

After surgery and histopathological assessment of the margins of excision of the primary tumour and after the evaluation of the involvement of the surroundings structures, adjuvant therapy was performed; radiotherapy for T4 tumours

Table I. Patient demographics and clinical characteristics.

	N (%)
Gender (male/female)	80/41 (66/34)
Male mean age, years (range)	63.10 (30-83)
Female mean age, years (range)	63.12 (25-86)
Primary T site	
Tongue	53 (44)
Floor of the mouth	23 (19)
Cheek	4 (3)
Trigone	17 (14)
Oropharynx	8 (7)
Palate	3 (2)
Fornix	10 (9)
Not specified	3 (2)
Histologic grade	
Low	35 (29)
Intermediate	65 (54)
High	21 (17)
AJCC stage	
I	11 (9)
II	30 (25)
III	28 (23)
IV	52 (43)

with free-surgical margins and/or ≥N2, and both radiotherapy and chemotherapy both for tumours with any N+ plus ECS, tumours with any T and positive or close margins or perineural invasion and/or neoplastic vascular embolization tumours T1-3 with free margins and pN0/pN1 were not enrolled for adjuvant treatments (12,13).

Since data refer to patients recruited from 1999 to 2004, prior to the last Cancer Staging Atlas publication, we considered the previous edition (2); hence, T4 tumours were not distinguished in T4a and T4b, consequently, stage IV has not been not subclassified into stages IVa, IVb and IVc (7).

Histopathological node metastasis classification. All 121 lymph node specimens dissected were histopathologically re-evaluated for the present study. In order to detect micrometastases and to confirm the involvement of lymph nodes, the standardized sectioning protocol was performed. One H&E stained section was prepared from each block and examined for the presence of nodal involvement by tumour. If present, metastatic disease was reported. If node was negative or equivocal for metastatic disease, or positive for micrometastases, the removed lymph nodes were also serially sectioned at 25-μm intervals 4 μm thick and alternately stained with H&E and immunohistochemical staining (IHC) using anti-cytokeratin and EMA antibodies (Fig. 1) as described below. This pattern was continued throughout the entire block. Each immunostained component was always compared with adjacent sections stained by H&E.

Woolgar's classification criteria were considered in order to classify the type of metastasis (21,22). Woolgar distinguished metastatic lymph nodes into two groups with different prognosis and features: typical metastatic pattern as 'orderly involvement of successive anatomical nodal levels, creating an inverted cone with maximum volume and maximum ECS at levels I or II and a gradual reduction in the volume/extent of metastasis at the numerically higher levels' (21), vs. atypical metastatic pattern, termed 'aberrant' by Woolgar, and characterized by various features. The ones referring to the atypical pattern and considered in the present study were the involvement of 'other' anatomical groups of nodes (including parapharyngeal, facial, buccal, lingual and sublingual nodes), involvement of controlateral cervical lymph nodes, skipping of anatomical levels other than level I and the presence of a single micrometastasis (21).

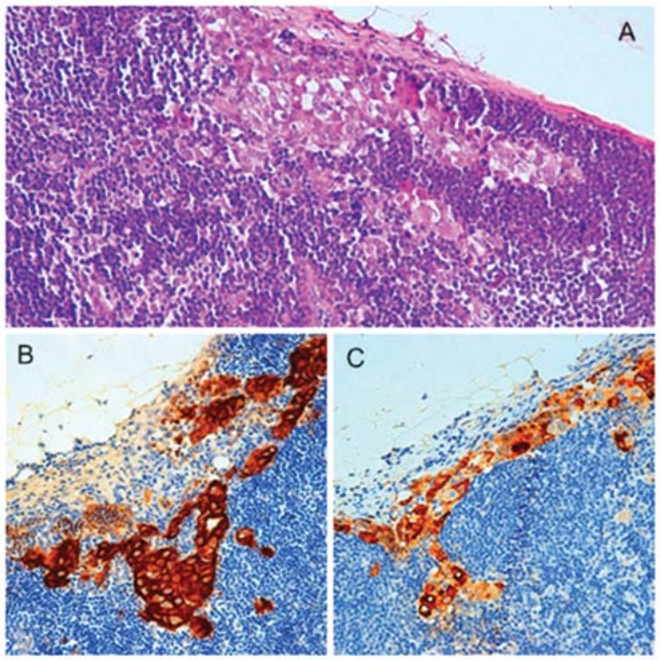


Figure 1. Immunohistochemical H&E staining of a node metastasis showing cytokeratin and EMA positivity confirming the presence of OSCC metastases in the lymph nodes evaluated.

Once defined, the histopathological features of node metastases were correlated with the clinical and histopathological features of the primary tumour in order to establish statistical and prognostic correlations.

Immunohistochemistry. Histological and immunohistochemical analyses were performed on formalin-fixed, paraffin-embedded tissue samples. Immunostaining was performed using the linked streptavidin-biotin horseradish peroxidase technique (LSAB-HRP). Antigen retrieval was performed by microwave heating, a first time for 3 min at 650 W, a second and a third time for 3 min at 350 W, the slides immersed in 10 mM citrate buffer pH 6.0. After heating, the sections were blocked for 60 min with 1.5% horse serum (Santa Cruz Biotechnology) diluted in PBS buffer before reaction with the primary antibody (Ab). The primary monoclonal antibodies anti CK AE1/AE3 (dilution 1:50, pH 6.0; Dako, Carpinteria, CA, USA) and EMA (dilution 1:75, with protein K; Dako) were incubated overnight. After two washes

with PBS, the slides were treated with biotinylated species-specific secondary antibodies and streptavidin-biotin enzyme reagent (Dako, Glostrup, Denmark), and the colour developed by 3,3'-diaminobenzidine tetrahydrochloride. Sections were counterstained with Mayer's hematoxylin and mounted using xylene-based mounting medium. In negative controls, the primary antibody was omitted. The results of the IHC were separately evaluated by two independent observers by carefully examining the entire section with an optical microscope (Olympus BX41). For each case, the presence and the extent of positive cells in all sections examined was determined. Isolated tumour cells (ITCs) are defined as tumour cell clusters that are not >0.2 mm in largest diameter and are denoted as lymph node negative (pN0[i+]). Micrometastases are defined as metastases that are >0.2 mm in diameter but ≤2 mm, denoted as lymph node positive (pN1mi). Carcinoma macrometastases measured >2 mm in maximum extent. Two investigators experienced in oral pathology blindly and independently examined the study sections initially, and then they evaluated together the histopathological and immunostained sections until they reached an agreement.

Statistical analysis. Data were analysed by the GraphPad Prism software version 5.0 for Windows (GraphPad Software, San Diego, CA, USA; www.graphpad.com) and Excel Microsoft Office. Differences among the groups were estimated using the one-way analysis of variance (ANOVA) and the Student-Newman-Keuls test. Only P-values <0.05 were considered significant. Overall survivals in the different groups were calculated by the Kaplan-Meier curves and log-rank (Mantel-Cox) test was applied for comparing survival probabilities. The pathological positivity of the ND (pN+) and the type of LNMs were correlated with the site of primary tumour. The percentages of positive node metastases (pN+) in elective, therapeutic and secondary to SLN+ NDs and the number of lymph nodes harvested were also evaluated.

Results

Differentiation degree, cTNM staging and pN status of 121 cases. Patient demographics and characteristics such as gender, OSCC site, primary tumour differentiation grading and cTNM staging according to the international guidelines (2) of the 121 OSCCs considered are shown in Table I.

At pre-surgical clinical-instrumental evaluation, 61/121 cases (50%) were considered positive (cN+) and 60/121 (49%) negative (cN0) to node metastases. The histopathological lymph node assessment subsequent to ND revealed at least one node metastasis in 56/121 NDs, thus considered pathologically positive lymph nodes (pN+) and no node metastasis in the remaining 65 cases, which were considered pathologically negative lymph nodes (pN0). The percentages of true positive (cN+ and pN+), true negative (cN0 and pN0), false positive (cN+ and pN0) and false negative (cN0 and pN+) were 87, 95, 13 and 5% respectively, as reported with details of accuracy, sensitivity, specificity, and positive and negative predictive values in Fig. 2.

The pN+ distribution according to the grading, staging MRND intent and, conversely, the pN+ frequency in each group are reported in Table II.

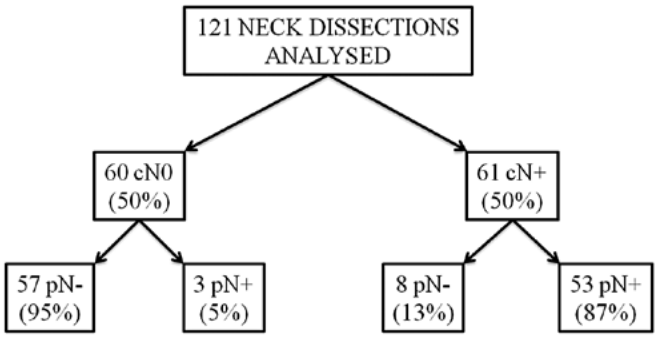


Figure 2. Flow chart showing the cases analysed in the study and the accuracy, sensitivity, specificity and predictive values of the clinical instrumental approach. Accuracy, 90.9%; sensitivity, 0.946; specificity, 0.877; PPV[1], 8.869; NPV[2], 0.950; [1]PPV, positive predictive value; [2]NPV, negative predictive value.

Distribution of 121 MRNDs according to intent to surgery and related pN+ frequencies. Among the 121 NDs considered, 61/121 (50%), presenting at least a clinical node involvement (cN+), were therapeutic NDs; 19/121 (16%), presenting a cT3/cT4 and cN0 were elective NDs; the remaining 41/121 (34%), presenting primary tumours small in size (cT1/cT2) and no evident clinical node metastases (cN0) but positive to sentinel lymph node metastases (SLN+) during the intraoperative assessment of sentinel lymph node, were NDs performed to establish the presence of other node metastases in addition to SLN+ (Table II). The distribution of 56 pN+ according to clinical-instrumental indications and, conversely, the pN+ frequency in each indication are reported in Table II.

pN+ pattern. After excluding 19 pN+ cases due to lack of data useful to classify the pN+ histopathological pattern, the remaining 37 pN+ NDs were distinguished into 17/37 with typical (46%) and 20/37 with atypical (54%) node metastases according to Woolgar's classification (21). The atypical pattern was largely represented by skip metastases [10/20 (50%)], followed by the frequency of bilateral metastases [5/20 (25%)], micrometastases [2/20 (10%)], involvement of other lymph nodes alone [2/20 (10%)], and 1/20 (5%) showing both micrometastases and other lymph nodes co-interested (Fig. 3A). According to primary tumour site, skip metastases indiscriminately involved any site of the oral cavity, except check and fornix, which, on the contrary, preferentially showed micrometastases; bilateral metastases were frequently detected in OSCCs affecting tongue as a single site or in association with floor of the mouth or trigone; 'other different lymph nodes' were involved in floor of the mouth tumours (Fig. 3B and C).

Among 56 pN+ cases, 15/56 pN+ (26.8%) involved levels I-III, 11/56 pN+ (19.6%) involved levels IV-V, and 30/56 (53.6%) pN+ were censored due to level not reported.

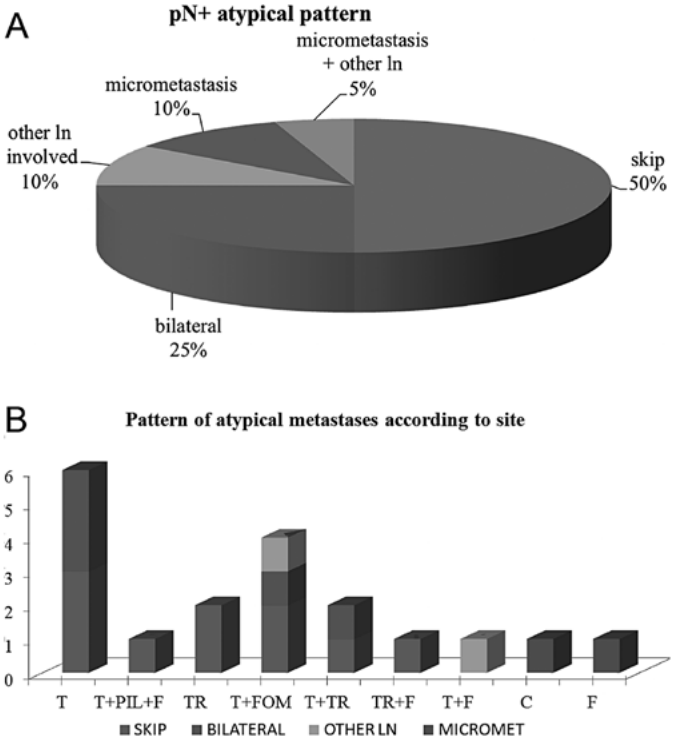
ND anatomical levels I-III were typically involved by node metastases while levels IV-V showed pN+ only for primary tumours of trigone, floor of the mouth plus tongue, tongue alone and multiple sites (data not shown).

Number of lymph nodes removed. A total of 3,390 lymph nodes were harvested in 121 NDs, mean 18.5±22.7 per ND,

Table II. pN+ distribution and frequency according to histological grading, AJCC staging and MRND intent.

Histological grade	Total ND cases (%)	pN+ distribution according to grade	Total pN+ cases in each group
Low	35 (29)	11/56 (20)	11/35 (31)
Intermediate	65 (54)	32/56 (57)	32/65 (49)
High	21 (17)	13/56 (23)	13/21 (62)
cTNM	**Total ND cases (%)**	**pN+ distribution according to cTNM**	**Total pN+ cases in each group**
Stage I	11 (9)	0/56 (0)	0/11 (0)
Stage II	30 (25)	2/56 (4)	2/30 (6.6)
Stage III	28 (23)	13/56 (23)	13/28 (46.4)
Stage IV	52 (43)	41/56 (73)	41/52 (79)

cT status	cN status	MRND clinically accorded	Total ND cases (%)	pN+ according to MRND intent	Total pN+ cases in each group
Any T	cN+	Therapeutic	61/121 (50)	53/56 (94)	53/61 (88.3)
T3 or T4	cN0	Elective	19/121 (16)	1/56 (2)	1/19 (5.3)
T1 or T2	cN0	Secondary to SLN+	41/121 (34)	2/56 (4)	2/42 (4.8)



C

Site	Skip	Bilateral	Other Ln	Micromet
T	3	3	0	0
T+PIL+F	1	0	0	0
TR	2	0	0	0
T+FOM	2	1	1	0
T+TR	1	1	0	0
TR+F	1	0	0	0
T+F	0	0	1	0
C	0	0	0	1
F	0	0	0	1

Figure 3. Atypical metastatic pattern frequencies (A) and their distributions (B and C) according to primary tumour site. (C) Distribution of the 19 pN+ atypical metastases according to pattern and primary tumour site. The case showing both micrometastases and other lymph nodes co-interested has not been included. Ln, lymph node; T, tongue; PIL, pillars; F, fornix; FOM, floor of the mouth; TR, trigone; C, cheek.

range 1-110. One hundred and sixty-two lymph nodes were pN+ in 56 NDs, mean 2.9±0.03, range 1-10.

Recurrence. Recurrence was observed in 8 cases, whose clinical, histological and lymph node features are shown in Table III.

Survival curves. Overall survival statistical significance and percentages of subjects alive at 1, 2 and 5 years from the diagnosis are reported in Table IV.

Overall survival was statistically different according to early AJCC vs. late AJCC stages (P=0.0004) with a 5-year

Table III. Clinical, histological and lymph node features in the 8 cases with recurrence.

Gender	Age (years)	T site	Histological grade	AJCC stage	pN status	Outcome
Female	80	FOM	Low	II	pN0	Alive
Female	83	FOM	Intermediate	III	pN+	Alive
Female	48	Tongue	Intermediate	IV	pN+	Alive
Female	70	Tongue	Low	I	pN0	Deceased
Male	64	Tongue	Intermediate	II	pN0	Deceased
Male	57	FOM, Tongue	Intermediate	IV	pN+	Alive
Male	70	Fornix	Intermediate	III	pN+	Deceased

survival of 78.34 and 46.16%, respectively, and according to absence/presence of nodal metastases (pN0 vs. pN+, P=0.0003) with a 1-5 year overall survival ranging between 97-74% in pN0 cases and between 69-54% in pN+ cases.

Overall survival according to histological grade and typical vs. atypical lymph nodal metastatic pattern did not reach statistical significance when independently considered or when together. When comparing pN0 subjects, pN+ with macrometastases or ECS and pN+ with micrometastases, patients reporting pN+ with micrometastases showed an intermediate probability of survival after 5 years and these data were statistically significant (P=0.004). With regard to the number of lymph nodes harvested, statistically significant different survivals (P=0.005) were found in cases with >30 lymph nodes harvested, whose 5-year survival was >80% compared to 46.93% in cases with <20 lymph nodes and 66.67% in the 20-30 lymph node group, independently of the pN status.

With regard to intent to surgery, overall survival among subjects who had undergone elective, therapeutic and after SLN+ NDs were always statistically significant with the worst prognosis in patients who had undergone therapeutic ND and the most positive one in patients who had undergone ND after SLN+. pN status did not appear to be responsible for differences in survival since patients with pN0/therapeutic MRND showed a 15% 5-year survival compared to pN+/therapeutic MRND patients with a 45.72% 5-year survival.

Discussion

In the present study, a descriptive and statistical retrospective study on 121 OSCCs who had undergone neck dissection (ND) was conducted, focusing on metastatic pattern (typical vs. atypical), number of lymph nodes harvested and node metastasis features in terms of size, anatomical extent and surgical decision orienting the ND (elective, therapeutic and after SLN+).

Correlation among histological malignancy grading in OSCC and different clinical parameters such as clinical staging, recurrence and prognosis have been published in different studies and a close relationship between the degree of histological differentiation and the incidence of lymph node metastasis (LNM) has been reported by several investigators in an attempt to identify a better prognosis. Our results are partly in accordance with previous literature (23).

Descriptive data showed, as expected, that the more the primitive tumour was towards undifferentiation and AJCC advanced staging, the more frequent the nodal metastases. Despite these findings, statistically significant differences in the overall survival were observed only in relation to staging and not according to grading.

Since 88.3% of NDs performed for therapeutic intent presented at least one pN+, the therapeutic value was confirmed. On the contrary, the low pN+ frequencies in elective NDs (5.3%) and in NDs secondary to SLN+ (4.8%) revealed an overtreatment in the remaining 94.7 and 95.2% of cases, respectively. pN+ was found in 2 out of 42 NDs performed after SLN+ (0/11, 0%, pN+ in cT1-cN0M0 NDs and 2/31, 6.45%, in cT2-cN0M0 NDs), thus confuting previous literature supporting its role as a diagnostic marker for other nodal metastases (24,25) and bringing the predictive role of SLN positivity into discussion, leading us to conclude that an ND secondary to SLN+ is an overtreatment in 100% of cT1-cN0M0 NDs and in 93.55% of cT2-cN0M0 NDs. We suggest conducting further biomolecular studies focusing on molecular markers able to predict occult metastatic disease in SLN biopsies, thereby improving the quality of the treatments (26).

The significant association between clinical staging and histopathological report, confirmed by high accuracy (90.9%) revealed the quality of the pre-surgical clinical and instrumental staging of the tumours.

With regard to the anatomical lymph nodal levels involved, results showing involvement of levels IV-V only for primary tumours of trigone, floor of the mouth plus tongue, tongue alone and multiple sites, express the major morbidity of the OSCCs of these primary sites, requesting an ND extended until level V and lead us to re-consider the extended ND in the cases of OSCC affecting different oral sites such as cheek, which never showed levels of IV-V involvement in the present study. Shah (27) provided evidence that the pattern of neck metastasis of carcinomas from upper aerodigestive tract is predictable based on the location of the primary lesion. Moreover, it has been shown that in patients with oral carcinoma and clinical evidence of neck disease, the rate of pathologic involvement of level V nodes was only 4%. In the present study, the percentage of pathologic involvement of level IV-V nodes was 19.6%, higher when compared with the 4% value reported by Shah (27).

Table IV. One-, 2- and 5-year overall survival and the statistical significance.

	1-year (%)	2-year (%)	5-year (%)	P<0.05
Stage I-II	90.00	87.50	78.34	Yes
Stage III-IV	76.16	50.78	46.16	
Low grade	83.24	68.65	68.65	No
Intermediate-high grade	81.11	64.95	51.45	
pN0	93.54	94.54	69.11	Yes
pN+	66.03	45.41	45.41	
pN+/Stage I-II[a]	0	0	0	Yes
pN+/Stage III-IV	67.46	46.20	46.20	
pN+/Low grade	50.00	41.66	41.66	No
pN+/Intermediate-high grade	69.35	44.56	44.56	
Typical pN+	50.89	44.53	44.53	No
Atypical pN+	72.22	41.27	41.27	
Typical pN+/Low grade	50.00	50.00	50.00	No
Typical pN+/Intermediate-high grade	51.56	51.56	51.56	
Atypical pN+/Low grade	78.57	34.37	34.37	
Atypical pN+/Intermediate-high grade	50.00	25.00	25.00	
pN+ with ECS/macrometastases	80.67	28.68	28.68	Yes
pN+ with micrometastases	80.00	40.00	40.00	
pN0	93.54	81.50	69.10	
LN<20	72.38	52.36	46.93	Yes
LN 20-30	88.80	66.67	66.67	
LN>30	96.29	87.59	80.60	
pN0/Elective	87.50	79.54	62.64	Yes
pN0/Therapeutic	87.50	30.00	15.00	
pN0/SLN+	100.00	94.51	84.63	
pN+/Elective	100.00	100.00	100.00	
pN+/Therapeutic	68.10	45.71	45.71	
pN+/SLN+[b]	0	0	0	
SLN+	95.00	89.79	80.40	Yes
E	88.23	80.88	65.36	
T	70.745	42.86	39.56	
pN+/SLN+	100.00	95.52	84.63	Yes
pN+/E	100.00	100.00	100.00	
pN+/T	68.11	45.72	45.72	
pN0/SLN+	100.00	94.52	84.63	Yes
pN0/E	87.50	71.59	62.64	
pN0/T	87.50	30.00	15.00	

[a]There were 2 pN^+/Stage I-II subjects. [b]The 2 patients pN^+/SLN^+ died after 9 months.

Recurrences, observed in 8 cases, mainly occurred in floor of the mouth and tongue OSCCs, at intermediate grade of differentiation and independently from the pN status.

The survival probability was in accordance with the number of lymph nodes harvested, as previously demonstrated by Amar *et al* (6), who found the larger number of lymph nodes dissected in the ND related to the group of better prognoses among pN0 cases, while we found this result independently from the pN status.

We also confirmed the statistically significant different survival probability of patients with micrometastases (5-year, 40%), intermediate among pN0 (5-year, 69.10%) and pN+ with macrometastases patients (5-year, 28.68%), as previously reported by Broglie *et al* (20) and Han *et al* (28).

Statistically significant difference in the overall survival was also found according to clinical intent to surgery independently from the pN0, with a better prognosis in patients who had undergone elective ND or after SLN^+ when compared with the ones who had undergone therapeutic ND, independently from pN status.

In conclusion, the surgical management of regional metastatic neck disease in patients with oral and oropharyngeal cancer remains a topic of debate and controversy. For several years classical comprehensive ND has been the mainstay of treatment. Selective and super-selective neck treatments were recently introduced and widely applied in order to reduce morbidity and mortality related to extensive ND, thus improving the postoperative quality of life after preservation of level V and the surrounding anatomical structures.

With regard to atypical metastases according to Woolgar's definitions, no statistically significant differences were found related to the overall survival of this group vs. typical metastatic pattern. However, we noted different atypical features related to different primary tumour sites. Our data suggest that enhancing our knowledge of these types of atypical patterns site-related, and further evaluations such as novel imaging techniques (29) and molecular analyses (30) may help us to understand if any behaviour and biomolecular differences exist among OSCCs according to site.

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