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Intra-Operative Per-Oral Ultrasonography to Guide Resection of the Deep Surgical Tumor- Free Margins in Carcinoma Tongue

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ABSTRACT

Introduction: *Squamous cell carcinoma(SCC) of the oral tongue is the second most common sub site in the oral cavity malignancy in India. Surgery being the first modality of treatment, needs a 1.5 cm three dimensional resection margins in order to achieve proper tumor oncological clearance. The deep margins are the one which is usually compromised. Can per-operative image guided excision be done to aid the surgeon in adequate resection? So as not to compromise on the specialized function of the tongue or the tumor clearance.*

Methods: *A prospective non-randomized pilot study with a sample size of 15 who were newely diagnosed SCC of oral tongue between June, 2013 and March, 2014. A finger probe was use to mark the deep soft tissue margin of 1.5 cm from the deep edge of the tumor. The depth of the tumor and the post operative resection margin was again measured sonographically immediately following the excision of the tumor specimen. This was correlated with the final histopathological depth of the tumor and the margin. The findings were analyzed using descriptive statistics and correlation co-efficient calculated using SPSS17.*

Results: *The mean deep soft tissue pathological margin was 1.2 cm (SD 4.1). Sonographically measured tumor depth had a positive correlation of 0.955while the deep soft tissue margin had a correlation of 0.261with the final histopathology.*

Conclusion: *Intra-operative sonography using the finger-probe is feasible and simple technique to measure the depth of tumor in the carcinoma of the oral tongue and helps achieving the desired resection margin.*

KEYWORDS :carcinoma tongue, ultrasonography, Squamous cell carcinoma (SCC)

Introduction

SCC of tongue is aggressive with regional lymph nodes spread and high local recurrence. Hence this malignancy has a low 5 year disease-free survival. Adequate loco regional surgical clearance is important to improve the outcome. The recommendation for resection of the SCC is excision of the primary with a three dimensional margins of 1.5 -2 cm and prophylactic/elective neck dissection followed by adjuvant radiotherapy.

Post –operative adjuvant treatment causes short and long term morbidity and worsens tongue function .Resection by clinical assessment varies according to surgical skills and it may impair the tongue's specialized functions, especially swallowing and speech. Frozen section biopsy for tumor clearance has several limitations like availability, cost and time. Hence it has limited utility in guiding the resection margins in SCC of the tongue.

Per-operative sonography to determine tumor depth has shown good correlation with histopathology .Trials using sonography in guiding the resection margins especially, the deep soft tissue margins have shown good correlation with histological margins. With sonography-guided resection, adjuvant therapy can be avoided, if uniform and reproducible tumor-free deep soft tissue margins can be ensured.

The purpose of this study was to objectively determine adequate and uniform margins of resection especially at the depth and to compare and correlate the margins of resection using sonography and with the pathological margins.

Material and methods

We decided to do a focus research on how imaging can improve surgical tumor clearance and decided to explore the role of intraopera-

tive intraoral sonography using a finger probe in marking the deep soft tissue resection margins and so improve local control rate.

Using the original work done by previous researcher where intraoperative real time use of sonography in measuring the depth of tumor invasion give a correlation coefficient of 0.8-0.9 when compared to pathological depth of tumor measurement (taken as the gold standard) .Then together with statistician we reviewed literature and designed a diagnostic prospective study and the protocol needed based on the paper by Yamane et al, on "Noninvasive quantitative assessment of oral tongue cancer by intraoral ultrasonography," Head and Neck, vol. 29, no. 4, pp. 307–314, 2007 which give a correlation of 0.9 and calculated our sample size which,needed to be statistically relevant was 59.

We decided to conduct a pilot study for a 1 year period with the sample size of 1/10th the required sample size which we agreed on 15 study cases. Till the later period of 2012 our institution has been resecting carcinoma tongue with a 1 cm resection margins, but our study has been planned with a resection margins of 1.5 cm as recommended by the AJCC through consensus so we could not plan for sensitivity and specificity analysis. We decided to do only a frequency analysis and Pearson correlation taking pathological margins of resection as the gold standard. We have involved senior radiologist and pathologist to help us in intraoperative sonography of the tongue and for processing and histopathology reporting of the specimen respectively.

Our study population was all previously untreated newly diagnose SCC of oral tongue, willing to be operated in our institution, after proper information and consent from the patient regardless of the tumor stage. Who had previous treatment elsewhere with any form of modality were excluded. Trismus less than 2cm central inter-incisor distance were also excluded.

We used an Aloka sonography machine- ALPHA A6,Aloka finger probe – UST-995-7.5;4-10 MHz,65 degree/20mm radius.

After the patient is anaesthetized and draped and after placing of buccal retractor and mouth gag and a throat pack, we place stay sutures on the undersurface tip of tongue to stabilize the tongue and also on the lesion for retraction during resection [Fig 1]. We mark the mucosa resection with a soft paper scale using cutting cautery .Then we place the probe on the dorsal and lateral surface to measure the depth of tumor and marked the vertical and horizontal deep soft tissue resection margins of 1.5cms using 8 to 10 cm diameter round body needle[Fig2]. Then we start resecting the lesion around the needle ,when the specimen is resected we repeat the ultrasound on the specimen to make sure that the desired excision was done before putting the specimen in formalin and sending to the pathologist. Analysis was done in SPSS software version 16.0 (licensed by IBM) with the help of the statistician. All study variables were described using descriptive statistical methods. Continuous variables were summarized using mean with a standard deviation.

The association between intraoperative sonography and pathology for depth of tumor and deep soft tissue resection margins were assessed using Pearson correlation coefficient.

Fig 1. Marking the mucosal margins and accessing the depth of the tumor

Fig 2. Curved round needle is being used to mark 1.5 cm from the deep margins of ulcer

Fig 3.Intra op USG needle can be seen

Fig4. USG of the resected specimen To confirm the depth

We also try to analyze other association which is not a part of my study in order to have an idea for further research. We also try to analyze the association of pre op MRI with contrast and pathology for depth of tumor in the patients who had an MRI done in the immediate preoperative period (within 1 week of surgery) using Pearson correlation coefficient

We also try to analyze if depth of pathological depth of tumor>4mm increase the likelihood of lymph node metastasis All cases had at least a prophylactic neck dissection(level 1a,1b,2a,2b and 3) on the same side of the tumor using a cross tabulation table

Results

Amongst the patients included in the study 12, (80%) are males with a mean age of 53 years and mean duration of non-healing ulcer of 5 months. Amongst the male patients in the study, 75% of them were more than 40 years of age, while all the female 3, (20%) patients were over 40 years of age.

The patients had varied occupations and most of them were from a low socio-economic status. Majority of the patients 6 (40%) were manual laborers. Majority of the patients 11(73.3%) had a history of exposure to risk factors. All patients presented with a suspicious non-healing ulcer over the tongue. None of them had a history suggestive of a premalignant condition. Amongst the patients 10(66.7%) patients had squalors cell carcinoma of moderate differentiation and 5 (33.3%) had of well differentiation. None of the patients had poorly differentiated carcinoma.

Among the patients 6 patients have high risk factors, 3(20%) patients with node positive for metastasis, one each(6.7%) had lymphovascular invasion , perineural invasion ,lymph node along with perineural invasion,9(60%) patients with no risk factor for adjuvant treatment. Amongst the patients, 7 (46.7%) and 6(40%) were pT1 and pT2 stages respectively; implying majority of the cases (86.7) had an early primary disease, 2(13.3) patient with pT3.

The mean sonographic depth of the tumor in 15 cases was 10.9 mm (S.D. 8.8) while the mean depth of tumor when assessed by MRI in 11 patients was 12.2 mm (S.D. 11.6). The real-time sonographic deep soft tissue margin was 13.7 mm (S.D. 2.2). The depth of tumor and deep soft tissue margin on final histopathology were 10.0 mm (S.D. 11.4) and 12.6 mm (S.D. 4.2), respectively. Intraoperative sonography real time measurement of depth of tumor invasion to soft tissue correlated reasonably well with histopathological depth of the tumor with a Pearson correlation of 0.995. Similarly, intra-operative real-time sonographic estimation of the deep soft tissue margin and its histopathological Pearson correlation was 0.261.

The deep margin was more than 5mm in all the patients recruited.

10 (66.67%) patients had a pathological deep margin of less than 1.2cm while 5 (33.33%) had more than 1.2 cm.

In a sub-group analysis of 5 patients who had pathological deep surgical margin over 12 mm, 4 of the 7 patients were in clinical T1 stage while there was 1 patient out of six clinical T2 stage. The mean excess pathologic margin over 12 mm was 5.8 mm in these 5 patients. When clinical T1-stage was compared with other stages, there was no statis-

tical correlation or significance between the number of patients with excessive margins and the clinical T1-stage of the disease.

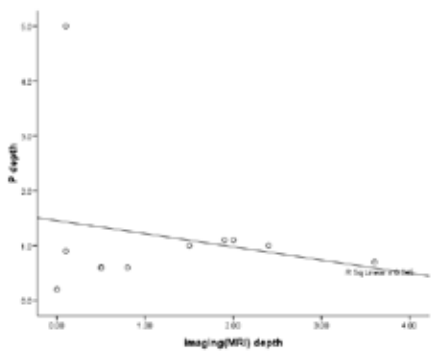
In all fifteen patients depth of tumor and deep resection margin was measured intra-operatively by ultrasound and post-operatively by pathological examination. A pre-operative assessment of tumor depth alone was done in 11 patients using MRI.

Comparison of tumor Depth on MRI and on histopathology:

Eleven patients had an MRI for confirmation of extent of the tumor. This was compared with the depth of tumor on histopathology. There was a negative correlation of -0.213 between the two that was not statistically significant. [Graph 1]

Modality	Number	Minimum mm	Maximum mm	Mean mm	Std. Deviation mm
USG depth	15	3.0	40	10.87	8.831
MRI depth	11	0.0	36	12.182	11.5829
Pathological depth	15	2.0	50	10.00	11.408
Pathological deep soft tissue margin	15	8.0	20	12.60	4.188
USG deep soft tissue margin	15	11.0.	18	13.67	2.225

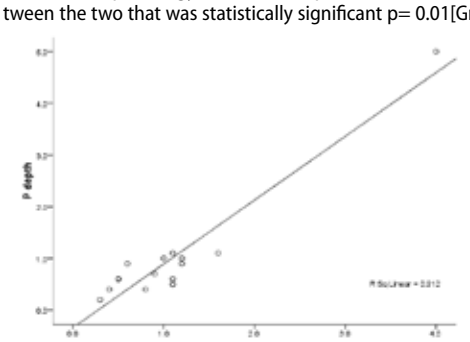
Table 1.



Correlation graph 1.

Comparison of tumor depth using Ultrasound imaging and Histopathology:

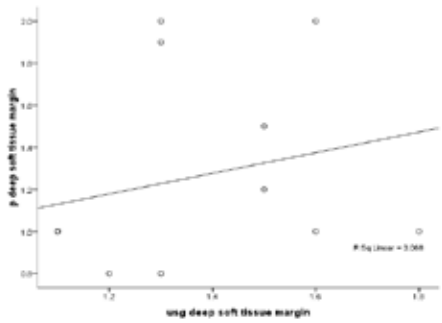
All fifteen patients had an intra-operative Ultrasound for confirmation of extent of the tumor. This was compared with the depth of tumor on histopathology. There was a positive correlation of 0.955between the two that was statistically significant p= 0.01[Graph 2]



Correlation graph 2

Comparison of deep soft tissue margin on Ultrasound imaging and on Histopathology:

All fifteen patients had an intra-operative Ultrasound to measure the deep soft tissue resection margin. This was compared with the deep soft tissue resection margin on histopathology. There was a positive correlation of 0.261between the two that was not statistically Vsignificant [graph3]



Correlation graph 3

The grade of tumor differentiation in SCC of oral tongue does seem to have an influence on lymph node metastasis although it is not statistically significant. Three patients had a tumor depth equal to or less than 4mm, and none of these had lymph nodal metastases, 5 out of the 12, who had a depth more than 4mm, had lymph nodal metastasis.

We would also like to report that although we achieved adequate resection on histopathology 6 patients received adjuvant Radiation therapy. The indications for Radiation therapy is the presence of other risk factors for loco regional recurrence on final histopathology report.

Out of 6 patients who had combined modality one patient develop loco regional recurrence within 6 months and it could be because he discontinued Radiation therapy after 50Gys in25#or may be because he has an aggressive disease.

Discussion

Head and neck accounts for 3-5 % of overall cancer in the whole body .Oral cavity malignancy accounts for1/5thof head and neck cancer. Men are two to three times more commonly affected than women and the incidence increases with age with almost 96per cent of cases occurring in patients over 40 years of age(1,5). The two most important factors in the etiology of head and neck cancer are tobacco and alcohol. There is a synergistic interaction between these two agents. In the UK, head and neck cancer represents 5—10 per cent of all tumors making it the eighth most common cancer in males and sixteenth most frequent in females(4).Human Papilloma Virus(HPV), predominantly strains 16 and 18 has also been studied for its association with tongue cancers(1,2).

Clinically SCC of oral tongue tend to present early compared to other subsites in head and neck cancers besides having an easy accessibility for self-examination (1,2).

Of all the tongue malignancies, SCC is the most common type of malignancy (90%) (2,4). Because of multiple factors they tend to spread early to the regional lymph nodes (15-30 % in the neck) and 15 % of them can have skip metastasis to level 4 cervical lymph at presentation(2). They also have a high loco-regional recurrence rate compared to other oral cavity sub site(2,6). The rate of distant metastasis at (10-20%) at presentation is the same as for other oral cavity sub sites (4).

Factors which predict lymph node involvement and loco-regional recurrence of disease and eventually influence management and overall disease survival are advanced primary disease, lymph node metastasis, perineural involvement, lymphovascular invasion, close and positive surgical margins, extra capsular spread(14, 11-22)

Management of the SCC of the oral cavity has followed the Halstedian principles of three dimensional oncological resection of the tumor with a margin of 1 cm of the normal adjacent tissue as per the recommendation for the skin non melanomatous SCC, Broadland and Zitelli et al could achieve tumor free margin of 0.5cm in more than 98.5% of their cases.(69) It is pertinent to note that the current National Comprehensive Cancer Network (NCCN) has recommended 1.5 to 2 cm margins from the visible and the palpable tumor (70)

Despite improved protocol and technical advances in adjuvant therapy, there has been no significant improvement in the local control rate of 50-60 % and an overall survival rate of 40%. Many centers have reported a high percentage of close pathological margins 30-40-% hence most head and neck surgeons and guidelines in this era by consensus recommends resection margins of 1.2 to 2 cm.. SCC of the tongue spreads locally by radial infiltrative growth (as for any other sub site in the oral cavity) and vertically along the planes of least resistance between the muscle fibers. This is the reason why many oncosurgeons believe that the compartmental resection of the tongue lesions may give a better oncological clearance especially for tumors which involve the extrinsic muscles of the tongue(7,8)

The prognostic factor depends on the Stage of primary disease, number and level of lymph node involvement, presence of distant metastasis and presence of co morbidities has been proven to affect the management and survival of patients with SCC(2,9,10).

Loco regional recurrence is the most common cause for treatment failure (30-40%) in SCC of oral tongue and is associated with a high mortality rate with a 5-year survival rate of less than 10 %. Surgical salvage procedure is possible in less than 50% of patients which brings a lot of pain and suffering to the patient(1,2,4,11-13,18,21,24).

Local recurrence can be because of many factors, both clinical and histopathological,primary site tumor risk factor are- higherT-stage(11,16,18,22,25) , poor differentiation of tumor(22,26) mode of local invasion(21,27) perineural invasion(28), lymph vascular invasion, depth of invasion(29), microsatellite lesion(30) ,field concretization(stem cell clones) at the margin of resection(39), presence of high risk molecular markers at the margins(32-36) ,and most importantly close or positive margins(37,39).

The principle of oncosurgery is to get tumor clearance and improve the patient's disease free Survival rate and eventually overall survival rate. From an oncosurgical perspective adequate tumor clearance is considered as the most important part of treatment. The reconstructive aspect is planned depending on the anatomical defect and function of the recipient organ, at the same time taking care of the aesthetic aspect as well(1,2,3).

Oncosurgeons at one time were resecting oral cavity malignancies with a 1cm resection margin to get at least more than 5mm margin on histopathology examination. This is, taking into account the normal tissue shrinkage of 30% after specimen processing for histo-pathologic studies40,41).Seventy percent of normal tissue shrinkage happen within one minute of resection and the rest thirty percent is due to formalin and other histopathological processing(40).

Most of these tumors with a close or positive resection margin share tumors with aggressive tumor biology and that they will need adjuvant treatment because of other risk factors even if we give wider margins which only compromise tongue function. This has been supported further by the fact that 20-50% of patients with a positive or close resection margins does not recur and the theories for this are(2,4) that the Heat generated by the cautery for resection inflicts collateral damage to the cancer cells as well which may contribute towards the non-recurrence of cancer. The microscopic cells left over after resection are taken care of by the body's immune system.

Though there are cases of 15-30% of patients with negative margins after resection develop recurrence(41,42) and the theories are microsatellite lesion around the margins of lesion(30) aggressive tumor biology(36) presence of MMPI,COL4A1,P4HA2,THBS2 molecular markers in cells at the margins of resection which are signature for local recurrence at the margin of resection (24,32-34)Field cancerization(31),Presence of Cancer Stem Cells(43)

Most of the local recurrences occur within the first two years of follow up and the earlier the recurrence of tumor the more likely the tumor is an aggressive one with a poor outcome (4,11).SCC of the oral cavity (including tongue) is resected with a recommended (level 5 evidence) radial 1.5cm unstretched normal margin in three dimensions. Resection margins on the mucosal surface is usually measured (with a soft paper scale) but it is usually left to the surgeon's clinical skills (which have been proven not to be reliable and replicable) in estimating the deep soft tissue margins (44).

There is a need for more investigational studies to get a better understanding of resection of cancers and how to manage them(26,34). Since the resection margins play a major role in the outcome of management of mucosal oral cavity cancers including tongue literature is replete with several techniques that have been tried to ensure negative pathological resection margins especially at the deep soft tissue margins. Multiple techniques including the use of Toluidine blue(44), Lugol's Iodine(46), intra-operative frozen biopsy, Moh's micrographic technique (75), gene probe assessment for P53 and imaging guided surgery(48)have been described.

Frozen(49-52) section is an attractive technique in objectively determining clear surgical clearance, especially at the mucosal level but frozen sections are also not cost effective has prolong operating time, and pose logistic difficulties hence it has fallen out of favour .

IMAGE GUIDED SURGERY

Imaging guided surgery has been studied and found to be useful in resection of tumors extending to the base of skull. MRI has been accepted as the preferred anatomical imaging in tongue to define the site and also the extent of tongue lesions because of its better soft tissue resolution, but it has its own limitations in detecting small surface lesion <5mm,it is costly and does not help to guide resection margins in real time.(53,54) .CT scan in tongue has a poor soft tissue delineation in tongue and is not commonly used(53). PET/CT Scan seems to have some role in calculating tumor volume to be treated in radiation therapy but has no role in guiding resection margins(55). Pre–operative ultrasound has been found to have a good correlation with final histopathology in determining depth of tumor in tongue but cannot give real time resection margins[56,58].

Intra operative or preoperative sonography using small high frequency intra cavitory probes have been found to give the best correlation with histopathology in delineating the deep soft tissue margins in SCC of the oral tongue with a Pearson correlation ranging from 0.7-0.9 in different studies. Some studies have found that this tool is even better than MRI (correlation of 0.54)[59-63].

In our study Intraoperative sonography real time measurement of depth of tumor invasion to soft tissue correlated reasonably well with histopathological depth of the tumor with a Pearson correlation of 0.995. Similarly, intra-operative real-time sonographic estimation of the deep soft tissue margin and its histopathological Pearson correlation was 0.261. Ultrasonography is an easy tool to use and it is noninvasive with no hazard to the patient. It is also rapid and easily repeatable SCC of the oral tongue is usually seen as a hypo echoic lesion.

Five trial studies have tried to use sonography in determining resection margins using different techniques:

Helbig M et al In 2001used Endo-ultrasound was use to mark resection margin with a suture and filling the mouth with saline and found to be useful but–difficult to perform[64].

Songra el al in 2006 small intracavitory probe was placed with metal reflectors to assess the margins for resection, but the resection itself was done by clinical assessment[65]

In 2007 a small sector probe was used to visualize the depth of tumor before resection and post resection sonography was performed in gelatin embedded specimen to confirm clearance but with no preoperative marking for resection margins[66].

Baek C et alIn 2008 small intracavitory probes was used to place 25 gauge spinal needle at the depth of resection with a high chance of canula displacement during resection[67]

Kodama et al study In 2010 depth was indicated with an IV canula and then post resection the specimen was embedded in gelatin for sonographic confirmation of adequate resection margins[68].

In our study we used a large curved round body needle 8 to 10 cm diameter which followed the natural curvature of three dimentional resection with reconfirmation of the margins on the ultrasound table for adequacy of the margins.

Conclusions

Intraoperative sonography real-time estimation of deep soft tissue margins and using sonography to mark the margins of 1.5 cm did ensure that no patients had a close resection margin which certainly does help in avoiding unnecessary adjuvant treatment for patients with not very aggressive tumors and without risk factors. This perhaps helped in reducing added morbidity from radiation therapy and also reduces cost of treatment and emotional trauma to the patient and the family.

Future directions

Base on the positive results from our pilot study (15 patients) we are encourage to approach the Institutional Review Board to continue this study and complete the statistically significant calculated sample size with a few minor adjustment in our technique in marking the estimated margins.

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