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# The Applications and Potential Developments of Ultrasound in Oral Cancer Management

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## Abstract

Oral cancer is endemic and causes a great burden in Southern Asia. It is preferably treated by surgery with/without adjuvant radiotherapy (RT) or chemoradiation therapy, depending on the stage of the disease. Close or positive resection margin and cervical lymph node (LN) metastasis are important prognostic factors that have been presented to be related to undesirable locoregional recurrence and poor survival. Ultrasound (US) is a simple, noninvasive, time-saving, and inexpensive diagnostic modality. It can depict soft tissues very clearly without the risk of radiation exposure. Additionally, it is real-time and continuous image is demonstrated during the exam. Furthermore, the clinician can perform US-guided fine needle aspiration (FNA) or core needle biopsy (CNB) at the same time. US with/without US-guided FNA/CNB is reported to be of value in determining tumor thickness (TT), depth of invasion (DOI), and cervical LN metastasis, and in aiding the staging of oral cancer. DOI has a relevant prognostic value as reported in the eighth edition of the American Joint Committee on Cancer staging of oral cancer. In the present review, we describe the clinical applications of US in oral cancer management in different phases and potential applications in the future. In the pretreatment and surgical phase, US can be used to evaluate TT/DOI and surgical margins of oral cancer in vivo and ex vivo. The prediction of a malignant cervical LN (nodal metastasis) by the US-based prediction model can guide the necessity of FNA/CNB and elective neck dissection in clinical early-stage oral cancer. In the posttreatment surveillance phase, US with/without US-guided FNA or CNB is helpful in the detection of nodal persistence or LN recurrence, and can assess the possibility and extent of carotid artery stenosis after irradiation therapy. Both US elastography and US swallowing assessment are potentially helpful to the management of oral cancer.

## Keywords

ultrasound, oral cancer, radiotherapy, chemoradiation therapy, fine needle aspiration, core needle biopsy, lymph node

## Abbreviations

CIMT, carotid intimal–medial thickness; CNB, core needle biopsy; CVD, cerebrovascular disease; DOI, depth of invasion; FNA, fine needle aspiration; LN, lymph node; PET/CT, positron emission tomography/computed tomography; RT, radiotherapy; TT, tumor thickness; US, ultrasound; MRI, magnetic resonance imaging; SLNB, sentinel LN biopsy.

## Introduction

The worldwide incidence rates (cumulative risk) of oral cancer for men and women are 0.66% and 0.26%, respectively.[1] Oral cancer is endemic and causes a great burden in Southern Asia because of habitual betel quid use, cigarette smoking, and chewing tobacco consumption.[1,2] Surgical resection of the primary malignancy with/without neck dissection has long been regarded as the best approach. The invasive nature of this disease makes it difficult to determine the margins, especially the deep margin, and the undesirable consequences of close or positive margins are still not uncommon, accounting for 11%-63% close margins and 7%-27% positive margins.[3–7]

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Neck lymph node (LN) metastasis is also one of the most important prognostic factors in the treatment of patients with oral cancer. Occult LN metastasis is estimated to be present in 23.9%-26.4% of clinical stage I/II oral cancer.[8,9] Efforts, therefore, are being made to detect indicators that can predict LN metastasis. Tumor thickness (TT), depth of invasion (DOI), and ultrasound (US) with/without US-guided fine needle aspiration (FNA) are parameters that have been studied for the prediction of nodal metastasis and correlate with locoregional recurrence.[8–14]

US is a simple, noninvasive, time-saving, and low-cost image modality. It illustrates cervical soft tissues very clearly and bears no risk of radiation exposure. Also, it exhibits a real-time and continuous image throughout the assessment. Besides, US-guided FNA or core needle biopsy (CNB) can be achieved in the meantime. One meta-analysis and systemic review show that both FNA and CNB have high sensitivity, specificity, and accuracy (all above 90%) in detecting head and neck malignancies.[15] US with/without US-guided FNA or CNB has been shown to be beneficial in assessing TT, DOI, and nodal metastasis, and in assisting the staging properly in oral cancer patients.[3–5,8–11,15–27] DOI has a relevant prognostic value as reported in the eighth edition of the American Joint Committee on Cancer staging of oral cancer.[28,29] In the treated neck of oral cancer patients, it is practical in early identifying a persistent nodal disease or cervical LN recurrence and in directing the need for salvage neck dissection.[30–35] Consequently, US can help the management of oral cancer in different scenarios. In this study, we aim to review the utility of US in oral cancer management in different phases (Table 1).

**Table 1.** The Applications of Ultrasound in the Assessment of Oral Cancer in Different Phases.

| Phase of oral cancer treatment | Ultrasound applications |
|---|---|
| Pretreatment assessment | Primary tumor TT/DOI assessment<br>Neck LN evaluation<br>Guidance of the necessity of US-guided FNA/CNB<br>Assist in clinical staging<br>PET/CT hot spot evaluation and confirmation |
| During surgery | Real-time TT/DOI measurement<br>In vivo and ex vivo resection margin assessment<br>Guide cN0 neck dissection |
| Posttreatment surveillance | Surveillance of neck nodal status<br>Guidance of the necessity of US-guided FNA/CNB<br>PET/CT hot spot evaluation and confirmation<br>Check the risk of CVD and guide management |

Abbreviations: TT, tumor thickness; DOI, depth of invasion; FNA, LN, lymph node; fine needle aspiration; CNB, core needle biopsy; PET/CT, positron emission tomography/computed tomography; CVD, cerebrovascular disease.

## Pretreatment and Surgical Phase

### *Intraoral US in Measuring TT and DOI of Oral Cancer*

In oral cancer, the mainstay of primary site treatment is complete surgical resection with adequate margins. In the past, the surgeon defines the tumor's dimensions by vision and manual palpation, and plans for resections allowing a minimal margin distance of $\geq$5 mm, which is essential for local control and disease-free survival.[6,36] This technique is often successful in determining the mucosal margins, while the deep margin in particular is often inadequate.[6] In one meta-analysis, margin revision of initially positive margins to clear margins based on frozen section guidance does not significantly improve local control and has a 2.5 times worse 5-year local recurrence-free survival compared to initially negative resection margins.[37] As a result, primary resection to obtain a negative margin ($\geq$5 mm) is critical. There are numerous studies suggested that preoperative or intraoperative US is reliable for the assessment of TT or DOI in oral cancer and can potentially guide the surgeon in the achievement of adequate resection margins, especially the deep margin (Figure 1A and B).[3,4,19–26,38] The correlation between the US-obtained and histology-obtained TT or DOI is good to strong with Spearman $R =$ 0.760-0.988,[3,4,8,19–26,38] and some studies show that US is better than computed tomography (CT) and magnetic resonance imaging (MRI) at determining the deep margins of oral cancer.[8,22,26,39,40] This technique is reported to be particularly reliable in tongue cancers with TT or DOI under 10 mm.[22,26] The head and neck surgeon can use real-time intraoperative (in vivo) US to assess the deep margin at the midpoint of the resection and reexamine (ex vivo) the resection specimens immediately after the completion of the resection.[20,24,38] Ex vivo examination by using US can be an adjunct to or even replace frozen section analysis and can guide an immediate re-resection, which further prevents local adjuvant treatment.

### *Assessment of Cervical LN Metastasis and Guidance of US-Guided FNA/CNB and Patient Surveillance*

It is important for clinicians to be able to identify US parameters of a LN regarding its likelihood of being benign or malignant. Size, shape, echogenicity, echogenic hilum, internal echo, necrosis, margin, vascular pattern, elastography, and grouping or matting are reported to be US features associated with malignant nodal disease.[16–18,41–46] The accuracy of differentiation between benign and malignant LN varies according to nodal size and the optimal cutoff differs at different neck levels.[42,43,47] Shape is usually described in terms of the ratio between the short-axis and long-axis diameters (S/L ratio). Normal LNs are usually elliptical with an S/L ratio $< 0.5$, whereas malignant cervical nodes are more likely to be round with an S/L ratio $\geq 0.5$.[16,17,42,43,46] Metastatic LNs are typically bigger in size with round shape, hypoechoic in echogenicity, missing of echogenic hilum, heterogeneous in internal echo, having abnormal vascular pattern other than hilar or avascular

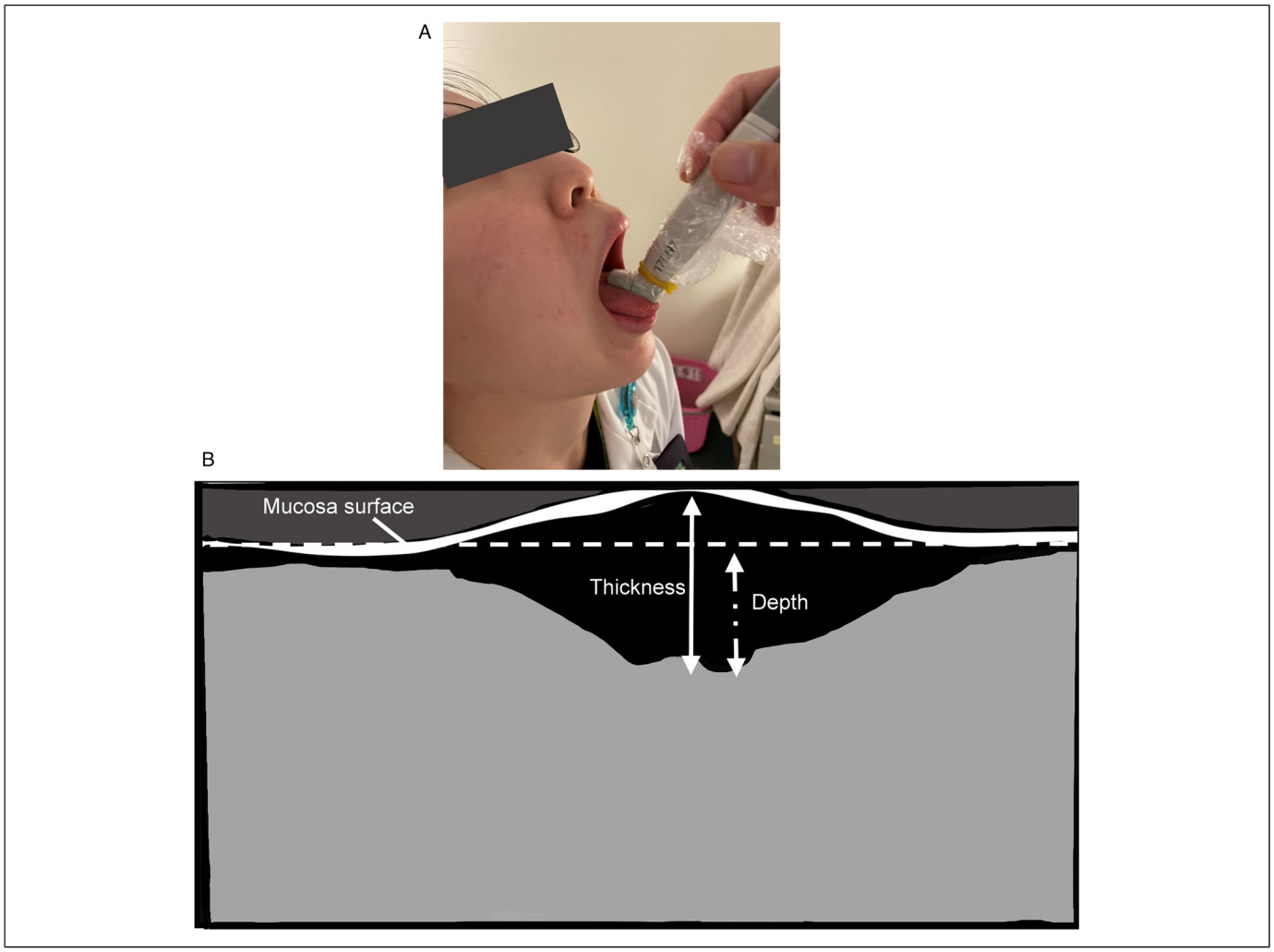


**Figure 1.** Real-time intraoral US (A) can be used to check oral cancer, it is reliable for the assessment of TT or DOI (B) in oral cancer and can potentially guide the surgeon in the achievement of adequate resection margins, especially the deep margin.
Abbreviations: US, ultrasound; TT, tumor thickness; DOI, depth of invasion.

pattern, and they may have intranodal necrosis, irregular margin, or present with groups of nodes. Elastography assesses LN elasticity and malignant nodal lesion tends to be stiffer than the benign LN.[17,46] Because there is no single US parameter that can both achieve good sensitivity and favorable specificity in the detection of cervical LN metastases, prediction models using clinical and sonographic features are created to assess malignant nodal disease (Table 2).[16,17,43,46,48] Our group have had proposed a predictive scoring model in predicting malignant cervical LNs,[16] which shows excellent results with c-statistic of 0.90-0.95 in the following internal validations.[17,46] This model is also validated externally at Mount Sinai Medical Center and displays good overall accuracy of 90%.[44] These data suggest that the prediction models can provide the physician reliable probability guidance for performing US-guided FNA/CNB (Figure 2A and B), and a promising method for initial nodal staging.[16,43] The predictive scoring model can also serve as an adjunctive tool in determining how closely a patient's neck should be surveyed.

US can also be used to assist in the evaluation of hot spots at positron emission tomography (PET)/CT. PET/CT is widely used in tumor staging and the evaluation of treatment response and recurrence.[49] However, since the principle of PET/CT is based on the physically 18-F fluorodeoxyglucose uptake, some inflammation may have a higher standardized uptake value and is deemed as malignancy. Yoon et al[50] have shown that subsequent US can help to differentiate the false-positive node and can also simultaneously obtain the US-guided FNA for further evaluation.

## *Guidance of Neck Dissection in Clinically N0 Neck in Early Oral Cancer*

The investigation and management of oral cancer patients with clinically N0 disease are controversial. Most medical centers electively treat the neck with surgery or radiotherapy (RT) because the risk of LN occult metastases is over 20%, even

though the majority of patients will encounter unnecessary neck surgery. Yesuratnam et al[8] have shown that intraoral US can be used for the assessment of TT of tongue cancer and can guide prophylactic neck dissection in early-stage disease. If US-measured TT is ≤4 mm, the LN metastases rate is 12.5%, compared to the LN metastases rate of 36.7% if TT is >4 mm obtained by US.[8] Terada et al[9] have studied the cutoff value of DOI for prophylactic neck dissection in clinical early-stage tongue cancer. The final data shows that the occult LN metastasis rate is 11.1% in patients with pathological DOI < 5 mm versus a rate of 42.1% in patients with pathological DOI ≥ 5 mm. It is reported that adding US in clinically N0 (under CT/MRI) oral cancer patients is able to reduce occult LN metastases from 31% to 18%.[18] Our group has performed a meta-analysis comparing different imaging modalities in the evaluation of clinically N0 neck in head and neck cancer patients.[51] The result shows that if the baseline possibility of clinical occult LN metastases is 30%, the negative predictive rate with a negative US result is 84%, which means the LN metastases rate is below 20%. Therefore, in some selected cases, a watchful waiting policy is feasible. There is one prospective study, including 90 clinically T1-3N0 oral cancer patients, using selected sonographic criteria to determine the cervical LNs.[27] The final results show that 33.7% of unnecessary elective neck dissection can be reduced in the truly negative neck and the occult LN metastases rate is 5.4% for the untreated neck. However, some studies advocate sentinel LN biopsy (SLNB) to detect occult metastasis to prevent unwanted neck dissection in early oral cancer.[52–54] Currently, the 2022 National Comprehensive Cancer Network guideline suggests that SLNB or DOI is the best predictor of neck occult metastasis. For primary tumors with DOI >3 mm, END is suggested as effective management; while for tumors with DOI < 4 mm without suspicious US characteristics of neck LN, close observation can be the feasible management.

**Table 2.** The Reported Prediction Models in the Assessment of Cervical LN.

| Author, year | Prediction model | Sensitivity (%) | Specificity (%) |
|---|---|---|---|
| *For cervical LN* | | | |
| Wu et al[48] | 1 × (age) + 2 × (vascularity index) + 3 × (short-axis) + 4 × (vascular pattern) + 4 × (internal echo) | 89.2 | 85.2 |
| Liao et al[16] | 0.06 × (age) + 4.76 × (S/L ratio) + 2.15 × (internal echo) + 1.80 × (vascular pattern) | 91.3 | 88.2 |
| Lai et al[43] | 2 × (age) + 2 × (S/L ratio) + 3 × (internal matting) + 3 × (vascular pattern) | 91.9 | 88.2 |
| Lo et al[46] | 0.04 × (age) + 2.28 × (S/L ratio) + 3.42 × (internal echo) + 2.29 × (elasticity indices) | 83.3 | 88.2 |
| *For post-RT node* | | | |
| Lo et al[33] | 1.35 × (L-axis) + 2.03 × (S-axis) + 2.27 × (margin) + 1.48 × (echogenic hilum) + 3.7 | 85.5 | 79.4 |

Abbreviations: LN, lymph node; RT, radiotherapy; S/L, the ratio between the short-axis and long-axis diameters.

## Posttreatment Phase

### *Detection of Nodal Malignancy by US in Treated Oral Cancer*

Early detection of regional recurrences is crucial during the follow-up programs for oral cancer patients. Neck US is

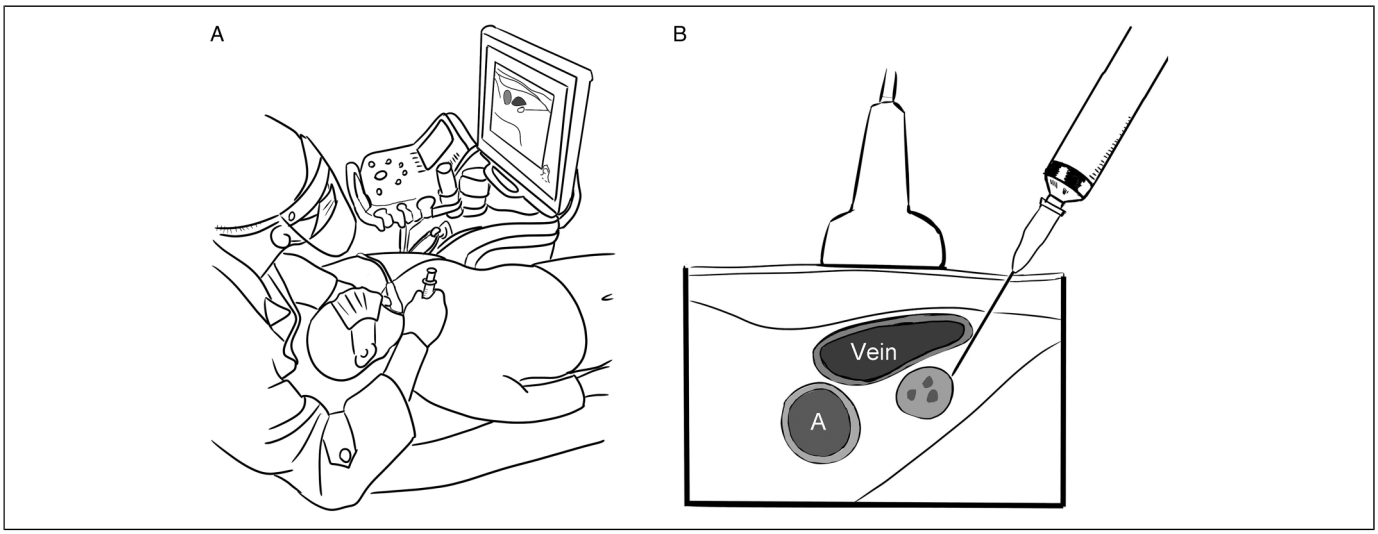


**Figure 2.** (A) Under the real-time guidance of ultrasound (US), FNA can be performed. (B) Large vessels could be visualized and incidental injury could be avoided under the guidance of US.
Abbreviations: US, ultrasound; FNA, fine needle aspiration.

reported to be effective in the posttreatment surveillance.[34,55] Lin et al[32] have displayed a short-axis diameter, S/L ratio (shape), heterogeneous internal echo, and irregular margin are practical US parameters in determining recurrent LNs in the treated neck. Our research group has revealed that RT had an influence on ultrasonographic features in treated oral cancer patients.[31] The recurrent cervical LNs in treated oral cancer patients with previous neck irradiation are smaller in size and have more signs of irregular margin and calcification under US than those without previous neck irradiation. As a result, we have then created a real-time predictive scoring model for the prediction of postirradiation malignant cervical LNs (Table 2).[33] We recommend proceeding to US-guided tissue sampling for the LN with a predictive score ≥6 in clinical use, corresponding to a sensitivity of 97.4% and a negative predictive value of 95.6%.

US-guided FNA/CNB has been shown to have good sensitivity and specificity in detecting nodal malignancy in treated head and neck cancer.[31–33,35,56,57] In the treated neck of head and neck cancer patients, the reported sensitivity and specificity for US-guide FNA are 71.4%-97.1% and 83.3%-100%, respectively.[31,32,56,57] While in US-guided CNB, the demonstrated sensitivity and specificity is 84.5% and 100%, respectively.[35] Although CNB has been considered to have a higher diagnostic rate in detecting true malignancy in the total head and neck regions, the sensitivity and specificity do not differ significantly between both methods in diagnosing squamous cell carcinoma.[15,58] In a treated neck, Lo et al[35] have shown that necrosis and fibrotic change of LNs have a significant adverse effect on the diagnosing performance of CNB with a negative predictive value of 54.7%. Accordingly, for the highly suspicious node in the treated neck, if FNA or CNB cannot provide a convincing answer, repeated FNA/CNB, PET/CT exam,[55] or surgical excision should still be suggested.

### *Doppler US for Follow-up Survey of Carotid Artery Stenosis After Neck Irradiation*

As demonstrated by one meta-analysis, RT to the neck can cause injury and stenosis of the carotid artery.[59] In head and neck cancer patients treated by RT, the prevalence of 50%-70% and ≥70% carotid artery stenosis are 25%-26% and 11%, respectively, and the cumulative incidence continuously increases over time.[59,60] One previous study has reported that screening for ≥60% carotid artery stenosis is cost-effective when the prevalence is more than 20%.[61] There is also at least a 2-fold risk of cerebrovascular disease (CVD) events in head and neck cancer patients treated by RT compared with a normal population. The diagnosis and screening of carotid artery stenosis mainly depend on high resolution and Doppler ultrasonography. Besides, we can obtain the carotid intimal–medial thickness (CIMT), which is the predictor for cardiovascular and stroke events and can further reflect the response of medical treatment by CIMT change.[62,63] Measurement of CIMT using US is useful for assessing CVD risk in oral cancer survivors after neck irradiation (Figure 3) and is promising to improve the CVD risk evaluation.[64] Lifestyle intervention and medical management, including antiplatelet, statins, and angiotensin-converting enzyme inhibitors, are indicated for patients who have atheromatous lesions. Carotid endarterectomy and carotid artery stenting are recommended in postirradiated patients with ≥70% carotid artery stenosis and should be considered in those with 50%-70% symptomatic stenosis.[65,66]

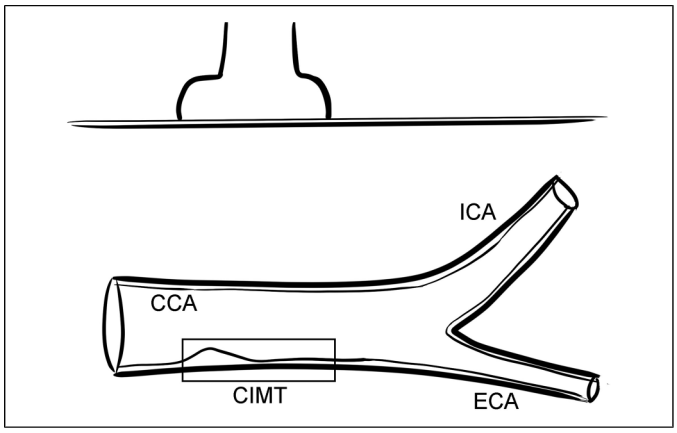


**Figure 3.** Measurement of CIMT using US is useful for assessing cardiovascular disease risk in oral cancer survivors after neck irradiation.
Abbreviations: CIMT, carotid intimal–medial thickness; US, ultrasound.

## Potential Application of US in the Assessment of Oral Cancer

### *US Elastography*

We have performed real-time and shear wave elastography in the assessment of malignant cervical LNs and showed slightly better performance of shear wave elastography, corresponding to a sensitivity of 83.3% and specificity of 64.7%.[17,46] However, if we incorporate real-time or shear wave elastography into our previously proposed predictive scoring model, the diagnostic performance is not significantly increased (Table 2).[16,17,46] Thus, we demonstrate that the parameters of a US-based model including grey-scale and Doppler US are basic and good at determining nodal malignancy. Shear wave elastography can be considered as having a complementary role in diagnosing malignant cervical LN beyond conventional US exams.[46,67]

### *US in Swallowing Assessment*

The presence of speech and swallowing problems in oral cancer patients following surgery or radiation has been well documented in the literature.[68,69] US can be used to assess the dynamic change and different phases of swallowing.[70] In the oral phase, US can evaluate the tongue muscle movement; in the pharyngeal phase, US can measure the movement of hyoid bone and thyroid cartilage, the constriction of the cricopharyngeus muscle, and can check the vocal fold movement.[71,72] Besides

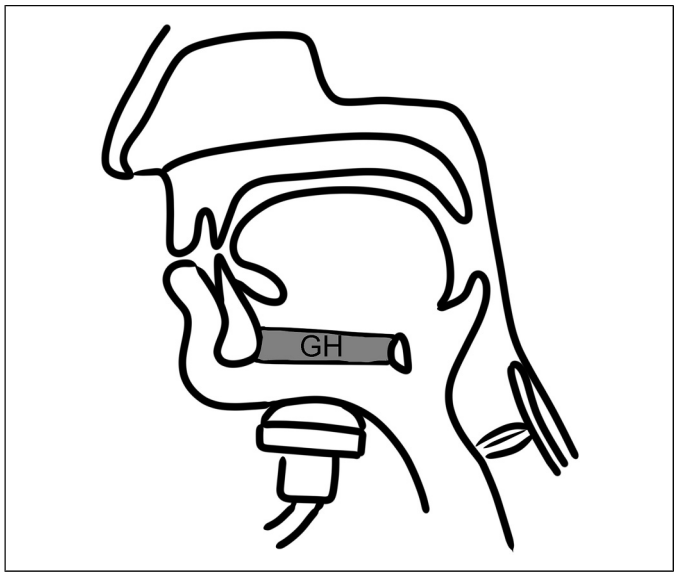


**Figure 4.** US also shows the potential in assisting swallowing rehabilitation in patients who received partial glossectomy by using US visual feedback during swallowing tasks. Tongue-strengthening exercise on the GH muscle may improve swallowing dysfunction.
Abbreviations: US, ultrasound; GH, geniohyoid.

the swallowing phase evaluation, US also shows the potential in assisting swallowing rehabilitation in patients who received partial glossectomy by using US visual feedback during swallowing tasks (Figure 4).[73]

## Conclusions

In the present review, we describe the clinical applications of US in oral cancer management in different phases and potential applications. In the pretreatment and surgical phase, US can be used to evaluate TT/DOI and surgical margins of oral cancer in vivo and ex vivo. The prediction of a cervical LN metastasis by the US-based prediction model can guide the necessity of US-guided FNA/CNB and elective neck dissection in clinical early-stage oral cancer. In the posttreatment surveillance phase, US with/without US-guided FNA or CNB is helpful in the detection of nodal persistence or LN recurrence, and can assess the possibility and extent of carotid artery stenosis after irradiation therapy. Both US elastography and US swallowing assessment are potentially helpful to the management of oral cancer. The clinical application of US in oral cancer should be advocated.

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### Author Contributions

W.C.L., C.M.C., and P.C.C. wrote the manuscript. P.W.C. and L.J.L. reviewed and edited the manuscript. W.C.L. and L.J.L. prepared the tables and figures. All authors reviewed and revised the manuscript.

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