When should elective neck dissection be considered for early-stage oral cavity tumors? Insights from a multicenter study of 1109 patients and development of a multiparametric predictive model

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Running title: Elective neck dissection for early-stage oral cavity tumors

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Abstract

Background: Nodal metastases significantly affect prognosis in oral cavity squamous cell carcinoma (OCSCC). In early-stage OCSCC (cT1-T2 cN0), management of the clinically negative neck (cN0) remains controversial. Depth of invasion (DOI) is a key determinant for END, but other histopathological parameters, such as grading, perineural invasion (PNI), lymphovascular invasion (LVI), and worst pattern of invasion (WPOI), are emerging prognostic factors.

Methods: This multicenter retrospective study analyzed 1,109 patients with cT1-T2 cN0 OCSCC treated at 30 Italian hospitals since 2017. Data on histopathological parameters, tumor characteristics, and patient outcomes were collected via the REDCap® platform. Simple and multivariable logistic regression models were developed to assess predictors of occult nodal metastases.

Results: A total of 585 patients were clinically classified as cT1 tumors (53%), 503 as cT2 (45%), and cTis (1.9%). Of the 1,109 patients,193 (28%) had occult nodal metastases, with DOI, LVI, PNI, WPOI and grading emerging as significant predictors. A predictive model integrating these variables demonstrated superior accuracy compared to a DOI-only model (AUROC comparison, $p < 0.01$).

Conclusion: This study highlights the importance of incorporating multiple histopathological parameters into risk models for occult nodal metastases, overcoming the fixed DOI as a cutoff. The proposed predictive model offers a more precise method for guiding END in early-stage OCSCC, allowing individualized risk estimation.

Introduction

The oral cavity is the most frequent site of head and neck squamous cell carcinoma. [1] Nodal metastases are a key prognostic factor in determining survival for patients with oral cavity squamous cell carcinoma (OCSCC). The presence of nodal metastases not only upstages the disease but also reduces survival rates by 50%. [2] Therefore, precise management of cervical nodal metastases is crucial for achieving effective locoregional control and enhancing survival outcomes. [3]

The management of the clinically negative neck (cN0) in T1-T2 (stage I-II) OCSCC is a subject of ongoing controversy, and numerous clinical studies and literature reviews have been conducted on this topic in recent decades. The main issue concerns the decision to perform, in addition to transoral resection of the primary tumor, a neck dissection, which would result a pN0 surgical specimen in majority of patients. [4] The literature reports that the prevalence of occult nodal metastasis in cT1-T2 cN0 OCSCC varies between 7.3% and 36.8%. [5,6] The rate of occult metastases is influenced by the effectiveness of preoperative clinical assessments, the diagnostic techniques used (such as computed tomography or magnetic resonance imaging), and the criteria for identifying pathological lymph node metastases in imaging studies. [7]

Management strategies for early-stage OCSCC include observational approaches with therapeutic neck dissection (TND) if metastases are detected, [8] elective neck dissection (END) concurrent with tumor resection, [9] and sentinel lymph node biopsy (SLNB) as a newer alternative. SLNB offers lower morbidity and good detection of micrometastases but requires specialized facilities. [10,11]

The largest prospective study in the literature today comparing observation with TND in case of nodal recurrence versus prophylactic END, involving 500 patients, is by D'Cruz et al. and demonstrated that END improved overall and disease-free survival in early-stage OCSCC patients defined according to the 6th Edition of the TNM Classification of Malignant Tumors. [12]

Considering recent findings on the treatment of OCSCC, one of the most commonly used criteria in the decision-making process between prophylactic END or an observational approach with close follow-up is the depth of invasion (DOI). It has been shown that DOI is directly related to the likelihood of cervical lymph node metastases. [13] The NCCN guidelines recommend END for tumors with a depth of invasion (DOI) ≥ 3 mm, as the aforementioned prospective study[12] shows a significant increase in cervical lymph node metastases as DOI increases from 3 mm (5.6%) to 4 mm (16.9%). However, the guidelines also state that "for cases with DOI between 2 and 4 mm, the decision for neck dissection should be based on clinical judgment".[10,14] Therefore, due to the absence of standardization for this cutoff, the guidelines reflect significant heterogeneity and suggest a potential knowledge gap in the recommended neck treatment for patients with OCSCC cT1-2 cN0.

Recent literature has increasingly shown that other histopathological parameters are also associated with the incidence of occult lymph node metastases in OCSCC: tumor site, grading, perineural invasion, perivascular invasion, tumor budding, and worst pattern of invasion (WPOI). [15,16,17]

Currently, there are few studies comparing all these histopathological variables with DOI, and the sample sizes in these studies are small. [18]

The primary aim of this study is to assess the incidence of occult metastases in cT1-T2 OCSCC, by correlating the presence of occult lymph node metastases with specific histopathological parameters of the primary tumor, including tumor site, grading, DOI, perineural invasion, perivascular invasion, and WPOI. The ultimate goal is to develop a statistical model that predicts the likelihood of occult lymph node metastasis based on the histopathological characteristics of the primary tumor. This model would help to determine the need for prophylactic END in cN0 patients and tailor surgical treatment to the specific features of the cancer. The model will be grounded in strong scientific evidence, supported by a large sample size, which is currently lacking in existing literature, and will be ensured by the study's multicenter design.

Methods

We conducted a multicenter retrospective study in 30 Italian hospital centers, including patients who underwent surgery for an OCSCC whose clinical staging was cT1-T2 cN0. All patients have been operated on since January 1, 2017, the year of introduction of the Union for International Cancer Control (UICC) Staging Manual 8th edition.[19]

Inclusion criteria:

- Patients 18 years old or older.
- Patients who underwent surgery for cT1-T2 stage OCSCC with clinically negative neck (cN0), staged according to the 8th edition of the Union for International Cancer Control staging manual. [19]
- Patients who underwent neck dissection at the time of primary tumour resection or within two months thereafter (no minimum follow-up required, as pathological nodal status was immediately available).

- Patients who did not undergo neck dissection but had a minimum clinical or instrumental follow-up duration of 12 months after primary surgery.
- Avaibility of anatomopathological data.

For patients who did not undergo END, a minimum follow-up of 12 months was required. This threshold was chosen a priori to allow sufficient time for occult metastases present at diagnosis to become clinically or instrumentally detectable, while minimizing the risk of including late recurrences or second primaries.

Exclusion criteria:

- Patients with histologies other than squamous cell carcinoma.
- Patients with a history of head and neck cancer prior to OCSCC.
- Patients who underwent radiotherapy as prophylactic neck treatment.

Anatomopathological and operating room records, outpatient reports, and admission paperwork were the sources of the retrospective data collection.

The absence of cervical lymph node metastases was confirmed for each patient clinically or instrumentally in the pre-operative course. The presence or absence of occult lymph node metastasis was evaluated on the outcomes of pathologic reports in patients undergoing END. In patients who did not undergo END, on the other hand, it was evaluated on the course of clinical and instrumental neck follow-up. The occurrence of pathologic lymphadenopathy within 12 months after diagnosis of the primary tumor was considered positive for the presence of occult metastasis at diagnosis. Absence of locoregional recurrence within 12 months of follow up was considered negative for the presence of occult metastasis at diagnosis. Data were collected in the different centers through REDCap® digital platform, including patients and tumor characteristics, clinical staging, surgical data anatomopathological data and follow-up.

Ethical Approval

This study was approved by the Provincial Ethics Committee of Bolzano (Protocol No. 0023477-BZ). The research was conducted ethically, with all study procedures being performed in accordance with the requirements of the World Medical Association's Declaration of Helsinki. Written informed consent was obtained from each participant/patient for study participation and data publication.

Statistical analysis

Continuous variables were reported using median and interquartile range (I–III quartile), and categorical variables with absolute number and percentage (relative frequencies).

To examine the association between the presence of occult metastases and the variables of interest, a logistic regression model was used. Predictors showing a statistically significant association or deemed clinically relevant were subsequently included in a multivariable logistic model. In all models, DOI was included as a continuous predictor, following good practice recommendations. The correlation between independent predictors was assessed using the Variance Inflation Factor (VIF) to check for multicollinearity. The performance of the final model, assessed in terms of receiver operating characteristic (ROC) curve and its corresponding area under the curve (AUC), was then compared with that of the model using DOI as the sole predictor through DeLong's test. Finally, the fitted model was presented graphically using a nomogram, a tool that allows the calculation of a score for each predictor in the model and subsequently provides the probability of the event of interest.

To account for missing values, random forest imputation technique was operated (MissForest).[20]

For all analyses, a two-sided $p<0.05$ was considered to be significant. Statistical analyses were performed in R System version 4.3.3,[21] using packages rms,[22] Hmisc,[23] pROC, missForest.[20]

Results

A total of 30 centers participated in this multicenter study. A total of 1,109 patients met the inclusion criteria and were included in the present study. The median age at diagnosis was 65 years, with 591

(53%) males and 518 (47%) females. Regarding risk factors, smoking status was available for 1,031 out of 1,109 patients; of these, 396 (38%) were non-smokers, 383 (37%) were active smokers, and 252 (24%) were former smokers. For smokers, the mean consumption was 30 pack-years (15–48). Regarding alcohol consumption, this data was reported in 982 cases: 709 were non-drinkers (72%), 248 (25%) were active drinkers, while 24 (2.4%) were former drinkers. Comorbidities were reported in 971 out of 1,109 reports and are described in Table 1. The ASA (American Society of Anesthesiologists) score for the majority of patients was ASA score 2 (60%), followed by ASA score 3 (26%) and ASA score 1 (14%), while only 0.4% of patients had an ASA score of 4.

Table 1. Patients characteristics

Patient Characteristic (Number of patients with available data)	N*
Age at surgery (1109)	65 (55,74)
Gender (1109)	
Male	592 (53%)
Female	519 (47%)
Smoke (1031)	
No	396 (38%)
Yes	383 (37%)
Previous	252 (24%)
Alcohol consumption (981)	
No	709 (72%)
Yes	248 (25%)
Previous	24 (2.4%)

Comorbidities (871)	568 (58%)
Diabetes	122 (11%)
Heart disease	268 (24%)
COPD	49 (4.4%)
Pulmonary disease (other than COPD)	37 (3.3%)
Chronic Kidney disease	25 (2.3%)
Liver failure	15 (1.4%)
HIV	8 (0.7%)
HCV	22 (2.0%)
Autoimmune disease	57 (5.1%)
Neurologic disease	32 (2.9%)
Other	221 (20%)
ASA score (753)	
1	106 (14%)
2	449 (60%)
3	195 (26%)
4	3 (0.4%)
Neutrophil-Lymphocyte Ratio (627)	2 (2, 3)

**Median (IQR); n (%)*

The median follow-up time for the entire cohort was 36 months (IQR 19–56), corresponding to 2.97 years (IQR 1.61–4.67). When stratified by treatment of the neck, the median follow-up was 35 months (IQR 20–55) [2.94 years (IQR 1.68–4.60)] for the END group and 37 months (IQR 19–57) [3.07 years (IQR 1.56–4.76)] for the non-END group (Table 2).

Table 2. Median follow-up time in the overall cohort and according to END status.

Characteristic	Overall (N = 1,109)	END (N = 682)	Non-END (N = 427)
Median follow-up, years (Q1–Q3)	2.97 (1.61–4.67)	2.94 (1.68–4.60)	3.07 (1.56–4.76)
Median follow-up, months (Q1–Q3)	36 (19–56)	35 (20–55)	37 (19–57)

A total of 585 patients were clinically classified as cT1 tumors (53%), 503 as cT2 (45%), and cTis (2%). The majority of tumors (73%) involved the mobile tongue, followed by the oral floor (10%) and buccal mucosa (9%), as described in Table 3. The preoperative evaluation of the tumor (cT) and lymph nodes (cN) was conducted according to different protocols depending on the patient's referral center, using one or a combination of the following techniques: 613 (55%) magnetic resonance imaging (MRI), 529 (48%) computed tomography (CT), 348 (31%) ultrasound, 101 (9%) positron emission tomography (PET), and in 76 (7%), only a clinical evaluation was performed preoperatively. In 26 (2%) patients, a fine needle aspiration cytology (FNAC) was necessary to rule out lymph node metastasis if suspected.

Table 3. Tumor characteristics

Clinical T stage (cT)	Number of patients (%)
cT1	585 (53%)
cT2	503 (45%)
cTis	21 (1.9%)
Oral cavity subsite	
Tongue:	808 (73%) 418 (59%)

• **Anterior border*** • **Posterior border*** • **Dorsum** • **Ventral** • **Tongue subsite not Available**	188 (27%) 33 (4.7%) 67 (9.5%) 102
Oral floor	107 (9.6%)
Buccal mucosa	96 (8.7%)
Upper gingiva	16 (1.4%)
Inferior gingiva	33 (3.0%)
Hard palate	7 (0.6%)
Retromolar trigone	42 (3.8%)

**Anterior border was defined as the anterior half of the mobile tongue (from the tip to the midpoint between the tip and the vallate papillae); posterior border referred to the posterior half (from this midpoint to the vallate papillae).*

Regarding the surgery on the primary tumor, a transoral approach was chosen in 973 cases (88%), while a transcervical pull-through approach was used in 136 cases (12%). In 427 out of 1,109 patients (39%), END was not performed, and they were followed up with clinical and ultrasound monitoring. A unilateral END was performed in 605 patients (55%), and a bilateral END in 77 patients (7%). A concomitant neck dissection alongside the resection of the primary tumor was performed in 541 patients, while a planned delayed neck dissection, scheduled within 45 days after the primary tumor resection based on histopathological findings, was carried out in 128 patients. Data regarding the type of dissection and the levels involved were available for 669 out of 683 patients. The type of END was a selective neck dissection (SND) in 621 patients (93%), and a modified radical neck dissection (MRND) in 48 patients. The levels dissected for each neck dissection and the pathological data related to the timing of neck dissection are summarized in Table 4 and 5.

Table 4. Neck dissection

Dissected Levels	**Number of patients (%)**
IA	590 (88%)
Ipsilateral levels	
IB	649 (97%)
IIA	664 (99%)
IIB	625 (94%)
III	650 (97%)
IV	390 (60%)
V	81 (13%)
Contralateral levels	
IB	76 (11%)
IIA	63 (9%)
IIB	58 (9%)
III	60 (9%)
IV	26 (4%)
V	3 (0%)

Table 5. Timing of neck dissection

	Concomitant Neck Dissection N = 541*	Delayed Neck Dissection N = 128*	Neck Dissection Not performed N = 427*
pT			
IS	6 (1.1%)	0 (0%)	36 (8.4%)
1	182 (34%)	41 (32%)	288 (67%)
2	271 (50%)	75 (59%)	86 (20%)
3	78 (14%)	11 (8.6%)	14 (3.3%)
4A	4 (0.7%)	1 (0.8%)	3 (0.7%)
Pathological DOI (mm)	6.0 (3.0, 8.0)	6.0 (4.0, 8.0)	3.0 (1.0, 4.0)
WPOI			
high risk	89 (40%)	18 (49%)	25 (21%)
low risk	136 (60%)	19 (51%)	92 (79%)
Unknown	316	91	310
PNI	152 (31%)	28 (24%)	34 (9.2%)
Unknown	58	10	59
LVI	80 (17%)	10 (8.6%)	12 (3.3%)
Unknown	66	12	59
Grading			
1	84 (17%)	36 (29%)	168 (44%)
2	331 (66%)	63 (50%)	175 (46%)
3	85 (17%)	26 (21%)	37 (9.7%)
Unknown	41	3	47
Recurrence	118 (22%)	26 (20%)	99 (23%)

**Median (IQR); n (%)*

In the histological examination, the tumor classification was pTis in 42 patients (3.8%), pT1 in 518 patients (47%), pT2 in 438 patients (39%), while the classification was upgraded to pT3 in 103 patients (9.3%) and to pT4a in 8 patients (0.7%). Regarding the neck status, the majority of patients (489; 72%) who underwent dissection were classified as pN0, while 193 patients (28%) had occult lymph node metastases on histological examination, and of these, 27 (4.0%) had extranodal extension (ENE). The remaining pathological data are summarized in Table 6.

Table 6. Anatomopathological data

Anatomopathological data (Number of patients with available data)	**Number of patients (%) Median (IQR)**
pT (1109)	
pTis	42 (3.8%)
pT1	518 (47%)
pT2	438 (39%)
pT3	103 (9.3%)
pT4a	8 (0.7%)
pT4b	0 (0%)
pN (682)	
pN0	489 (72%)
pN1	102 (15%)
pN2a	12 (1.8%)
pN2b	48 (7.0%)
pN2c	4 (0.6%)
pN3a	0 (0%)

pN3b	27 (4.0%)
Grading (1017)	
1	290 (29%)
2	576 (57%)
3	151 (15%)
Perineural invasion (980)	216 (22%)
Linfovascular invasion (970)	104 (11%)
Margins status (1107)	
R0	922 (83%)
R1	51 (4.6%)
R2	7 (0.6%)
R close (<5mm)	127 (11%)
Depth of invasion DOI (mm) (1084)	4 (2, 7)
Worst pattern of invasion WPOI (301)	
1	34 (11%)
2	83 (28%)
3	67 (22%)
4	77 (26%)
5	40 (13%)

In the postoperative period, a total of 194 patients (18%) underwent adjuvant therapy. Of these, 150 (14%) received radiotherapy, 2 (0,2%) received chemotherapy, and 42 (3.8%) received both radiotherapy and chemotherapy. Data were available for 122 patients who underwent adjuvant radiotherapy; all had the tumor within the irradiated field, 118 patients had the ipsilateral neck irradiated, and 23 patients also had the contralateral neck irradiated.

Regarding follow-up, 99 patients (8.9%) had a local recurrence, 115 (10%) had nodal recurrence, 33 (3.0%) had both local and regional recurrence, and 22 (2.0%) had distant metastases.

The median time to first recurrence for the entire cohort was 324 days (interquartile range, IQR, 192–632 days). Stratified by treatment, the median time to recurrence was 322 days (IQR 196–619) in the END group and 334 days (IQR 188–730) in the non-END group. According to adjuvant therapy, the median time to recurrence was 378 days (IQR 266–622) with adjuvant treatment and 312 days (IQR 182–670) without. The median time to second recurrence was 620 days (IQR 377–1209) overall, 476 days (IQR 362–1114) in END patients, and 846 days (IQR 494–1552) in non-END patients. In patients who received adjuvant treatment, the median time to second recurrence was 491 days (interquartile range [IQR], 360–1050) compared with 630 days (IQR, 401–1421) in those without adjuvant therapy (Table 7).

Table 7. Median time to first and second recurrence, overall and stratified by treatment (END vs. non-END; adjuvant vs. no adjuvant therapy).

Characteristic	N	Overall	END	Non-END	Adjuvant Yes / No
Time to first recurrence (days), Median (Q1–Q3)	242	324 (192–632)	322 (196–619)	334 (188–730)	378 (266–622) / 312 (182–670)

Time to second recurrence (days), Median (Q1–Q3)	53	620 (377–1209)	476 (362–1114)	846 (494–1552)	491 (360–1050) / 630 (401–1421)

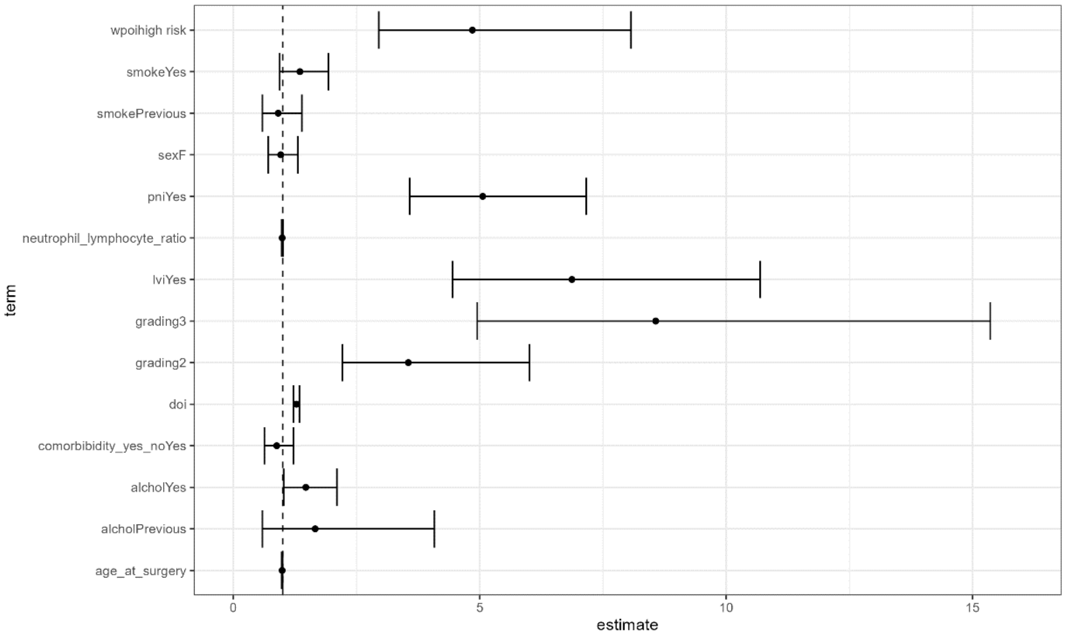
Logistic regressions on various predictors are summarized in Table 8 and graphically represented in Figure 1 usinga forest plot. Factors most strongly associated with the presence of occult metastasis were grading, DOI, lymphovascular invasion (LVI), perineural invasion (PNI), and worst pattern of invasion (WPOI). Active alcohol consumption was also found to be statistically associated, although with a lower odds ratio (OR) compared to the other factors. In contrast, associations with age, sex, and smoking habits were not found to be statistically significant.

Table 8. Univariable models for the occurrence of occult metastasis

	OR	**95% CI**	**p-value**
Age at surgery	0.99	0.98, 1.00	0.3
Sex			
M	—	—	
F	0.96	0.71, 1.31	0.8
Smoke			
No	—	—	
Yes	1.35	0.94, 1.93	0.10
previous	0.91	0.59, 1.39	0.7
Alchol			
No	—	—	
Yes	1.47	1.02, 2.10	0.035
previous	1.66	0.59, 4.08	0.3

Comorbibidity			
No	—	—	
Yes	0.88	0.63, 1.22	0.4
Neutrophil Lymphocyte Ratio	0.99	0.98, 1.01	0.3
Pathological DOI	1.28	1.22, 1.34	<0.001
LVI			
No	—	—	
Yes	6.87	4.45, 10.7	<0.001
Grading			
1	—	—	
2	3.55	2.21, 6.01	<0.001
3	8.57	4.95, 15.4	<0.001
WPOI risk			
low risk	—	—	
high risk	4.85	2.95, 8.07	<0.001
PNI			
No	—	—	
Yes	5.06	3.58, 7.16	<0.001

Figure 1. Forest plot of the univariable models



The following variables were selected for the multivariable regression model: pDOI, LVI, PNI and grading. We decided not to use WPOI, despite its statistical correlation, due to the low number of patients (301) for whom this data was available, which would have affected the overall power and generalizability of the model.

Figures 2 and 3 graphically represent the final model. By knowing the tumor grading and the presence or absence of LVI, it is possible to plot different risk curves for occult metastasis based on pDOI. This approach allows for both the calculation of the risk of occult metastasis for each patient based on these three variables and a more precise indication for END, without setting a fixed pDOI cut-off but rather adjusting it according to grading and LVI. Figure 4 shows the nomogram for risk calculation. When also including PNI, risk curves demonstrated an additional stratification of risk across DOI, grading, and LVI (Figure 5). We have also developed an online calculator (See legend Figure 6).

Comparing the standard approach and estimated model (Model with just p DOI as predictor vs Model with LVI, PNI, grading, pDOI as predictors, a seen in Figure 7, performance of the fitted model was significantly higher than the performance of the model with only the pDOI parameter. ROC curves and their AUC show that the performance of model 2 is superior to model 1 performance, with a statistically significant difference (Delong's p.val< 0.01). Although the improvement from the DOI-only model (AUC 0.77) to the multivariable model (AUC 0.81) may appear modest, it was statistically significant and can be clinically relevant, particularly for patients close to the 20% threshold commonly used to recommend END. Importantly, the additional predictors (grading, LVI, and PNI) are routinely available in pathology reports and therefore do not require extra diagnostic work-up. To further support clinical applicability, we developed a user-friendly Shiny web calculator, which provides rapid individualized risk estimates and makes the model easier to use in daily practice.

Figure 2. Risk curves based on pDOI and grading. The green, blue, and red curves identify grades 3, 2, and 1, respectively. The x-axis represents the pDOI measurement in millimeters. The dashed line is set at a 20% risk of occult metastasis (the commonly accepted threshold to indicate an END).

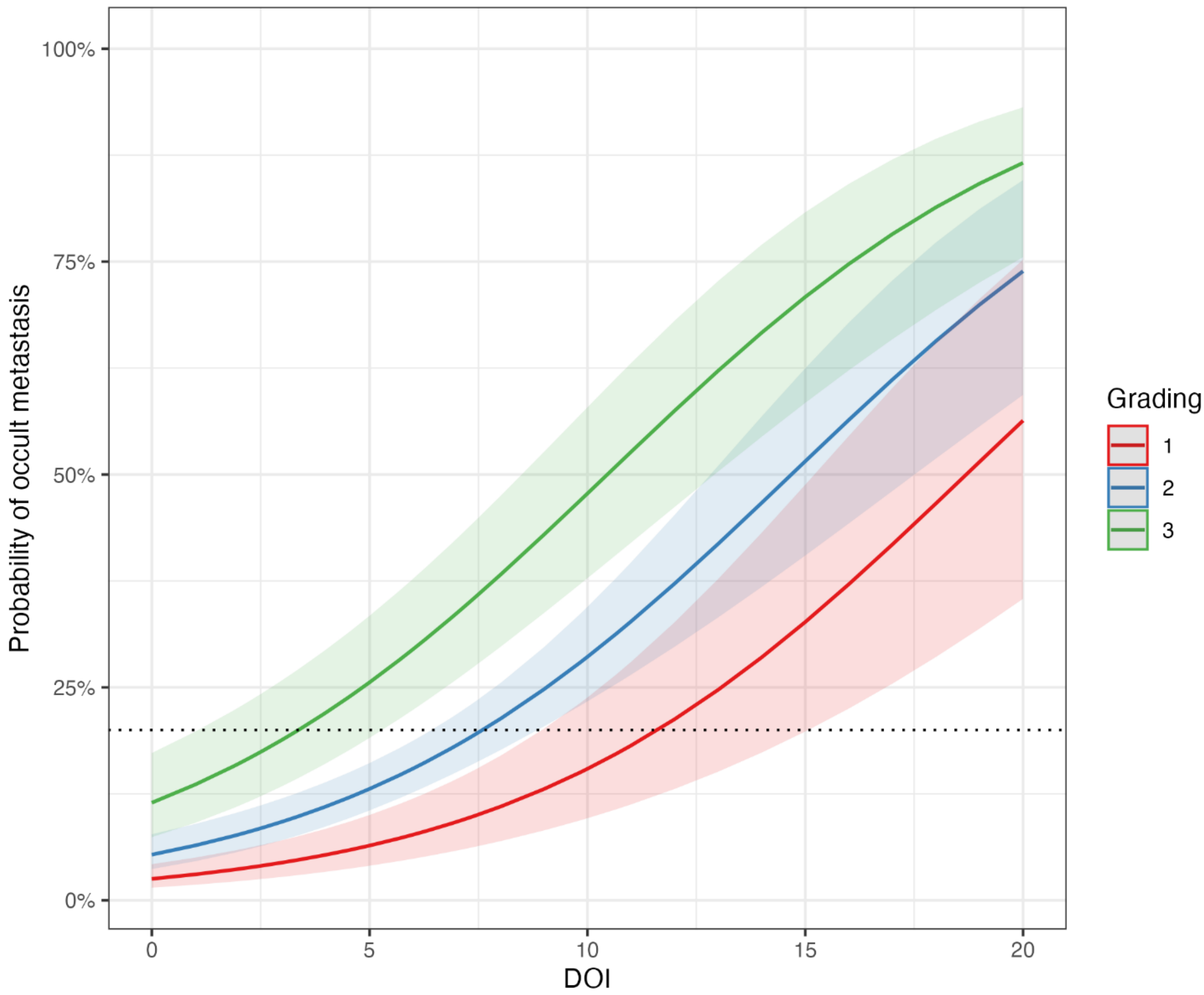


Figure 3: Risk curves based on pDOI, grading, and LVI. The panel on the left shows the curves in the absence of LVI, while the panel on the right shows them in the presence of LVI. The green, blue, and red curves identify grades 3, 2, and 1, respectively. The x-axis represents the pDOI measurement in millimeters. The dashed line is set at a 20% risk of occult metastasis (the commonly accepted threshold to indicate an END).

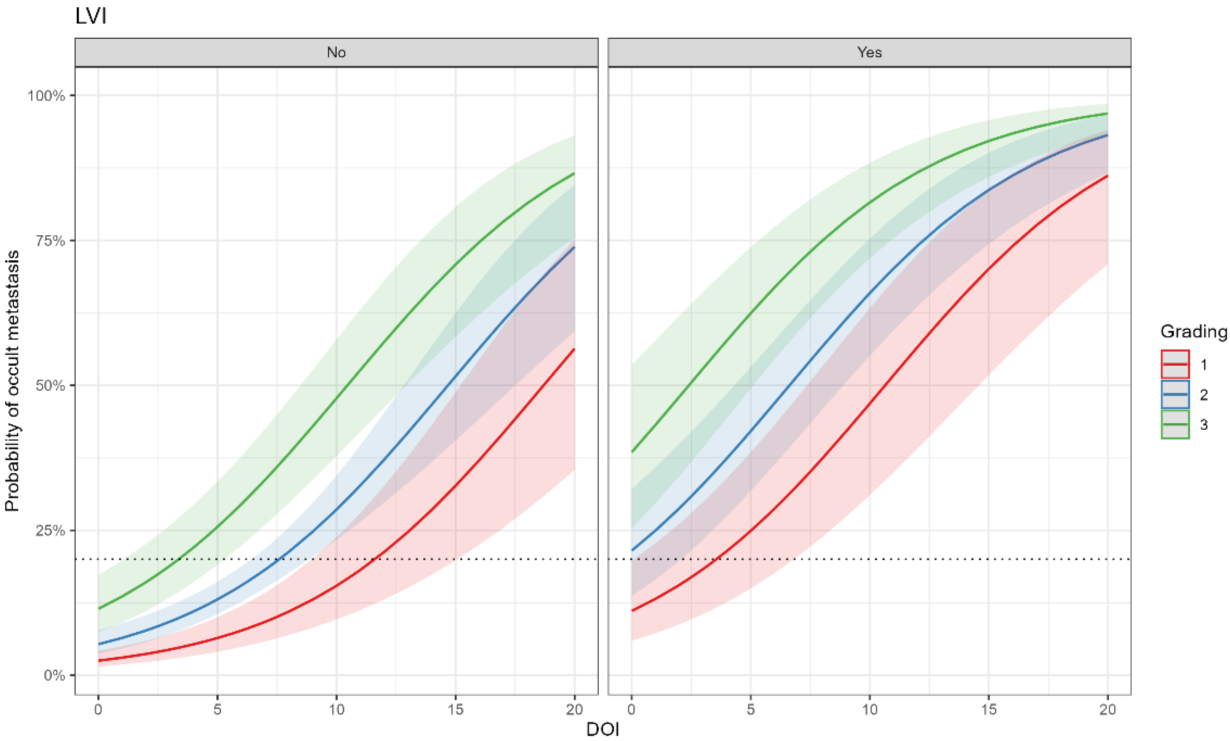


Figure 4: Risk curves based on pDOI, grading, and LVI. The panels, from left to right, represent the curves according to grading: grading 1 on the left, grading 2 in the middle, and grading 3 on the right. In each panel, the left side shows the curves in absence of LVI, while the right side shows them when LVI is present. The blue and red curves identify the presence or absence of LVI, respectively. The x-axis represents the pDOI measurement in millimeters. The dashed line is set at a 20% risk of occult metastasis (the commonly accepted threshold to indicate an END).

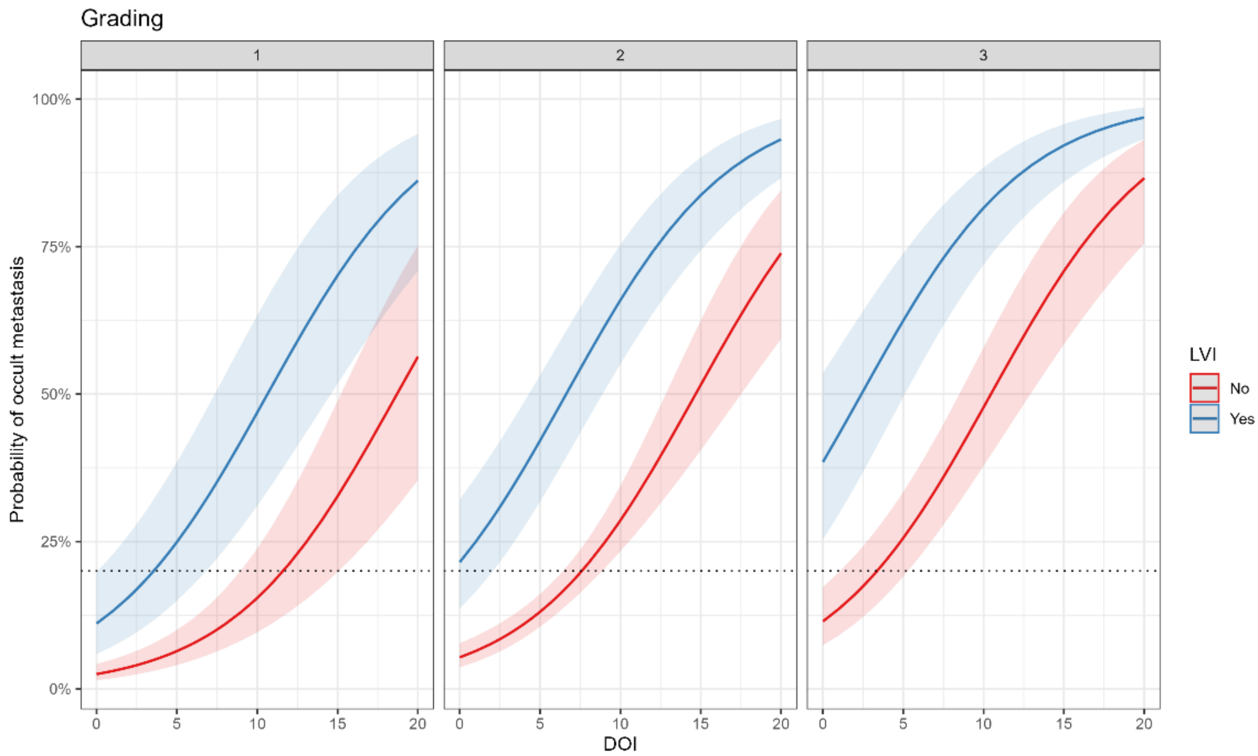


Figure 5: Risk curves based on pDOI, grading, PNI and LVI. Predicted probability of occult metastases according to depth of invasion (DOI), stratified by grading, lymphovascular invasion (LVI), and perineural invasion (PNI). Each panel shows risk curves for grading 1 (red), grading 2 (blue), and grading 3 (green). Shaded areas represent 95% confidence intervals. The dashed line is set at a 20% risk of occult metastasis (the commonly accepted threshold to indicate an END).

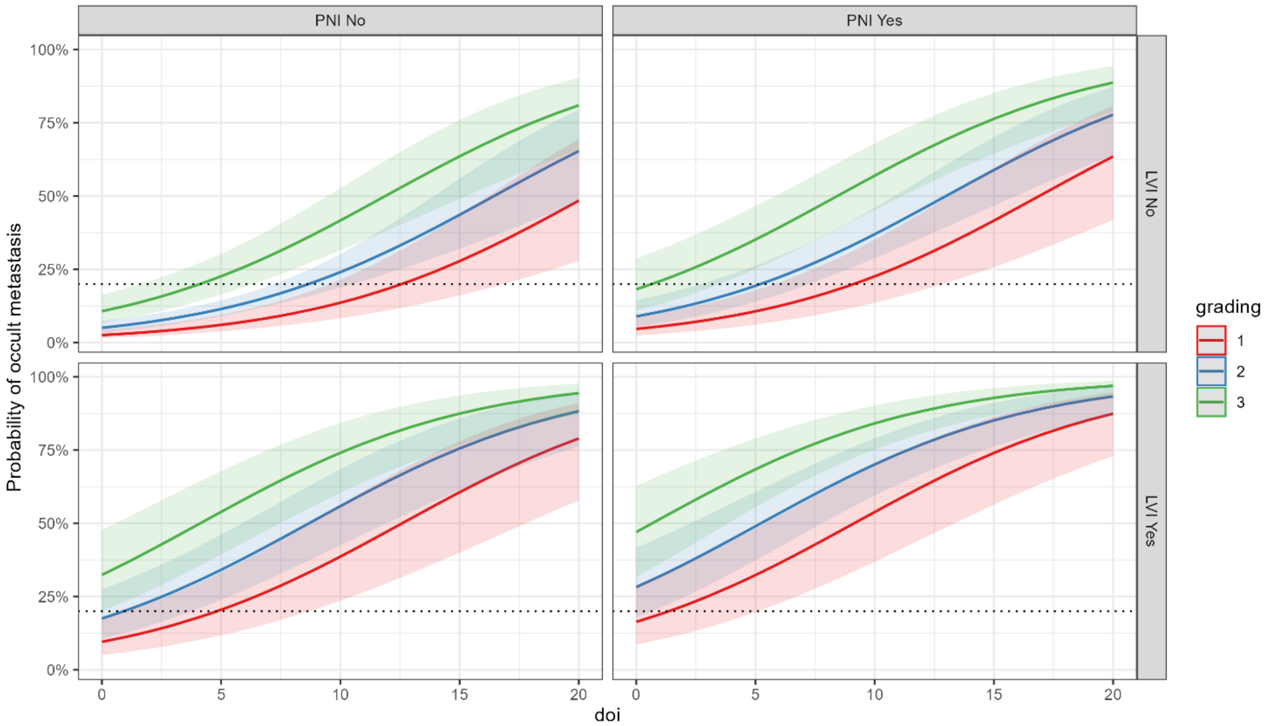


Figure 6: Nomogram of the predictive model.

Calculation of the risk of occult metastasis can easily be performed by following these steps:

1. In the top row, assign points to each variable.
2. In rows 2 to 4 (pDOI, LVI, PNI and grading), evaluate the variables. Each variable is compared to the top row to determine the points.
3. Sum the points obtained from all three variables and mark this total on row 5 (Sum of points).
4. Transfer the corresponding point value by drawing a perpendicular line between the sum of points and the predictive value. This will give the predicted risk value for occult metastasis.

An alternative method is to use the online calculator available at the following address (https://r-ubesp.dctv.unipd.it/shiny/etca/)

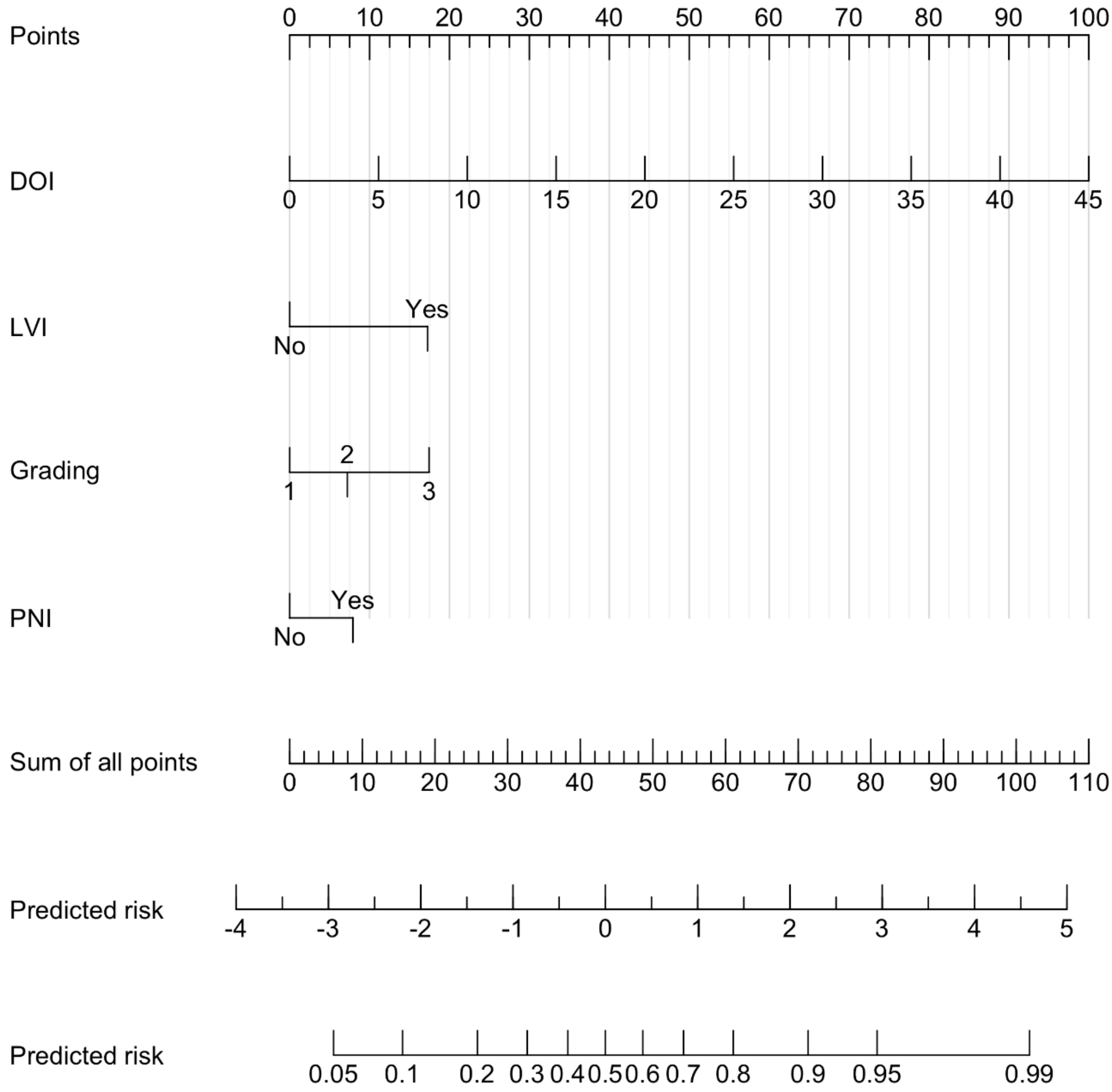
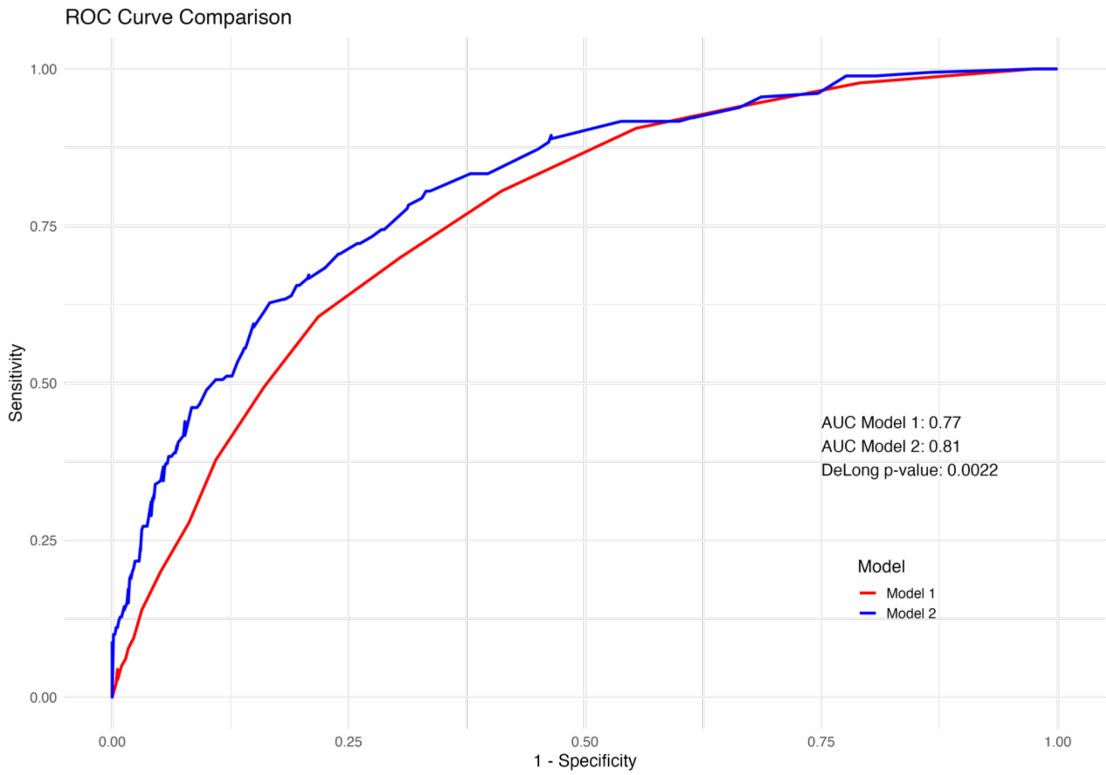


Figure 7. Comparison between standard approach and estimated model. Model 1. Model with DOI as predictor (Red line). Model 2. The comprehensive and final Model including LVI, PNI, grading, DOI as predictors (Blue line)

The ROC curves and their AUROC show that the performance of Model 2 is superior to Model 1 performance, with a statistically significant difference (Delong's p.val< 0.01).



Discussion

Nowadays, the necessity of END in T1-T2 OCSCC is still debated, although the risk of occult nodal metastasis in cN0 T1-T2 OCSCC is estimated up to 30%. [24] The first reference point that justifies END in such patients is the randomized controlled trial published by D'Cruz et al. in 2015, where the authors demonstrated that OCSCC patients treated with END had an improved overall and disease-free survival compared to those undergoing follow-up and TND in case of nodal relapse. [12] This result may also be explained, by the fact that END permits a more precise pathological staging of the disease, that is missed when END is not performed leading to an underestimation of the needed adjuvant therapies. [7] Also, tumor relapses in cases where END was not performed are often more aggressive and difficult to treat compared to pN0 cases. Finally, the percentage of pN+ cases in patients undergoing END are underestimated. In fact, not all the harvested lymph nodes are sectioned by the pathologist, and in such cases END is therapeutic for any potential occult micro metastasis. [25] On the other hand, it must be considered that END is not a morbid-free procedure and can be associated with important complications and worsening of the patient's quality of life. [26,27,28] Postoperative spinal accessory nerve deficiency is reported to occur in up to 30% of patients undergoing END. [29] This is relevant considering that END could be avoided in 70-80% of patients. In any case, it must be kept in mind that SND is reported to be associated with less postoperative morbidity than RND, and that END on a cN0 neck leads to less complications compared to TND performed in case of a regional relapse. [12]

In this setting, current guidelines suggest two alternatives for the neck management in cN0 T1-T2 OCSCC patients. [10] In particular, END is recommended in case of a DOI over 4 mm, while the indication for END in case of a DOI between 2 and 4 mm is left to clinical discernment. As an alternative, in such patients current guidelines suggest performing SLNB. SLNB owns many advantages, as its mini-invasiveness, avoidance of a useless END and the possibility to reveal lymph nodes in atypical sites. [30,31] However, as for now SLNB is reliable only in 80-90% of cases. [32] Also, when positive, it requires a second neck operation on a scar resulting from the sentinel lymph node harvesting. Furthermore, SLNB does not permit any pathological neck staging, differently from END. Finally, although some randomized studies have confirmed the equivalence in terms of survival between END and SNB, some trials are still ongoing (NCT04333537) with a larger patient cohort compared to previous studies. It will be necessary to await their results to draw definitive conclusions. [33]

As a result, it is fundamental to better understand for which patients END is indicated, and for which it can be safely avoided. [34] In the literature, many different parameters have been associated to the risk of occult neck metastasis, as DOI, LVI, tumor thickness and WPOI. Moreover, some studies have demonstrated that the combination of such parameters is a better indicator of risk compared to the single parameters alone. [35]

Our results have confirmed that DOI, LVI, PNI, WPOI, and grading are important predictors of occult lymph node metastases. We have developed a multivariable model that allows us to calculate the risk of occult metastases in a more accurate way. As seen from the graphical representation of the model, it is reductive to rely solely on DOI for deciding on whether or not performing END. Indeed, the curves relating DOI to the percentage of metastases are significantly shifted and modulated based on grading and LVI. Once the cutoff percentage of metastases beyond which we recommend END (commonly accepted at 20%) is set, we can intercept the various curves, noting how the corresponding DOI threshold changes significantly. There are various nuanced scenarios ranging from well-differentiated G1 neoplasms without LVI, where END could potentially be spared even in patients with DOI significantly greater than the 4 mm cutoff currently used, to poorly differentiated G3 tumors with LVI, where END would be indicated regardless of DOI. Thus, the predictive model represents a significant improvement over the simple measurement of DOI, allowing for a more appropriate selection of patients for whom the risk of occult lymph node metastases justifies END. Moreover, by using the nomogram and the online calculator, it is possible to obtain not just an indication for END, as it was for DOI threshold, dividing patients into high risk, where dissection is performed, and low risk, where it is not, but rather a precise percentage of the risk of metastases, allowing for a case-by-case decision on the best choice based on the patient's specific characteristics. This provides more accurate information to the patient and a more informed decision, considering the commonly adopted 20% percentage for recommending END only as a guideline, but evaluating the pros and cons of END even with percentages above or below this threshold based on the patient's needs, expectations, characteristics, and comorbidities. [36]

The limitations of this study include its retrospective nature and the fact that data were collected in a multicentric setting, with variability in patient management protocols across participating centers. Additionally, patients who did not undergo neck dissection but were managed with clinical follow-up were included, and those without evidence of nodal disease after 12 months of follow-up were considered negative for occult metastases. This could introduce a limited bias, as not all patients had histopathological data at time zero, relying instead on the follow-up results. The decision to include these patients was made to avoid excluding all early-stage tumors with a low depth of invasion (DOI), for which prophylactic neck treatment is not indicated. According to the authors, such an exclusion would have introduced a greater bias in the outcome calculations. Moreover, the histopathological data itself may also be subject to bias, as an occult micrometastasis might not be included in the examined section, potentially leading to a falsely negative result in the final histological assessment of the specimen. A potential limitation of the predictive model in the application in the clinical practice is that information regarding pDOI, PNI, LVI, and grading is reliably obtained from the final histological assessment, whereas it may be challenging to acquire from a preoperative biopsy. Some authors, on the contrary, argue that certain histopathological parameters obtained from preoperative biopsy may serve as reliable predictors of the final histological examination. Further studies will be necessary to assess the actual reliability of preoperative biopsy. [37,38,39] This raises future practical considerations regarding whether the model should be used strictly for prognostic purposes or whether it may have a predictive preoperative value. This opens some scenarios in clinical practice for applying the model according to different strategies:

• The first scenario is applicable in cases where it is possible to obtain the necessary pathological data for the model's risk calculation (DOI, LVI, and Grading) from a punch biopsy. [37,38] In this case, it is possible to be guided in the decision regarding END already, at the time of the primary tumor surgery. In this case, close collaboration between the surgeon and the pathologist is essential to obtain pathological information whenever possible from the preoperative biopsy.

• The second scenario for possible application of the model is for patients that were preoperatively under-staged based on cDOI. In these patients, where the risk of occult metastases is low, guidelines recommend resection of the primary tumor followed by close follow-up of the neck. However, after the primary tumor resection, in some cases, the histopathological examination of the surgical specimen may reveal a pDOI greater than expected or other high-risk factors (such as G3 grading, LVI, or PNI), increasing the risk of occult metastases. In these cases, if the risk calculated using the predictive model is high enough to justify an elective neck dissection (END), this information should be discussed with the patient, and a delayed END could be considered.

• The third scenario is the application of the so-called "deferred neck dissection strategy" already implemented in some centers. [40,41] This involves initially treating the primary tumor with transoral surgery, without addressing the neck. Based on the results of the histological examination, the need for dissection is determined later, within 30-60 days of the primary tumor surgery. This organizational strategy is very similar to what is already validated in the clinical practice with the SNB, where if the sentinel lymph node is positive for metastases, a deferred END is performed. Although this method leads to the need for a second surgery with consequent double general anesthesia in about 20-30% of cases, it has significant advantages. The first advantage is that surgical dissection will be performed in super-selected and real benefits patients, reducing the unnecessary procedures and improving the quality of life of patients who might otherwise undergo not required neck dissection. Furthermore, it allows for END in patients who were clinically under-staged, and in the final histopathological examination, present high-risk features, possibly improving their overall prognosis.

Future developments of this model include integrating WPOI, which is an extremely relevant parameter for the presence of occult lymph node metastases but is not currently reported as a standard in all pathological reports. Since WPOI was available in only 301 out of 1109 patients and to make the model more accessible to centers where WPOI is not available, we removed this parameter from the equation. Should there be broader adoption of WPOI in the future, integrating it into the model could be beneficial.

Additionally, to definitively confirm the precision of this model, a prospective validation study will be essential.

Conclusions

This multicentric study on a large cohort of patients with early OCSCC (cT1-T2 N0) demonstrates that it is possible to predict the risk of occult lymph node metastasis more accurately than relying solely on a DOI cutoff. The predictive model developed by combining DOI, grading, and LVI allows for an accurate estimation of the risk of occult metastasis and can prove to be a useful tool for selecting patients who should undergo END.

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Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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