Significance of Intraoral Elastography in the Evaluation of Muscular Invasion of Early-stage Tongue Carcinoma

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Statement of Clinical Relevance

Elastography is an ultrasonographic technology that enables visualization of tissue elasticity. Muscular invasion of the early-stage tongue carcinomas significantly relates to cervical lymph node metastasis. Intraoral elastography suggested to be a promising method to evaluate the muscular invasion of tongue carcinoma through the comparison between preoperative elastography and histopathological findings.

ABSTRACT

Objective. Cervical lymph node metastasis is the most important prognostic factor in patients with tongue carcinoma. Several studies advocate that the muscular invasion of the primary tumor significantly relates to cervical lymph node metastasis. Elastography is an ultrasonographic technology that enables visualization of tissue elasticity. In this preliminary study, we estimated the usefulness of intraoral elastography for the evaluation of muscular invasion of early-stage tongue carcinoma by comparison between preoperative elastography and histopathological findings.

Study Design. Twenty five patients with early-stage tongue carcinomas (Tis, T1, T2) were included (10 females and 15 males; age range 38–85 years). Preoperative intraoral ultrasonography was performed with an intraoperative probe. We evaluated the differences in margins between the hypoechoic tumorous area on B-mode images and the blue hard area on elastographic images.

Results. Among 20 cases with muscular invasion, exudation of the blue hard area around the margin of the hypoechoic tumorous area was observed. In contrast, in five cases with non-invasive carcinoma, the margins of the hard area corresponded almost exactly with those of the hypoechoic tumorous area.

Conclusions. Although the present study included a limited number of cases, it was suspected that intraoral elastography is a promising method to evaluate the muscular invasion of tongue carcinoma.

Cervical lymph node metastasis is a crucial factor in the prognosis of patients with tongue carcinoma. Several studies revealed that lymph node metastasis in tongue carcinoma is associated with the primary tumor thickness (or depth of invasion) and the muscular invasion[1-7]. Thus, the assessment of the extent of tumor in the pre-treatment processes is essential.

Currently, computed tomography (CT), magnetic resonance (MR), and intraoral ultrasonography could be applied for evaluating the extent of tongue carcinoma. In these imaging modalities, intraoral ultrasonography can visualize the whole tumor clearly. By using the significantly high-resolution images obtained by intraoral ultrasonography, the morphological feature of the invasion front of the tongue carcinoma on ultrasonography has been evaluated[8-11].

Commonly, biopsy is applied to confirm a definitive diagnosis for oral cancer including tongue carcinoma. However, it is not easy to obtain adequate specimens which include the invasion front of the tongue carcinoma and even the incision for biopsy itself may be a risk factor for dissemination of cancer cells to surrounding tissue[12]. In contrast, intraoral ultrasonography is a noninvasive and accurate examination for the evaluation of the extent of tumor.

In recent years, ultrasound elastography has been introduced as ultrasound technology that enables the visualization of tissue elasticity, which is used to assess the degree of invasion of carcinoma[13]. Elastography is proved to be significant for differentiating benign from malignant in breast and thyroid gland lesions and assessing liver fibrosis[13-19]. Therefore, elastography combined with conventional intraoral ultrasonography might be also useful to assess the extent of infiltration of tongue carcinoma. However, to the best of our knowledge, no published study has addressed these possibilities. In this preliminary study, we estimated the usefulness of intraoral elastography for the evaluation of muscular invasion of early-stage tongue carcinoma by a side-by-side comparison between preoperative elastography and histopathological findings.

MATERIALS AND METHODS

This retrospective study was approved by the institutional review board. The routinely acquired clinical imaging data was used for this study and any information that can identify individual patients were removed.

From January 2013 to December 2014, 25 consecutive patients with a clinical diagnosis of tongue carcinoma were enrolled. Tumors were staged according to the TNM clinical staging system proposed by the International Union against Cancer. Patients who received preoperative chemotherapy and radiotherapy were excluded. The patients consisted of 15 males and 10 females, with a median age of 64 years (range, 38–85 years). Of the 25 patients, disease stage was Tis in 5 cases, T1 in 7, and T2 in 13; nodal status was N0 in all cases.

Preoperative intraoral ultrasonography and elastography were performed on all the patients by one expert oral and maxillofacial radiologist with 28 years of experience. The ultrasonographic equipment used was the HI VISION Preirus (Hitachi-Aloka Medical, Tokyo, Japan), which had a 7-13 MHz, hockey-stick shaped intraoperative linear probe (EUP-O54J) (Fig. 1). Intraoral ultrasound examination was performed with a probe in which its entire tip was covered with a 3 or 5 mm thickness acoustic coupling polymer gel (“SONAGEL”; Takiron, Tokyo, Japan), with a fingertip or plastic wrap, and the examiner placed the probe on the tumor surface of the tongue. During examination, patients were instructed to protrude the tongue, which was held with a gauze by the examiner for stable data acquisition (Fig. 2). The sonographic structural layers of the normal tongue mucosa from the lateral surface to the deeper layer were detected in a transverse section using acoustic coupling polymer gel as follows: hypoechoic acoustic coupling polymer gel, hyperechoic (white) mucosal surface underlying the acoustic coupling polymer gel, hypoechoic (black) the mucosal layer underlying the mucosal surface, and the mixed hyperechoic and hypoechoic submucosal and muscular layers underlie the mucosal layer (Fig. 3).[7] Typically, carcinoma tissue appeared as a focal hypoechoic area that was contiguous with the surrounding normal mucosal layer on B-mode images. The deep margin of the lesion was commonly ill-defined and irregular (Fig. 4).

The examination procedures are summarized as follows: conventional B-mode images were initially obtained. The probe was moved around the tumor surface until the thickest portion of the hypoechoic lesion was identified; thereafter, the image was frozen and tumor thickness was measured (Fig. 4). Tumor thickness was defined as the distance from the surface of the tumor to the invasion front of the tumor. Then, the operation mode was switched to elastography and intraoral elastography was performed at the thickest portion.

Two different types of ultrasound elastography are currently available: strain imaging and shear wave imaging. The former is based on the comparison of tissue ultrasound echo signals before and after compression, whereas the latter is based on measuring the propagation speed of shear waves that are generated by the acoustic radiation force for quantitative assessment of tissue stiffness. In this study, we employed strain elastography, which was based on the fact that stiff tissues show less displacement than soft ones under the compression. Strain elastography was easy to perform and provided qualitative information through real-time visualization of the stiffness distribution. The major disadvantage of the technique was the lack of quantification methods.

Each pixel of the image was assigned one of 256 specific colors, depending on the degree of strain within the region of interest (ROI). The scale ranged from red for components with the greatest strain (i.e., softest components) to blue for those with no strain (i.e., hardest components). Green indicated average strain in the ROI. These color-scale elasticity images were converted to translucent images and were superimposed on the corresponding B-mode images so that the investigator could easily recognize at a glance the relationship between strain distribution and B-mode characteristics. Color images were constructed automatically with the same image processing settings throughout the study.

In obtaining elasticity images, ROI included the acoustic coupling polymer gel on the top and the deep part of the muscular layer at the bottom. In a normal intraoral elastography, the blue area was limited within the mucosal layer. The target tumor was vertically compressed with light pressure using the ultrasound probe to show the fat-containing muscular layer as mixed red and green (Fig. 5). Elastography images were obtained as motion images, and typical frames were extracted as representative images. Image interpretations were independently performed by three oral and maxillofacial radiologists with three years or more experience on intraoral ultrasonography. All elastography images were evaluated in consensus by them and the typical static frames were chosen for analysis. Both motion and static images were stored in the hard drive of the equipment.

For the side-by-side comparative study, we evaluated the differences in tumor margins between the hypoechoic tumorous area on B-mode and the blue hard area on elastography (Fig. 6) and compared these with muscular invasion on histopathological findings. We defined the word "exudation" on intraoral elastography as more than 1 mm extension of the blue hard area from the margin shown on the B-mode image (Fig. 6). The presence or absence of exudation on elastography was compared with the presence or absence of muscular invasion on histopathology of the excised surgical specimens.

RESULTS

Surgical resections were carried out on all patients, and we compared between preoperative ultrasonography/elastography and histopathological findings of the surgical specimens. Among the 25 cases, 20 were proven to be squamous cell carcinoma (SCC) and five carcinoma in-situ (CIS).

Average tumor thickness on ultrasonography was 5.3 mm (range, 2–12 mm) in patients with SCC and 1.5 mm (range, 1–3 mm) in patients with CIS.

In all 20 cases with muscular invasion on histopathological sections, the range of the hypoechoic lesions on B-mode images were discordant with that of the blue hard areas on elastography, which showed exudation of the blue hard area around the margins of the hypoechoic tumorous area. In contrast, the margins of the hard area corresponded almost exactly with that of the hypoechoic tumorous area in the five cases with non-invasive carcinoma (Table 1, Fig. 7 and Fig. 8).

In four patients with T2 disease, cervical lymph node metastasis subsequently developed after initial surgery at a median duration of 4 months (range, 2–9 months). In these cases, marked muscular invasion was observed histopathologically, and exudation of the elastography blue hard area around the margins of the B-mode hypoechoic tumorous area was observed.

DISCUSSION

Cervical lymph node metastasis is one of the most important prognostic factors in patients with tongue carcinoma. In particular, tongue carcinoma has a comparably high incidence rate to metastasize to cervical lymph nodes compared with those of other subsites of the oral cavity. Several studies revealed that cervical lymph node metastasis had an incidence of approximately 20%–40% in early T1–2 tongue carcinoma,[20-23] and reduced patient survival rates.[24] Therefore, prediction of subclinical lymph node metastasis before treatment is crucial not only to improve the prognosis but also to establish an appropriate treatment plan. Several authors advocated that primary tumor thickness (or depth of invasion) and muscular invasion are significantly related to lymph node metastasis in tongue carcinoma.[1-7]

Currently, computed tomography (CT), magnetic resonance (MR), and intraoral ultrasonography could be applied for imaging evaluation of tumor thickness and muscular invasion of tongue carcinoma. Although modern CT systems provide 0.5- mm isotropic voxel data, the images tend to be easily degraded by metallic artifacts from metal dental prosthesis and restorations in most cases. The soft tissue contrast of routine MR examination is significant enough to delineate tumor extent; however, it is not always easy to clearly define the deepest tumor margin because of the volume averaging effect that arises from a relatively large pixel size and slice thickness. In contrast, intraoral ultrasonography can clearly visualize the whole tumor by direct contact of the ultrasonographic probe to the tumor surface. By using significantly higher resolution images obtained by intraoral ultrasonography, some studies investigated the correlation between sonographic morphological feature of the invasion front of the tongue carcinoma and histopathological findings.[8-11]

Like other carcinomas, tongue carcinoma needs a definitive diagnosis to establish the treatment plan. As the oral cavity is readily accessible for the examination and detection of mucosal malignancies, biopsies of tongue lesions are relatively easy to perform. Although histopathological examination was also useful to determine about the malignant potential of carcinoma tissue, biopsy specimens have often been inadequate for appropriate estimation[25]; moreover, incision for biopsy itself may lead to seeding of cancer cells to surrounding tissue[12]. In contrast, intraoral ultrasonography has been reported to be a noninvasive and accurate examination for the evaluation of tumor thickness and showed significant correlation with histopathological findings.[2,10,11,26,27] Therefore, preoperative intraoral ultrasonography is considered to be mandatory for deciding the extent of resection. However, it is not so easy to estimate the muscular invasion accurately with conventional B-mode images only and few studies evaluated the correlation between on ultrasonography images and histopathological findings of the surgical specimens with regard to muscular invasion.

In recent years, ultrasound elastography has been introduced as a complementary modality that enabled visualization of tissue elasticity, which is used to assess the degree of carcinoma invasion.[13] This technique is based on the fact that carcinoma tissue is harder than the surrounding normal tissue. Elastography can depict tissue stiffness noninvasively and has been proven to be significant in differentiating benign from malignant breast and thyroid gland lesions as well as in the assessment of liver fibrosis,[13-19] and evaluating histological information by depicting the distribution of tissue stiffness[28-31]. Therefore, assessment of tissue stiffness by elastography combined with conventional intraoral ultrasonography may be useful to evaluate the muscular invasion of tongue carcinoma.

In all cases with non-invasive carcinoma, the margins of the hard area on elastography corresponded almost exactly or within 1 mm of the hypoechoic margins on B-mode. On the other hand, exudation of the blue hard area around the margins of the hypoechoic tumorous area was observed in all cases with muscular invasion. This finding appeared to be primarily caused by an interstitial reaction against cancer invasion. Cancer tissue becomes harder as the density of blood vessels and cells increases; this hardening process may begin in the early stages of cancer. Many malignant lesions have higher stiffness not only within the lesions but also within the surrounding tissue. A desmoplastic reaction is characterized by dense fibrosis around neoplasms. Some studies have reported that the high stiffness of tissue surrounding malignant lesions in breast cancers may be caused by desmoplastic reaction or by infiltration of cancer cells.[13, 32] The degree of fibrosis was also known to be correlated with stiffness in thyroid and liver diseases.[16, 19] It has been reported that cancer tissue becomes harder as tumor invasion progresses and stimulates interstitial reaction to cause more fibrosis. Moreover, because the high stiffness value of cancer tissues was reported to correlate with high histological grades, the evaluation of tissue stiffness may potentially grasp the invasive characteristics of cancer tissue.[32]

In the present study, our image interpretation for the evaluation of muscular invasion was based on the elasticity score, which has been applied to differentiate malignant from benign breast lesions.[13] According to this scoring system, the blue area shown on elastography was considered to correspond to the spread of breast cancer. In our study, the margins of the blue hard area on elastography corresponded almost exactly with that of the hypoechoic tumorous area on B-mode images in cases without histopathologic evidence of muscular invasion, whereas exudation of the blue hard area around the margins of the hypoechoic tumorous area was revealed in cases with histopathological muscular invasion. These findings suggested that intraoral elastography estimates the presence or absence of histological muscular invasion in early-stage tongue carcinoma. We were able to differentiate tongue carcinomas with muscular invasion from those without muscular invasion even with same thickness demonstrated on B-mode images when intraoral elastography was added (Figs. 7 and 8). This meant that in early-stage tongue carcinoma with a thickness of 3 mm or less, elastography may help detect pathological muscular invasion, which is difficult to estimate on CT or MRI.

Based on this study, we advocate that intraoral ultrasonography may be advantageous for clinicians in several ways. First, this technique can provide useful information, such as tumor extent, by clearly visualizing even small or thin lesions with crucial findings of muscular invasion; this can aid in deciding the treatment strategy. Second, the spread of this alternative non-invasive technique may reduce the risk of the dissemination of cancer cells to surrounding tissue by biopsy, which should be avoided in patients with poor general conditions or those on antithrombotic therapy. Third, the reproducibility of this technique can enable early detection of malignant transformation from pre-cancerous lesions, like leukoplakia, during follow-up examination.

This study have several limitations. We did not evaluate interobserver and intraobserver variability in data acquisition and interpretation. Although ultrasound is a common technique, elastography may be operator dependent and may require experience in obtaining reproducible results. Static elastography images selected from motion images often tended to be subjectively affected by the examiner’s experience. To overcome this problem, all the intraoral ultrasonographic examinations were performed by a single investigator who was an expert in oral and maxillofacial radiology; image interpretations were independently made by three oral and maxillofacial radiologists with three years or more experience on intraoral ultrasonography and any discrepancies between interpretations were resolved by consensus. Of note, surgical intervention should be avoided before imaging studies including intraoral ultrasonography. Early tongue carcinoma appears as a focal hypoechoic area that is contiguous with the surrounding normal mucosal layer on B-mode images. Alteration of the structural layer by biopsy may interfere with the evaluation of cancer tissue invasion. Additionally, the variable stiffness caused by scarring in healing process after biopsy may influence the strain images.

CONCLUSIONS

Although the present study included a limited number of cases, intraoral elastography may be a promising method for the evaluation of muscular invasion of early-stage tongue carcinoma. Further studies are required to validate its clinical application in the future. The strain elastography was valuable for "at-a-glance" visualization of stiffness distribution of stiffness within ROI, however, this method lacked objectivity because of relative stiffness. To evaluate tissue stiffness quantitatively, strain ratio assessment is utilized by the evaluation of average strain through comparison of cancer tissue and the surrounding normal tissue. For better acquisition of strain ratio data, acoustic coupling polymer gel is recommended as the reference material because its acoustic impedance is similar to that of the living body. Therefore, we intend to use this principle to objectively quantify the stiffness of cancer tissue and its surrounding tissue and to differentiate cancer tissue from inflammatory reaction. Furthermore, we aim to formulate the evaluation criteria for predicting subclinical lymph node metastasis based on studies on intraoral ultrasonography combined with elastography.

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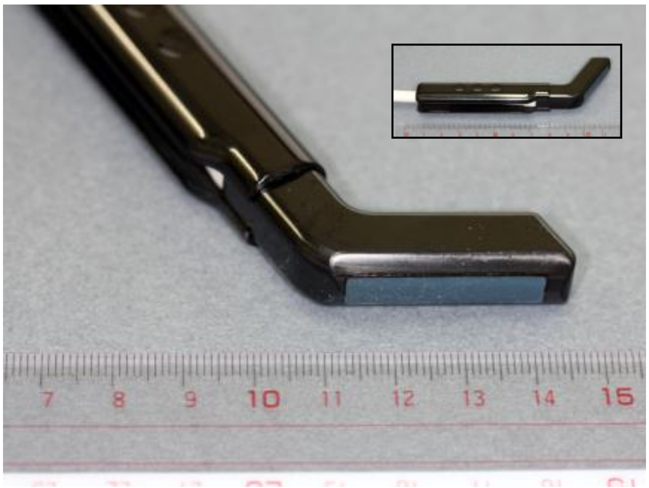

Fig. 1. A 7-13 MHz, hockey-stick shaped intraoperative linear probe (EUP-O54J).

Fig. 2. Intraoral application: The entire tip is covered with a plastic wrap including an acoustic coupling polymer gel. Then the probe is placed on the lateral surface of the tongue.

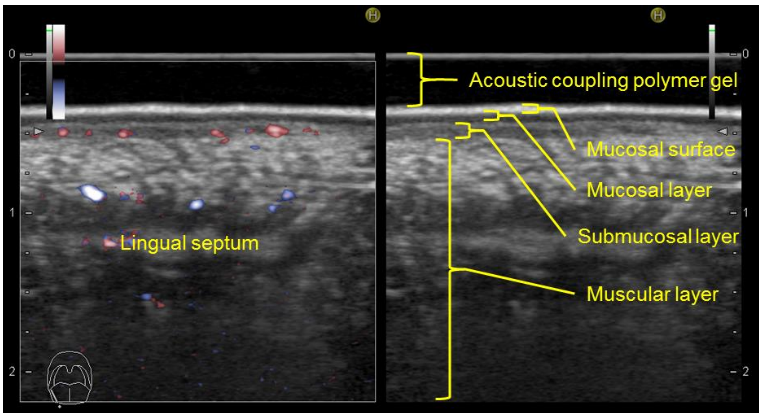

Fig. 3. The sonographic structure of the normal mucosa at the lateral surface of the tongue in a transverse section using acoustic coupling polymer gel.

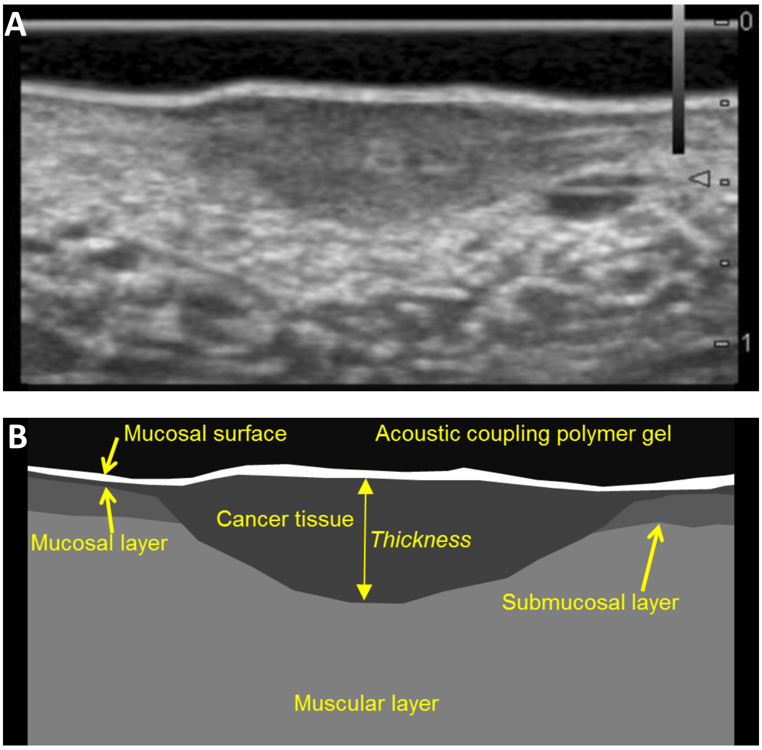

Fig. 4. One of the typical sonographic findings of squamous cell carcinoma of the tongue. **A**, The B-mode ultrasonography. **B**, The schematic drawing of corresponding B-mode image.

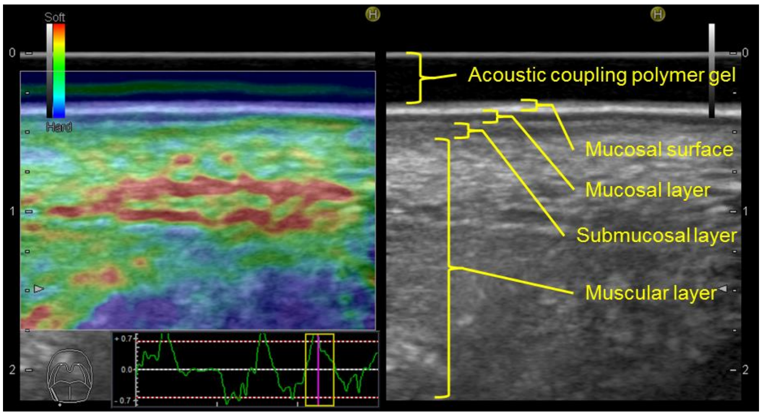

Fig. 5. A normal intraoral elastography of the lateral surface of the tongue in a transverse section. Note the hard, blue area is limited to within the mucosal layer.

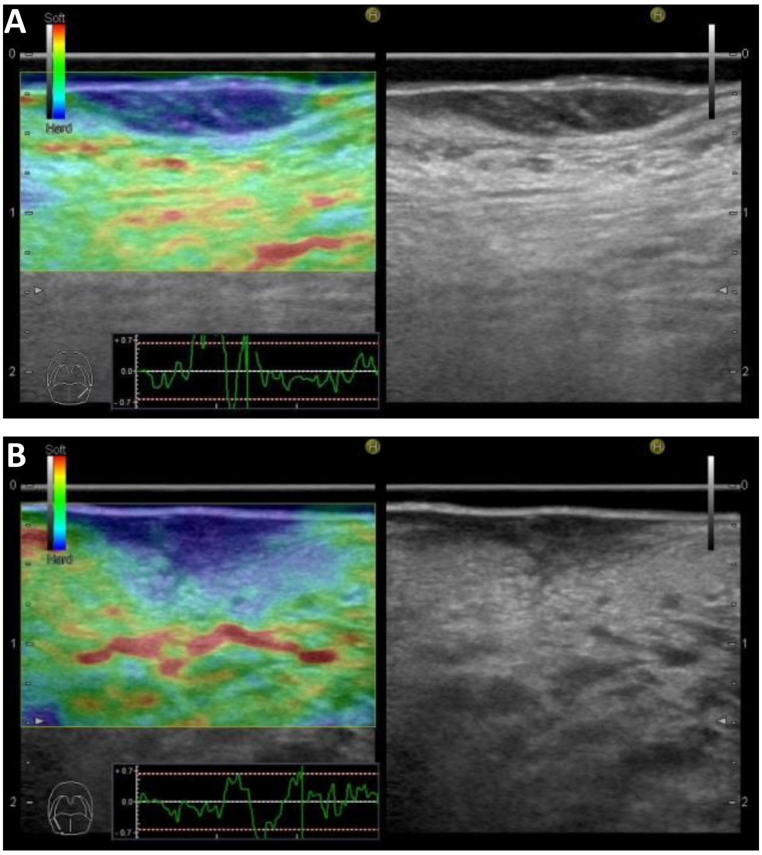

Fig. 6. The intraoral elastography of tongue carcinomas in a transverse section. **A**, The margin of the blue hard area on elastography corresponds almost exactly with that of the hypoechoic tumorous area on B-mode. **B**, The margin of the hypoechoic lesion on B-mode image is discordant with that of the blue hard area on elastography. The "exudation" of the blue hard area around the margin of the hypoechoic tumorous area is observed.

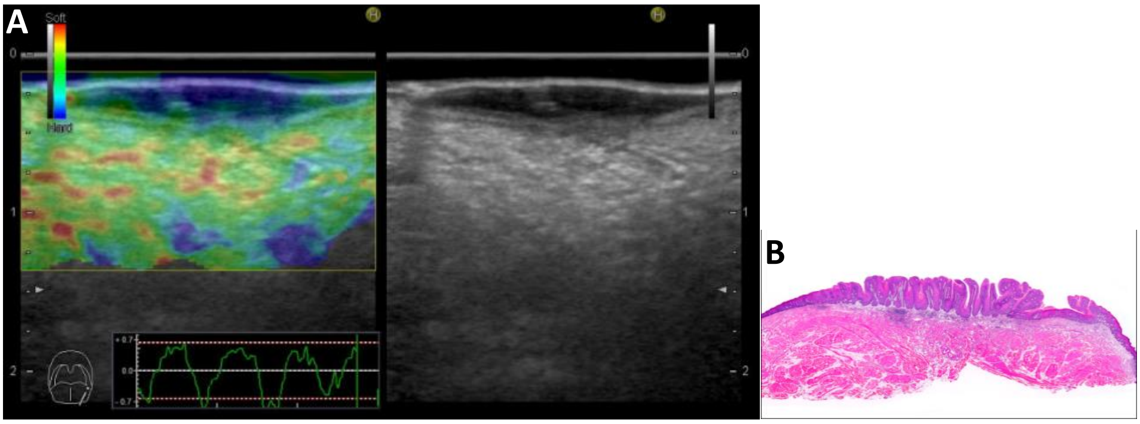

Fig. 7. A case of untreated Tis tongue carcinoma. **A**, An intraoral elastography in a transverse section. No apparent exudation of the blue hard area on elastography around the margin of the hypoechoic lesions on B-mode image is demonstrated. **B**, Histopathological specimen in a frontal section. Pathologically, the lesion was confirmed as carcinoma-in-situ, without muscular invasion.

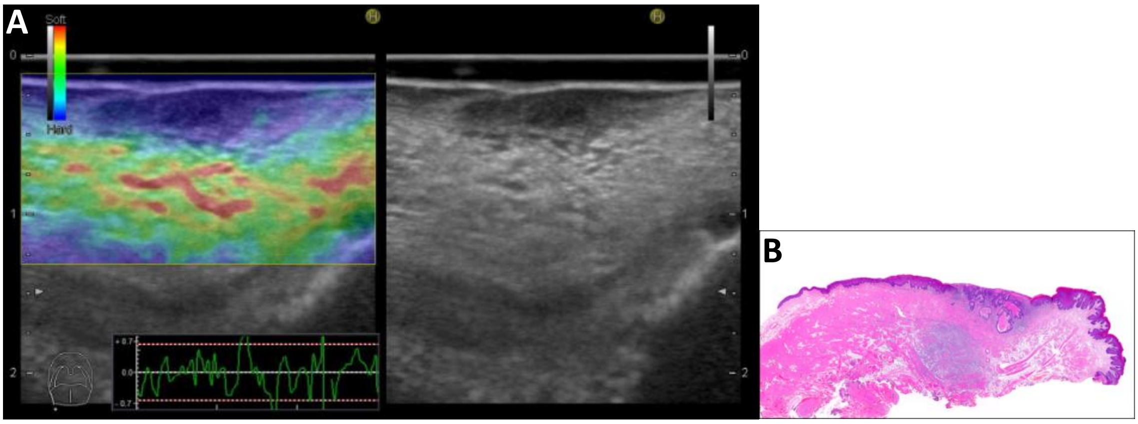

Fig. 8. A case of untreated T2 tongue carcinoma. **A**, An intraoral elastography in a transverse section. An exudation of the blue hard area on elastography around the margin of the hypoechoic lesion on B-mode image is demonstrated. **B**, Histopathological specimen in a frontal section. Pathologically, the lesion was confirmed as squamous cell carcinoma with muscular invasion.

Table 1. A summary of the cases.

Case no.	Gender	Age (years)	Histopathological diagnosis	Tumor thickness on B-mode(mm)	Muscular invasion on histopathology	Exudation on elastography
1	Male	40	CIS	1	No	No
2	Male	78	CIS	3	No	No
3	Male	63	CIS	2	Yes	Yes
4	Female	68	CIS	1	No	No
5	Female	67	CIS	2	No	No
6	Male	38	SCC	3	Yes	Yes
7	Female	80	SCC	2	Yes	Yes
8	Female	60	SCC	6	Yes	Yes
9	Male	70	SCC	3	Yes	Yes
10	Female	40	SCC	1	Yes	Yes
11	Male	71	SCC	4	Yes	Yes
12	Male	51	SCC	7	Yes	Yes
13	Female	57	SCC	4	Yes	Yes
14	Male	63	SCC	3	Yes	Yes
15	Male	68	SCC	9	Yes	Yes
16	Male	74	SCC	8	Yes	Yes
17	Female	60	SCC	5	Yes	Yes
18	Male	64	SCC	4	No	No
19	Male	43	SCC	4	Yes	Yes
20	Male	85	SCC	6	Yes	Yes
21	Female	52	SCC	12	Yes	Yes
22	Female	65	SCC	6	Yes	Yes
23	Male	80	SCC	5	Yes	Yes
24	Male	58	SCC	9	Yes	Yes
25	Female	74	SCC	4	Yes	Yes