Ultrasonography use for tongue cancer management: A scoping review

Luiz Cláudio Pires Duarte [1], Karlayle Teixeira [1], Barbara Magalhães Figueiredo Dias [1], Felipe Paiva Fonseca [1], Denise Vieira Travassos [2], Chané Smit [3], Maurício Augusto Aquino de Castro [1], Aline Araujo Sampaio [1,*]

[1] Department of Oral Surgery and Pathology, School of Dentistry, Universidade Federal de Minas Gerais, Belo Horizonte, Brazil.

[2] Department of Public Health, School of Dentistry, Universidade Federal de Minas Gerais, Belo Horizonte, Brazil.

[3] Department of Oral and Maxillofacial Pathology, University of Pretoria, Pretoria, South Africa.

* Correspondence: Aline Araujo Sampaio, Department of Oral Surgery and Pathology, School of Dentistry, Universidade Federal de Minas Gerais, Av. Antônio Carlos, 6627, 31270-901, Pampulha. Belo Horizonte, MG, Brazil. Email: alinea.sampaioufmg@gmail.com

ABSTRACT

Background: Tongue cancer is associated with debilitating diseases and poor prognostic outcomes. The use of imaging techniques like ultrasonography to assist in the clinical management of affected patients is desirable, but its reliability remains debatable. Therefore, the aim of this study is to investigate the importance of ultrasound use for the clinicopathological management of tongue cancer.

Methods: A scoping review was carried out using specific search strategies in the following electronic databases: PubMed/MEDLINE, Scopus, Web of Science, and Google Scholar. Collected data included bibliographical information, study design, ultrasound equipment, the aim of the ultrasonography use, the timing of ultrasound use during oncological treatment (pre-, trans-, and/or post-operatively), and the advantages and disadvantages of the use of the ultrasound.

Results: A total of 47 studies were included in this review after following the selection process. The majority of the studies investigated the use of ultrasound pre-operatively for the investigation of lymph node metastases or to determine the tumor thickness and depth of invasion. The sensitivity, specificity, and accuracy of ultrasound to determine clinical lymph node metastases ranged from 47% to 87.2%, from 84.3% to 95.8%, and from 70% to 86.2%, respectively. The sensitivity and specificity to determine the microscopic depth of invasion were 92.3% and from 70.6% to 82.1%, respectively.

Conclusion: Ultrasonography seems to be a reliable imaging technique for the investigation of important prognostic parameters for tongue cancer, including depth of invasion and lymph node metastases.

Keywords: depth of invasion; metastasis; tongue cancer; ultrasonography; ultrasound.

1 INTRODUCTION

Oral cancer represents a major public health issue in many parts of the world. The International Agency for Research on Cancer estimated for 2020 that approximately 377 713 new cases would be diagnosed worldwide, with 177 757 associated deaths.[1, 2] The tongue is the most common subsite affected in the oral cavity and squamous cell carcinoma represents over 95% of all cases diagnosed. This malignancy is strongly associated with tobacco use and mainly affects patients over the age of 45 years. Despite improvements in the understanding of the biological basis of the disease and the development of new technologies for therapeutic and diagnostic assistance, there has not been much improvement in the survival rates of patients affected by tongue cancer. Surgery with or without adjuvant radiotherapy remains the main therapeutic modality. Clinical features like tumor size (T-stage) and the presence of lymph node metastases (N-stage) remain the key parameters for stratifying patients according to therapeutic responses, to estimate survival rates and to determine how patients will be managed.[3-5]

Although clinical parameters like the occurrence of lymph node metastases and the presence of positive surgical margins are known to negatively impact patients' survival, many efforts have been made to improve these algorithms.[3] For instance, the last edition of the American Joint Committee on Cancer (AJCC) recommended the use of depth of invasion as an important microscopic finding associated with patients' prognosis.[6] However, assessing clinical and microscopic features either pre-operatively or trans- and post-operatively may be very difficult and the use of imaging techniques has been considered potential auxiliaries. Computed tomography (CT) and magnetic resonance imaging (MRI) are modern techniques that are not widely available for patients from developing countries, whereas ultrasound is a more accessible approach. However, the advantages and the reliability of ultrasound to accurately determine tongue cancer characteristics that could contribute to patients' management remains debatable.[6]

Therefore, the aim of this study is to investigate, through a scoping review of the literature, the reliability of ultrasonography to contribute to the clinical management of patients affected by tongue cancer.

2 MATERIALS AND METHODS

2.1 Study design

This study used the Preferred Report Items for Systematic reviews and Meta-Analyses (PRISMA) statement following an extension for scoping review protocol (PRISMA-ScR) intending to investigate the utility of ultrasonography for tongue cancer clinicopathological management.[7, 8]

2.2 Search strategy

An electronic search was carried out in April 2023 with no time restriction. The following electronic databases were assessed: PubMed/MEDLINE, Web of Science, and Scopus. Gray literature was assessed using the Google Scholar database up to the 10th page of results. The

search strategy used in all databases comprised the following Medical Subject Headings: (ultrasound or ultrasonography or “ultrasound diagnosis”) and (“tongue cancer” or “tongue tumor” or “tongue neoplasia”).

2.3 Eligibility criteria

2.3.1 Inclusion criteria

All studies investigating the importance of ultrasonography use for tongue cancer clinicopathological characterization in humans were included. Randomized and controlled clinical trials, cohort studies, cross-sectional studies, case–control studies, case series, and case reports published in English, Portuguese, or Spanish languages were screened.

2.3.2 Exclusion criteria

Literature review publications or studies investigating ultrasonography use in animals were excluded.

2.4 Study selection

Two previously trained authors independently screened the titles and abstracts of all articles yielded from the initial search. The calibration between the authors started with 10% of the references, and Cohen's κ value of 0.91 was obtained, indicating a high level of reliability between the authors' recommendations. The studies that fulfilled the inclusion criteria, and those that did not present sufficient information in their title or abstract, were fully assessed. A cross-check assessment of articles was performed by a third author to ensure the correctness of included studies, as per the inclusion and exclusion criteria. Duplicate references were initially identified and removed using the EndNote program (EndNote®; Clarivate Analytics, Toronto, Canada), after which a manual review was done to remove other duplicates not initially recognized by the software.

2.5 Data extraction

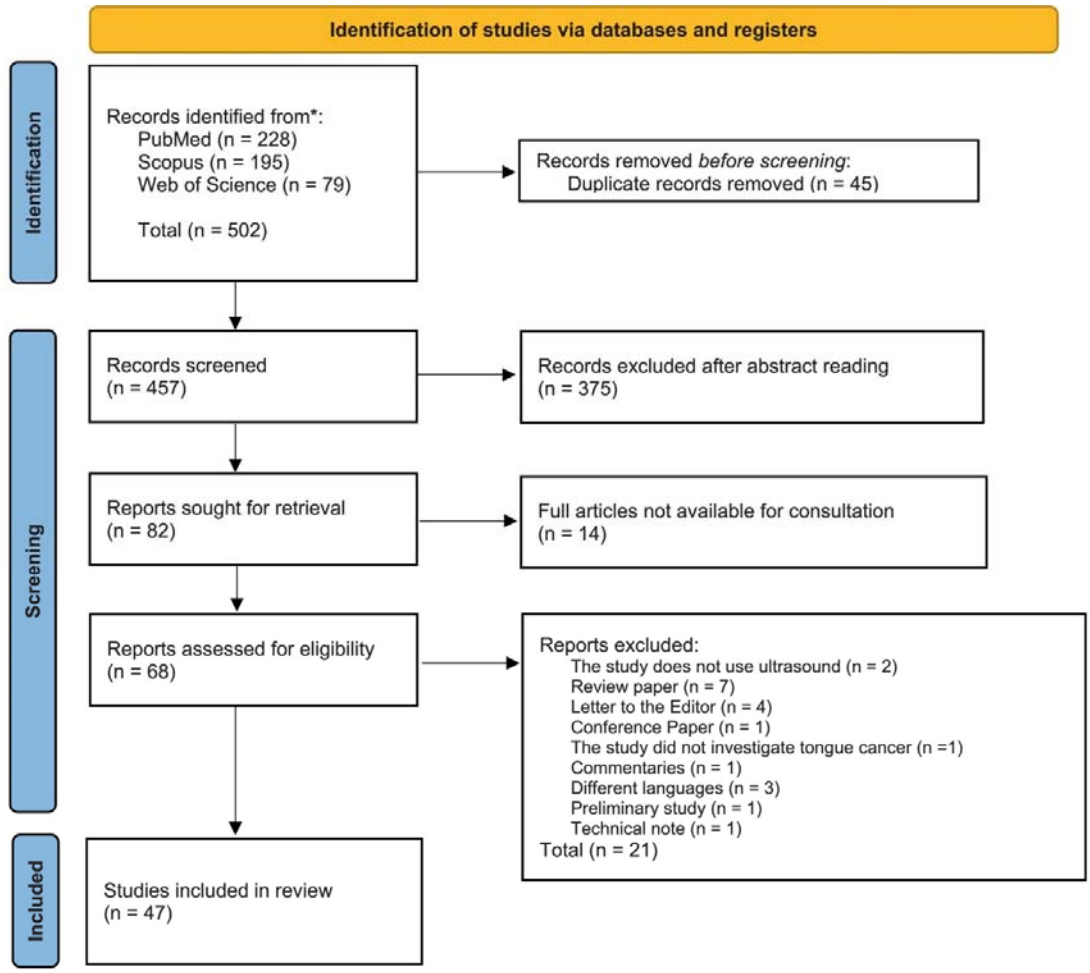
Three authors independently extracted the following data from the included studies: study reference (authors, year, country where the study was done, and article title), study design, ultrasound equipment used and whether it was intraoral or extraoral, approach, timing of the ultrasound used during oncological treatment (pre-, trans-, and/or post-operatively), advantages and disadvantages of the use of the ultrasound for tongue cancer management and the reasons for the use of the ultrasonography. Data was gathered in a Microsoft Excel® spreadsheet and disagreements were jointly settled with the project members.

3 RESULTS

3.1 Studies selection

The study selection process is summarized in Figure 1. The search strategy identified a total of 502 articles, of which 45 were duplicated. Out of the 457 articles remaining, 375 were excluded after the authors accessed the abstract. Another 14 articles were excluded because

the full manuscripts were not available for consultation even after email contact with the authors and 21 studies were further excluded due to different specific reasons. Therefore, 47 articles met the inclusion criteria to be included in this scope review[6, 9-45] (File S1). The studies included in this review were published between 1986 and 2022, being geographically distributed more frequently in Japan (*n* = 19), followed by USA (*n* = 8), China (*n* = 5), Republic of Korea (*n* = 3), India (*n* = 3), Netherlands (*n* = 3), Switzerland (*n* = 2), Turkey (*n* = 1), Brazil (*n* = 1), Australia (*n* = 1), and Italy (*n* = 1).



*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).

**If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

FIGURE 1. PRISMA 2020 flow diagram containing the results obtained for the current scope review.

3.2 Data description

The objective of the use of ultrasound and the description of the articles included in this review are described in Table S1. The extraoral ultrasound probe was used in 13 studies, while intraoral ultrasonography was used in 27 studies, demonstrating that both modalities are useful for managing tongue cancer patients. In seven studies, it was not possible to reliably

identify the type of ultrasound probe used by the authors. Moreover, many different ultrasonography models are currently available and were used by the studies, with different frequencies that ranged between 3 and 20 MHz. The studies included, used the ultrasound at three different stages: pre-, trans-, and/or post-operatively. Those studies that evaluated the use of ultrasound before surgery investigated the presence of lymph node metastases, blood flow through Doppler analysis, tumor thickness, and depth of invasion of the primary tumor. In addition, it was also used for diagnostic purposes, to determine the surgical margins, to evaluate the lingual artery, to guide fine needle aspiration biopsy, and for the analysis of the hardness of the tumor. Regarding the trans-operatory use of the ultrasound, authors used this technique to establish the depth and extension of surgical margins, to investigate possible metastatic islands and to administer iode 125. Finally, in the studies that used ultrasound post-operatively, authors used this approach for screening of lymph node metastases during patients' follow-up, analysis of the surgical margins in surgical specimens, and evaluation of the size of the neoplasm surgically removed.

The sensitivity, specificity, and accuracy of ultrasound to determine clinical lymph node metastases were shown to range from 47% to 87.2%, from 84.3% to 95.8%, and from 70% to 86.2%, respectively. Meanwhile, the sensitivity and specificity values for the potential of ultrasonography to determine the microscopic depth of invasion were 92.3% and from 70.6% to 82.1%, respectively (Table 1).

TABLE 1. Values of sensitivity, specificity, and accuracy of intraoral ultrasonography to determine the occurrence of lymph node metastases and to determine the histological depth of invasion.

	Lymph node metastasis			**DOI**		
	Sensitivity	**Specificity**	**Accuracy**	**Sensitivity**	**Specificity**	**Accuracy**
Yamane et al. (20077)[15a]	87.2%	84.3%	85.3%	–	–	–
To et al. (2003)[25]	47%	93%	70%	–	–	–
Kawano et al. (2022)[60]	53.6%	95.8%	86.2%	–	–	–
Iida et al. (2018)[61b]	–	–	–	92.3%	70.6%	–
Caprioli et al. (2022)[23c]	–	–	–	92.3%	82.1%	–
Chammas et al. (2010)[38d]	63%	91%	79%	–	–	–
Byers et al. (1998)[62]	52%	95%	70%	–	–	–

- *Note*: Superscript numbers cited in the table are references present in File S1.
- Abbreviation: DOI, depth of invasion.
- [a] Intraoral ultrasonography versus ultrasonography used in conjunction with a computer-aided diagnosis (CAD) system.
- [b] DOI ≤5 versus >5 mm.
- [c] DOI >4 mm.
- [d] Values obtained for 2 cm tumor thickness.

Different studies described improvements in the clinical management of patients by using ultrasonography. For instance, Yoon et al.[6] found a statistically significant correlation between ultrasound and histologic depth of invasion, while Takamura et al.[13] demonstrated that ultrasound overestimated the depth of invasion by an average of 0.2 mm, which was much lower than CT and MRI that overestimated the depth of invasion by an average of 2–

3 mm. Moreover, Nair et al.[11] demonstrated that ultrasonography is a reliable and cost-effective tool to measure tumor thickness, while de Koning et al.[21] demonstrated that ultrasound-guided tumor resections improved surgical margin status, and Konishi et al.[22] demonstrated that the occurrence of irregular lesion margins assessed using intraoral ultrasonography may serve as an effective predictor of late cervical lymph node metastasis.

4 DISCUSSION

Tongue cancer represents a public health problem worldwide, with an unsatisfactory survival rate. Seeing as squamous cell carcinoma represents over 95% of all cases in this site, tongue cancer is strongly associated with smoking habits. The search for new clinicopathological parameters that contribute to stratifying patients according to their risk of death or response to therapy is desirable, and the use of imaging technologies has been an important auxiliary for patients' management. Although ultrasonography is a well-known technique, is usually available in many oncological centers and its use for tongue cancer management has been investigated previously, its reliability in estimating tongue cancer pathological parameters remains highly debatable, especially when compared to CT and MRI. However, ultrasonography can be more widely applied to presurgical procedures and post-surgical follow-up. Therefore, in this scoping review, it was demonstrated that the currently available literature supports the use of ultrasound to reliably estimate important prognostic determinants like tumor thickness, depth of invasion, and lymph node metastases, consequently leading to improvements in patients' outcomes.

In addition to the various medical indications of ultrasonography, this technique has extensively been used for the diagnosis of different oral and maxillofacial diseases like salivary gland-related conditions, lymph node-related diseases, subcutaneous diseases, and tongue-related diseases, although an important percentage of dentists still does not know its diagnostic utilities.[9, 46] More recently, Doppler ultrasound that demonstrates the flow in blood vessels, have also been applied to improve the recognition of oral diseases.[46] Intraoral ultrasonography is a noninvasive, real-time, cost-effective diagnostic approach that uses an L-shaped facility, which, however, demands the presence of an acoustic medium to obtain an appropriate image.[6, 10, 11, 47] Moreover, it is important to consider that ultrasonography is a highly operator-dependent technique that might provide incorrect results if there is inadequate contact with the lesion, possibly due to pain on contact, limited mouth opening or if the lesion is located where the transducer does not reach.[12, 13, 46, 48] Moreover, the potential for prolonged trans-operative times and the degree of compression of the tissue interface with the ultrasound probe that may cause erroneous values for tumor thickness may also represent possible limitations.[14]

The use of intraoral ultrasonography for the diagnosis and clinical management of tongue cancer has been widely investigated in recent years, but its reliability remains to be fully validated. Compared to normal tissue, ulcerative tongue cancer lesions are abnormally hypoechoic, distorting the surrounding normal tongue architecture, and since malignant cells infiltrate normal adjacent structures, the tumor contour on ultrasonic images shows an irregular shape and unsharp borders.[6, 12] In addition, normal lymph nodes have extensive vascularity originating in the hilus and branching radially toward the periphery, whereas

metastatic lymph nodes reveal peripheral vasculature that runs along the periphery of nodes and no vasculature around the hilus.[46]

As demonstrated in the current scoping review, ultrasound has been advocated to be used pre-, trans-, and post-operatively for tongue cancer patients. Numerous studies investigated the ability of ultrasonography to estimate tumor size and thickness before surgery,[10, 15] to assist in real-time tumor resections trans-operatively[16] and to screen for subclinical cervical lymph node metastases after initial therapy.[12] According to available studies, it seems that ultrasound-guided surgery is associated with a lower frequency of positive surgical margins, decreasing the necessity for adjuvant radiotherapy.[16, 49] A number of studies suggested that ultrasound was significantly superior to manual palpation and other imaging modalities (CT and MRI) for demarcating the margins of tongue cancer, especially the deep margins.[14, 46] Although some studies used braided surgical sutures or drive needles to determine the deep margins of tumors, the use of ultrasound trans-operatively without the use of any invasive method to mark the resection margin has been proven accurate.[14]

As an attempt to improve the risk stratification of tongue cancer patients, the eighth edition of the AJCC recommended the use of depth of invasion in clinical staging. This histological parameter should be differentiated from tumor thickness because it uses the basal membrane of adjacent normal mucosa as a reference, while tumor thickness may be increased in exophytic lesions or decreased in ulcered tumors. The majority of the studies included in the current scoping review demonstrated a reliable potential of intraoral ultrasound to more efficiently estimate depth of invasion and tumor thickness pre-operatively, demonstrating lower overestimations than CT and MRI, which are more strongly affected by peritumoral edema and reactive inflammation.[11, 13, 16-19] Moreover, the occurrence of metal artifacts is frequently reported as an important limitation of CT, which precludes detailed tongue cancer analyses in a large number of patients that often carry amalgam dental restorations.[6, 13]

It is known that the higher the depth of invasion of tongue cancer, the higher the frequency of metastases to the cervical lymph nodes.[13] The use of ultrasound to estimate the risk of nodal metastases has also been investigated and Shinozaki et al.[20] showed that cases with tumor thickness >3 mm detected using ultrasonography had a higher potential for cervical lymph node metastasis. Moreover, different studies demonstrated that ultrasound scanning has a diagnostic accuracy rate of approximately 90% for cervical lymph node staging, representing a better diagnostic approach than CT and direct palpation,[20] which should still be further validated by studies directly comparing ultrasonography and CT. Yamane et al.[12] found a diagnostic sensitivity, specificity, and accuracy for the prediction of subclinical lymph node metastasis of 87.2%, 84.3%, and 85.3%, respectively, but To et al.[50] found sensitivity, specificity, and accuracy of 47%, 93%, and 70%, respectively, which according to the authors would not allow ultrasonography to be used in isolation to determine if elective neck dissections were recommended. The use of Doppler ultrasound attempts to improve these values, and Yamamoto et al.[10] reported that blood flow signal number ratio and blood flow signal width ratio on the invasion front of tongue cancer would be important predictors for cervical lymph node metastasis.

The variability in the results obtained for sensitivity, specificity, and accuracy among different studies that evaluate the ability of ultrasonography to determine the risk of lymph node metastases or the depth of invasion might be explained due to the lack of a strict standardization regarding tumor characteristics since some studies evaluate only patients affected by specific tumor sizes and others do not use this feature as an inclusion criterium. Moreover, the cut-off value used to investigate the ability of ultrasonography to determine the depth of invasion also varies from study to study. Therefore, the reliability of ultrasonography as an auxiliary for the clinical management of tongue cancer still demands more studies, and this technique should be used together with other clinical and microscopic parameters.

In conclusion, this scoping review demonstrated the availability of scientific data supporting the use of ultrasonography for the clinical management pre-, trans-, and post-operatively of patients affected by tongue cancer. The use for the depth of invasion, tumor thickness determination, risk and diagnosis of lymph node metastases, and the control of appropriate surgical margins showed accuracy values similar to or higher than other imaging techniques, supporting the use of ultrasound during oncological treatment. Taken together, these features will improve patients' prognosis and survival.

AUTHOR CONTRIBUTIONS

Luiz Cláudio Pires Duarte: Data curation; formal analysis; investigation; methodology; writing – original draft; writing – review and editing. **Karlayle Teixeira:** Data curation; formal analysis; investigation; methodology; writing – original draft; writing – review and editing. **Felipe Paiva Fonseca:** Data curation; formal analysis; investigation; project administration; supervision; writing – original draft; writing – review and editing. **Barbara Magalhães Figueiredo Dias:** Data curation; formal analysis; investigation; methodology; writing – original draft; writing – review and editing. **Denise Vieira Travassos:** Formal analysis; investigation; methodology; writing – original draft; writing – review and editing. **Chané Smit:** Formal analysis; investigation; methodology; visualization; writing – original draft; writing – review and editing. **Maurício Augusto Aquino de Castro:** Conceptualization; formal analysis; investigation; methodology; writing – original draft; writing – review and editing. **Aline Araujo Sampaio:** Conceptualization; data curation; formal analysis; funding acquisition; investigation; methodology; project administration; resources; software; supervision; validation; visualization; writing – original draft; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Full data is available in Table S1.

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