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Understanding approaches to measurement and impact of depth of invasion of oral cavity cancers: A survey of American Head and Neck Society Membership

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ABSTRACT

Objectives: To investigate methods used by head and neck surgeons to pre-operatively measure depth of invasion (DOI) in light of the new staging for oral cavity squamous cell carcinoma (OCSCC).

Materials and methods: A survey was designed and sent to all American Head and Neck Society (AHNS) members via an email link. The last response was recorded on January 16, 2019.

Results: We received 185 (13.3%) responses from 184 surgeons and 1 radiation oncologist. The majority of surgeons correctly identified DOI (78.9%) and indicated measuring DOI pre-operatively (86%). The most common methods for measuring DOI were manual palpation (32.5%) and full thickness biopsy (25.2%). In addition, most surgeons (84.7%) reported using a DOI threshold (in mm) as their primary criterion in their decision to pursue a neck dissection in the N0 neck. The most common reported threshold was 4 mm (37.4% of those that reported using DOI), however, the range varied from 2 to > 10 mm. Two-thirds of surgeons considered DOI an important indicator for adjuvant therapy.

Conclusion: DOI is believed to be an important prognostic indicator guiding neck dissection and the need for adjuvant therapy. While most surgeons currently measure DOI pre-operatively, most use subjective methods. Future studies are needed to establish objective pre-operative DOI measurement techniques and to better inform the decision to perform prophylactic neck dissection, given the current majority practice of prophylactic neck dissection for DOI of 4 mm or greater.

Introduction

Oral cavity squamous cell carcinoma (OCSCC) constitutes about one-third of all head and neck cancers [1]. OCSCC is primarily managed with surgical resection of the primary tumor augmented with a neck dissection and adjuvant therapy depending on pathologic findings. The decision to pursue a neck dissection or adjuvant therapy depends on several factors including tumor stage, histopathologic features, and patient preference. Although pre-operative clinical staging plays an important role in guiding treatment, imaging and clinical examination are limited in their ability to predict the presence of occult lymph node (LN) metastasis and the need for neck dissection [2–6]. Despite a clinically negative neck, occult LN metastases have been reported in up to 42% of T1/2N0 OCSCC patients [7]. As a result, many studies have explored other pre-operative variables which may better predict occult nodal disease and oncologic outcomes. Tumor thickness (TT) and depth of invasion (DOI) are two such factors that have consistently been associated with occult nodal metastasis and survival [8].

In light of this research, the American Joint Committee on Cancer (AJCC) has included DOI as a clinical and pathologic T-staging parameter in its most recent iteration of the TNM staging manual (8th edition) [9,10]. While accurate DOI measures can easily be obtained post-operatively using standard histopathology, methods of measuring DOI pre-operatively for clinical T-staging are not as clear. In particular, the pre-operative evaluation must not confuse DOI and TT. There is a tendency in the field to use the terms DOI and TT interchangeably

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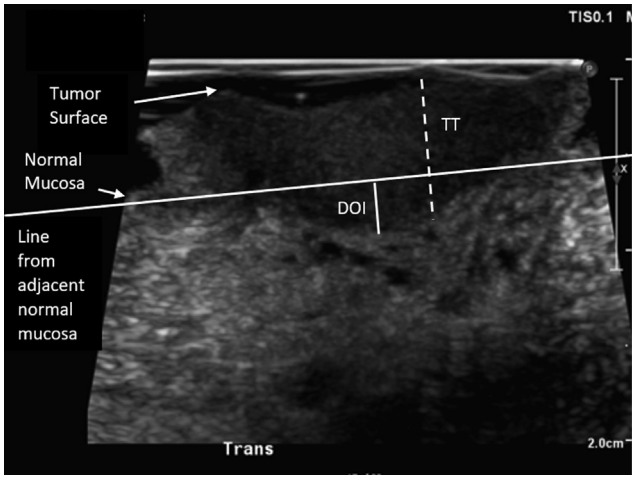

Fig. 1. Ultrasonographic image of an exophytic oral tongue tumor showing the discrepancy between DOI (vertical solid line) and TT (vertical dashed line). A DOI of 2 mm and TT of 6 mm was reported on final pathology.

despite them being distinct pathologic measures [8,11]. DOI is the distance from the basement membrane of adjacent normal mucosa to the deepest point of invasion of the tumor. TT on the other hand is the distance from the mucosal surface of the tumor to the deepest point of invasion (Fig. 1) [12]. TT is therefore greater than DOI when tumor is exophytic, however, DOI may be greater with ulcerative tumors. DOI was recently assessed in a large multicenter retrospective study which found that DOI predicts disease specific survival (DSS) and addition to the T-staging complements its prognostic ability [6]. More importantly, the most reliable method of pre-operative clinical and radiologic modalities for assessing DOI is still an area of continued debate. Manual palpation, ultrasound, MRI, CT and biopsies have all been identified in the literature as approaches to measuring DOI or TT pre-operatively [8,11,13].

To understand how the head and neck surgical community has adopted and integrated this new addition to the cTNM staging system, we performed a survey of the American Head and Neck Society (AHNS) membership. This survey primarily focused on understanding how surgeons define DOI in their clinical practice and how they approach measuring DOI preoperatively in OCSCC patients that present to them for treatment.

Materials and methods

We designed a web-based survey with a total of 24 questions investigating the approach of surgeons to DOI and margin assessment. The survey was distributed via an email link to AHNS members after review and approval by the AHNS Research Committee. Ten questions were concerned with DOI and 14 questions were concerned with margin assessment. In this study, we report only the results of the questions pertaining to DOI. The DOI questions focused on five domains: definition of DOI, current methods of DOI measurement, future methods of DOI measurement, determinants of neck dissection in the N0 neck and the effect of DOI on treatment. Descriptive statistics were used to define the study population (Microsoft Excel 2016).

Results

The survey was sent to 1392 AHNS members. One hundred eighty-five (13.3%) members responded by the final access date, February 12, 2019. Respondents consisted of 166 attending surgeons, 9 fellows, 9 residents and 1 radiation oncologist.

Definition of DOI

One hundred forty-six (78.9%) respondents correctly identified DOI, whereas 34 (18.4%) confused TT for DOI. Five (2.7%) members indicated that they did not believe that the difference between the two definitions was meaningful (Fig. 2).

Pre-operative assessment of DOI

One hundred fifty-nine (86%) respondents indicated that they measure DOI pre-operatively. The most common method to measure DOI (Fig. 3) was manual palpation (32.5%) followed by full thickness biopsy (FTB, 25.2%). Respondents who chose “other” reported using multiple modalities. Amongst respondents that reported a practice of DOI measurement, rates of implementing this practice varied based on tumor subsite (Fig. 4).

Criteria for neck dissection of the N0 neck

Seventeen (9.3%) respondents reported that they perform neck dissections on all patients with OCSCC, 11 (6%) reported using sentinel lymph node biopsy (SLNB) to identify cases that needed it and 155 (84.7%) indicated that they used a DOI threshold or other criteria to

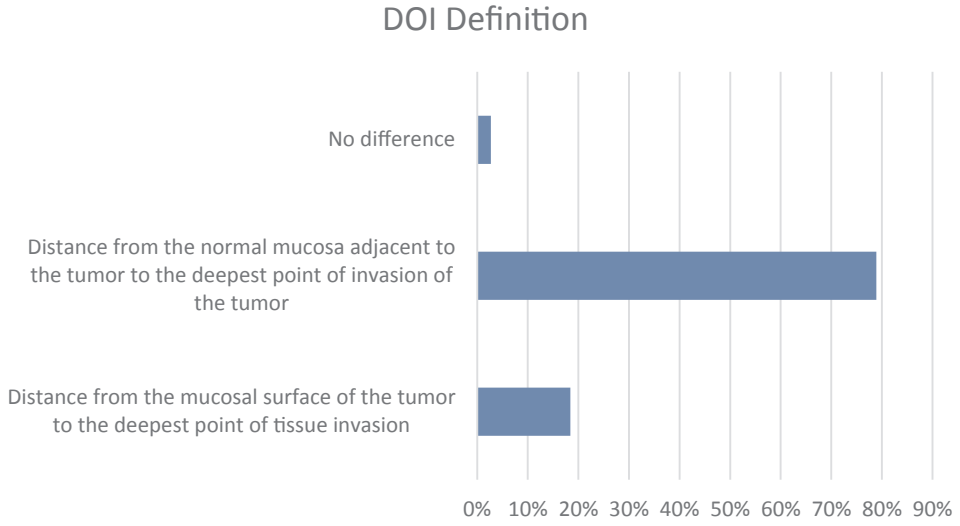

Fig. 2. Bar graph showing response to question: *How do you define DOI?*

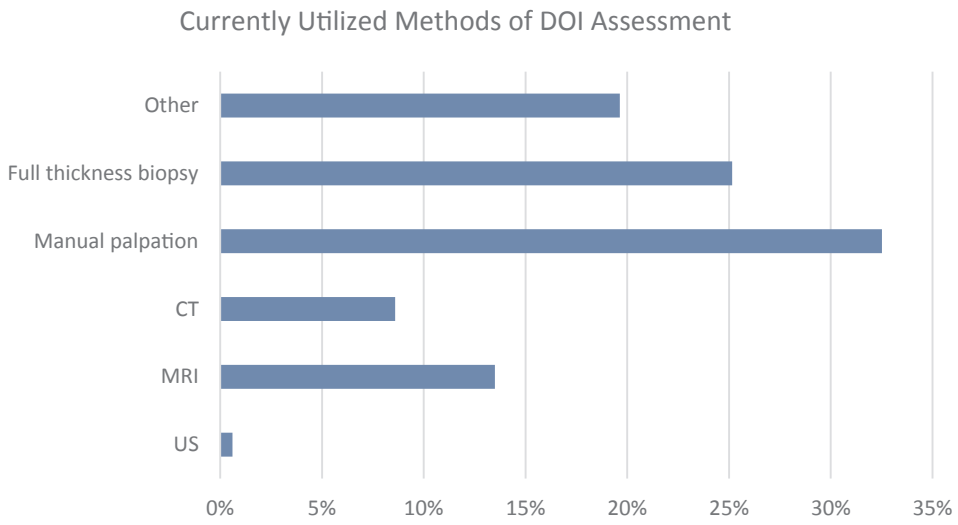

Fig. 3. Bar graph showing response to question: H*ow do you assess the depth of invasion pre-operatively?*

guide neck dissection decision. Of the latter group, 134 (86.5%) reported using a single DOI threshold to determine the need for neck dissection, while 21 (13.5%) reported using other criteria including T-stage, different DOI thresholds depending on subsite (threshold for floor of mouth lesions was reported to be lower than the tongue) or other histopathological features (grade, muscle invasion, etc.). The most commonly reported DOI threshold was 4 mm, however the range varied from 2 to > 10 mm (Fig. 5).

Future trends in pre-operative DOI assessment

When asked about considering measuring DOI in light of the new staging system, 38.5% of those who do not currently measure DOI pre-operatively indicated willingness to measure DOI pre-operatively. The most commonly proposed method was FTB (32.7%) as a sole measurement tool followed by manual palpation (23.8%) (Fig. 6). Again, those who chose "other" reported using multiple modalities. Reasons reported for the low dependence on imaging included no accurate modality available (most common response) and limited utility (Fig. 7). Most of those saying "other" indicated that FTB is better and more reliable approach.

Effect of DOI on treatment

Two-thirds of respondents believed that DOI > 1.0 cm (T3 as per the new staging) warrants adjuvant therapy even in the absence of any other adverse feature. Of those, one hundred eleven (91%) thought that radiotherapy would be sufficient, while 11 (9%) thought there may be a need for chemoradiation.

Discussion

In our survey of AHNS membership we report current practice and attitudes towards DOI measurements and how they impact surgical practice in light of the changes made to the AJCC staging criteria for OCSCC. While most respondents identified DOI correctly, a small proportion still uses DOI interchangeably with TT or do not believe that the difference is clinically meaningful. While this may certainly be true for select cases, measuring TT rather than DOI can lead to incorrect T-staging under the new criteria and inappropriate changes to treatment plans (using TT can lead to upstaging of exophytic tumors or downstaging of ulcerative tumors and thus overtreatment or undertreatment, respectively). Furthermore, Kane et al reported that DOI not TT is the

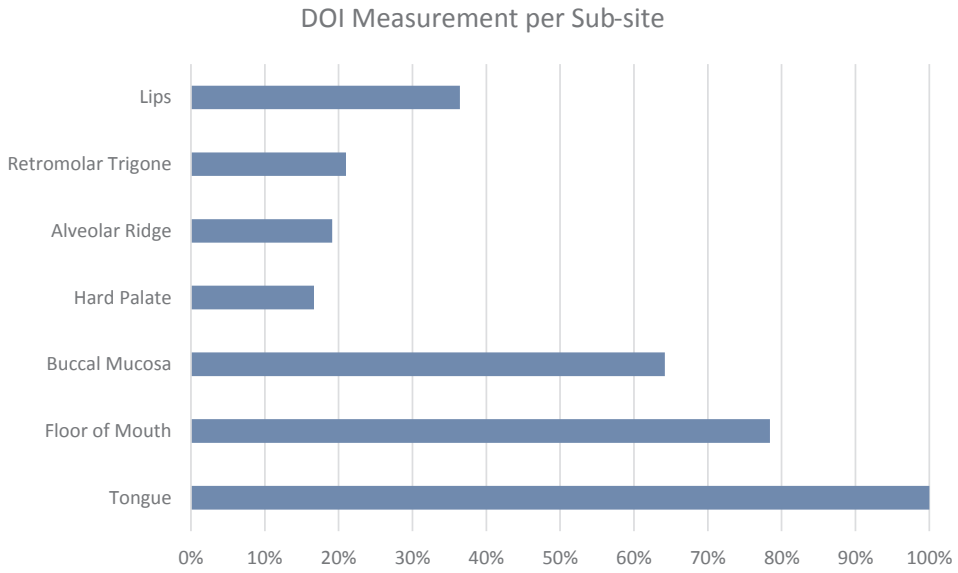

Fig. 4. Bar graph showing response to question: *For what oral sub-sites do you assess DOI? (Check all that apply).*

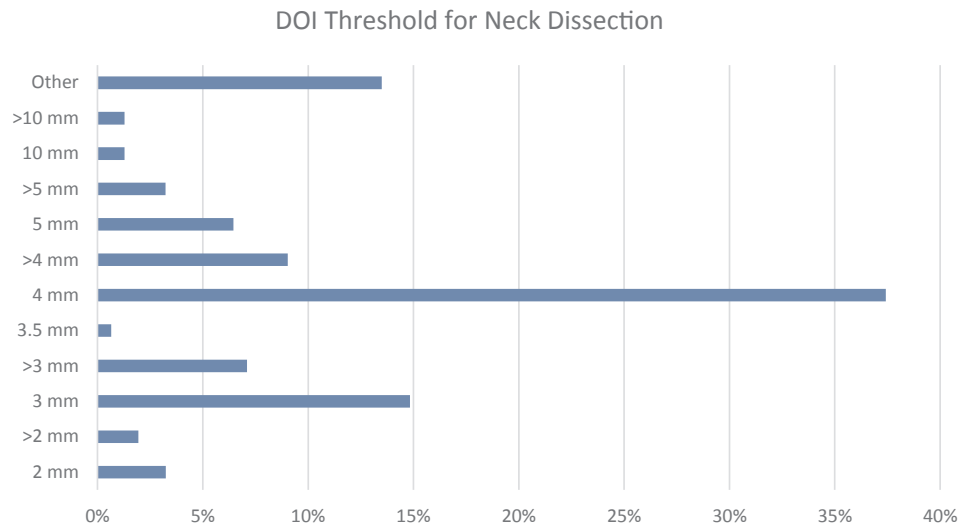

Fig. 5. Bar graph showing the DOI thresholds (mm) for neck dissection. This is the subset of respondents that chose "DOI of (please type the DOI in mm) or other criteria you use" in the question: *How do you determine when to do a neck dissection of the N0 neck?*

only predictor of cervical LN metastasis [14].

Most respondents indicated using manual palpation or FTB as the sole measurement technique to assess DOI pre-operatively. These findings highlight the lack of a consensus in the field regarding the most reliable approach to preoperative DOI measurements for clinical staging. A large portion of surgeons reported using manual palpation as their primary method of DOI measurement. Although manual palpation might be subjective, Alsaffar et al showed that measurements of DOI by manual palpation correlate well with histopathologic and MRI measurements in oral tongue carcinoma ($r = 0.78$; $p < 0.001$ and $r = 0.731$; $p < 0.001$, respectively). The correlation holds only when tumors are ≥ 5 mm but not for tumors < 5 mm. However, there was no measurement of inter-rater reliability between surgeons; this should be incorporated in future studies to investigate how subjective manual palpation is [13]. The second most commonly used method for assessing DOI among respondents was FTB. While FTB is a more objective measure, only TT, not DOI, can be acquired using this method as there is usually no surrounding mucosa to use as a reference point for the measurement. Furthermore, de Visscher et al. [15] reported that FTB can predict TT accurately only for lesions < 3 mm thick, limiting its ability to stage a large portion of OCSCC. Therefore, only FTB that includes excision to the depth of the center of the lesion with a margin of surrounding normal tissue can provide what is needed to determine DOI preoperatively; such an extensive preoperative biopsy may be impractical in many cases.

The literature pertaining to clinical DOI measurement suggests that radiographic tools provide the most promise for accurate clinical measurements of DOI. Studies correlating DOI or TT on imaging to histologic DOI or TT report strong correlations between radiographic and histologic measurements [16]. US appears to be particularly useful and correlates more closely with histologic measures than MRI or CT [17]. Furthermore, neither MRI nor CT can detect lesions with TT $<$ 5 mm [17]. In a recent meta-analysis, pre-operative TT measurements on US were highly correlated with final pathologic TT measurements ($r = 0.95$) [11]. Although most of the included studies in this meta-analysis measured TT, we can still make an inference that US can be used for accurate measurement of DOI.

When asked about the criteria used to determine the need for neck dissection in the N0 neck, the majority of respondents indicated that DOI is the only parameter they use to make their decision. We observed a wide variety of DOI thresholds as indications for neck dissection in the responses ranging from 2 to > 10 mm. The most common response for DOI threshold value was 4 mm. This threshold is likely derived from a number of retrospective studies [18,19] and a meta-analysis which

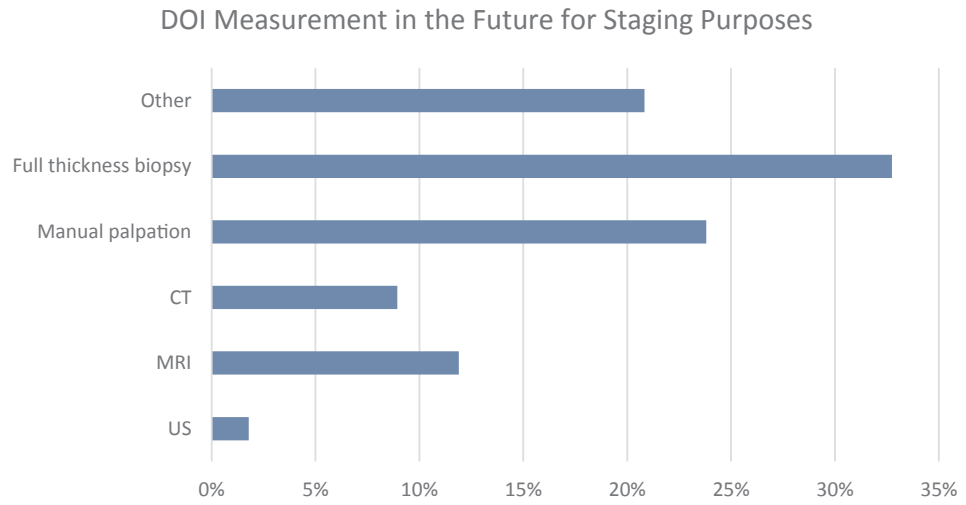

Fig. 6. Bar graph showing response to question: *How do you plan on obtaining DOI measures for staging/neck dissection purposes (given the updated T-staging)?*

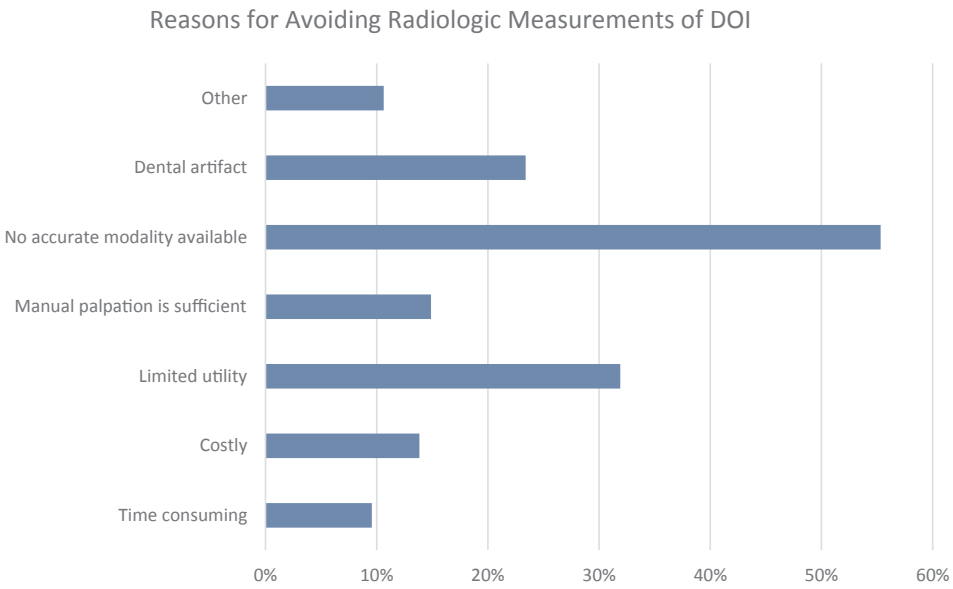

Fig. 7. Bar graph showing the response to question: *If you do not use any radiologic assessment of DOI pre-operatively, please specify the reason. (Check all that apply).*

combined a number of studies and found 4 mm to be the optimal DOI threshold for neck dissection [20]. This was reaffirmed by the D'Cruz et al. trial [21], where in post hoc subgroup analysis they showed that a DOI of 4 mm increased positive LN rate from 5.6% to 16.9% as compared to a DOI of 3 mm. Interestingly, the goal of that study was to compare patients with clinically N0 necks receiving elective neck dissection (END) to those receiving a therapeutic neck dissection and the recommendation based on the study results was to perform END for all patients with OCSCC and N0 necks as END improves survival [21]. Despite the robust evidence the trial provides for performing END, only a small portion of respondents to our survey indicated doing END for all OCSCC patients. The large variety in DOI thresholds observed in the responses is probably due to studies in the literature exploring associations between DOI and TT thresholds and occult lymph node metastasis and subsequently recommending thresholds above which neck dissections should be performed [8]. Unfortunately, many of these studies suffer from the following limitations: (1) TT and DOI are used interchangeably [22]; (2) no mention of how TT or DOI were measured [23,3,24]; and (3) the retrospective design of these studies limiting their ability to make clinical recommendations. SLNB use was reported by a minority of respondents although studies have shown accuracy of this technique [25–27] and it is now one of the options in the NCCN guidelines [28].

When asked about the need for adjuvant therapy for patients with DOI $>$ 10 mm (T3 per the AJCC TNM 8) in the absence of any other adverse features, around two-thirds of the respondents agreed that this warranted adjuvant therapy probably because this upstages a tumor to T3 with the majority considering only adjuvant radiation. However, a recent study by Ebrahimi et al concluded that patients with no other adverse features (defined as margin $<$ 5 mm and/or positive nodes) but with DOI $\geq$ 10 mm had equal locoregional and disease specific survival to patients with DOI $<$ 10 mm even in the group without adjuvant therapy. Nevertheless, there was no data on perineural invasion, lymphovascular invasion or tumor grade which might limit the interpretation of the results [29].

The results of our study confirm the need for more systematic multicenter prospective studies investigating the most accurate pre-operative modality for measuring DOI given the importance of DOI as a threshold for neck dissection and the importance of adjuvant therapy in tumors with high DOI in the absence of any other adverse feature.

Limitations of our study include but are not limited to: (1) cross-sectional design allowing assessment in a single point in time only; (2) acceptable but low response rate; (3) survey based data which lacks objective information; (4) lack of data on respondent demographics; and (5) selection bias (those that responded tend to be more academic or interested in latest literature).

Conclusion

TT and DOI have been reported to be important predictors of survival and occult LN metastasis. While they are still used interchangeably, it is important to recognize the difference and increase the awareness given the need to rely on DOI for staging purposes and because the subtle differences between the two can affect treatment decisions for individual patients. DOI can be measured pre-operatively with a number of tools, most accurately by radiologic imaging as evidenced by the high correlation between radiologic DOI (namely by US) and histologic DOI. Although the correlation is very strong, based on the results of this survey, there may be underutilization of radiologic approaches. Most surgeons polled felt tumors with $>$ 10 mm of DOI, widely clear margins and no other adverse features warrant adjuvant therapy. In light of the new staging system, these specific pathologic criteria need to be evaluated prospectively to determine their individual impact.

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Declaration of Competing Interest

None declared.

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