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Review

Intraoral ultrasonography to measure tumor thickness of oral cancer: A systematic review and meta-analysis

Thomas J.W. Klein Nulent[a,b,*,1], Rob Noorlag[a,b,1], Ellen M. Van Cann[a,b], Frank A. Pameijer[c], Stefan M. Willems[d], Adrian Yesuratnam[e], Antoine J.W.P. Rosenberg[a], Remco de Bree[b], Robert J.J. van Es[a,b]

[a] Department of Oral and Maxillofacial Surgery, University Medical Center Utrecht, Utrecht, The Netherlands
[b] Department of Head and Neck Surgical Oncology, UMC Utrecht Cancer Center, University Medical Center Utrecht, Utrecht, The Netherlands
[c] Department of Radiology, University Medical Center Utrecht, Utrecht, The Netherlands
[d] Department of Pathology, University Medical Center Utrecht, Utrecht, The Netherlands
[e] Department of Radiology, The Royal Melbourne Hospital, University of Melbourne, Parkville, Victoria, Australia

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ABSTRACT

Early oral cancer is preferably treated by surgery. Its complete removal is essential for locoregional control and disease-free survival. Inadequate resection margins require adjuvant therapy such as re-resection or (chemo) radiation, that causes extra morbidity and oral discomfort. Intraoral ultrasonography (US) is reported to be of value in determining tumor thickness. Intraoperative visualization of the tumor may facilitate the resection and ensure adequate surgical margins. Furthermore, accurate prediction of tumor thickness could help determine the treatment strategy of the clinically node-negative neck, as thickness and depth of invasion are predictors of cervical metastasis as well as prognosticators of survival. The 8th edition of the American Joint Committee on Cancer staging system for oral squamous cell carcinoma has included depth of invasion as parameter for cT-stage. The aim of this review is to analyze the accuracy of intraoral US in determining tumor thickness in oral cancer.

A systematic search was conducted, and the quality of the included papers was assessed using the QUADAS-2 tool for diagnostic accuracy studies. Subsequently, a meta-analysis was performed on the available individual participant data of 240 patients.

Most of the twelve included studies focused on T1-2 tongue cancer (n = 129). Meta-analysis showed a high correlation in tumor thickness within this subgroup as measured by intraoral US and histopathology ($r = 0.82$, $p < .001$), with minor overestimation of 0.5 mm on US. It is concluded that intraoral US is very accurate in determining tumor thickness in early oral tongue cancer.

Introduction

Head and neck cancer is the sixth most common malignancy worldwide of which approximately one third consists of oral squamous cell carcinoma (OSCC) [1,2]. For early OSCC (Stage I-II), surgery is the preferred treatment choice. Its complete removal is essential for locoregional control and disease-free survival [3]. Most authors agree that adequate histopathological resection margins are crucial, although it is debated how wide surgical margins should be [4–9]. For all T-stages, free margins of at least 5 mm to the tumor invasive front are accepted as "negative" resection margins. Resection margins between 1 and 5 mm are considered "close" and resection margins less than 1 mm "positive". In early OSCC a 3 mm clear margin proves to be as safe as 5 mm [4,9].

"Unfavorable growth patterns" of the tumor front, such as non-cohesive growth, perineural invasion and lymphovascular invasion may increase the risk of residual microscopic disease. Re-resection or adjuvant (chemo)radiation is indicated in case of positive resection margins and/or close margins in combination with one or more unfavorable growth patterns. Routine clinical follow-up is justified in case of negative margins and close margins without unfavorable growth patterns [10].

Adjuvant radiotherapy may cause significant morbidity and (oral) discomfort affecting quality of life: patients may experience acute and

* Corresponding author at: Department of Oral and Maxillofacial Surgery, University Medical Center Utrecht, G05.129, Heidelberglaan 100, 3584 CX Utrecht, The Netherlands.
E-mail address: t.j.w.kleinnulent@umcutrecht.nl (T.J.W. Klein Nulent).
[1] Contributed equally to this work.

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late reactions such as mucositis, xerostomia, fibrosis of the soft tissues and osteoradionecrosis, even when treated with intensity modulated radiation (IMRT) [11,12]. Moreover, nausea and vomiting, bone-marrow suppression and skin lesions are frequently reported when chemotherapy or monoclonal antibodies are added to radiotherapy [13].

Resection margins in OSCC are often inadequate and the main indication to apply adjuvant treatment. A retrospective analysis of surgically treated patients with early OSCC revealed 63% close margins and 11% positive margins. Especially deep resection margins often appeared close or positive [9]. These results are in line with reports from comparable institutes, that report 42–48% close resection margins and 28–36% positive resection margins in early oral cancers [14].

New diagnostic and therapeutic methods for better margin control in early OSCC management are necessary and may reduce the need for adjuvant treatment. In T1-2 invasive breast cancer, ultrasound (US) guided surgery reduced the number of positive margins, the volume of healthy breast tissue resected and the number of patients who need adjuvant radiotherapy, leading to improved cosmetics and quality of life [15]. These results raised the question whether intraoral US is of value in determining tumor thickness in oral cancer, and whether intraoperative visualization by US leads to more accurate resection margins. In addition, accurate prediction of histopathological thickness may help to decide on the treatment strategy of the clinically node-negative neck, as depth of invasion and tumor thickness are predictors of the presence of cervical metastasis as well as prognosticators of survival [16–19].

The recent 8th edition of the American Joint Committee on Cancer (AJCC) staging system for OSCC includes depth of invasion as parameter to adjust the T-stage [20]. It should be noted that tumor thickness differs clearly from depth of invasion and that these terms are often used interchangeably, which is incorrect. Tumor thickness is defined as the distance from the tumor surface to the deepest level of invasion, while depth of invasion defines the distance from the reconstructed mucosal surface to the deepest level of invasion [21].

The application of intraoral US for oral cancers has initially been described by Shintani et al. in 1997. Earlier publications described only extraoral visualization of the tumor due to the large size of the US probe [22]. Since 1997, comparative studies on this topic have been published and seem promising, but a review is lacking. The aim of this systematic review is to analyze the accuracy of intraoral US in determining tumor thickness in oral carcinoma, when compared to thickness measured at histopathology. The outcome of this review could delineate new treatment modalities in order to obtain better margin control in OSCC, resulting in a decrease of morbidity and improvement of quality of life.

Materials and methods

Search strategy

A systematic search was conducted in the PubMed (MEDLINE), Embase and Cochrane databases for original articles published until the 6th of July 2016. Search terms included “oral cancer” and “ultrasonography” and their synonyms in title and abstract fields. The search syntax is shown in Supplementary Table 1. Duplicates were extracted manually using RefWorks (ProQuest, Michigan, USA). Two authors (TKN and RN) independently screened all titles and abstracts for relevance using predefined inclusion and exclusion criteria. Subsequently, the full text of relevant studies was screened for final selection. Discordant judgments were resolved by consensus discussion. A reference check and citation check of the selected articles was performed to identify potentially missed relevant studies.

Inclusion and exclusion criteria

Articles were selected when (1) the studied population consisted of patients with OSCC; and (2) preoperative or intraoperative measurement of tumor thickness or tumor margin measurement was performed by intraoral US; and (3) when these measurements were compared with histopathological tumor thickness or margin width as reference standard.

Exclusion criteria were (1) duplicate articles that contained all or some of the original publication data; (2) reviews, book chapters, cases reports, editorials, oral presentations, technical notes and poster presentations; (3) articles analyzing head and neck squamous cell carcinoma without subgroup analysis of OSCC and (4) articles in a language other than English or German.

Critical appraisal

The included studies were ranked, based on standardized criteria for diagnostic research using the QUADAS-2 tool for quality assessment of diagnostic accuracy studies [23]. All included studies were appraised by both authors (TKN and RN) separately and subsequently merged by consensus. Risk of bias was scored on the following items: (1) patient selection: a consecutive or random sample of patients, avoidance of case-control study design and avoidance of inappropriate exclusions; (2) index test: preoperative or intraoperative intraoral US; (3) reference standard: validity of the reference standard and blinding of the pathologist to US and (4) flow and timing: time span between US and histopathology, standardization of study protocol and missing data. Subsequently, applicability was evaluated on the first three items: (1) patient selection: patients with primary and not previously treated OSCC; (2) index test: pre- or intraoperative measurement of tumor thickness or margin measurement by intraoral US and (3) reference standard: histopathological tumor thickness or margin width. All items were scored as low (+) or high (−) risk of bias, or unclear (?) if the item was not mentioned.

Data extraction and analysis

The following data were extracted from the included articles: number of included patients, tumor site, TNM-stage according to the 7th edition AJCC staging system for OSCC, US device and type of probe, time span between US and histopathology and the number of patients on which the correlation between US and histopathology could be made. When individual measurements were not given, authors were contacted and requested to provide their source data. Subsequently, individual patient data were pooled and subjected for meta-analysis when possible. Pearson’s correlation coefficient was (re)calculated per study, tumor site and when possible per tumors cT-stage. For subgroup analysis, a one-sample T-test was used to describe the mean differences of US compared to histopathology.

Differences per study in thickness measurement of all tongue tumors were visualized in a forest plot. Of the early OSCC subgroup, a scatter plot was drawn to visualize the correlation between histopathology and US. The absolute difference between histopathology and US was calculated for each individual patient and plotted against the reference standard in a modified Bland-Altman plot [24]. Accuracy of thickness estimation within and between different subsites was calculated using a one-way ANOVA analysis of variance.

All statistical tests for meta-analyses were performed using IBM SPSS Statistics for Windows, Version 21.0, 2012. All plots were drawn using GraphPad Prism for Windows, Version 6.02, 2013. P-values $<$ .05 (two-tailed) were considered statistically significant. The PRISMA-P 2015 statement was adopted for a complete and transparent report of the systematic review and meta-analysis [25].

Results

Search strategy and article selection

The search revealed 6442 citations (Fig. 1). After removing duplicates, titles and abstracts were screened by two authors independently according to the inclusion and exclusion criteria.