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The role of ultrasound, MRI, and CT imaging in the assessment of the depth of invasion (DOI) in oral tongue squamous cell carcinoma (OTSCC) and its clinical implications

Rola badań obrazowych (USG, MRI, CT) w ocenie głębokości naciekania (DOI) raka płaskonabłonkowego części ustnej języka (OTSCC) i implikacje kliniczne

Authors' Contribution:
A – Study Design
B – Data Collection
C – Statistical Analysis
D – Data Interpretation
E – Manuscript Preparation
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ABSTRACT:

Introduction: Oral tongue squamous cell carcinoma (OTSCC) presents a diagnostic and therapeutic challenge. The eighth edition of the AJCC/UICC guidelines on the TNM staging system introduced the depth of invasion (DOI) as an independent prognostic factor determining the risk of occult metastases and disease-specific survival (DSS). As of the present, no standardized imaging modality has been established for preoperative DOI measurement.

Aim: The aim of this review article is to identify the optimal imaging modality for measuring depth of invasion, used to determine tumor stage, define the deep resection margin, and guide decisions regarding the need for neck dissection and further therapeutic options, whose standardized implementation could improve prognosis in patients with squamous cell carcinoma of the oral tongue.

Materials and methods: The review is based on scientific articles available from the PubMed database.

Results: A total of 20 papers were returned as a result of the database query.

Conclusions: Intraoral ultrasound (IOUS), magnetic resonance imaging (MRI), and computed tomography (CT) remain the three complementary imaging modalities for the assessment of the depth of invasion in cases of oral tongue squamous cell carcinoma. While MRI and CT scans are recommended for the evaluation of the primary focus and neck structures, recent scientific studies point to intraoral ultrasound as an increasingly important alternative, especially in early T1–T2 N0 stages of OTSCC, shallow lesions confined to the mucosa and having the DOI of < 5 mm, and micrometastases smaller than 3 mm, as well as with regard to the determination of deep resection margins and real-time determination of the resection boundary between the tumor and the healthy tissue. IOUS facilitates effective determination of the clinical stage and the deep resection margin, as well as contributes to the decision-making regarding elective neck dissection. Standardized use of IOUS, as well as standardization of the other imaging modalities, might contribute to a reduction in the extent of resections with simultaneous reduction in the number of R1 resections, translating to a reduced need for resurgeries and adjuvant therapies, better prognosis, and longer recurrence-free survival.

KEYWORDS: AJCC/UICC, CT, deep resection margin, DOI, elective neck dissection, MRI, oral tongue squamous cell carcinoma, OTSCC, depth of invasion, ultrasound

STRESZCZENIE:

Wstęp: Rak płaskonabłonkowy części ustnej języka (OTSCC) stanowi wyzwanie diagnostyczne i terapeutyczne. Zaimplementowana przez AJCC/UICC ósma wersja wytycznych wprowadziła do określania stopnia zaawansowania OTSCC głębokość naciekania (DOI) jako niezależny czynnik rokowniczy, warunkujący ryzyko ukrytych przerzutów i przeżycie specyficzne dla choroby. Obecnie brakuje wystandaryzowanej metody obrazowania do przedoperacyjnego pomiaru DOI.

Cel: Celem niniejszego artykułu przeglądowego jest znalezienie optymalnej metody obrazowania do pomiaru głębokości naciekania, wykorzystywanej do określania stopnia zaawansowania nowotworu, wytyczania marginesu głębokiego resekcji

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oraz podejmowania decyzji o potrzebie operacji węzłowej szyi i dalszych opcjach terapeutycznych, której wystandaryzowana implementacja mogłaby wpłynąć na poprawę rokowania u pacjentów z rakiem płaskonabłonkowym części ustnej języka.

Materiały i metody: Podstawę opracowania stanowią artykuły naukowe bazy PubMed.

Wyniki: Łącznie 20 publikacji spełniło kryteria wyszukiwania.

Wnioski: Trzy metody obrazowania: ultrasonografia przezustna (ioUSG), obrazowane metodą rezonansu magnetycznego (MRI) oraz tomografia komputerowa (CT) pozostają komplementarne w ocenie głębokości naciekania raka płaskonabłonkowego części ustnej języka. Chociaż MRI i CT są zalecane do obrazowania ogniska pierwotnego i szyi, najnowsze badania naukowe dowodzą, że szczególnie we wczesnych T1–T2 N0 stadiach OTSCC, w przypadku płytkich zmian ograniczonych do błony śluzowej o DOI <5 mm, mikrometastaz mniejszych niż 3 mm, wyznaczania marginesu głębokiego resekcji i granicy resekcji między guzem a zdrową tkanką w czasie rzeczywistym, ioUSG jest zyskującą na znaczeniu alternatywą. Skutecznie określa ona stopień zaawansowania klinicznego, margines głęboki resekcji oraz ułatwia podjęcie decyzji o elektywnej dyssekcji szyi. Wystandaryzowana implementacja ioUSG i standaryzacja pozostałych metod może przyczynić się do ograniczenia rozległości resekcji, przy jednoczesnym zmniejszeniu liczby resekcji R1, a co za tym idzie uniknięcia reoperacji, konieczności terapii adjuwantowej oraz lepszego rokowania i dłuższego przeżycia bez nawrotu choroby.

SŁOWA KLUCZOWE: AJCC/UICC, CT, DOI, elektywna dyssekcja szyi, głębokość naciekania, margines głęboki resekcji, MRI, OTSCC, rak płaskonabłonkowy części ustnej języka, USG

ABBREVIATIONS

ADC – apparent diffusion coefficient
AJCC – American Joint Committee on Cancer
CT – computed tomography
DFS – disease-free survival
DOI – depth of invasion
DSS – disease-specific survival
DWI – diffusion weighted imaging
e-THRIVE – enhanced T1 high resolution isotropic volume excitation
IOUS – intraoral ultrasound
LRFS – local recurrence-free survival
MAR – metallic artifact reduction
ML – machine learning
MRI – magnetic resonance imaging
NCCN – National Comprehensive Cancer Network
OS – overall survival
OTSCC – oral tongue squamous cell carcinoma
SII – subtraction iodine imaging
TNM – the TNM cancer staging system
TT – tumor thickness
UICC – Union for International Cancer Control
US – ultrasound

INTRODUCTION

Oral squamous cell carcinoma is one of the most common cancers of the head and neck region, the oral part of the tongue being its most common location [1].

The tongue is a small yet functionally important organ, responsible for speech, swallowing, intake of food, and protection of the respiratory tract, among others. When performing the resection of oral tongue squamous cell carcinoma (OTSCC), it is important that the radical removal of the tumor with an adequate negative margin be balanced against the maximum possible preservation of the function of the portion of the organ not affected by the disease [2].

The TNM staging system, as introduced by the American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control (UICC), is a widespread and widely accepted tool used to describe the extent of the disease and, above all, to estimate the prognosis of patients with cancer on the basis of the anatomical characteristics of the tumor. Until 2018, the T component had been traditionally determined on the basis of the superficial dimensions of the tumor. The eighth edition of the AJCC/UICC guidelines introduced the depth of invasion (DOI) as the third dimension taken into consideration in the determination of the T component and an independent prognostic factor determining the risk of occult metastases and disease-specific survival (DSS) [3].

DOI is a histopathological variable measured perpendicularly from the level of the hypothetical line running through the basal lamina of the mucosa adjacent to the tumor to the deepest point of tumor infiltration. Unlike DOI, the previously used parameter of tumor thickness (TT) was measured from the surface of the tumor to the deepest point of tumor infiltration. In practice, this means that the DOI measurement includes the concave parts of endophytic tumors while disregarding the convex parts of exophytic tumors. Compared to DOI, TT is therefore increased by the convex portion and decreased by the concave portion of the lesion [1, 2].

As of the present, no standardized imaging modality has been established for preoperative DOI measurement [4, 5].

AIM

The aim of this review article is to identify the optimal imaging modality for measuring depth of invasion, used to determine tumor stage, define the deep resection margin, and guide decisions regarding the need for neck dissection and further therapeutic options, whose standardized implementation could

improve prognosis in patients with squamous cell carcinoma of the oral tongue.

MATERIAL AND METHODS

A query of the PubMed database using the keywords "*ultrasound*", "*depth*", and "*tongue cancer*" returned a total of 25 results, including 18 full-text articles available in the open access model and related to the subject matter of this review. The subsequent queries using the keyword sets of "*mri*", "*depth*", and "*tongue cancer*" as well as "*ct*", "*depth*", and "*tongue cancer*" returned a total of 19 and 6 results, respectively, including 2 non-duplicate papers related to the subject matter of this review. All papers were published in the period of 2016 through 2023.

RESULTS

A total of 20 papers met the criteria of the database query; these included 4 prospective studies, 15 retrospective studies, and 1 case series. Ultrasound imaging alone was used in 3 studies, US/MRI were used in 2 studies, and US/MRI/CT were used in 1 study. MRI alone was used in 13 studies, while CT alone was used in 1 study. Four articles were published before the latest version of the AJCC/UICC guidelines.

CLINICAL IMPLICATIONS OF DOI MEASUREMENTS

The gold standard of treatment for oral tongue cancer consists of complete resection of the primary focus with adequate margins and neck dissection based on the status of lymph nodes and the risk factors for occult nodal metastases [6].

Depth of invasion *vs.* TNM staging

According to the AJCC/UICC guidelines, the DOI values determine the division of the T parameter into T1 for lesions with DOI of ≤ 5 mm, T2 for lesions with DOI of > 5 mm and ≤10 mm, and T3 for lesions with DOI of > 10 mm, with each 5-mm increment in DOI increasing the T parameter by one [3].

Depth of invasion *vs.* deep resection margin

Palpation remains the main technique for determining the resection margin and the boundary between the tumor and healthy tissue, although its accuracy in this regard is limited [2]. In oral cancers, the negative resection margin is 1 cm macroscopically and 0.5 cm microscopically [2, 6]. R0 resection on intraoperative histopathology is crucial, as an R1 resection, even when subsequently revised to R0, results in a 2.5-fold reduction in local recurrence-free survival (LRFS). Tongue cancers are third to ovarian and prostate cancers in terms of the percentage of positive margins. According to the literature, positive margins are detected in up to 23% of oral and pharyngeal cancer resections; of these, deep margins account for 87% of cases [6].

Depth of invasion vs. elective neck dissection

Cervical lymph node metastasis is the most important prognostic factor in OTSCC [7], and nodal recurrence is the most common cause of surgical failure [5]. The decision regarding elective nodal neck surgery is based on preoperative clinical and radiological evaluation of tumor size and depth of invasion, as well as the risk factors for occult nodal metastases. The National Comprehensive Cancer Network (NCCN) guidelines recommend elective neck dissection for DOI ≥ 4 mm [5] as this is the value at which the risk of occult nodal metastasis of early-stage oral squamous cell carcinoma (pT1/pT2) exceeds 20% [8, 9].

IMAGING STUDIES IN THE ASSESSMENT OF DOI

Intraoral ultrasound

Intraoral ultrasound (IOUS) has been highlighted as a tool to assess the depth of invasion in OTSCC in the literature published from 2020 onward [1]. The conclusions include the presence of a strong correlation between the depth of invasion as measured on ultrasound and during histopathological examination [1, 2, 6]. The mean difference between the DOI values as measured by ultrasound and histopathology for Tis, T1, and T2 stage lesions was 0.7 mm, as compared to a 1.6 mm difference between MRI and histopathology [1]. In an earlier study, the disparity was even greater as the differences amounted to 0.2 mm and 2 mm, respectively [4]. The measurements of DOI by means of ultrasound and palpation were more accurate compared to MRI [10]. Ultrasound was also shown to be superior to MRI in the evaluation of the primary focus [1, 10], especially when the depth of invasion, as measured intraoperatively, is less than 5 mm, and the invasion is limited to the superficial mucosal layers [1, 4]. Another conclusion is that ultrasound examination is suitable for determining the T component of the TNM classification system. A relationship has been demonstrated between the T component as assessed on ultrasound and in histopathological examination, with ultrasound facilitating correct determination of the T component in 70.7% of cases [1]. Thirdly, intraoral ultrasound facilitates resection with negative deep margins [2, 6, 11]. On top of that, the sensitivity and specificity of ultrasound for determining the cutoff point for elective nodal surgery, or DOI ≥ 4 mm, were determined at 92.31% and 82.14%, respectively [1].

The use of a compact linear high-frequency hockey stick probe facilitates visualization of the entire tumor, determination of infiltration depth, deep margins and the resection boundary between the tumor and healthy tissue in real time; at the same time, the overestimation bias and the susceptibility to artifacts for shallow lesions with DOI of < 5 mm are lower than in the case of MRI and CT [1, 10, 11]. Other advantages of ultrasound include its wide availability, non-invasiveness, safety, and low cost [2, 4, 6]. Intraoperative use of ultrasound has been shown to slightly increase the duration of surgery by 5–10 min [2, 6].

For tumors with a DOI of ≥ 5 mm, the measurements are less accurate due to the lower penetrability of ultrasound [1, 4]. Other limitations to the use of the modality include lockjaw, tongue root infiltration, and painfulness [4]. However, the latter can be mitigated

by the use of local anesthesia such as carbocaine with epinephrine, lingual nerve block, or general anesthesia [10]. Finally, one should keep in mind that ultrasound remains a subjective examination, especially in the case of tumors of highly irregular shapes, and that the precision of the measurements depends on the experience of the operator [2].

As suggested by the aforementioned evidence, intraoral ultrasound is most appropriate in the assessment of T1 and T2 stage OTSCC [1, 4, 12]. Preoperatively, the modality can be used to determine the stage of the tumor and guide the decision regarding elective neck resection. Intraoperatively, its use may result in fewer cases of positive resection margins and thus fewer revision surgeries, lower requirement for adjuvant therapy, and better functional and oncological outcomes [6].

Magnetic resonance imaging

Traditionally, MRI has been considered the modality of choice for the evaluation of OTSCC [1, 13]. The technique is helpful in preoperative determination of the extent and DOI of the tumor [5]. The relationship between the DOI of OTSCC as measured on MRI and in histopathological examination was established in 2016 [5] and confirmed in subsequent years [8, 13, 14, 15]. The comparisons included T1- and T2-weighted, DWI, and dynamic contrast-enhanced (e-THRIVE) sequences to show that the DOI as measured within 1 minute following the administration of the contrast agent using the e-THRIVE sequence had the best relationship to the DOI as measured on histopathology. The results were slightly worse for DWI sequences, while T1- and T2-weighted sequences presented the highest overestimation bias. Both the e-THRIVE and DWI sequences facilitate good differentiation between the tumor and the surrounding inflammatory tissue. The e-THRIVE sequence was considered best for the evaluation of the T component, with DWI providing an alternative option in cases where contrast agents are contraindicated [15]. As found in one of the studies, 96% of OTSCCs undetectable on MRI had a DOI of < 4 mm and required no elective nodal surgery [5]; however, tumors with a DOI as low as 3 mm could be detected in newer studies carried out using 7T MRI systems [16, 17]. Evidence was obtained to confirm a correlation between the depth of invasion as measured by MRI, and the presence of cervical lymph node metastases [18]. One study reported the presence of nodal metastases in 71% of lesions with a DOI of > 9 mm and attempted to differentiate between benign and malignant nodes on the basis of the apparent diffusion coefficient (ADC) [14]. Most studies, however, show a moderate correlation between the lymph node status as determined by MRI and the histopathological outcomes [8, 12]. The sensitivity of MRI in the detection of pathological lymph nodes is estimated to be around 60% [8], and the attempts to develop machine learning (ML) models to improve our ability to preoperatively detect occult nodal metastases have led to mediocre results [12]. Given the above, nodal status as assessed by MRI should not be the sole criterion when determining the need for neck nodal surgery [8, 12].

The advantages of MRI include its applicability in preoperative OTSCC staging [2, 12, 15] as well as its ability to provide information on resection margins. While the high positive predictive value of the modality in tumors with DOI of ≥ 3 mm makes it possible to predict a particular margin being too small, the low negative predictive value translates to histopathological examination remaining the gold standard in cases where confirmation of margin sufficiency is required [16]. MRI is characterized by excellent resolution in soft tissues [8, 15] and is widely used, in addition to palpation [7], particularly in more advanced tumors with DOI of ≥ 5 mm [1, 7, 10, 12], infiltrating into the bones and/or the floor of the mouth, and accompanied by lymph node enlargement [1, 12]. New studies on magnetic resonance measurements are focusing on analyzing variables that improve the prognostic value of the modality as a survival assessment tool in OTSCC patients. For example, multi--parametric analysis revealed that tumor thickness of > 23 mm as measured on T1-weighted sequences following the injection of a contrast agent was associated with worse overall survival (OS) while age was associated with worse local recurrence-free survival [13]. Optimized radiomic models (involving computerized analysis of diagnostic images) are also being sought for the prediction of survival in OTSCC [19, 20]. An interesting example is provided by the CRprim+10 model enhanced by clinicopathological features such as DOI and extended to include peritumoral tissue within 10 mm of the primary focus, which presents with increased sensitivity in detecting occult nodal metastases and provides an independent predictor of worse overall survival and disease-free survival (DFS) [20].

The disadvantages of both MRI and CT include the undetectability of micrometastases smaller than 3 mm [16, 20] and shallow lesions, limited to the mucosa and having the DOI of < 5 mm [4, 7]. In addition, both methods tend to overestimate the DOI relative to histopathological examination, with an average difference of about 2–3 mm [4]. This is particularly significant in early T1/T2 stages of OTSCC [1] and due firstly to shrinkage occurring during formalin fixation of the biopsy specimen as well as in the course of its further processing [1, 13, 15], and secondly to the presence of peritumoral edema and inflammation [1, 4, 15], especially in cases of diagnostic tumor biopsies collected prior to the imaging examination [17]. For this reason, measurements taken before the diagnostic biopsy, adjusted for the shrinkage factor (ranging from 10 to 30% according to different sources) are believed to provide the greatest accuracy in assessing the DOI [4, 17]. In the order of increasing overestimation bias, the imaging techniques can be listed as follows: MRI using the e-THRIVE sequence, MRI using the DWI sequence followed by the T1-weighted sequence similar to contrast-enhanced CT, and, lastly, MRI using the T2-weighted sequence [4]. Compared to CT, MRI scans are characterized by inferior spatial distribution [4, 15] but superior resolution within the soft tissues [5, 8, 15] and lower susceptibility to artifacts from metallic materials used in dentistry [4,5].

Computed tomography

The current guidelines recommend that preoperative imaging of the primary focus and neck be pursued with contrast-enhanced CT and/or MRI with and without contrast [4]. While tumor size and DOI are crucial for OTSCC staging, CT frequently fails as an appropriate evaluation tool due to the presence of artifacts from dental materials. Although improvements in image quality

can be achieved through metallic artifact reduction (MAR), the use of image reconstruction algorithms with the subtraction of iodine contrast-containing structures (subtraction iodine imaging; SII) is superior in this regard. SII has been shown to improve the detectability and measurability of tumor size and DOI in OTSCC, albeit to an extent lesser than that provided by MRI. SII can be particularly useful in cases when MRI evaluation is contraindicated or impossible due to motion artifacts [21].

CONCLUSIONS

IOUS, MRI, and CT remain the three complementary imaging modalities for the assessment of the depth of invasion in cases of oral tongue squamous cell carcinoma. Although the latter two methods are recommended in the current guidelines for the imaging of the primary focus and neck, one should remember that these modalities are insufficient in cases of shallow lesions confined to the mucosa and having the DOI of < 5 mm, and micrometastases smaller than 3 mm, as well as with regard to the determination of deep resection margins and real-time determination of the resection boundary between the tumor and the healthy tissue. While the usefulness of these modalities can be increased thanks to the more recent techniques such as diffusion-weighted imaging, dynamic sequences with contrast enhancement, or image reconstruction algorithms with the subtraction of iodine contrast-containing structures, intraoral ultrasound can provide a valid alternative, especially in early T1–T2 N0 stages. According to recent scientific reports, IOUS facilitates effective determination of the stage of the tumor and delineation of deep resection margins, as well as contributes to the decision-making regarding elective neck dissection. Widespread use of IOUS might contribute to a reduction in the number of R1 resections with optimum conservation of organ function, translating to a reduced need for resurgery and adjuvant therapy, better prognosis, and longer recurrence-free survival.

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