Tumor depth of invasion versus tumor thickness in guiding regional nodal treatment in early oral tongue squamous cell carcinoma

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Objectives. Tumor thickness (TT) and tumor depth of invasion (DOI) correlate with the risk of regional lymph node metastases in early oral tongue squamous cell carcinoma (OTSCC). We aimed to determine optimal cutoff points to guide elective nodal treatment in early OTSCC.

Study Design. This retrospective study included 145 patients treated between 1995 and 2012 for histologically proven OTSCC (<4 cm). The minimum *P* value method was used to calculate the cut-point values of TT and DOI that predicted for nodal disease. The utility of the DOI cut-point value and the 5-mm DOI currently used for staging were then compared.

Results. Logistic regression analysis demonstrated that DOI ($P = .00036$) and TT ($P = .0001$) were highly correlated with nodal disease and each other. The cut-points that best predicted for nodal disease were 4.5 mm for DOI and 8 mm for TT. There was no difference in utility between DOIs of 4.5 mm and 5 mm.

Conclusions. TT and DOI were highly correlated with nodal risk but had different cut-points for prediction. Our findings highlight the need to recognize these parameters as discrete entities and to report them appropriately. This study's findings support the use of the 5-mm DOI, currently used for staging, as also the threshold value to guide elective nodal treatment. (Oral Surg Oral Med Oral Pathol Oral Radiol 2020;129:45−50)

Research over the past 2 decades has demonstrated that tumor thickness (TT) and depth of invasion (DOI) are correlated with the risk of regional metastases and poorer survival outcomes in oral tongue squamous cell carcinoma (OTSCC).[1-5] Recent research focused on the stratification of tumor (T) stage based on DOI has led to the incorporation of tumor DOI into the revised 8th edition of the *American Joint Committee on Cancer (AJCC) Staging Manual*.[6,7] In addition to their value in prognostication, TT and DOI have clinical utility in guiding management in early OTSCC, particularly in relation to the clinically and radiologically negative neck nodes (clinically, N0).

Decisions on elective nodal treatment in early OTSCC are usually based on the probability of occult metastases in the regional neck nodes exceeding a threshold value of around 20%.[8] Various groups, including our own, have determined and reported cut-points, for TT and DOI, at which the risk of occult regional nodal metastasis exceeds the threshold value.[1,9,10] The cut-points derived from these studies have been used to guide decisions regarding when the regional lymph nodes should be electively treated. Although 4 mm is often considered the most robust cut-point at which the risk of occult nodal disease appears to exceed 20%, the cut-point values reported in the literature vary widely, from 2 mm to 10 mm.[1,5,11] Part of the reason for this wide range is the ambiguity in the definitions of TT and DOI.

TT is a term that is often used by clinicians during clinical assessment of the primary tumor. It is also a

Statement of Clinical Relevance

Our findings highlight that depth of invasion and tumor thickness are different entities that should be quantified uniformly and confirm the utility of the 5-mm depth of invasion threshold in guiding elective regional nodal treatment in early oral tongue SCC.

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term used by pathologists during macroscopic description of the tumor specimen after excision. Unfortunately, it is a term that is often incorrectly interchanged with tumor DOI. Reviews of the literature conducted by Huang et al. and Pentenero et al. highlighted the discrepancies around this issue.[1,2] They noted that most authors did not clearly describe the measurement techniques they used when assessing and reporting TT and DOI. Indeed, in introducing DOI to the staging of TSCC, the 8th edition of the *AJCC Staging Manual* clearly makes the distinction between TT and DOI and emphasizes that the T stage classification of the primary tumor is based on DOI and not TT.[6,7]

We aimed to examine the histologic measurement and reporting of both TT and tumor DOI at our institution to determine the most appropriate parameter and the most appropriate threshold cut-point to guide elective management of the clinically N0 neck. We also aimed to examine the potential use of the 5-mm DOI value adopted by the current 8th edition of the *AJCC Staging Manual* for the elective management of clinically N0 neck.

PATIENTS AND METHODS

Patients with OTSCC, treated with primary surgical resection during the 17-year period between February 1, 1995, to January 31, 2012, were identified from a prospectively maintained, institutional (Westmead Hospital, Sydney, Australia) database and records of the Institute of Clinical Pathology and Medical Research at Western Sydney Local Health District (New South Wales, Australia). Patients, age 18 years and greater at time of diagnosis, were included if they had histologically proven OTSCC measuring less than 4 cm (T1 or T2 according to the 7th edition of the *AJCC Staging Manual*)[12] and were treated with curative intent through primary surgical excision with or without neck dissection. Information on patient, tumor, and treatment characteristics was extracted from the database and review of patient medical records, including correspondence, histopathology, and surgical reports. Data concerning TT and DOI were identified and recorded according to the historical histopathology reports. The TT and DOI values extracted were rounded up to the nearest 0.1 mm because differences in the TT and DOI values of less than 0.1 mm were not felt to be clinically or histopathologically significant and, therefore, considered equivalent.

Logistic regression was used to examine correlations between each of the 2 parameters (TT and DOI) and subsequent regional nodal recurrence. The minimum *P* value method was used to calculate cut-point values of TT and DOI that predicted for regional nodal disease (occult disease on neck dissection or subsequent neck relapse).[13] The negative predictive values (NPVs) of the 2 cut-points obtained, using the minimum *P*-value method, were then calculated and compared to select the ideal cut-point (i.e., the DOI cut-point vs the TT cut-point).

For comparison of the ideal cut-point derived from these data and the 5-mm DOI value currently used by the AJCC for staging, the samples were classified into 3 subgroups: (1) those that had both TT and DOI below the cut-point derived from these data; (2) those that had both TT and DOI above the cut-point derived from these data; and (3) those that had both measures reported but only 1 below the cut-point derived from these data. The above classification was performed, given that the data collection period in this study spanned a 17-year period and it was possible that the terms DOI and TT may have been used interchangeably during reporting in the early period of the study. To avoid ambiguity around the use of these terms affecting the results, we excluded those cases where DOI and TT straddled the cut-point derived from the data (group 3). The management decisions made in the groups regarding regional neck treatment were collected and examined together with the disease outcomes obtained. This was then repeated for the DOI value of 5 mm, which is used in the current AJCC staging system. To perform a direct comparison between the treatment outcomes for the 2 threshold values (cut-point derived from our data and the AJCC DOI of 5 mm), we modeled the proportions of patients who may be undertreated and overtreated if the above-mentioned threshold values were used for clinical decision making regarding elective regional nodal treatment.

RESULTS

A total of 145 potentially eligible cases were identified. Fifteen cases were excluded from the current analysis because no residual malignancy was seen on histopathologic examination of the resected specimen. Of the remaining 130 patients, 109 (84%) had both TT and DOI reported. Patient, tumor, and treatment characteristics of these 109 eligible cases are presented in Table I. The median age at time of diagnosis was 64 years (range 25−89 years). The majority (59%) of patients were males. Most (76%) were age 50 years or older. Tumors measuring less than 2 cm (T1 according to the 7th edition of the AJCC manual) accounted for 97 (67%) of cases, with the majority (79%) excised with clear margins of greater than 2 mm. Seventy-six patients (70%) had undergone neck dissections and had been pathologically staged as N0.

Of the 109 cases that had both TT and DOI parameters reported, there were 58 cases (53%) where TT and DOI were assigned identical values (n = 37) or were assigned values that differed by less than 0.1 mm (n = 21). Fifty-one (47%) cases had TT and DOI values

Table I. Patient, tumor, and treatment characteristics of the study cohort

Characteristics	*Both TT and DOI reported (Total = 109)*	*(%)*
Sex		
Male	64	59%
Female	45	41%
Age (median = 64; range 25−89)		
<30	2	2%
30−49	24	22%
50−69	46	42%
70−79	27	25%
>80	10	9%
Tumor pathology		
T stage		
≤2 cm	73	67%
>2 cm but <4 cm	36	33%
Primary excision margin status		
Clear (≥2 mm)	86	79%
Close (<2 mm)	22	20%
Involved	1	1%
Perineural invasion at primary site		
Not identified	71	65%
Present	36	33%
Did not specify	2	2%
Lymphovascular invasion seen in primary excision specimen		
Not identified	98	90%
Present	8	7%
Did not specify	3	3%
N stage		
Nx (No ipsilateral neck dissection)	5	5%
N0	76	70%
N1	17	16%
N2	11	10%
Extracapsular extension seen in neck dissection specimen		
Not identified	27	25%
Present	11	10%
N/A (no neck dissection or no nodal involvement on neck dissection)	71	65%

DOI, depth of invasion; *TT*, tumor thickness.

that differed by greater than 0.1 mm. The majority had been assigned TT values larger than those of DOI, with only 10 cases assigned DOI values larger than those of TT, where most of these tumors were described as being ulcerated. The median difference between TT and DOI was 0.5 mm (range 0−20 mm), and the average difference was 1.7 mm. On logistic regression analyses, both DOI ($P = .00036$) and TT ($P = .0001$) were highly correlated with risk of nodal disease and with each other ($P < .001$) (Figure 1).

Cutoff points for DOI and TT that predicted for nodal disease

A value of 4.5 mm was identified as the most optimal cutoff point for DOI that predicted for a higher risk of regional nodal disease. This cutoff point would yield a NPV of 88% (positive predictive value [PPV] of 55%). For TT, the ideal cut-point was determined to be 8 mm, with a NPV of 75% (PPV of 66%).

Comparison of 4 mm versus 5 mm as the threshold cutoff point to guide elective nodal treatment

Of the 51 cases (47%) where DOI and TT differed by greater than 0.1 mm, 9 cases had both TT and DOI parameters less than 4 mm, and 34 had both TT and DOI of 4 mm or greater (Figure 2). The 2 parameters straddled the 4-mm cutoff in 8 cases (17%), and these cases were excluded from this analysis to avoid ambiguity around these measures. If a 4-mm cutoff for either TT or DOI was used to guide elective nodal treatment, the rate of undertreatment would have been 11% (1 of 9). The rate of over treatment would have been 47% (16 of 34).

If the above analysis were repeated based on a 5-mm threshold for either TT or DOI, the rate of under treatment would have been 19% and the rate of overtreatment would have been 49% (Figure 3).

DISCUSSION

Our study has reinforced the findings from previous studies indicating that both TT and DOI are highly correlated with the risk of regional nodal disease and with each other.[1-5] Importantly, it has highlighted that TT and DOI need to be recognized as 2 discrete entities and that the 2 terms should not be used interchangeably. These parameters should be measured and reported in a manner that ensures consistency and quality. Adherence to guidelines, such as those recommended by the 8th edition of the AJCC manual and the recent publication by Lydiatt et al., is crucial for consistent and quality reporting of primary OTSCC specimens, particularly given the prognostic and clinical management implications of DOI.[6,7]

Although DOI, based on its prognostic value on overall disease outcomes, has been incorporated into the current AJCC staging system such that it upstages an OTSCC from T1 to T2 stage if DOI is greater than 5 mm, the question of whether a DOI threshold of 5 mm should also be used to guide clinical decisions regarding elective nodal treatment is of importance. With regard to cut-point calculation using our data set, the DOI cut-point was identified as the ideal cutoff point that predicts for regional nodal disease. The 55% PPV of this DOI cut-point of 4.5 mm and its 88% NPV, in our opinion, provide superior clinical utility compared with the cut-point for TT, which had a lower

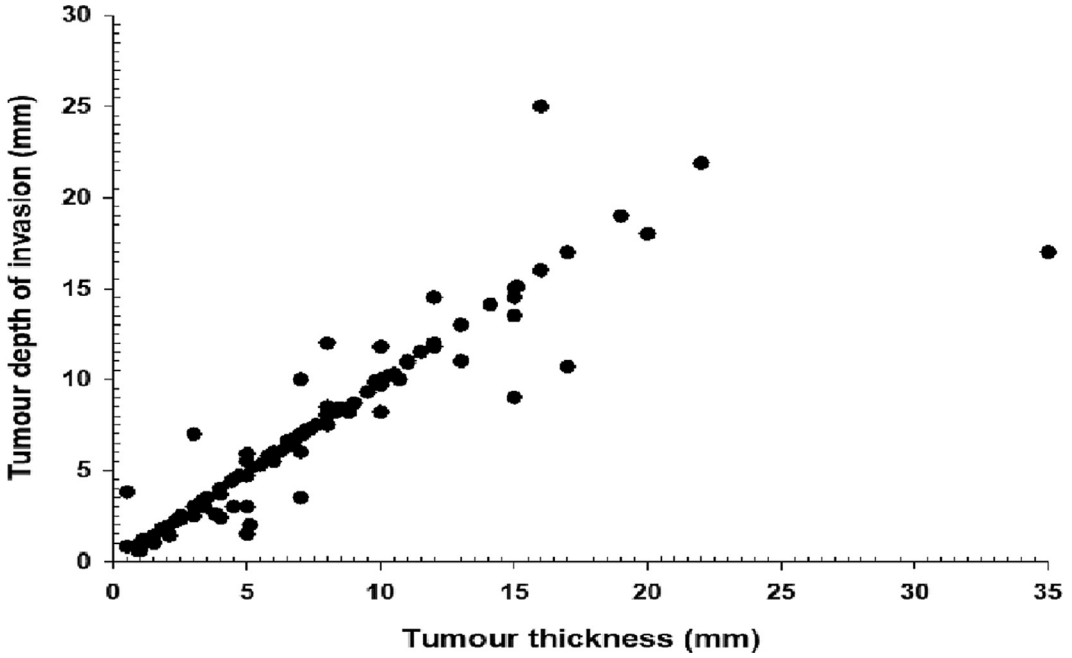

Fig. 1. Correlation of depth of invasion (DOI) with tumor thickness (TT).

NPV. Considering this, we have chosen to employ the DOI threshold (rather than the TT threshold) to guide our future clinical decision making regarding elective nodal treatment.

Undertreatment of the regional nodal basin as a result of inaccurate assessment of local invasion at the primary site may lead to subsequent regional nodal failure and impact survival outcomes. Similarly, overtreatment of the regional nodal basin places patients at risk of increased treatment-related morbidity. On the basis of a previously published series by Veness et al., our service has been employing a 5-mm threshold to guide elective neck dissections in the clinically node negative neck.[10] Similarly, other groups have used a 4-mm threshold, based on their own series data, to guide their clinical decisions regarding elective nodal treatment.[9] It is acknowledged that in many of these series, the term TT was used to describe what likely was a measure of tumor DOI. Terminology notwithstanding, it is reassuring that the present study demonstrated little difference between the 4-mm and 5-mm threshold values for DOI in the modeled rates of overtreatment and undertreatment of the regional neck nodes.

Previous studies have reported that DOI and TT perform similarly in terms of their utility in prognostication and use in current staging.[4,14] However, these findings

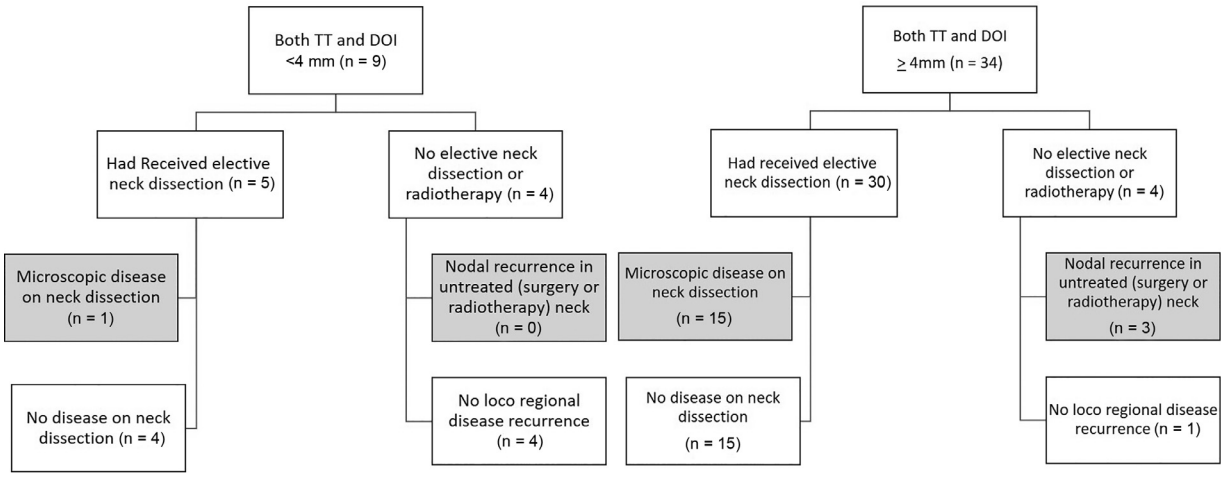

Fig. 2. Patterns of nodal disease if using primary site DOI 4 mm as threshold.

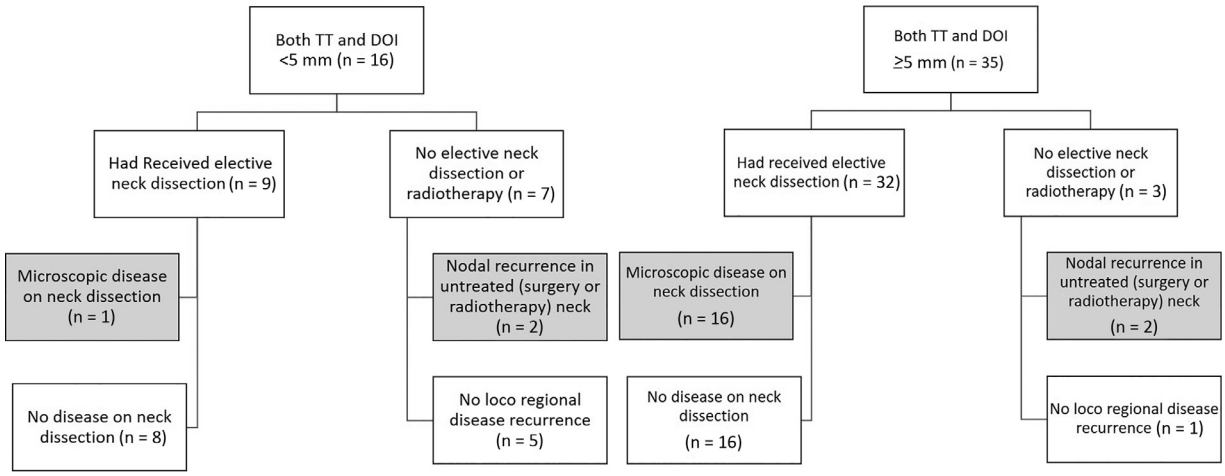

Fig. 3. Patterns of nodal disease if using primary site DOI 5 mm as threshold.

cannot be directly extrapolated to guide clinical decisions regarding the management of the clinically N0 neck. The decision to proceed with elective nodal dissection is often a clinical decision that is made at the time of initial clinical assessment of the primary OTSCC. The histopathologic assessment of DOI after surgical excision may lead to a subsequent staged neck dissection or radiation therapy, but this scenario is less common. This raises the question as to whether a difference in DOI up to 1 mm is clinically detectable in those preoperative scenarios of clinical decision making regarding elective nodal treatment and whether small discrepancies in histopathologic assessment of DOI are relevant in decision making regarding subsequent staged elective nodal treatment. Our data suggest that the impact of small discrepancies (up to 1 mm) in the estimation of DOI would not be expected to significantly impact on regional nodal failure.

Although elective nodal dissection has been shown to improve both overall and disease-free survival in patients with early oral cavity cancer, it is acknowledged that it carries significant morbidity and cost.[15] Sentinel lymph node biopsy (SLNB) offers a way to meticulously conduct a detailed examination of the most appropriate lymph node for a particular oral cavity cancer while avoiding the morbidity and cost of a neck dissection.[16] Given this, SLNB for oral cavity cancers has been incorporated into the UK and the National Comprehensive Cancer Network guidelines on the management of these cancers.[17,18] We have published a report of our own experience in the technique and have confirmed that SLNB for the treatment of oral cavity cancers is feasible and, if done properly, is reliable, with a low false-negative rate.[19] There is future potential for the use of SLNB in combination with the DOI threshold cut-point identified in this study to improve the rates of overtreatment and undertreatment of the clinically N0 neck.

The limitations of this study include its use of retrospective data, although much of the data were prospectively collected and maintained. Thus, the possible inherent biases associated with this study design warrant consideration. There were no measures in place for standardized reporting of histopathologic specimens during the whole period of treatment of the patients included in this study. We acknowledge that there may have been interobserver and possibly intraobserver variabilities in terms of histopathology reporting and quantification of the DOI/TT values used in this study. Nevertheless, this study has been able to highlight the ambiguity that has existed in the assessment and reporting of tumor DOI/TT in OTSCC and has yielded useful insights that may guide future local practice. We also acknowledge that ideally, the DOI cut-point identified in this study should be validated in a future collaborative effort on an independent data set, given that the minimum *P*-value method used in this study is data driven. Another limitation of this study is that it did not address some variables, such as growth pattern or host response (presence of inflammatory cells), given the inconsistencies in data collection around these variables, particularly in the early period of this study. We recognize that it would be important to include these other tumor-related variables in any future predictive models.

CONCLUSIONS

This study has demonstrated the need for clarity around the use of the terms *tumor DOI* and *TT* in OTSCC as well as the importance of adhering to published guidelines on the measurement and reporting of these parameters such that outcomes arising from their use in clinical decision making may be monitored meaningfully. The 5-mm DOI cut-point identified in this study was superior to the TT cut-point. In addition to its

prognostic utility (as in the 8th edition of the AJCC manual for T staging), this DOI cut-point has utility in guiding decisions regarding elective nodal treatment.

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