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Tumour thickness in oral cancer using an intra-oral ultrasound probe

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Abstract *Objectives* To investigate tumour-thickness measurement with an intra-operative ultrasound (US) probe. *Methods* A retrospective data analysis was undertaken for a total of 65 patients with a T1-2 oral cavity cancer, who were seen at a tertiary referral centre between 2004 and 2010. The correspondence between tumour thickness measured by ultrasonography and histopathology was assessed by Pearson's correlation coefficient, and also between tumour thickness and the development of neck metastasis. *Results* In 11 cases, intra-oral measurement was not optimal due to limited mouth opening ($n=2$) or impossibility to depict the lesion ($n=9$). Tumour thickness measured by US correlated well with histopathology ($n=23$, $R=0.93$). Tumour thickness of ≤7mm carries a risk of lymph node metastasis of 12%, whereas in tumours exceeding 7mm this risk is 57% ($p=0.001$). Twenty-five percent developed neck metastasis and 19% had local recurrence. *Conclusion* Tumour thickness is an important predictive marker for lymph node metastases. As such, it can help in decision-making with regard to management of the primary tumour and neck. Based upon our findings, a wait-and-see policy is only warranted for superficial lesions with tumour thickness of less than 7mm, but only if regular follow-up using US-guided aspiration of the neck is ensured.

Keywords Intra-oral ultrasonography · Tumour thickness · Head and neck · Cervical metastasis · MR imaging

Introduction

Predicting the risk of lymph node metastases in clinically N0 patients with oral cancer is very important in treatment planning for the neck. Tumour thickness has been shown to be one of the most important features in predicting lymph node metastases in oral cancer. Since 1986 several studies have focused on tumour thickness [1–3]. In 2005, Pentenero et al. [4] showed in a large review cut-off points as prognostic factors ranging from 2 mm to 10 mm. Table 1 shows cut-off values for all studies used in this article and studies performed after the review of Pentenero et al. [4]. Tumour thickness is not the only important

Table 1 Reviewed articles: from 1986 to 2009, displayed with number of patients, TNM stage, studied site, and cut-off values found by ultrasound for N0 versus pathological N+ (*FOM* floor of mouth, *N+* tumour thickness significant for nodal involvement)

Reviewed articles	Year	Number patients	TNM	Site	N+	Survival
Spiro et al. [1]	1986	92	Any TN	Oral cavity	2 mm	2 mm
Mohit et al. [14]	1986	84	T1-2N0	FOM	1.5 mm	–
Rasgon et al. [3]	1988	22	Any TN	Oral cavity	5 mm	–
Woolgar et al. [15]	1995	50	T2	Tongue	8 mm	8 mm
Martinez et al. [16]	1995	126	Any TN	Oral cavity	7 mm	–
Fukano et al. [13]	1996	34	Any TN	Tongue	5 mm	–
Shintani et al. [10]	1997	53	Any TN	Oral cavity	8 mm	–
Byers et al. [17]	1998	91	Any TN	Tongue	4 mm	–
Scheer et al. [18]	2005	64	Any TN	Oral cavity	13 mm	14 mm
Veness et al. [19]	2005	99	Any TN	Tongue	5 mm	5 mm
Jing et al. [20]	2006	45	Any TN	Oral cavity	5.2 mm	–
Clark et al. [21]	2006	105	Any TN	Oral cavity	5 mm	–
Wallwork et al. [22]	2007	53	Any TN	FOM	7.5 mm	–
Suzuki et al. [23]	2007	48	T1-2N0	FOM	5 mm	–
Okura et al. [24]	2008	43	Any TN	Tongue	9.7 mm	–
Kim et al. [25]	2008	82	Any TN	Oral cavity	8 mm	8 mm
El-Okeily et al. [26]	2008	124	T1-3N0	Oral cavity	6.5 mm	6.5 mm
Natori et al. [27]	2008	110	Any TN	Tongue	8 mm	8 mm
Huang et al. [2]	2009	1,136	Any TN	Oral cavity	4 mm	–

predictive factor; other important characteristics of the tumour are: epidemiologic parameters such as age, sex, race, alcohol, and/or tobacco intake, clinical parameters (TNM stage, site) and histopathological parameters such as the tumour border, being either infiltrative or more pushing, perineural invasion and vascular invasion [4–6]. Recently, it has also been shown that gene expression of the primary tumour correlates with the risk of cervical metastases [7].

Separate from predicting the development of lymph node metastases, the measurement of tumour thickness may have implications for the treatment of the primary tumour as well. Limited oral cancer in general is treated surgically, using postoperative radiotherapy or chemoradiation in the case of unfavourable histopathological features. In superficial oral cancer, apart from local excision, CO_2 laser resections and photodynamic therapy (PDT) have also been shown to yield excellent results [8].

However, the results of these alternative treatments are very much dependent on the amount of tumour infiltration (i.e. tumour thickness). Although depth of infiltration is predictive for the chance of local recurrence as well [6], it is not routinely used as an indication for postoperative radiotherapy in most clinics. A recent study showed that tumour thickness is also predictive for the risk of contralateral cervical metastasis in tongue carcinoma [9].

To measure tumour thickness, different techniques are available. Several studies have compared intra-oral ultrasound (US) with magnetic resonance imaging (MRI) or computed tomography (CT) [10, 11]. In 1989, Iro and Nitsche [12] showed that using a miniaturised transducer enables the depiction of tumours of the anterior tongue and the floor of the mouth without artefacts. They found this method to be superior to conventional US for this region.

Since June 2007 we have been using a new intraoperative transducer (Philips IU-22 L 15-7; 7–15 MHz). In this study, we present our results with respect to the feasibility of US measurement of intra-oral tumour thickness, correlation with the presence of lymph node metastases as well as correlation with MRI, with histopathology as the "gold standard".

Patients and methods

Ethical considerations

This was a retrospective study with anonymous evaluation of data; therefore, written informed consent was not required.

Selection criteria

All patients with stage T1–T2 oral cancer planned for transoral excision or photodynamic therapy (PDT) in our department were included (*n*=65). All patients were seen between 2004 and 2010.

Participants

Ages ranged from 42 to 89 years (mean 65 years) and the sex ratio was 34 men to 31 women. The cancers were localised in the tongue (*n*=38), the floor of the mouth (*n*=22) and elsewhere in the mouth (*n*=5).

Clinical T-stages of the 65 patients were as follows: T1 (*n*=50), T2 (*n*=15); N-stages were: N0 (*n*=59), N1 (*n*=4) and N2 (*n*=2).

Intra-oral US was used in all 65 patients, and MRI was performed in 36 cases. MRI was only performed as part of the preoperative treatment planning, in patients possibly applicable for transoral excision. In 13 cases the lesion was not found on MRI, because of superficial growth. These lesions were interpreted as minimal lesions of less than 1-mm thick.

Patients underwent transoral excision (n=30), CO_2 laser excision (n=3) or photodynamic therapy (PDT) (n=29), or a combination of surgery with postoperative radiotherapy (n= 3). Within the group of patients treated with PDT (n=29) the localisations were as follows: 13 tumours of the tongue, 13 in the floor of the mouth and three elsewhere in the mouth.

Twelve patients underwent a primary neck dissection.

Histopathological data on thickness were available in all 33 surgically treated patients.

Current treatment protocol

US measurement of tumour thickness is currently used to select patients treatable with PDT. In tumours of less than 5-mm thick, PDT treatment can be used as light penetration up to 1 cm. We chose PDT especially in cases where surgery carried a risk of Warthin's duct obstruction or a marginal mandibulectomy. For thicker tumours, we always perform a local excision. The neck is staged using US-guided aspiration cytology (USgFNAC) and a sentinel node procedure in the case of a negative USgFNAC and treatment of the primary with transoral excision. For negative sentinel nodes, a wait-and-see policy is the standard. In the case of positive sentinel nodes or a positive USgFNAC, a neck dissection is carried out.

Measurement of tumour thickness

For US measurement of tumour thickness, an intra-operative transducer (Philips IU-22, L15-7; 7–15 MHz) was used (n=44). Before June 2007, a small parts transducer probe (5–7 MHz) was used in 21 patients. Tumour thickness was measured by placing the probe directly on the lesion. The same radiologist performed all intra-oral measurements on the outpatient clinic, 1 or 2 weeks before surgery without anaesthesia.

Using an US probe or MRI, the thickness of the tumour is measured and not the depth of infiltration from an imaginary line at the level of the mucosal surface. So, in this study we measured maximal tumour thickness also with histopatho-logical sections, and not the depth of infiltration.

On histological sections, the tumour thickness was measured using the ocular micrometer. MRI examinations were performed at 3.0 T (Philips Achieva release 3.2.1, Philips Medical Systems, Best, The Netherlands) using a dedicated 16-channel SENSE neurovascular coil.

The following series were acquired: STIR TSE COR, TR (repetition time), IR (inversion time), TE (echo time) 3,880/180/20 ms, ETL: 12, FOV 300/228/40 mm, matrix: 320/320, 2 nex, slice thickness 4 mm; STIR TSE TRA, TR/IR/TE 4,228/180/20, ETL: 12, FOV: 180/200/80 mm, matrix 300/312, 2 nex, SW 3.5 mm, T1 TSE TRA, TR/ TE: 780/10, ETL: 5, FOV 180/180/80, matrix 384/384, 2 nex, slice thickness: 3.5 mm; T1 3D Thrive [performed after intravenous injection of 15 cc gadoterate meglumine (Dotarem)], TR/TE: 5/2,22, ETL:90, TA: 10, FOV 230/ 272/220, matrix 288/288, 2 nex, slice thickness: 0.8 mm;

T1 TSE COR (post contrast): TR/TE: 812/10, ETL: 6, FOV: 180/150/96 mm, matrix: 320/320, 3 nex, slice thickness 3.5 mm.

The US findings of the patients treated with PDT and CO_2 laser could not be correlated with histopathological measurements, for obvious reasons. Figure 1 shows the measurement of a tumour using the three techniques.

Statistical analysis

The correlation between tumour thickness as measured by US, MRI and in the histopathological sections was evaluated. Pearson's product correlation analysis was performed on all data in order to determine the overall correlation between them. The correlation between tumour thickness and the presence of lymph node metastases was analysed using the chi-squared test.

Results

Tumour thickness

For all 65 patients, US measurement of the oral lesion was obtained. For 11 cases, intra-oral measurement was not optimal due to limited mouth opening (n=2) or the impossibility of depicting the lesion (n=9). There was no difference between the old and the new transducer probe (four versus seven cases). Tumour thickness ranged from 1 mm to 35 mm, with an average of 8 mm.

MRI was performed on 36 patients. Tumour thickness ranged from 1 mm to 24 mm, with an average of 5 mm.

On histopathology (n=33), tumour thickness ranged from 1 mm to 35 mm with an average of 8 mm.

Correlation with histopathology

Correlation between US and histopathology could be made in 31 cases. For two surgically treated patients, US could not be performed. Correlation between MRI and histopathology could be made in 22 cases. Pearson's product correlation (Figs. 2, 3) between US and MRI imaging was significantly different. With a correlation product of R=0.87, US correlated better with histopathology than MRI (R=0.54). Comparing the old transducer used before 2007 and the new intra-oral probe, the Pearson's product was respectively 0.05 versus 0.93 (Fig. 4)

Neck node metastases

In total, 12 patients (N0=6, N1=4, N2=2) initially underwent 12 neck dissections, six therapeutic and six elective. Of these 12 neck dissections, nine were patho-logical N+ (pN+). In total, 53 clinically N0 patients did
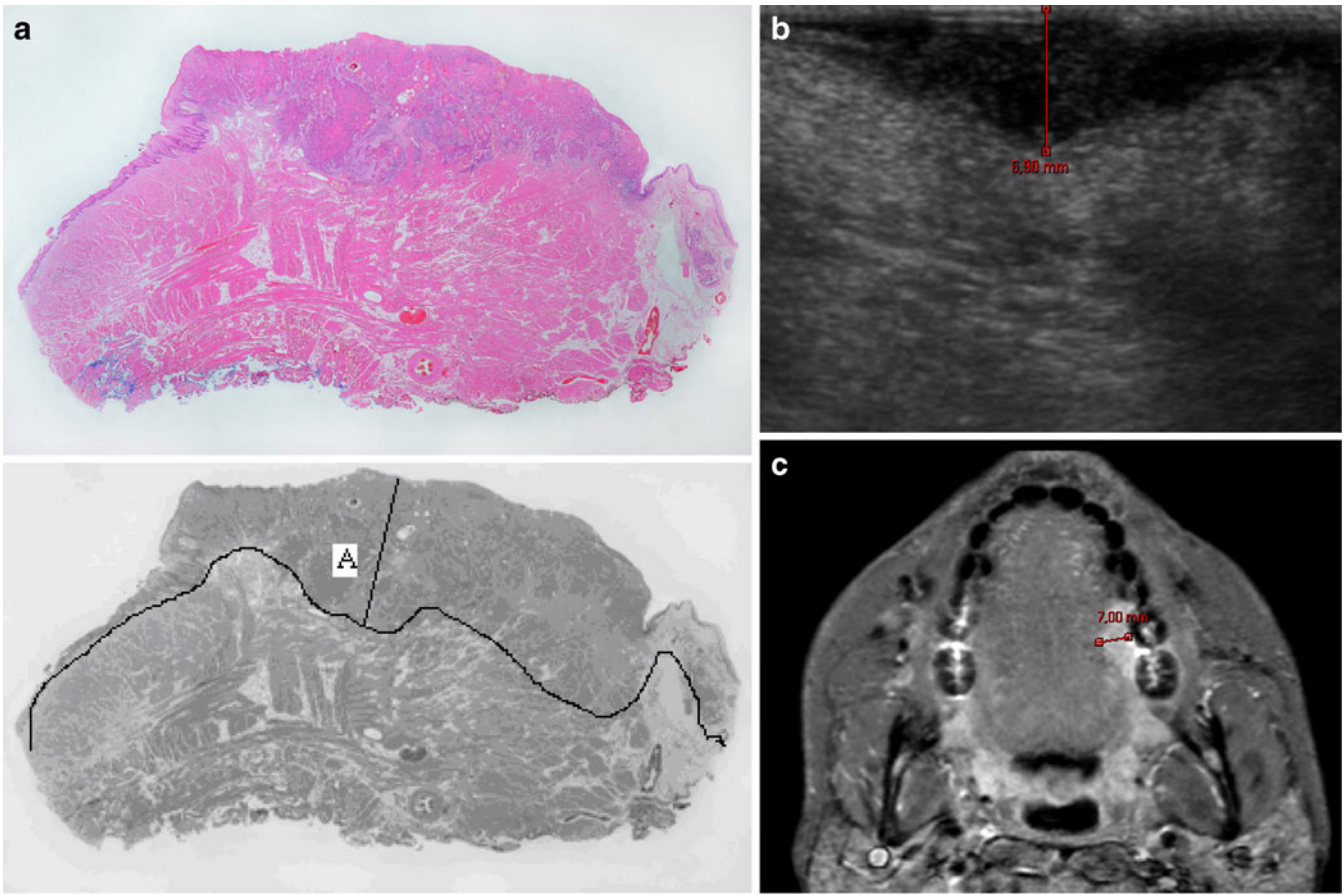
Fig. 1 Tumour thickness on histology, US and MRI. **a** Histological section showing a tumour of the tongue. Tumour thickness is 8 mm (*A* indicates diameter). **b** US picture of the same tumour of the tongue. **c** Tumour thickness measured on MRI

not undergo a neck dissection initially. During follow-up, seven patients in this wait-and-see group developed a neck node metastasis. Of these seven patients, three also had local recurrence. Thus, a total of 16 of the 65 (25%) patients were pN+. Of these 16 patients, US could be performed in 13 cases.

Correlation of tumour thickness and lymph node involvement

In the patients with available histopathological measurement, histopathologically measured tumour thickness was used to correlate with lymph node metastasis. For
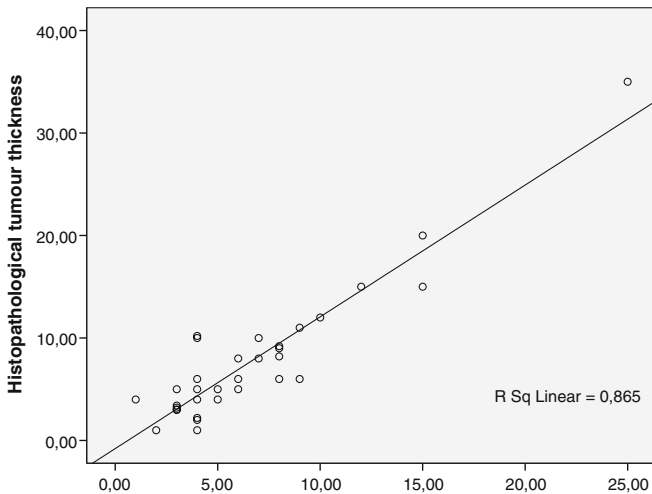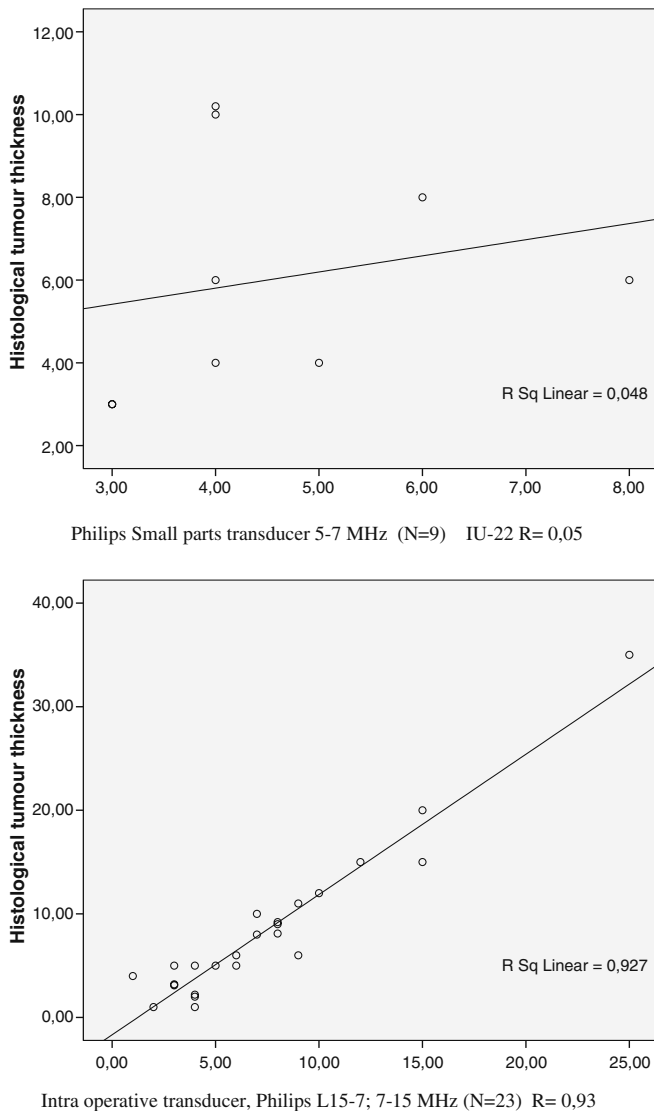

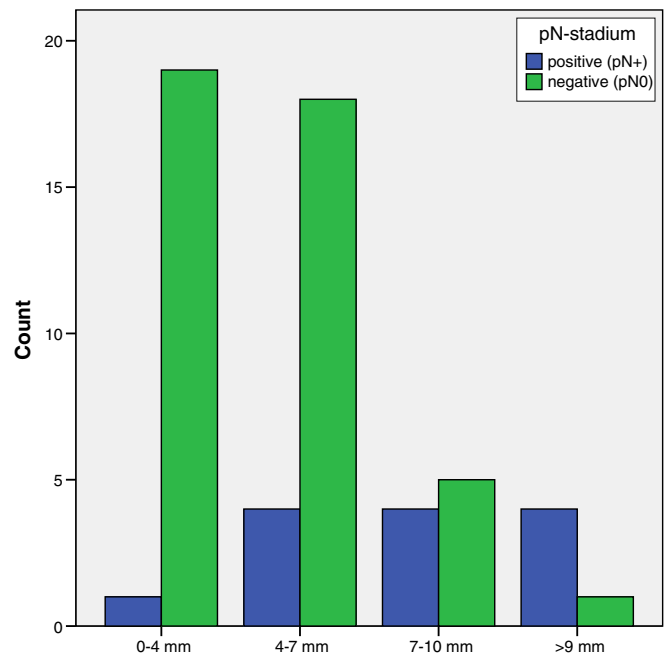**Fig. 2** Correlation between tumour thickness on histological section and by US; $n=32$, Pearson's product $R=0.87$
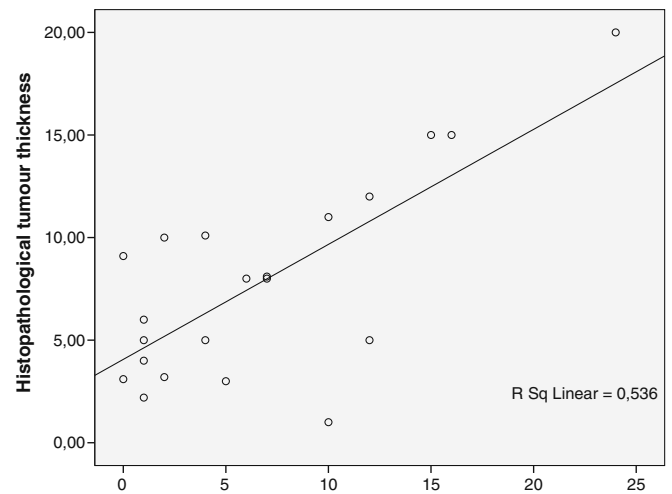
Fig. 3 Correlation between tumour thickness on histological section and by MRI; $n=22$, Pearson's product $R=0.54$

Philips Small parts transducer 5-7 MHz (N=9)   IU-22 R= 0,05

Intra operative transducer, Philips L15-7; 7-15 MHz (N=23) R= 0,93

Fig. 4 Correlation between tumour thickness on histological section and by US. Sub-selection between a Philips small-parts transducer probe (5–7 MHz) and the intraoperative transducer probe, Philips IU-22)

Fig. 5 Relationship between tumour thickness and cervical metastases (*n*=56). Tumour thickness measured by intra-oral US probe, if not available measured by histopathology *N*=56. *Green* represents the patients with no neck metastasis within the 2-year follow-up period; *blue* represents the patients with positive neck nodes during the follow-up period

the 32 cases in which histopathology was not possible, the US-measured thickness was used (only measured with the new intra-oral transducer probe). Therefore in total, correlation was possible in 56 patients (Fig. 5). One metastasis (1/20=5%) was found in patients with a histological tumour thickness of 3 mm or less. Four patients had cervical metastasis with tumour thickness between 4 and 7 mm (4/22=18%). When the tumour thickness exceeded 7 mm, the cervical metastases rate increased to 57% (8/14). The difference in metastasis for 7-mm tumour thickness was significant at $p=0.001$. Table 2 shows sensitivity and specificity by cut-off value.

Correlation of tumour thickness and lymph node involvement by site

Within the group of tongue carcinomas (*n*=36), none of the patients had cervical metastasis with histological tumour thickness of 3 mm or less (Fig. 6). Three patients had cervical metastasis with tumour thickness between 4 and 7 mm (3/18=17%). When the tumour thickness exceeded 7 mm, the cervical metastasis rate increased to 44% (4/9). The difference in metastasis for 7-mm tumour thickness is significant with $p=0.03$.

Within the group of floor of mouth carcinomas (*n*=15), none of the patients had cervical metastasis with histological tumour thickness of 7 mm or less. When the tumour thickness exceeded 7 mm, the cervical metastasis rate increased to 80% (4/5). The difference in metastasis for 7-mm tumour thickness is significant at $p=0.001$.

Local recurrence versus tumour thickness

Tumour thickness measured by histopathology was used for correlation with local recurrences. In our series, 12 patients (12/65=19%) had a local recurrence within the follow-up period. In five cases, recurrences occurred at a thickness of 0–4 mm (5/20=25%), none in the 4–7-mm group, two in the 7–10-mm group (2/7=22%) and no local recurrence occurred in the group with tumour thickness of >9 mm.

Table 2 Sensitivity, specificity and significance level versus cut-off points for tumour thickness

Cut-off point	Sensitivity	Specificity	p value
Total group (n=56)			
≥3 mm/<3 mm	90%	26%	0.275
≥4 mm /<4 mm	95%	33%	0.016
≥5 mm/<5 mm	88%	39%	0.019
≥6 mm/<6 mm	90%	53%	0.001
≥7 mm/<7 mm	88%	57%	0.001
≥8 mm/<8 mm	87%	64%	<0.001
Tongue carcinomas (n=36)			
≥3 mm/<3 mm	100%	21%	0.374
≥4 mm /<4 mm	100%	26%	0.089
≥5 mm/<5 mm	89%	29%	0.153
≥6 mm/<6 mm	92%	42%	0.017
≥7 mm/<7 mm	89%	44%	0.029
≥8 mm/<8 mm	86%	43%	0.081
Floor of mouth carcinomas (n=15)			
≥3 mm/<3 mm	100%	40%	0.099
≥4 mm /<4 mm	100%	50%	0.029
≥5 mm/<5 mm	100%	67%	0.004
≥6 mm/<6 mm	100%	80%	0.001
≥7 mm/<7 mm	100%	80%	0.001
≥8 mm/<8 mm	100%	100%	<0.001

There was no significant correlation between chance of local recurrence and tumour thickness.

Discussion

Synopsis of key/new findings

Although this is a retrospective study, all measurements were performed only once and by the same observer, and histology was not available in all patients, this study demonstrates that the measurement of tumour thickness with the new generation of intra-oral US transducers correlates well with histopathological thickness in oral cavity cancer ($R=0.93$). Between 2004 and 2007, we used a non-dedicated small-parts transducer for measurement and this yielded inferior results ($R=0.05$). This clearly shows that it is necessary to use a dedicated small-parts transducer to obtain reliable measurements.

In our study, MRI correlated less well with histopathology than US ($R=0.54$). Worldwide, MRI measurements are regularly performed in patients with oral cancer. In our series, 13 of the 36 patients had lesions that could not be measured by MRI because of superficial growth, and these were treated with PDT. Therefore, histopathological measurement could not be performed. We were able to perform correlation in 26 cases; in those cases whereboth MRI and histopathological measurements were available, the correlation was only $R=0.54$.

In this study, the risk of metastasis in the neck with tumour thickness of 6 mm or less was 12% (five out of 42), whereas when tumour thickness was 7 mm or more this risk was 57% (eight out of 14). For tongue carcinoma, the risk of metastasis in the neck with tumour thickness of 6 mm or less was 11% (three out of 27), whereas when tumour thickness was 7 mm or more this risk was 44%

(four out of nine). For floor of mouth carcinoma, the risk of metastasis in the neck with tumour thickness of 6 mm or less was 0% (none out of ten), whereas when tumour thickness was 7 mm or more this risk was 80% (four out of five). From these data we conclude that within the overall group 7-mm tumour thickness is the cut-off value that optimally stratifies patients at a low versus high risk of development of neck node metastases ($p=0.001$). However, as shown in Table 2, it is a matter of compromise between the sensitivity and specificity of a given cut-off value to make a choice for the optimal value. With a cut-off point of 7 mm, the sensitivity in our study was 88% and the specificity 57% (Table 2). By dividing the group by site, the optimal cut-off value would be 7 mm for both groups, although this was determined within small groups ($n=36$ vs $n=15$).

Comparisons with other studies

Our findings, using the dedicated intra-oral/intra-operative probe confirm those published by Iro and Nitsche [12]. Rasgon et al. [3] showed that the percentage of cervical lymph node metastases in lesions less than 5-mm thick was significantly lower compared with those with lesions with a thickness more than 5 mm. Also, Shintani et al. [10], who studied 24 patients, found a strong correlation between tumour thickness measured with US and histology (Pearson's product $R=0.98$). They found that tumours thicker than 20 mm showed discordant results, possibly caused by tissue constriction during fixation with formalin. Lesions smaller than 10 mm showed a significantly better correlation.

Shintani et al. [10] also compared the accuracy of US and MRI in assessing tumour thickness. They found that US and MRI correlated well with histopathology. However, MRI could not identify most of the tumours less than 5.0-mm
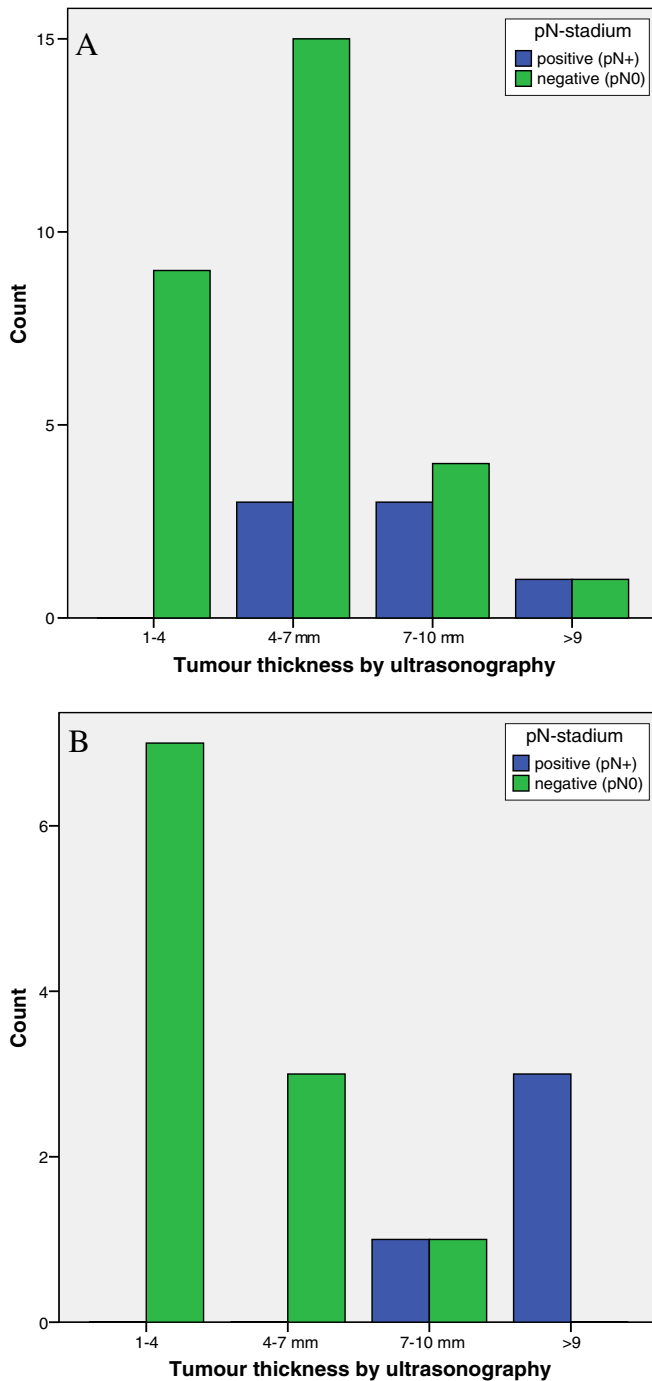
Fig. 6 Relationship between tumour thickness and cervical metastases divided by site. Tumour thickness measured by intra-oral US probe, if not available measured by histopathology. *Green* represents the patients with no neck metastasis within the 2-year follow-up period; *blue* represents the patients with positive neck nodes during the follow-up period. **a** The group with tongue carcinoma (*n*=36); **b** the group with floor of mouth carcinoma (*n*=15)

thick. Preda et al. [11] showed a significant direct correlation between the measured histological and measured MRI tumour thickness (correlation coefficient=0.80, *p*<0.0001).

In the literature, discussion remains as to which cut-off point is optimal [1–4, 10–30], and in the more recent literature, cut-off points range between 3 and 8 mm [2, 13].

In a large clinical review by Pentenero et al. [4], tumour thickness was shown to be an important parameter for predicting nodal metastases and for survival. They showed that in the literature the cut-off thickness predicting neck metastasis and survival varied from 1.5 mm to 10 mm. Thus, it remains difficult to choose a reliable cut-off point for elective neck treatment and/or adjuvant radiotherapy.

The indication for elective neck treatment is mainly based on the expected risk of occult metastases. With respect to this risk assessment, Spiro et al. [1] retrospectively analysed tumour thickness in 92 patients treated with surgery for tongue and floor of mouth carcinomas. They concluded that for clinically N0 oral cancer, elective neck dissection was indicated in patients with depth invasion of more than 2 mm because in these tumours the risk of metastases reached 40%. Fukano et al. [13], on the other hand, showed that tongue tumours exceeding 5 mm carried a risk of 65% for neck metastases, whereas those infiltrating 5 mm or less had a risk of only 6% (significant difference, *p*=0.0003).

A meta-analysis by Huang et al. [2] showed an association between tumour thickness and cervical lymph-node involvement and they stated that the optimal cut-off point for tumour thickness is 4 mm. For oral cavity tumours thicker than 4 mm, prophylactic neck management should generally be recommended according to this study.

At present, little is known about the correlation between tumour thickness and local recurrences of oral cavity carcinomas. In our study, there was no significant difference in local recurrences using the cut-off point for tumour thickness of more or less than 7 mm. Yuen et al. [6] showed in 2002 that tumour thickness is prognostic for both nodal and local recurrence in oral carcinomas. With a tumour thickness less than 3 mm, 0% had local recurrences and 8% had nodal metastases; tumour thickness of more than 3 mm and up to 9 mm had 44% subclinical nodal metastasis and 7% local recurrence; tumour thickness of more than 9 mm had 53% subclinical nodal metastasis and 24% local recurrence. In our series, not enough patients with tumour thickness of 10 mm or more were included to compare these results. Extracting the results from Spiro et al. [1], local recurrence occurred in 5% of the group of tumours with thickness <2 mm (2/40), 9% (3/35) within the group 3–8 mm thick and 25% (4/17) for the group with thickness >9 mm. Local recurrence occurred significantly more in the group with tumour thickness of more than 8 mm, at *p*=0.035. Yet more factors like perineural invasion, radical operation, postoperative treatment and N-staging should also be considered in relation to local recurrence [6].

Clinical applicability of the study

From this and other studies, it is clear that state-of-the-art US has a high correlation with histopathological thickness [10, 12]. US thus seems to be the optimal technique in patients with no limited mouth opening or base of tongue involvement. US measurement is more reliable than MRI for the measurement of tumour thickness, especially in superficial lesions.

All currently available literature shows depth of invasion or tumour thickness measurements of the primary tumour, most often only in small groups. The identification of a cut-off with adequate utility for clinical decision-making requires large studies and independent validation.

making with regard to management of the primary tumour and neck. Based upon our findings, a wait-and-see policy is only warranted in superficial lesions with tumour thickness less than 7 mm, but only if regular follow-up using US-guided aspiration of the neck is ensured [31, 32].

Conclusion

Tumour thickness is an important predictive marker for lymph node metastases. As such, it can help in decision-

References

1. Spiro RH, Huvos AG, Wong GY, Spiro JD, Gnecco CA, Strong EW (1986) Predictive value of tumor thickness in squamous carcinomas confined to the tongue and floor of the mouth. Am J Surg 152:345–350
2. Huang SH, Hwang D, Lockwood G, Goldstein DP, O'Sullivan B (2009) Predictive value of tumor thickness for cervical lymph-node involvement in squamous cell carcinoma of the oral cavity. Cancer 115:1489–1497
3. Rasgon BM, Cruz RM, Hilsinger RL, Sawicki JE (1988) Relation of lymph-node metastasis to histopathologic appearance in oral cavity and oropharyngeal carcinoma: a case series and literature review. Laryngoscope 99:1103–1110
4. Pentenero M, Gandolfo S, Carrozzo M (2005) Importance of tumor thickness and depth of invasion in nodal involvement and prognosis of oral squamous cell carcinoma: a review of the literature. Head Neck 27:1080–1091
5. Brandwein-Gensler M, Teixeira MS, Lewis CM et al (2005) Oral squamous cell carcinoma: histologic risk assessment, but not margin status, is strongly predictive of local disease-free and overall survival. Am J Surg Pathol 29:167–178
6. Po Wing Yuen A, Lam KY, Lam LK et al (2002) Prognostic factors of clinically stage I and II oral tongue carcinoma-A comparative study of stage, thickness, shape, growth pattern, invasive front malignancy grading, Martinez-Gimeno score, and pathologic features. Head Neck 24:513–520
7. Roepman P, de Jager A, Groot Koerkamp MJ, Kummer A, Slootweg PJ, Holstege FC (2006) Maintenance of head and neck tumor gene expression profiles upon lymph node metastasis. Cancer Res 66:11110–11114
8. Biel MA (2007) Photodynamic therapy treatment of early oral and laryngeal cancers. Photochem Photobiol 83:1063–1068
9. Bier-Laning CM, Durazo-Arvizu R, Muzaffar K et al (2009) Primary tumor thickness as a risk factor for contralateral cervical metastases in T1/T2 oral tongue squamous cell carcinoma. Laryngoscope 119:883–888
10. Shintani S, Yoshihama Y, Ueyama Y et al (2001) The usefulness of intraoral ultrasonography in the evaluation of oral cancer. Int J Oral Maxillofac Surg 30:139–143
11. Preda L, Chiesa F, Calabrese L et al (2006) Relationship between histologic thickness of tongue carcinoma and thickness estimated from preoperative MRI. Eur Radiol 16:2242–2248
12. Iro H, Nitsche N (1989) Intra-oral sonography in neoplasms of the mouth and base of the tongue. HNO 37:329–332
13. Fukano H, Matsuura H, Hasegawa Y, Nakamura S (1997) Depth of invasion as a predictive factor for cervical lymph node metastasis in tongue carcinoma. Head Neck 19:205–210
14. Mohit-Tabatabai MA, Sobel H, Rush BF, Mashberg A (1986) Relation of thickness of floor of mouth stage I and II cancers to regional metastasis. Am J Surg 152:351–353
15. Woolgar JA, Scott J (1995) Prediction of cervical lymph node metastasis in squamous cell carcinoma of the tongue/floor of mouth. Head Neck 17(6):463–472
16. Martínez-Gimeno C, Rodriguez E, Vila CN, Varela CL (1995) Squamous cell carcinoma of the oral cavity: a clinicopathologic scoring system for evaluating risk of cervical lymph node metastasis. Laryngoscope 105:728–733
17. Byers RM, El Naggar A, Lee YY et al (1998) Can we detect or predict the presence of occult nodal metastases in patients with squamous carcinoma of the oral tongue? Head Neck 20:138–144
18. Scheer M, Kubler A, Manawi NN, Reuther T, Zöller JE (2005) Endosonographic imaging of tumor thickness in oral squamous cell cancer and its effect on the incidence of lymph node metastases. Mund Kiefer Gesichtschir 9:282–289
19. Veness MJ, Morgan G, Sathiyaseelan Y, Gebski V (2005) Anterior tongue cancer and the incidence of cervical lymph node metastases with increasing tumour thickness: should elective treatment to the neck be standard practice in all patients? ANZ J Surg 75:101–105
20. Jing J, Li L, He W, Sun G (2006) Prognostic predictors of squamous cell carcinoma of the buccal mucosa with negative surgical margins. J Oral Maxillofac Surg 64:896–901
21. Clark JR, Naranjo N, Franklin JH, de Almeida J, Gullane PJ (2006) Prognostic variables in N0 oral carcinoma. Otolaryngol Head Neck Surg 135:748–753
22. Wallwork BD, Anderson S, Coman WB (2007) Squamous cell carcinoma of the floor of the mouth: tumour thickness and the rate of cervical metastasis. ANZ J Surg 77:761–764
23. Suzuki M, Suzuki T, Asai M et al (2007) Clinicopathological factors related to cervical lymph node metastasis in a patient with carcinoma of the oral floor. Acta Otolaryngol Suppl 559:129–135
24. Okura M, Iida S, Aikawa T et al (2008) Tumor thickness and paralingual distance of coronal MR imaging predicts cervical node metastases in oral tongue carcinoma. AJNR Am J Neuroradiol 29:45–50
25. Kim SY, Roh J, Kim JS et al (2008) Utility of FDG PET in patients with squamous cell carcinomas of the oral cavity. Eur J Surg Oncol 34:208–215

26. El-Okeily M, El-Bouihi M, Ricard AS et al (2008) Mouth floor and mobile tongue epidermoid carcinomas thickness: prognostic value. Rev Stomatol Chir Maxillofac 109:81–85

27. Natori T, Koga M, Anegawa E et al (2008) Usefulness of intra-oral ultrasonography to predict neck metastasis in patients with tongue carcinoma. Oral Dis 14:591–599

28. Jones KR, Lodge-Rigal R, Reddick RL et al (1992) Prognostic factors in the recurrence of stage I and II squamous cell cancer of the oral cavity. Arch Otolaryngol Head Neck Surg 118:483–485

29. Hosal AS, Unal O, Ayhan A (1998) Possible prognostic value of histopathologic parameters in patients with carcinoma of the oral tongue. Eur Arch Otorhinolaryngol 255:216–219

30. Nathanson A, Agren K, Biorklund A et al (1989) Evaluation of some prognostic factors in small squamous cell carcinoma of the mobile tongue: a multicentre study in Sweden. Head Neck 11:387–392

31. Van den Brekel MW, Stel HV, Castelijns JA, Croll GJ, Snow GB (1991) Lymph node staging in patients with clinically negative neck examinations by ufltrasound and ultrasound-guided aspiration cytology. Am J Surg 162:362–366

32. Van den Brekel MW (1996) US-guided fine-needle aspiration cytology of neck nodes in patients with N0 disease. Radiology 201:580–581