ORIGINAL RESEARCH

Laryngoscope
Investigative Otolaryngology

Patients of stage I oral cancer with pathologically low-risk feature managed by primary tumor resection alone: Impact of depth of invasion and a nomogram analysis

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Abstract

Objectives: To evaluate the importance of depth of invasion (DOI) in patients with pathologically low-risk feature stage I oral squamous cell carcinoma (OSCC) managed by primary tumor resection alone.

Methods: Patients with stage I OSCC, at pathologically low risk, underwent primary tumor resection without neck dissection were enrolled retrospectively between 2007 and 2015. Low risk was defined as the absence of positive or close margins, lymphovascular invasion, perineural invasion, worst pattern of invasion-5, and poor differentiation in histologic grade. The primary endpoints included overall survival (OS), cancer specific survival (CSS), local recurrence free survival (LRFS), and regional recurrence free survival (RRFS). A nomogram based on the DOI was established for predicting RRFS.

Results: A total of 198 patients were enrolled in this study. DOI was the only prognosticator to achieve statistical significance in all primary endpoints according to univariate analysis. Patients with DOI <3 mm tumor showed better five-year OS, CSS, LRFS, and RRFS than those with DOI ≥3 mm tumor. The concordance index of the nomogram model without DOI was 0.684, which could increase to 0.733 when DOI was included in the calculation.

Conclusion: Patients with pathologically low-risk stage I OSCC correlate with a higher chance in occult neck metastasis if increasing DOI (≥3 mm) is noticed. Indeed, the chance of occult neck metastasis is significantly higher in this group (14% vs. 2%) than in those with DOI <3 mm. Elective neck dissection is advised if DOI is ≥3 mm to achieve better clinical outcomes.

Level of Evidence: 4.

KEYWORDS
depth of invasion, neck dissection, outcome, regional recurrence, stage I oral cancer

1 | INTRODUCTION

Oral squamous cell carcinoma (OSCC) is an aggressive head and neck malignancy and also the fifth most common cancer in males in Taiwan.[1] Early detection of OSCC is important but local or regional failure may appear in this cohort after treatment. Local invasion and neck lymph node metastasis are two common causes for treatment failure in OSCC. Because neck nodal metastasis has been shown to be one of the most significant prognostic factors of survival for patients with OSCC, elective neck dissection (END) has been strongly recommended to provide precise pathologic examination, better neck control rate, and survival.[2] Generally, END will increase postoperative morbidity, including shoulder problems and pain; thus, it has a great impact on the quality of life in these patients.[3] Some studies have described neck management with a watch-and-see strategy that could be equal in survival compared with END in selected patients with early stage OSCC.[4]

Studies have reported that adverse pathologic features, including grade of differentiation, perineural invasion (PNI), lymphovascular invasion (LVI), and worst pattern of invasion-5 (WPOI-5) are markers that increase the risk of locoregional recurrence in stage I/II OSCC.[5–8] In the eighth edition of the American Joint Committee on Cancer (AJCC),[9] depth of invasion (DOI) has become a factor influencing T classification in OSCC. A DOI value >4 mm was shown to be associated with a higher rate of recurrence and worse outcomes in stage I/II OSCC.[10–13]

However, only a few studies had focused on patients diagnosed with stage I OSCC. It was unclear whether neck dissection should be performed in patients with low-risk stage I OSCC treated only with primary tumor resection. The aims of this study were to determine whether DOI can predict local or regional recurrence and impact survival in this cohort. In addition, we generated a prognostic nomogram that incorporated DOI and clinicopathological features to investigate whether DOI can be used to estimate the five-year regional recurrence free survival (RRFS) rates in our cohort.

2 | MATERIAL AND METHODS

2.1 | Study population

In total, 198 consecutive patients with stage I OSCC (based on the eighth edition of the AJCC Staging), who underwent primary tumor resection alone with low-risk pathological features at Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Taiwan, were enrolled retrospectively between January 2007 and June 2015. Data were

TABLE 1 Patient characteristics ($n = 198$)

Characteristics		Value	%
Median age (range), std, year		53 (23, 85)	11.4
Median follow-up time (range), std, months		79.3 (1.5, 156.1)	39.3
Sex	Male	181	91.4
	Female	17	8.6
Smoking habit	Yes	170	85.9
	No	28	14.1
Betel but habit	Yes	131	66.2
	No	67	33.8
Alcohol drinking habit	No	72	36.4
	Yes	126	63.6
Cancer location	Tongue	79	39.9
	Buccal	80	40.4
	Other subsites	39	19.7
Histologic grade	WDSCC	144	72.7
	MDSCC	54	27.3
Depth of invasion	<3 mm	105	53.0
	≥3 mm	93	47.0
Tumor greatest size	≤10 mm	115	58.1
	>10 mm	83	41.9
Recurrence	No	167	84.3
	Yes	31	15.7
Recurrent location	Local	16	51.6
	Regional	15	48.4

Abbreviations: MDSCC, moderately differentiated squamous cell carcinoma; WDSCC, well differentiated squamous cell carcinoma.

TABLE 2 Association between different depth of invasion and other clinical-pathological factors

Variable		Depth of invasion		p value
		<3 mm (N = 105)	≥3 mm (N = 93)	
Age	<53	51	46	.9
	≥53	54	47	
Smoking habit	No	18	10	.198
	Yes	87	83	
Betel but habit	No	41	26	.1
	Yes	64	67	
Alcohol drinking habit	No	42	30	.258
	Yes	63	63	
Cancer location	Tongue	50	29	.032
	Buccal	34	46	
	Other subsites	21	18	
Histologic grade	WDSCC	76	68	.907
	MDSCC	29	25	
Tumor greatest size	≤10 mm	79	36	<.001
	>10 mm	26	57	

Abbreviations: MDSCC, moderately differentiated squamous cell carcinoma; WDSCC, well differentiated squamous cell carcinoma.

TABLE 3 The characteristic of patients with regional recurrence (n = 15)

No.	Tumor subsite	DOI (mm)	Location of recurrence	Salvage treatment	Status while last visit
1	Tongue	5	Ipsilateral, I + II + III	Salvage neck dissection then CCRT	DOD
2	Tongue	3	Ipsilateral, I + II + III	Salvage neck dissection then CCRT	DOD
3	Tongue	3	Ipsilateral, II	Salvage neck dissection then CCRT	NED
4	Buccal	3	Ipsilateral, I	Salvage neck dissection alone	NED
5	Buccal	5	Ipsilateral, I + II	Salvage neck dissection then CCRT	NED
6	Buccal	5	Ipsilateral, I + II + III	Salvage neck dissection then CCRT	NED
7	Buccal	5	Ipsilateral, I + II	Salvage neck dissection alone	NED
8	Buccal	4	Ipsilateral, I + II	Salvage neck dissection then CCRT	DWOD
9	Buccal	4	Ipsilateral, I + II + III	Salvage neck dissection then CCRT	DOD
10	Buccal	1	Ipsilateral, I	Salvage neck dissection then CCRT	DWOD
11	Buccal	2	Ipsilateral, I	Salvage neck dissection then CCRT	NED
12	Buccal	4	Ipsilateral, I + II	Salvage neck dissection then CCRT	DOD
13	Buccal	5	Ipsilateral, I	Salvage neck dissection then CCRT	DOD
14	Buccal	5	Ipsilateral, I	Salvage neck dissection then CCRT	DWOD
15	Hard palate	3	Ipsilateral, I	Salvage neck dissection then CCRT	DOD

Abbreviations: DOI, depth of invasion; CCRT, concurrent chemoradiotherapy; DOD, died of disease; NED: no evidence of disease; DWOD, died without disease.

collected from the cancer database of Kaohsiung Chang Gung Memorial Hospital, Taiwan. Clinical N0 was defined as no palpable neck lymphadenopathy in a clinical examination and absence of enlarged lymph nodes on imaging study. All patients included in this study had clinical N0 disease preoperatively, with detailed clinical and pathological information available for review. Low-risk tumor is defined as a pathologic feature without the presence of PNI, LVI, WPOI-5, poorly differentiated squamous cell carcinoma, and neither close nor positive margins in surgical resection specimen. Patients who had (a) a history of any cancer, (b) prior treatment for head and neck cancer, (c) a positive lymph node, (d) nonsquamous cell carcinoma, and (e) received adjuvant treatment, such as radiotherapy alone or concurrent chemoradiotherapy, were excluded from this study. This yielded a homogenous patient population to evaluate DOI alone as the major prognostic factor in oncologic outcomes.

2.2 | Statistical analysis

Statistical analyses were performed using SPSS 25.0 software (Armonk, NY: IBM Corp.). Outcomes of interest investigated included five-year rates of overall survival (OS), cancer specific survival (CSS), local recurrence free survival (LRFS), and RRFS. OS was calculated as the interval from the date of radical surgery to the date of death due to any cause. CSS was calculated as the interval from the date of radical surgery to the date of death from oral cancer. LRFS referred to as the interval from the date of radical surgery to the date of local recurrence. RRFS was calculated as the interval from the date of radical surgery to the date of regional recurrence. The Kaplan–Meier method was used to estimate the probabilities of survival in each categorized factor. The log-rank test account for each stratification factor was considered statistically significant using two-tailed tests at p values less than .05.

In addition, we created a prognostic nomogram that incorporated cancer location, histological grade, greatest size of tumor, and DOI by using the R software "rms" package (Version 5.1–0, Vanderbilt University, Nashville, TN, USA) with endpoints of five-year RRFS rates. To ascertain the RRFS prediction accuracy of the nomogram, the concordance index (C-index) was derived for the proposed nomogram models with and without the DOI; C-index values of 0.5 and 1.0 were considered to signify random and perfect predictability, respectively. A calibration plot was used to determine whether the predicted survival rate was consistent with the actual observed survival rate. This study was approved by the Medical Ethics Committee and Human Clinical Trial Committee, Chang Gung Memorial Hospital (Ethical Application Reference number: 202100663B0).

3 | RESULTS

A total of 198 patients were enrolled in this study. The clinical characteristics of patients are summarized in Table 1. The median age of patients was 53 years (range: 23–85). The study sample included
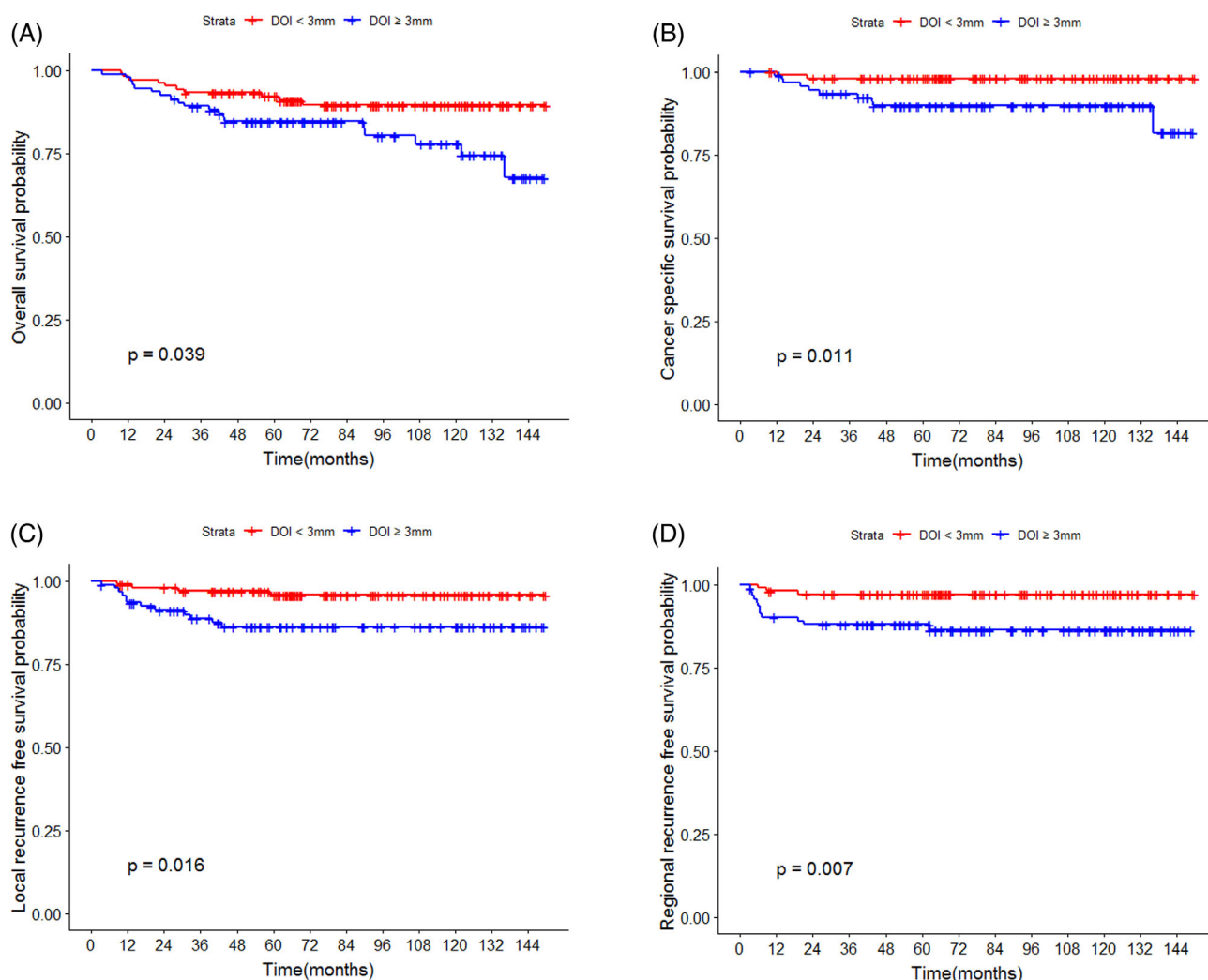

FIGURE 1 Kaplan–Meier survival curves according to different depth of invasion. (A) Overall survival curves, (B) cancer-specific survival curves, (C) local recurrence free survival curves, and (D) regional recurrence free survival curves

181 (91.4%) male and 17 (8.6%) female patients. Squamous cell carcinoma was the only histopathological cancer type in this population. The buccal mucosa (N = 80, 40.4%) was the most common tumor subsite, followed by the tongue (N = 79, 39.9%), lower lip (N = 13, 3.8%), lower gum (N = 10, 3.8%), mouth floor (N = 6, 3.8%), retromolar trigone (N = 4, 2.0%), hard palate (N = 4, 2.0%), upper lip (N = 1, 0.5%), and upper gum (N = 1, 0.5%). All the patients received primary tumor resection alone without END. No patient received adjuvant radiotherapy or concurrent chemoradiotherapy. The average greatest size of primary tumor was 9.5 mm (range: 1–20 mm). The average DOI was 2.6 mm (range: 1–5 mm)—105 (53%) and 93 (47%) patients had DOI values <3 mm and ≥3 mm, respectively. In this cohort, a cutoff of DOI = 3 mm was set for further analyses. Patients with DOI ≥3 mm in primary tumor had significantly higher rates of large tumor size and occurrence over buccal area (Table 2).

Patients were followed up for a median of 78.1 months in this cohort. Tumor recurrence occurred in 31 (15.7%) patients and included local recurrence (N = 16) and regional recurrence (N = 15). In a subgroup of patients with regional failure (N = 15), the nodal recurrence region was ipsilateral neck, and salvage neck dissection was

performed in all. Extranodal extension pathologically was shown in 13 patients (86.7%) (Table 3).

In a subgroup of patients with DOI ≥3 mm (N = 93), 13 (14.0%) had regional recurrence, whereas only 2 (2/105 = 2.0%) with DOI <3 mm had regional recurrence. Of the 13 patients with DOI ≥3 mm, who experienced regional recurrence, 10 had neck failure within the first year after primary treatment and 6 died of the disease.

The five-year OS, CSS, LRFS, and RRFS rates in this cohort were 88.6%, 94.2%, 91.4%, and 92.9%, respectively. We were interested in the effects of the clinicopathological factors, especially the role of DOI in the primary tumor. DOI itself might have an impact on survival. Five-year survival rates of OS, CSS, LRFS, and RRFS were calculated for all factors and listed in Table 3. These results revealed that patients with DOI ≥3 mm over the tumor were significantly associated with lower rates of five-year OS (p = .039), five-year CSS (p = .011), five-year LRFS (p = .016), and five-year RRFS (p = .007) than those with DOI <3 mm. Survival curves of DOI strata for each outcome were drawn (Figure 1). Both cancer location over buccal mucosa and tumor size (>10 mm) were significant prognostic factors of poorer

TABLE 4 Univariate analysis of factors impacting survival (n = 198)

Variable	N	5 year OS (%)	p	5 year CSS (%)	p	5 year LRFS (%)	p	5 year RRFS (%)	p
Age (median)									
< 53	97	90.5	.579	95.7	.591	93.6	.314	91.7	.396
≥53	101	86.9		93.9		89.1		94.0	
Smoking habit									
no	28	92.6	.216	92.6	.89	91.8	.809	92.9	.904
yes	170	88.0		94.5		91.3		92.9	
Betelnut chewing habit									
no	67	89.5	.913	93.9	.922	90.5	.801	94.0	.91
yes	131	88.1		94.2		92.0		92.3	
Alcohol drinking habit									
no	72	88.8	.644	94.2	.705	92.6	.661	93.0	.77
yes	126	88.6		94.2		90.6		92.8	
Cancer location									
tongue	79	91.0	.225	94.9	.74	97.5	.052	96.2	.022*
buccal	80	84.8		93.2		86.0		87.3	
other subsites	39	91.5		94.1		88.8		97.4	
Histologic grade									
WDSCC	144	89.3	.676	94.9	.558	90.6	.457	94.4	.221
MDSCC	54	87.0		92.5		93.2		88.8	
Depth of invasion									
<3 mm	105	92.2	.039*	98.1	.011*	95.8	.016*	97.1	.007*
≥3 mm	93	84.4		89.8		86.2		88.0	
Tumor greatest size									
≤10 mm	115	89.3	.869	96.3	.098	93.7	.24	95.6	.039*
>10 mm	83	87.7		91.3		88.1		89.0	

*statistically significant p < 0.05.
Abbreviations: CSS, cancer specific survival; LRFS, local recurrence free survival; MDSCC, moderately differentiated squamous cell carcinoma; OS, overall survival; RRFS, regional recurrence free survival; WDSCC, well differentiated squamous cell carcinoma.
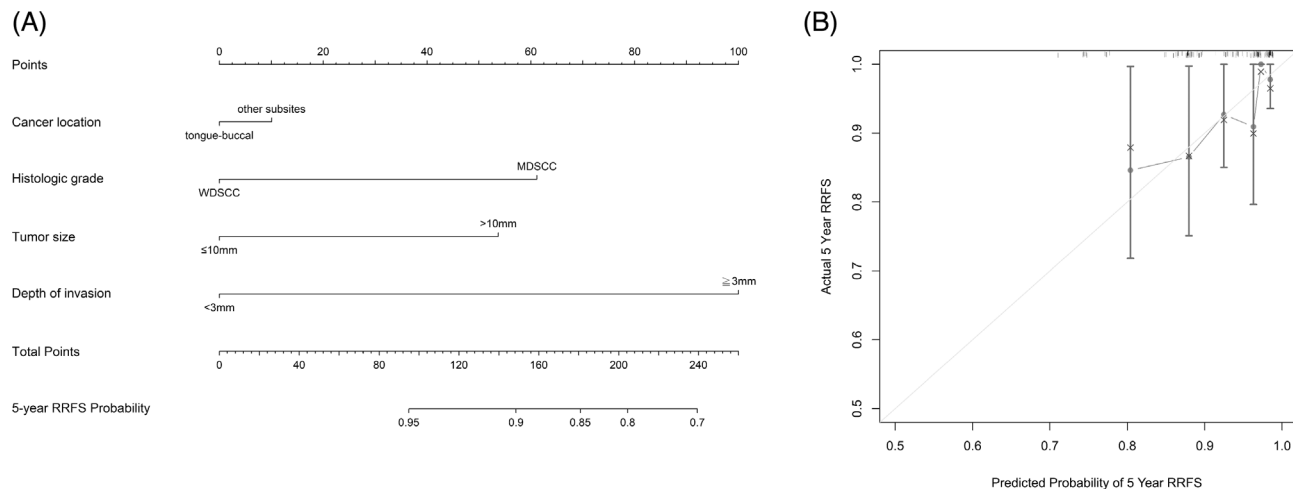
(A)

(B)

FIGURE 2 Nomogram and survival predictions. (A) Nomogram for predicted RRFS rate. A vertical line is drawn from each factor to the point score. By adding the points from all the factors, a total points score is reached, which is translated into five-year RRFS rates by drawing a vertical line to its axis. (B) Calibration plots of the nomogram to predict five-year RRFS rate. The diagonal line indicates ideal prediction, and the dark gray line indicates the predictive ability of our proposed nomogram. Gray dots with bars represent the performance and 95% CI of the nomogram when applied to the surviving cohorts. MDSCC, moderately differentiated squamous cell carcinoma; RRFS, regional recurrence free survival; WDSCC, well differentiated squamous cell carcinoma

outcomes for the RRFS rate in the univariate analysis (Table 4). However, further multivariate analysis revealed that no factor had statistical significance in RRFS (DOI, $p = .081$; cancer location, $p = .107$; tumor size, $p = .35$).

We analyzed the effect of DOI in primary buccal cancer ($N = 80$). The result showed that patients with buccal cancer and DOI ≥3 mm were significantly associated with lower rates of survival on five-year CSS than those with DOI <3 mm (88.3% vs. 100%, $p = .046$). At other endpoints, patients with DOI ≥3 mm buccal cancer showed inferior survival than those in control groups of five-year OS (80.1% vs. 91.2%, $p = .239$), LRFS (80.9% vs. 93%, $p = .109$), and RRFS (82.3% vs. 94%, $p = .069$), but these clinical outcomes did not achieve significance statistically (Table S1).

A nomogram that incorporated with cancer location, histological grade, greatest size of tumor, and DOI was developed for predicting individualized five-year RRFS rates in this cohort (Figure 2A). Another nomogram that incorporated with cancer location, histological grade, and tumor size was also implemented for comparison. The C-index (95% CI) derived for the nomogram that incorporated with several clinicopathological features without DOI was 0.684 (0.545–0.823), whereas the C-index (95% CI) derived for the nomogram model that incorporated with DOI and several clinicopathological features was 0.733 (0.615–0.851). These results indicate that the nomogram that incorporated with clinicopathological factors, including DOI, had a better performance in predicting the RRFS rate of patients with pathologically low risk, stage I oral cancer by primary tumor resection alone than the nomogram model with no DOI incorporated.

4 | DISCUSSION

To our best knowledge, our study is the first large case study to evaluate the pathologically low-risk stage I OSCC patients who were treated

by primary tumor resection alone. The aim of this study is to identify that DOI could be a sole factor for recurrence and survival prediction in this unique low-risk cancer population and provide information on their outcomes while there is no data exist to guide clinical decision making. Other high-risk pathologic features would likely have a dominating effect in our statistical models, and were therefore excluded.

In early stage (T1/T2) OSCC, DOI >4 mm had been shown to be associated with a worse outcome, and clinically, it was a strong predictor of occult metastatic neck disease.[13-16] Many studies have been published to discuss this issue although most of these studies had included both T1 and T2 OSCC. However, patients with cT1N0 and cT2N0 OSCCs have significantly different risks of local recurrence, neck lymph node metastasis, and different prognosis.[17,18] In oral cancer with stage of cT1N0, Low et al. noted that four or more adverse pathologic features and tumor thickness more than 5 mm signified an increased risk of locoregional failure.[19] Tai et al. revealed that perineural invasion was associated with a higher rate of occult nodal metastasis and poor outcomes in 146 patients diagnosed with T1N0 OSCC.[20] Zhang et al. studied a cohort of 65 patients with cT1N0 oral tongue cancer and found that tumors with DOI >3 mm were associated with higher occult neck metastasis rates.[21] Our study demonstrated that the variable, DOI ≥3 mm is a negative prognosticator of five-year OS, five-year CSS, five-year LRFS, and five-year RRFS rates in patients with stage I oral cancer with low-risk pathological feature. These findings further recognize the impact of DOI on locoregional recurrence and clinical outcomes.

To date, no study has constructed a DOI-based nomogram that predicts survival in this unique population. Our study established the multivariate nomogram that by integrating the clinicopathological variables, including location, histologic grade, tumor size, and DOI could yield a feasible result (c-index: 0.733). The nomogram can provide more accurate prediction over five-year RRFS rates in patients with

pathologically low risk, stage I oral cancer managed through primary tumor resection alone than the nomogram model without DOI incorporated. It could help surgeons to identify patients at higher risk of regional failure. Based on our nomogram prediction, for a case with pathologically proven low-risk stage I OSCC, who received primary tumor excision alone, with tumor location over tongue (score: 0), tumor size >10 mm (score: 53.72), moderately differentiated squamous cell carcinoma (score: 61.16), and DOI ≥3 mm (score: 100), the predicted five-year RRFS rate would be 77.0%. However, under the same conditions, but with DOI <3 mm, which received a score of 0 instead of 100, the predicted five-year RRFS rate would be 93.4%. Perhaps, END is advised if DOI is ≥3 mm in the image study or staged neck dissection is considered after primary tumor surgery.

Sentinel lymph node biopsy (SLNB) may be another treatment opinion other than END strategy. Sentinel lymph nodes, the first nodes to drain cancer cells, are at highest risk for metastasis.[22] In some cancers, such as melanoma and breast cancer, SLNB is widely used to identify whether lymph node metastasis is present. A negative SLNB result indicates that elective lymph node dissection is unnecessary, thereby sparing patients unnecessary surgery and avoiding surgical morbidity, while accurately upstaging malignancies.[23] For oral cavity cancer, the concept of SLNB has evolved during the last decades. Many large single and multicenter studies, in which treatment of the neck was only performed after positive SLNs, have shown high sensitivities and negative predictive values.[24–27] Results from a meta-analysis comprising 98 studies demonstrated the high specificity of SLNB and showed that SLNB is an accurate diagnostic tool that can be used in clinical practice to identify occult lymph node metastasis in early stage OSCC.[28] There is an ongoing randomized phase II/III trial (NCT04333537)—SLNB versus END—for early oral cancer, with the collaboration of the American National Cancer Institute. The trial started on April 3, 2020, and planned to enroll 618 patients. The endpoints of this trial will compare both arms in patient-reported neck and shoulder function, disease free survival, OS, local regional failure, distant metastasis, patient-reported shoulder-related quality of life, functional impairment and disability, general quality of life, nodal metastasis detection rate, pathologic false omission rate, and post-surgery patient-reported outcome. Hopefully, SLNB will become the solid evidence in the management of early oral cancer.

Our study has some limitations. First, it is a retrospective study and all the patients underwent surgical procedures at a single institution by different head and neck surgeons. Thus, the study is prone to have a selection bias. Second, the issue of preoperative imaging study exists, which may lead to different judgments in neck management. Some patients underwent CT scans for evaluation, whereas others received MRI studies. Third, the study's results were not validated by using an independent dataset. External validation of the results by using an independent patient cohort can strengthen the derived evidence.

5 | CONCLUSIONS

Our findings revealed that a tumor with DOI ≥3 mm was a negative prognostic factor in five-year OS, CSS, LRFS, and RRFS rates among patients of oral cancer staged as pT1cN0 with low-risk pathologically. An increasing DOI in patients of pT1cN0 with low risk in primary tumor should consider the need of neck dissection for regional control and better clinical outcomes.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.