The Indications for Elective Neck Dissection in T1N0M0 Oral Cavity Squamous Cell Carcinoma

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Purpose: The management of the clinically node-negative neck in T1 oral cavity squamous cell carcinoma (SCC) is controversial. The purpose of this study was to investigate tumor characteristics of surgically managed patients with T1N0 oral cavity SCC and determine the possible benefits of elective neck dissection (END).

Materials and Methods: A retrospective cohort study was conducted assessing outcomes for patients with stage I oral SCC at Waikato Hospital, New Zealand, between 2008 and 2018. Clinical staging was based on the American Joint Committee on Cancer Cancer Staging Manual, 8th Edition. Patients with T1N0 SCC either had an END or had the neck observed. These data were used to determine the rate of occult nodal disease, recurrence rate, and survival. Data collected included patient demographics, location, tumor characteristics including differentiation, depth of invasion (DOI), perineural invasion (PNI), lymphovascular invasion, closest histologic margin, management of the neck, the number of pathologic lymph nodes, adjuvant treatment, recurrence, and survival.

Results: A total of 70 patients were included in the study (40 male, 30 female; age range 30 to 91; mean age 65 years). Twenty-seven (38.6%) patients underwent END, whereas 43 patients (61.4%) were observed. Occult nodal metastases were diagnosed in 6 of 27 (22.2%) patients who underwent END. Regional relapse occurred in 7 of 43 (16.3%) patients who were observed. Risk factors for nodal disease included increasing DOI $\geq$ 3 mm (P = .049), poor tumor differentiation (P = .003), and presence of PNI (P = .002). Negative prognostic factors for overall survival included male gender (P = .02, hr = 3.55, CI for HR (1.18, 10.65)), presence of PNI (P = .001, hr = 4.52, CI for HR (1.77, 11.57)), and locoregional recurrence (P < .005, hr = 6.55, CI for HR (2.69, 15.98)). Six of the 7 tumors that relapsed in the neck after observation had a primary tumor DOI < 3 mm.

Conclusions: There is little data published for management outcomes of the node-negative neck in stage I oral squamous cell carcinoma. Given salvage neck dissection carries a poorer prognosis, END should be recommended for all T1N0 oral SCC with DOI $\geq$ 3 mm. In cases of DOI < 3 mm undergoing primary ablation only, a staging neck dissection as a second procedure should be considered in the presence of poor tumor differentiation or PNI on final histology.

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Oral squamous cell carcinoma (OSCC) accounts for 40% of all head and neck cancers[1] and continues to be challenging to manage across the world. Despite advances in diagnosis and management strategies, disease-free survival (DFS) and overall survival (OS) have not significantly improved.

OSCC most commonly metastasizes to the cervical lymph nodes. It is well documented that this can occur in early-stage cancer in a clinically node-negative neck (cN0). Despite clinical examination and exhaustive imaging investigations, occult metastatic disease still occurs in 20-30% of cN0 necks.[2] This micrometastatic disease is detected after histopathologic examination of a neck dissection specimen. A significant independent prognostic factor for patients with OSSC is the presence of metastatic disease of the cervical lymph nodes, which reduces survival by up to 50%.[3]

Management options for the node-negative neck include observation, elective neck dissection (END), elective radiotherapy, and sentinel lymph node biopsy (SLNB). Neck dissection allows pathologic staging of cervical lymph nodes, facilitates regional control of disease, and guides decision-making with regard to adjuvant treatment as well as aiding prognostication. Neck dissection carries small but significant risks of complications and morbidity, including shoulder dysfunction and facial weakness, as well as cost of additional hospital time and resources. The premise behind advocating for END has been strengthened by the results of a recent randomized controlled trial favoring END,[2] although this study incorporated T2 tumors as well, and there was no statistical significance for T1 tumors. An alternative to surgery in the cN0 neck includes a watch and wait approach. If a patient relapses in the neck during a period of surveillance, then a therapeutic neck dissection should be considered, but this can be technically more difficult than an END with greater potential morbidity. Controversy remains regarding the management of the cN0 neck with differing head and neck guidelines from respected organizations such as National Institute for Health and Care Excellence (NICE)[4] and National Comprehensive Cancer Network (NCCN).[5] While NICE no longer advocate a watch and wait approach, even in early-stage OSCC, NCCN adopt a similar statement for T1/2 OSCC but suggest for a depth of invasion (DOI) less than 2 mm, elective neck dissection is only recommended in highly selective situations.

The dilemma for a number of years was to determine in a cN0 neck, who would qualify for or benefit from an END. It was widely accepted that if the risk of occult disease was greater than 20%, then an END should be performed.[6] Increasing tumor size and DOI have been well-reported to increase the likelihood of regional nodal disease.[7-9] Other adverse histologic features which influence risk of nodal disease and survival include perineural invasion (PNI), lymphovascular invasion (LVI), and tumor differentiation. A recent study suggested that risk of nodal disease is increased when 2 or more adverse features are present on histology.[10] In recent times, SLNB has been advocated as a minimally invasive alternative, and while the research is promising with regard to reduced morbidity and comparable OS, SLNB is not universally the current standard of care and is still considered a diagnostic modality.[11,12]

It is well known that the risk of occult neck disease increases as the size of the tumor increases from T2 to T4 disease, and there is certainly agreement for END in such cases. Furthermore, for T1 tumors, DOI 4 mm or greater has been accepted as a threshold for END in many centers.[7,8] The challenge remains in managing T1N0 OSCC with a DOI less than 4 mm, as END carries a greater potential of overtreatment, while observation carries the risk of under treatment and reduced survival. Very few studies have analyzed this specific cohort of T1N0M0 (stage 1) patients with OSCC using the American Joint Committee on Cancer (AJCC) 8th Edition Staging Manual to determine whether other factors from clinical or histological examination can guide treatment outcomes. The purpose of this study was to investigate tumor characteristics of surgically managed patients with cT1N0 oral cavity SCC based on the AJCC 8th Edition and determine the possible benefits of END. The investigators hypothesize that END in T1N0 OSCC detects occult nodal disease in greater than 20% of cases, and confers a DFS and OS benefit. Furthermore, the specific aims of the study were to determine whether DOI per millimeter increment influenced nodal metastasis, recurrence, and survival.

Materials and Methods

To address the research purpose, the investigators designed and implemented a retrospective cohort study assessing outcomes for patients with stage I (T1N0M0) OSCC at Waikato Hospital, New Zealand, between 2008 and 2018. The study was granted exemption and approved in writing by the New Zealand Health and Disability Ethics Committee and approved by the local Waikato District Health Board. Patient information was reviewed using the head and neck cancer registry at the hospital.

The inclusion criteria were patients who were clinically staged with T1N0M0 oral cavity SCC based on the AJCC Cancer Staging Manual, 8th Edition, and had surgical intervention. Patients were staged as having a cN0 neck after unremarkable physical examination and radiologic investigations of the neck. All patients were then presented at a weekly head and neck multidisciplinary meeting. The recommendation

to perform END over surveillance was based on a combination of factors including DOI, adverse features, age, and comborbidities. While a cutoff of >3 mm was used to recommend END, this was not universal when accounting for the aforementioned factors. Patients were excluded if they did not have a diagnosis of SCC, had a DOI >5 mm and were therefore upstaged to ≥ T2, had previous treatment for oral SCC with surgery, radiotherapy and/or chemotherapy, or if records were not complete. The standard follow-up protocol is to monitor patients for a period of 5 years. In the study's cohort, patients were followed for a minimum period of 24 months, with a median follow-up of 55 months.

The primary predictor variable assessed in the study was modality of treatment—comparing END with surveillance of the neck. The outcome variables included recurrent disease and OS. A number of tumor factors were assessed to determine the influence on the outcome variables. As such data collected included patient demographics, location, tumor characteristics on final histology including differentiation, DOI, PNI, LVI, closest margin, management of the neck, number of pathologic lymph nodes, adjuvant treatment, recurrence, and survival. Histopathological margins were defined as clear (≥5 mm), close (2-5 mm), or involved (<2 mm). A single histopathologist reviewed all pathology cases which were originally reported as tumor thickness (TT), and re-evaluated as DOI for standardization. In addition, on histology review, if specimens were noted to have DOI >5 mm, then they were excluded. Nodal disease was either identified after an END or in patients who were observed in the neck and subsequently developed pathologic neck disease and underwent a therapeutic neck dissection.

Deidentified patient variables were analyzed using descriptive statistics. The variable nodal disease was defined as patients with pathologic positive node after either END or neck recurrence that occurred within 2 years in the observation group. Time-related outcomes in the model were OS, DFS, and regional recurrence. The Pearson χ^2 and Fisher exact tests for categorical analysis were used to determine the influence of patient variables on node status. Cox's proportional hazard model was used to compare patient variables against DFS, OS, and regional recurrence. The Kaplan-Meier survival method was used to analyze the survival probability and plot survival charts. Confidence intervals of 95% are used for the Cox hazard model and Kaplan-Meier survival method. A P value less than 0.05 was considered statistically significant.

Results

A total of 70 patients were included in the study (40 male, 30 female; age range 30 to 91; median age 65 years). Forty-eight (68.5%) cases involved the lateral tongue, 20 (28.5%) cases involved the buccal mucosa, and 1 (1.4%) case involved floor of the mouth, and 1 (1.4%) case involved the ventral tongue. Based on the current AJCC Cancer Staging Manual, 8th Edition, an additional 10 cases not included in the study had a DOI greater than 5 mm and would have been upstaged to T2 or 3, and therefore excluded from the final analysis. All 10 of these cases underwent END and were node positive.

Of the 70 patients in our cohort, nodal disease occurred in 13 patients (18.6%)—6 cases in the END group, and 7 cases in the observed group. Patient factors and tumor adverse features were assessed to determine a relationship with nodal disease. The results are summarized in Table 1. When the primary tumor factors were assessed in the 70 cases, DOI>3 mm (P = .049), poorly differentiated SCC (P = .003), and presence of PNI (P = .002) were statistically significant for risk of nodal disease. DOI was assessed in 1 mm increments and compared with the incidence of nodal disease in all 70 patients. The results are summarized in Table 2. The hypothesis that there is a relationship between DOI and nodal metastatic disease was tested by comparing the mean DOI of the node-positive patients (3.0 mm) to the mean DOI of the node-negative patients (2.1 mm) and determined to be significant (P = .03).

With regard to management of the cN0 neck, 27 (38.6%) patients underwent END, whereas 43 patients (61.4%) were observed. Occult nodal metastases were diagnosed in 6 of 27 patients (22.2%) who underwent END. Neck relapse was diagnosed in 7 of 43 patients (16.3%) in the observed group who subsequently underwent therapeutic neck dissections. In addition, DOI was assessed to determine the frequency of occult metastatic disease for the END group and the results are summarized in Table 3.

Of the 70 patients included in our study group, 69 patients were followed for a minimum of 2 years and there were 4 local recurrences and 8 regional recurrences. Regional recurrence was 3.7% in the END group and 16.7% in the observed group, but this was not found to be statistically significant (P = .163). Of the 8 regional recurrences, 1 had previously undergone END and was salvaged. Six of the remaining 7 were from the observed group and underwent therapeutic neck dissection, having a primary tumor DOI of ≤ 2.5 mm. Of the regional recurrences, 1 was well-differentiated, 4 were moderately differentiated, and 3 poorly differentiated OSCC. Poor tumor differentiation was found to be associated with a higher risk of regional recurrence (P = .02). Cox's proportional hazard model was used to estimate the hazard based on the predictor variables. These results are shown in

Table 1. FACTORS AFFECTING CERVICAL NODAL METASTASIS IN CT1N0 OSCC

		END		Observation		
Nodal Status	Cases (n = 70)	Present	Absent	Present	Absent	*P* Value
Sex						
Female		1	11	2	16	.13
Male		5	10	5	20	
Age (years)						
< 55	14	2	5	2	5	.28
≥ 55	56	4	16	5	31	
DOI						
< 3 mm	49	1	13	5	30	.049
≥ 3 mm	21	5	8	2	6	
Differentiation						
Well/moderate	65	5	20	4	36	.003
Poor	5	1	1	3	0	
PNI						
Present	10	3	3	3	1	.002
Absent	60	3	18	4	35	
LVI						
Present	5	0	2	2	1	.23
Absent	65	6	19	5	35	
Smoking						
Current	17	1	5	3	8	.44
Ex-smoker	32	3	8	4	17	
Never	21	2	8	0	11	
Alcohol						
Yes	57	5	16	6	30	.60
No	13	1	5	1	6	

Abbreviations: DOI, depth of invasion; END, elective neck dissection; LVI, lymphovascular invasion; OSCC, oral squamous cell carcinoma; PNI, perineural invasion.

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Table 4—bivariate analysis and Table 5—multivariate analysis.

OS was 87.0% at 2 years, and based on the Kaplan-Meier survival regression model, the probability of survival at 5 years was 72.4%. DFS was 79.7% at 2 years and the probability of DFS at 5 years was 64.6%. Negative prognostic factors for OS included male gender (P = .02, hr = 3.55, CI for HR (1.18, 10.66)), presence of PNI (P = .001, hr = 4.52, CI for HR (1.77, 11.57)), and locoregional recurrence (P < .005, hr = 6.55, CI for HR (2.69, 15.98)). Results for OS and DFS at 2 years are shown in Tables 6-9, respectively. Univariate and multivariate analyses were performed. Performing an END conferred an improved DFS by 2.9% at 2 years but had no impact on OS. Survival curves are shown in Figures 1-11.

Table 2. FREQUENCY OF NODAL DISEASE IN ALL CT1N0 PATIENTS BY 1 MM DOI INCREMENTS

Depth of Invasion	Cases (n = 70)	Nodal Disease Present	Nodal Disease Absent	% Node Present	% Node Absent
0 to <1 mm	15	1	14	7%	93%
1 to <2 mm	28	4	24	14%	86%
2 to <3 mm	11	2	9	18%	82%
3 to <4 mm	7	2	5	29%	71%
4 to ≤5 mm	9	4	5	44%	56%
All	70	13	57	19%	81%

Abbreviation: DOI, depth of invasion.

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Table 3. FREQUENCY OF OCCULT NODAL DISEASE IN ELECTIVE NECK DISSECTION GROUP

Depth of Invasion	Cases (n = 27)	Nodal Disease Present	Nodal Disease Absent	% Node Present	% Node Absent
0 to <1 mm	2	1	1	50%	50%
1 to <2 mm	9	0	9	0%	100%
2 to <3 mm	5	0	5	0%	100%
3 to <4 mm	4	1	3	25%	75%
4 to ≤5 mm	7	4	3	57%	43%
All	27	6	21	22%	78%

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Discussion

In the patient with OSCC, every effort should be made to detect occult nodal metastatic disease as it affects patient management and is negatively prognostic for DFS and OS.[3] While NICE and NCCN have recommended guidelines,[4,5] there is no universal consensus with regard to management of the node-negative neck in T1 tumors. While most head and neck surgeons agree that END be recommended for increasing DOI of the primary tumor,[2,7-9,13] others argue that observation of thin tumors prevents overtreatment of 70-80% of patients.[14,15] This ongoing dilemma with regard to treatment indications and decisions is reaffirmed in a recent perspective article in a request to cease combining T1 and T2 data which clouds the evidence.[16] The present study examined the clinical outcomes of patients with stage I (T1N0M0) OSCC based on AJCC 8th Edition guidelines to determine whether patient factors, surgical margins, histopathological features and END influence occult nodal disease, recurrence, and overall prognosis.

With the introduction of the AJCC Cancer Staging Manual 8th Edition in 2017, tumors with a DOI > 5 mm are now upstaged to ≥ T2. Over the 10-year period, tumor depth was not consistently reported, and nearly a half of the histopathology was reported as TT. To comply with the new AJCC guidelines, all

Table 4. BIVARIATE ANALYSIS FOR RISK FACTORS AFFECTING REGIONAL RECURRENCE AT 2 YEARS IN CT1N0 OSCC

Predictor	Values	HR	95% CI	*P* Value
Treatment	Observed	Reference		
	END	0.23	0.028-1.83	.16
Sex	Female	Reference		
	Male	5.49	0.67- 44.6	.11
Age (years)	< 55	Reference		
	≥ 55	0.67	0.14-3.34	.63
DOI	Shallow < 3	Reference		
	Deep ≥ 3	.309	0.038-2.51	.272
Differentiation	Well/moderate	Reference		
	Poor	9.24	2.19-39.02	.0025
PNI	Present	Reference		
	Absent	4.31	1.027-18.05	.046
LVI	Present	Reference		
	Absent	4.22	0.85-20.92	.078
Smoking	Never	Reference		
	Current or	2.96	0.36-24.10	.31
	Ex-smoker			
Alcohol	No	Reference		
	Yes	1.733	0.21-14.09	.61
Margin	Clear	Reference		
	Close	0.45	0.11-1.82	.27
	Positive	2.72×10^{-7}	0	.99

Abbreviations: DOI, depth of invasion; END, elective neck dissection; LVI, lymphovascular invasion; OSCC, oral squamous cell carcinoma; PNI, perineural invasion.

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Table 5. MULTIVARIATE ANALYSIS FOR REGIONAL RECURRENCE AT 2 YEARS IN CT1N0 OSCC

Predictor	Values	HR	95% CI	*P* Value
Differentiation	Well–moderate	Reference		
	Poor	11.21	2.01-66.45	.0058
PNI	Absent	Reference		
	Present	4.27	0.79-23.00	.091
Closest margin	Baseline	Reference		
	Per mm increase	1.23	1.07-1.41	.0042

Abbreviations: OSCC, oral squamous cell carcinoma; PNI, perineural invasion.

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TT specimens were reviewed and adjusted to DOI. With an initial data set of 80 patients, 10 cases with a DOI > 5 mm were upstaged and excluded from the study. Of note, they all underwent END and were all node positive. Based on the AJCC 7th Edition, the occult nodal disease rate would have been significantly higher (AJCC 7th 43.2% vs AJCC 8th 22.2%) suggesting that the addition of DOI in staging has reduced the rate of occult nodal disease in stage I OSCC. These findings align with the updates to the AJCC Cancer Staging Manual 8th Edition by including DOI in the staging system, as increasing DOI is an independent negatively prognostic factor for nodal disease and survival.[17-20]

Adverse features on histology have been widely investigated in the literature. The presence of LVI, PNI, and poor differentiation on histology suggest these features are part of a high-grade tumor that are biologically more aggressive and may metastasize to regional lymph nodes earlier.[17-19,21,22] In our study, these variables were assessed to determine whether there was a correlation with nodal disease and recurrence. The most significant findings were that poorly differentiated OSCC (*P* = .003) and presence of PNI

Table 6. BIVARIATE ANALYSIS FOR RISK FACTORS AFFECTING OVERALL SURVIVAL AT 2 YEARS IN CT1N0 OSCC

Predictor	Values	HR	95% CI	*P* Value
Sex	Female	Reference		
	Male	3.55	1.18-10.66	.02
Age (years)	< 55	Reference		
	≥ 55	0.99	0.32-3.01	.98
DOI	Shallow < 3	Reference		
	Deep ≥ 3	1.41	0.57-3.46	.45
Differentiation	Well/moderate	Reference		
	Poor	2.27	0.66-7.80	.19
PNI	Present	Reference		
	Absent	4.53	1.77-11.57	.002
LVI	Present	Reference		
	Absent	2.43	0.71-8.35	.16
Smoking	Never			
	Current or	Reference		
	Ex-smoker	1.79	0.60-5.38	.30
Alcohol	No	Reference		
	Yes	2.01	0.46-8.73	.35
Margin	Clear	Reference		
	Close	1.73	0.57-5.27	.33
	Positive	3.17	0.58-17.32	.18
Treatment	Observed	Reference		
	END	1.38	0.57-3.33	.48
Recurrence	None	Reference		
	Locoregional	6.55	2.69-15.98	<.005

Abbreviations: DOI, depth of invasion; END, elective neck dissection; LVI, lymphovascular invasion; OSCC, oral squamous cell carcinoma; PNI, perineural invasion.

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Table 7. MULTIVARIATE ANALYSIS FOR RISK FACTORS AFFECTING OVERALL SURVIVAL AT 2 YEARS IN CT1N0 OSCC

Predictor	Values	HR	95% CI	*P* value
Sex	Female	Reference		
	Male	2.36	0.75-7.45	.14
PNI	Absent	Reference		
	Present	42.41	0.85-6.87	.097
Any recurrence	None	Reference		
	Locoregional	3.92	1.41-10.87	.008

Abbreviations: OSCC, oral squamous cell carcinoma; PNI, perineural invasion.

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(*P* = .002) were found to be associated with a higher risk of nodal disease which is supported by other authors.[17,23] PNI was identified in 14.2% of patients. While that rate is high, it is supported in a study assessing PNI in OSCC, and found an overall incidence of 40%, and 22.2% in T1 OSCC.[24] A recent study found a correlation between PNI and pathologic nodal disease and extranodal extension (ENE).[25] The authors found that most PNI positive cases were associated with thicker tumors which would have been recommended for END based on DOI as a primary indicator. As such they concluded that PNI status added no value in decision-making. Detecting PNI on preoperative imaging or biopsy can be challenging and as such may be less significant than other adverse features. The presence of PNI on final histology, however, can influence postoperative management including consideration for a staging neck dissection as a second procedure or consideration of adjuvant radiotherapy.[25]

Weiss advocated performing END if the risk of occult nodal disease was greater than 20%,[6] although more recently other authors have suggested reducing this threshold to 15%.[26] There is little argument regarding the benefit of END in T3-T4 disease, and many T2 tumors would require neck access for free-flap reconstruction and therefore have an END concurrently. However, controversy remains over the management of the neck in early T1N0 OSCC. DOI has

Table 8. UNIVARIATE ANALYSIS FOR RISK FACTORS AFFECTING DISEASE-FREE SURVIVAL AT 2 YEARS IN CT1N0 OSCC

Predictor	Values	HR	95% CI	*P* Value
Sex	Female	Reference		
	Male	3.80	1.42-10.18	.008
Age (years)	< 55	Reference		
	≥ 55	0.90	0.34-2.42	.84
DOI	Shallow < 3	Reference		
	Deep ≥ 3	1.42	0.63-3.19	.39
Differentiation	Well/moderate	Reference		
	Poor	6.02	2.20-16.46	<.005
PNI	Present	Reference		
	Absent	3.75	1.55-9.10	.003
LVI	Present	Reference		
	Absent	2.03	0.60-6.82	.25
Smoking	Never			
	Current or	Reference		
	Ex-smoker	1.06	0.44-2.54	.89
Alcohol	No	Reference		
	Yes	1.09	0.37-3.21	.87
Margin	Clear	Reference		
	Close	1.33	0.52-3.39	.55
	Positive	2.28	0.46-11.38	.31
Treatment	Observed	Reference		
	END	1.05	0.47-2.35	.90

Abbreviations: DOI, depth of invasion; END, elective neck dissection; LVI, lymphovascular invasion; OSCC, oral squamous cell carcinoma; PNI, perineural invasion.

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Table 9. MULTIVARIATE ANALYSIS FOR RISK FACTORS AFFECTING DISEASE-FREE SURVIVAL AT 2 YEARS IN CT1N0 OSCC

Predictor	Values	HR	95% CI	*P* Value
Sex	Female	Reference		
	Male	4.30	1.57-11.77	.045
Differentiation	Well to moderate	Reference		
	Poor	7.00	2.23-21.96	<.005
PNI	Absent	Reference		
	Present	3.15	1.21-8.19	.018

Abbreviations: OSCC, oral squamous cell carcinoma; PNI, perineural invasion.

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been a commonly accepted variable to guide END recommendations with authors over the years proposing a cutoff of 2-4 mm.[7,9,13] Kligerman found that END conferred a DFS benefit of 23% (72% vs 49%) for T1/2 tumors in particular when DOI > 4 mm.[27] A recent meta-analysis supported END concluding that it could significantly reduce recurrence and improve DFS in early-stage OSCC.[28] The D'Cruz study was included in that meta-analysis and recommended END for all T1 and T2 OSCC regardless of depth given they found a 12.5% 3 year OS benefit,[2] although there was no statistically significant benefit in T1 tumors and when DOI ≤ 3 mm. There were a number of limitations in that study, including that over 55% of the cohort had a T2 tumor. Furthermore, only 14.3% of the patients had DOI ≤ 3 mm compared with 70% from the present study. As such, the RCT is unable to offer strong evidence to support END in T1 tumors. Most other studies examining cN0 patients include large patient numbers of T2 and even T3 tumors,[2,28,29] which skews the recommendation for END. By contrast, a recently published study by Feng also analyzing T1N0M0 SCC found a low occult nodal disease rate of 14.1% after END and 2-year nodal recurrence of 11.3%. They recommend a watch and wait approach for superficial disease dependent on subsite,[30] except in the tongue with a cutoff of 2 mm. In fact, in the 2 to <3 mm group, Feng reported an incidence of 18.2% in the tongue and concluded that this was adequate to recommend END.[30] Interestingly, in our study in the same 2 to <3 mm DOI group, the frequency of nodal disease was also 18% although the authors do not draw the same conclusions due to small numbers. The present study assessed only T1 tumors and found the occult nodal disease rate in patients with END was 22% which meets the 20% cutoff threshold. Furthermore, an assessment of DOI in our patient cohort identified a threshold of ≥ 3 mm to optimize outcomes and

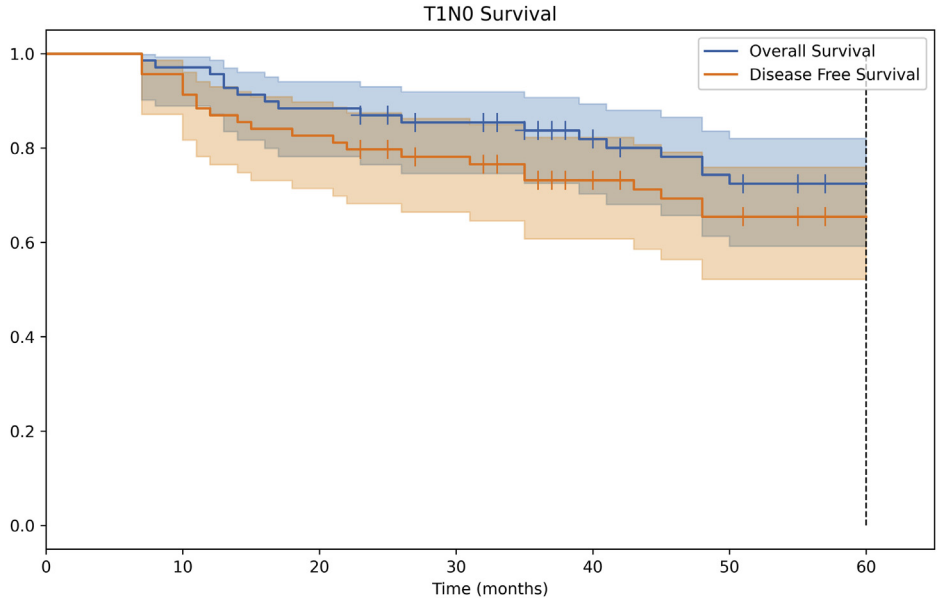

FIGURE 1. Comparison of T1N0 oral SCC DFS with OS. Abbreviations: DFS, disease-free survival; OS, overall survival; SCC, squamous cell carcinoma.

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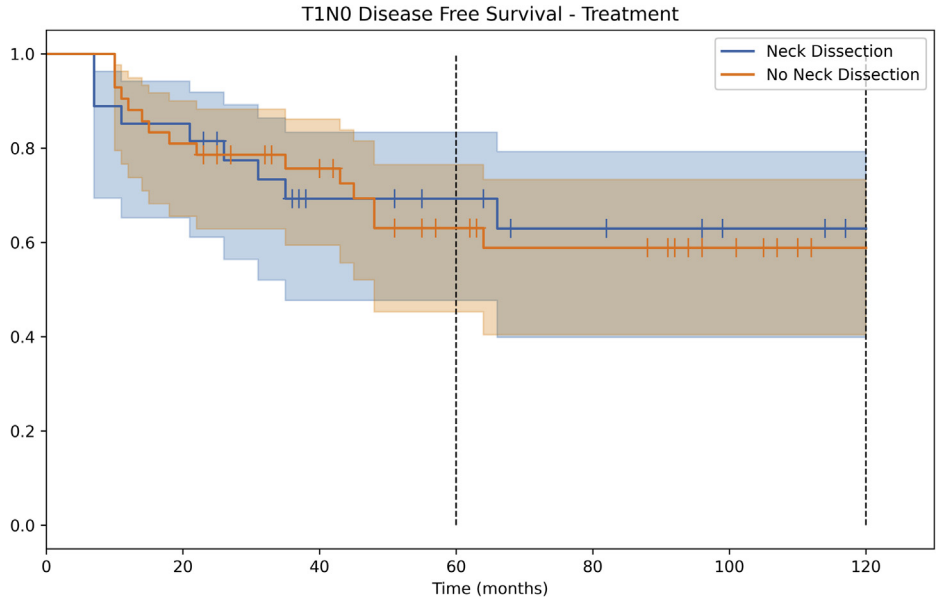

FIGURE 2. Comparison of DFS between END group and observation group. Abbreviations: DFS, disease-free survival; END, elective neck dissection.

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minimize the morbidity associated with overtreatment of END (P = .049). The present study found that END reduced regional recurrence compared with the observation group (3.7 vs 16.3%) which was clinically significant. While our findings were not statistically significant, the trend certainly supports END to adequately stage the neck and achieve regional control in occult disease, in particular when DOI $\geq$ 3 mm.

A clear histological margin is a modifiable factor that is key to minimizing locoregional recurrence. Iseli et al defined involved margins as <1 mm, and found that this resulted in higher recurrence and worse OS.[31] These findings lead to the author advocating for wider surgical margins to reduce the risk of local recurrence. A recent study examined surgical margins in relation to recurrence and survival after primary resection of OSCC. They defined margins as clear, close, or involved and found 5-year OS to be 81, 75, and 54%, respectively.[32] In the present study, a positive margin was found in 4 cases, and given small numbers, close

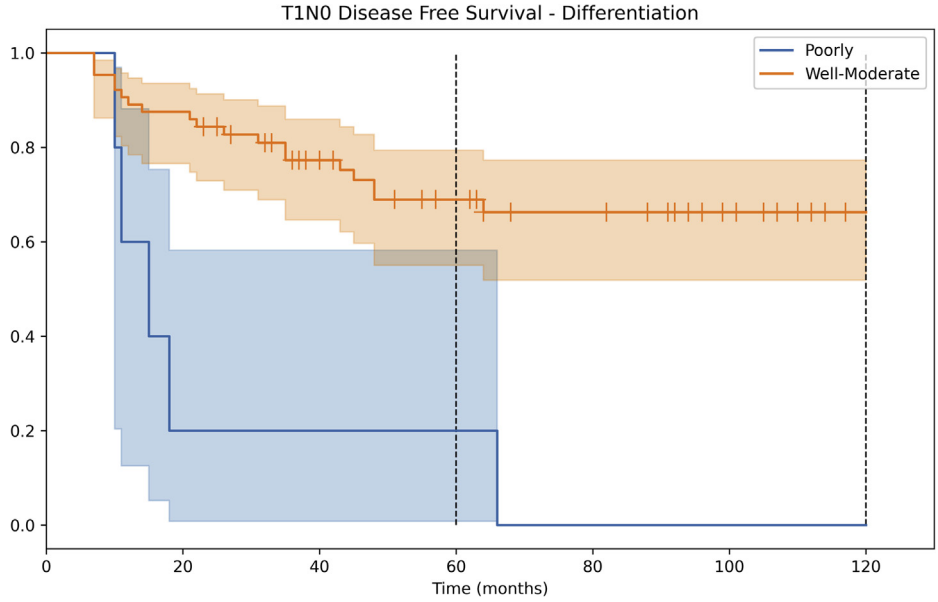

FIGURE 3. Comparison of DFS between poor and well-moderate tumor differentiation groups. Abbreviation: DFS, disease-free survival.

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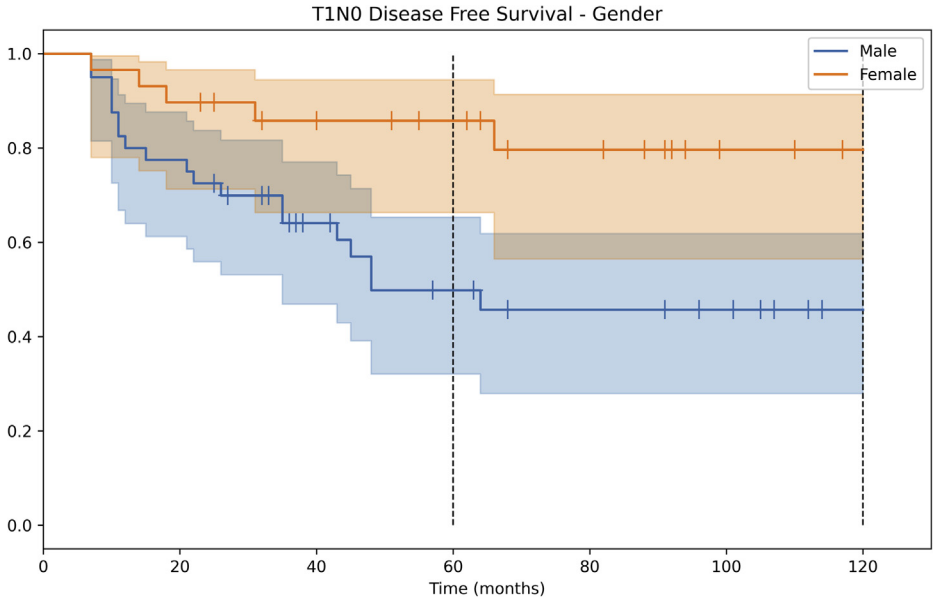

FIGURE 4. Comparison of DFS between male and female groups. Abbreviation: DFS, disease-free survival.

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and involved margins were grouped for analysis. There was no correlation between histologic margin status and locoregional recurrence. However, there was a clinically significant predicted OS benefit of 12.4%, and DFS benefit of 7.4% if a clear margin was achieved compared with a close or involved margin (DFS: clear 70.3% vs not clear 62.9%), (OS: clear 81.0% vs not clear 68.6%).

On further analysis of the regional recurrences, all cases which had primary observation of the neck had a DOI ≤ 4 mm. In fact, 6 of the 7 cases had a DOI <2.5 mm, and most cases being moderately or poorly differentiated SCC. The mortality in the recurrence group was 67%. The literature is clear that regional recurrence is negatively prognostic and that salvage options also carry a poor prognosis.[33,34] While the results from this study did not demonstrate a statistically significant survival benefit from END, it did demonstrate better regional control which other authors have found.[35] The authors advocate performing END in T1 tumors with DOI ≥ 3 mm. However, given regional recurrences occurred in tumors ≤3 mm,

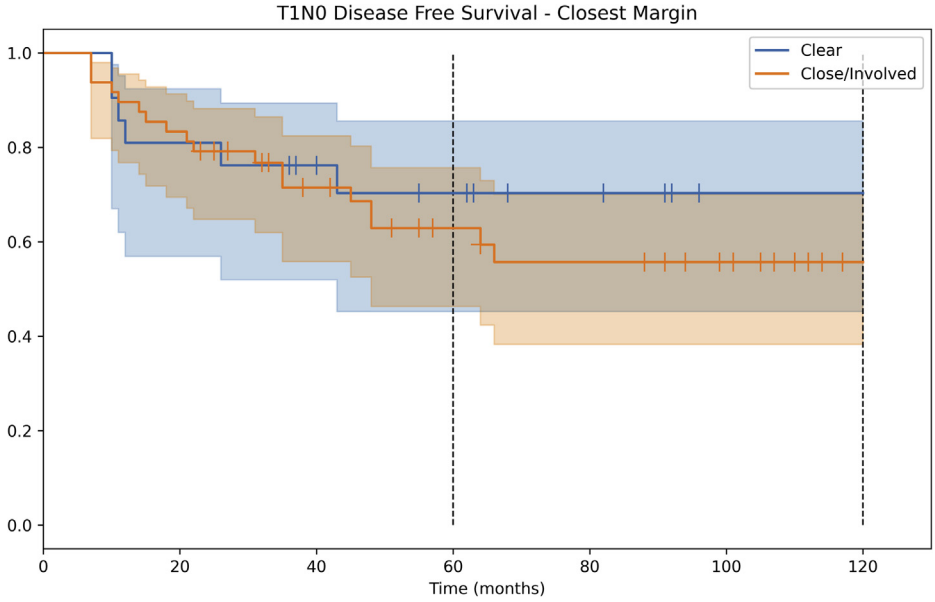

FIGURE 5. Comparison of DFS based on closest histological margin. Abbreviation: DFS, disease-free survival.

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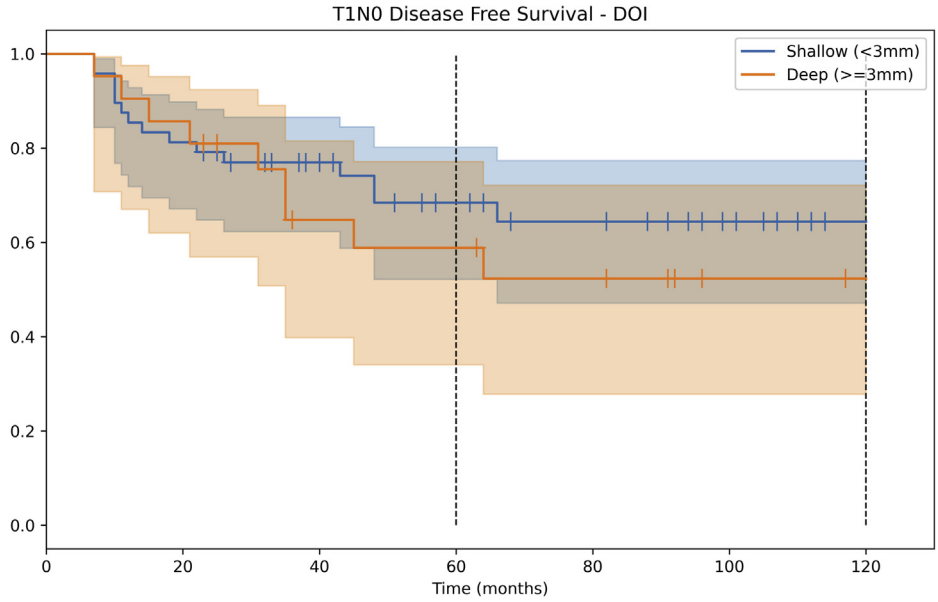

FIGURE 6. Comparison of DFS in relation to tumor depth of invasion. Abbreviation: DFS, disease-free survival.

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which would be observed in many centers, careful consideration should be made to perform END on cases with thinner tumors in the presence of adverse features. The challenge for surgeons is to determine these adverse factors to guide clinical decision-making. Our findings of adverse features are based on retrospective review of final histology, and while it is difficult to diagnose LVI and PNI on incisional biopsy, it is important to acquire a representative histological sample and to examine for these adverse features prior to definitive surgery. However, just as importantly, in cases where DOI <3 mm and the patient does not undergo END, the detection of poor prognosticators such as poor differentiation and PNI on final histology should influence the surgeon to consider performing a staging neck dissection as a second operation.

For stage I OSCC, the results from the present study showed a lower 2-year and projected 5-year DFS and OS in comparison with the literature quoted in the

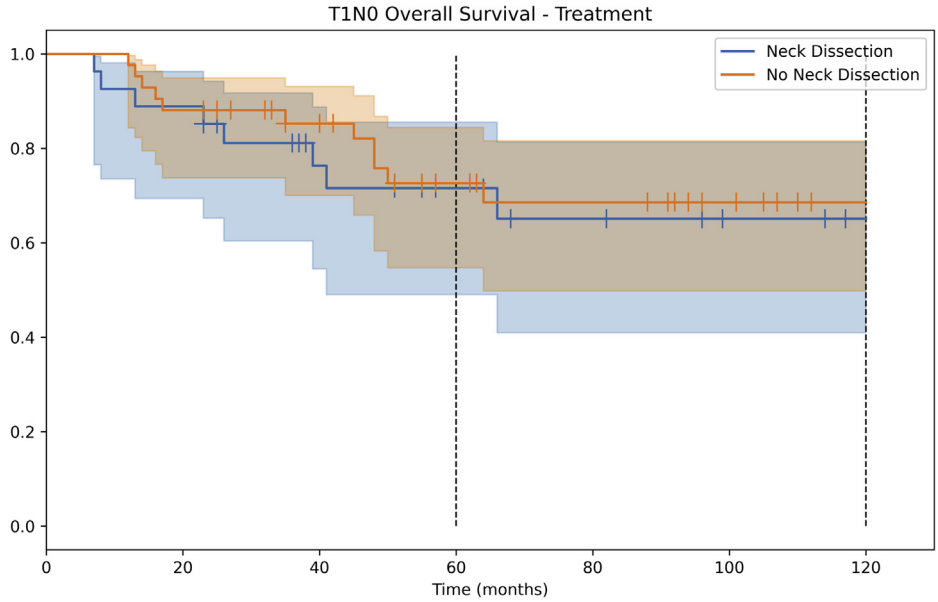

FIGURE 7. Comparison of OS between END group and observation group. Abbreviations: END, elective neck dissection; OS, overall survival.

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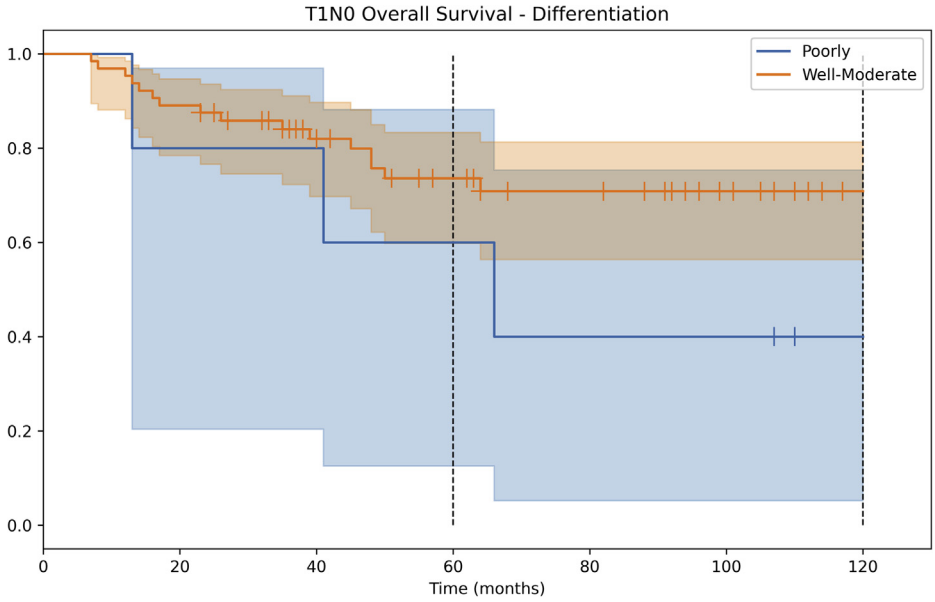

FIGURE 8. Comparison of OS between poor and well-moderate tumor differentiation groups. Abbreviation: OS, overall survival.

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AJCC Cancer Staging Manual, 8th Edition. However, the survival figures are comparable with the results from the largest RCT at 3 years.[2] Tumor subsite has been shown to influence patient outcomes,[36] in particular, tongue and buccal mucosa which can be highly aggressive due to anatomic location and lymphatic drainage pathways. In our patient cohort, there were no gingival primary tumors which normally have a better prognosis. The lower survival rates may have been influenced by the fact that all but 2 cases were either tongue or buccal mucosa primaries.

Prognostic factors for survival have been studied and patient and histologic factors including smoking and alcohol status, increasing tumor DOI, adverse features including PNI, LVI, and poor differentiation have been reported.[3,32,37,38] Increasing DOI was associated with an increased risk of nodal disease, and reduced DFS and OS although the latter was not statistically significant. Furthermore, a recent study found no correlation between DOI and recurrence or survival.[10] Instead they found 2 or more adverse pathologic features including PNI, LVI, and worst pattern of infiltration,

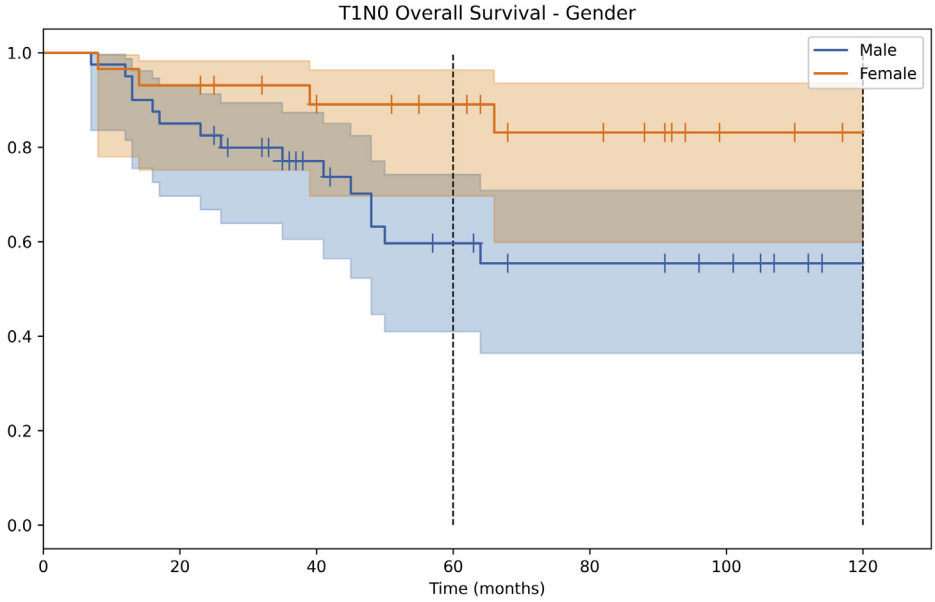

FIGURE 9. Comparison of OS between male and female groups. Abbreviation: OS, overall survival.

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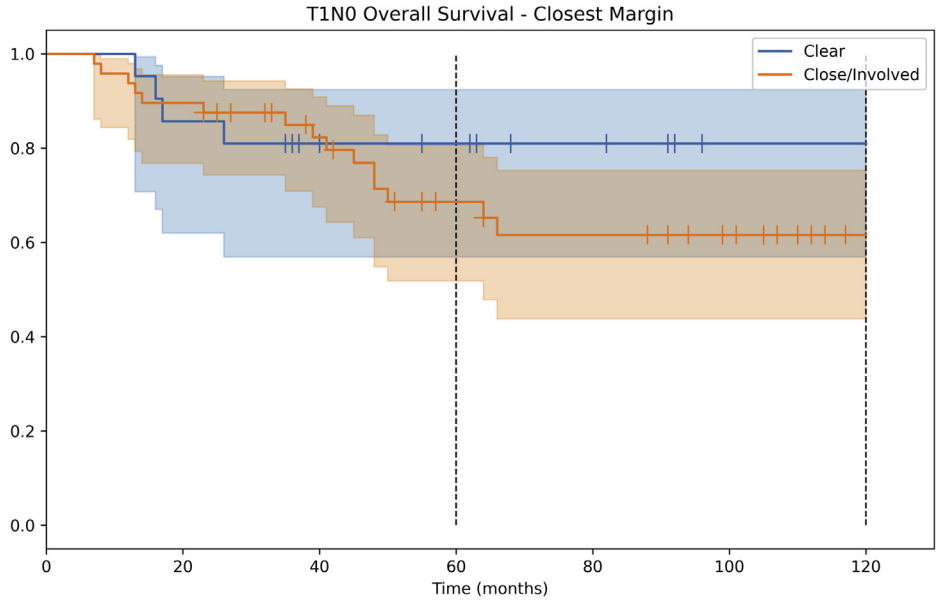

FIGURE 10. Comparison of OS based on closest histologic margin. Abbreviation: OS, overall survival.

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in combination with a DOI >4 mm to be negatively prognostic. In our study, negative prognostic factors for survival included male gender, any evidence of locoregional recurrence, a positive margin, and poorly differentiated OSCC.

The present study is one of a few in the literature to address only stage I OSCC outcomes, as most combine T1 and T2 patient cohorts to draw meaningful conclusions. There are however limitations with this study. First, it is a retrospective cohort study. Second, with a data set of 70 patients, it is challenging to draw statistical conclusions and the number of variables incorporated into study models is limited. Third, given that the END and observation groups were not randomized, the selection bias influenced the treatment arm (38.6% END vs 61.4% observation). It is likely that the patients at higher risk of nodal disease received an END and therefore conferred a benefit from that treatment arm, while patients in the surveillance cohort may have benefited from observation. While there is a trend, the results over the 10 year period did demonstrate that a DOI cutoff was not

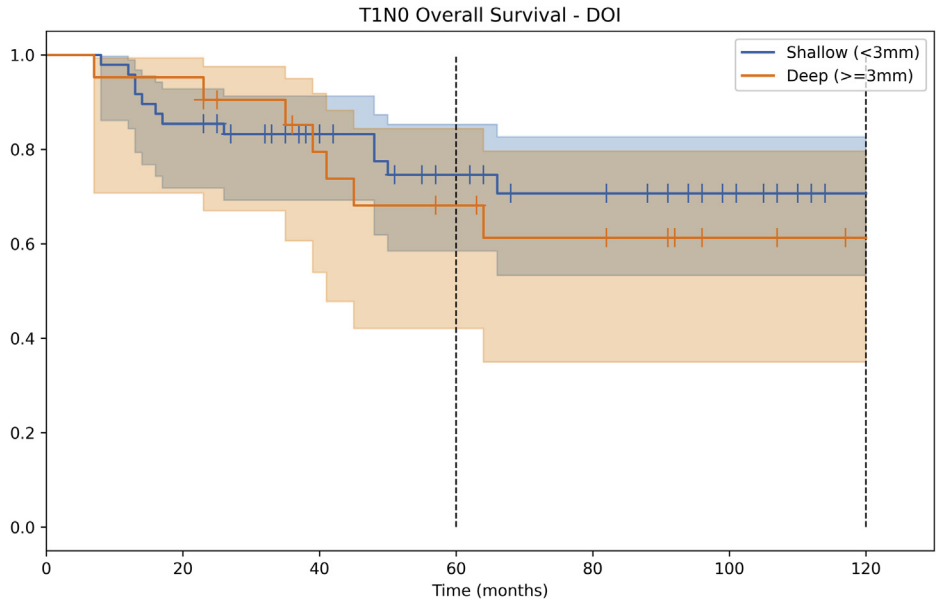

FIGURE 11. Comparison of OS in relation to tumor depth of invasion. Abbreviation: OS, overall survival.

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consistently used to guide END decisions in our institution, especially as histological analysis referred to TT at times rather than DOI. The findings of this study reaffirms the need to continue research into the management of T1N0 OSCC, and exclude T2N0 patient cohorts in future studies which have clouded the interpretation of benefits of END, ultimately in an effort to improve long-term patient outcomes.

In conclusion, there is little data published for management outcomes of the node-negative neck in stage I OSCC. Risk factors for nodal disease included increasing DOI, poor tumor differentiation, and presence of PNI. Negative prognostic factors for survival included male gender, positive margin, poor tumor differentiation, and locoregional recurrence. END reduced regional recurrence by 12.6% and improved DFS by 6.2%. Six of the 7 tumors that relapsed in the neck after observation had a primary tumor DOI < 3 mm. Given salvage neck dissection carries a poorer prognosis, END should be recommended for all T1N0 oral SCC with DOI ≥ 3 mm. In cases of DOI < 3 mm undergoing primary ablation only, a staging neck dissection as a second procedure should be considered in the presence of poor tumor differentiation or PNI on final histology.

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References

1. Dobrossy L: Epidemiology of head and neck cancer: Magnitude of the problem. Cancer metastasis Rev 24:9, 2005
2. D'Cruz AK, Vaish R, Kapre N, et al: Elective versus therapeutic neck dissection in node-negative oral cancer. The New Engl J Med 373:521, 2015
3. Cerezo L, Millan I, Torre A, et al: Prognostic factors for survival and tumor control in cervical lymph node metastases from head and neck cancer. A multivariate study of 492 cases. Cancer 69:1224, 1992
4. National Institute for Health and Care Excellence Guideline. Cancer of the Upper Aerodigestive Tract: Assessment and Management in People Aged 16 and over (Version February 2016).
5. National Comprehensive Cancer Network. Head and Neck Cancers (Version 3. 2019).
6. Weiss MH, Harrison LB, Isaacs RS: Use of decision analysis in planning a management strategy for the stage N0 neck. Arch Otolaryngology–Head Neck SURG 120:699, 1994
7. O'Brien CJ, Lauer CS, Fredricks S, et al: Tumor thickness influences prognosis of T1 and T2 oral cavity cancer–but what thickness? Head & neck 25:937, 2003
8. Huang SH, Hwang D, Lockwood G, et al: Predictive value of tumor thickness for cervical lymph-node involvement in squamous cell carcinoma of the oral cavity: A meta-analysis of reported studies. Cancer 115:1489, 2009
9. Brockhoff HC 2nd, Kim RY, Braun TM, et al: Correlating the depth of invasion at specific anatomic locations with the risk for regional metastatic disease to lymph nodes in the neck for oral squamous cell carcinoma. Head & neck 39:974, 2017
10. Larson AR, Kemmer J, Formeister E, et al: Beyond depth of invasion: Adverse pathologic tumor features in early oral tongue squamous cell carcinoma. The Laryngoscope 130:1715, 2020
11. Schilling C, Stoeckli SJ, Haerle SK, et al: Sentinel European node trial (SENT): 3-year results of sentinel node biopsy in oral cancer. Eur J Cancer 51:2777, 2015
12. Cramer JD, Sridharan S, Ferris RL, et al: Sentinel lymph node biopsy versus elective neck dissection for stage I to II oral cavity cancer. The Laryngoscope 129:162, 2019
13. Kuan EC, Mallen-St Clair J, Badran KW, St John MA: How does depth of invasion influence the decision to do a neck dissection in clinically N0 oral cavity cancer? The Laryngoscope 126:547, 2016
14. Flach GB, Tenhagen M, de Bree R, et al: Outcome of patients with early stage oral cancer managed by an observation strategy towards the N0 neck using ultrasound guided fine needle aspiration cytology: No survival difference as compared to elective neck dissection. Oral Oncol 49:157, 2013
15. Massey C, Dharmarajan A, Bannuru RR, Rebeiz E: Management of N0 neck in early oral squamous cell carcinoma: A systematic review and meta-analysis. The Laryngoscope 129:E284, 2019
16. Ward BB: Time to Start Asking the Right Question or at Least Admit We do not have the Answer-indications for elective neck dissection in early-stage oral cavity cancer. J Oral Maxill Surg 78:2108, 2020
17. Subramaniam N, Murthy S, Balasubramanian D, et al: Adverse pathologic features in T1/2 oral squamous cell carcinoma classified by the American Joint Committee on Cancer eighth edition and implications for treatment. Head & neck 40:2123, 2018
18. Spiro RH, Huvos AG, Wong GY, et al: Predictive value of tumor thickness in squamous carcinoma confined to the tongue and floor of the mouth. Am J Surg 152:345, 1986
19. Sparano A, Weinstein G, Chalian A, et al: Multivariate predictors of occult neck metastasis in early oral tongue cancer. Otolaryngology–Head and Neck Surgery 131:472, 2004
20. Murthy S, Low TH, Subramaniam N, et al: Validation of the eighth edition AJCC staging system in early T1 to T2 oral squamous cell carcinoma. J Surg Oncol 119:449, 2019
21. Wu K, Wei J, Liu Z, et al: Can pattern and depth of invasion predict lymph node relapse and prognosis in tongue squamous cell carcinoma. BMC cancer 19:714, 2019
22. Tai SK, Li WY, Chu PY, et al: Risks and clinical implications of perineural invasion in T1-2 oral tongue squamous cell carcinoma. Head & neck 34:994, 2012
23. Low TH, Gao K, Gupta R, et al: Factors predicting poor outcomes in T1N0 oral squamous cell carcinoma: Indicators for treatment intensification. ANZ J Surg 86:366, 2016
24. Varsha BK, Radhika MB, Makarla S, et al: Perineural invasion in oral squamous cell carcinoma: Case series and review of literature. J Oral Maxill Pathol 19:335, 2015
25. Alzahrani S, Feng Z, Cheng A, et al: Is perineural invasion a Reasonable indicator for neck dissection in cT1N0M0 squamous cell carcinoma of the oral cavity? J Oral Maxill Surg 6: 31105, 2020
26. Ferlito A, Silver CE, Rinaldo A: Elective management of the neck in oral cavity squamous carcinoma: Current concepts supported by prospective studies. The Br J Oral Maxill Surg 47:5, 2009
27. Kligerman J, Lima RA, Soares JR, et al: Supraomohyoid neck dissection in the treatment of T1/T2 squamous cell carcinoma of oral cavity. Am J Surg 168:391, 1994
28. Abu-Ghanem S, Yehuda M, Carmel NN, et al: Elective neck dissection vs observation in early-stage squamous cell carcinoma of the oral tongue with No clinically Apparent lymph node metastasis in the neck: A systematic review and meta-analysis. JAMA Otolaryngology–Head Neck Surg 142:857, 2016
29. Ding Z, Xiao T, Huang J, et al: Elective neck dissection versus observation in squamous cell carcinoma of oral cavity with clinically N0 neck: A systematic review and meta-analysis of prospective studies. J Oral Maxill Surg 77:184, 2019
30. Feng Z, Cheng A, Alzahrani S, et al: Elective neck dissection in T1N0M0 oral squamous cell carcinoma: When is it Necessary? J Oral Maxillofacial Surg 78:2306, 2020

31. Iseli TA, Lin MJ, Tsui A, et al: Are wider surgical margins needed for early oral tongue cancer? The J Laryngol otology 126:289, 2012
32. Mitchell DA, Kanatas A, Murphy C, et al: Margins and survival in oral cancer. The Br J Oral Maxill Surg 56:820, 2018
33. Kowalski LP: Results of salvage treatment of the neck in patients with oral cancer. Arch otolaryngology–head neck Surg 128:58, 2002
34. Jones AS, Tandon S, Helliwell TR, et al: Survival of patients with neck recurrence following radical neck dissection: Utility of a second neck dissection? Head & neck 30:1514, 2008
35. Hughes CJ, Gallo O, Spiro RH, Shah JP: Management of occult neck metastases in oral cavity squamous carcinoma. Am J Surg 166:380, 1993
36. Farhood Z, Simpson M, Ward GM, et al: Does anatomic subsite influence oral cavity cancer mortality? A SEER database analysis. The Laryngoscope 129:1400, 2019
37. Huang TY, Hsu LP, Wen YH, et al: Predictors of locoregional recurrence in early stage oral cavity cancer with free surgical margins. Oral Oncol 46:49, 2010
38. Woolgar JA: Histopathological prognosticators in oral and oropharyngeal squamous cell carcinoma. Oral Oncol 42:229, 2006