Prognostic Value of Frozen Section in T1, T2 Carcinoma of Oral Cavity

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Abstract Complex anatomy of oral cavity makes it difficult for a surgeon to assess margins of oral cancer accurately and positive margins compromise loco regional disease control, thus surgeon may rely on frozen section assessment for marginal status. We discussed the prognostic value of frozen section in early carcinoma of oral cavity. 90 patients with pT1 and pT2 oral cavity cancer operated from January 2010 to December 2011 under single consultant surgeon were retrospectively evaluated. Log rank test and multivariate cox regression model was used for testing frozen section against the survival and recurrence free status. Survival of patients with positive or negative frozen section was significant ($p = 0.037$), Survival of patients with positive or negative histology report was significant ($p = 0.004$), however; prognosis of patients with positive margins despite revision under frozen control was poorer to the patients with negative margin. Frozen section assessment is accurate but their use in the surgery

of oral cavity cancer might not improve loco regional disease control or survival when used routinely.

Keywords Frozen section · Histopathology · Locoregional recurrence

Introduction

Complex anatomy of oral cavity makes it difficult for a surgeon to accurately assess clinical margins of oral cancer resections, positive margins compromise loco regional disease control. For this surgeon may rely on frozen section assessment of marginal status. Frozen section assessment of margins is a very accurate diagnostic tool with an accuracy of 96.8–98 % in most of the studies [1–3]. The specificity is high than sensitivity and false positive results were less than 1 % in most of the studies [4]. Involved histopathological margins is associated with high rate of recurrences [5]. Since the accuracy of frozen section assessment is good, it may be assumed that this would reflect on over all prognosis of the patients.

Treatment planning of the patient of oral cancer depends upon tumor staging. Role of adjuvant therapy becomes important depending on tumor stage, status of cervical lymph nodes and status margins. Thus it becomes important that patients not intend to receive adjuvant therapy (T1 and T2 carcinoma oral cavity) are to be cleared of disease by single surgical modality of treatment. It is also clear that the efficacy of frozen section assessment is proportional to number of margins assessed which is easier in T1 and T2 carcinoma of oral cavity and becomes difficult with increase in tumor volume. Frozen section assessment is one of the widely available rapid tools which probably could help surgeon to completely remove tumor with adequate

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margins specifically in early carcinoma ie T1 and T2 cases which are treated solely by surgery.

Known factors effecting prognosis of patients with oral cavity cancer include tumor stage, thickness, margin status, regional spread, extracapsular spread, perineural invasion, lymphovascular invasion, and adjuvant treatment [6]. One of the important prognostic factors is margin status. Margin within 5 mm of the lesion of whether it is invasive carcinoma or carcinoma in situ/severe dysplasia are associated with approximately 80 % incidence of recurrent disease [5]. Involved margins are reported with high rate of recurrence despite post operative adjuvant therapy. Recurrence is 100 % when tumor is encountered in the margin and left unrevised or addressed by adjuvant therapy [4]. Even though re-excision is ideal, it is very difficult to reorient the margins at later date.

Although many guidelines have been defined, it is accepted that 5 mm of histological margin three dimensionally is adequate in curative surgery of oral cavity [7], but difficulty in identifying adequacy of margin intra operatively persists. Though frozen section analysis is possible it is an expensive tool, and prolongs operative period.

It is emphasized that the wider the margin better is the disease control locally but considering the morbidity associated and difficulties encountered in reconstructive options in oral cavity cancer, it is sufficient to optimize negative margin with 1 cm clearance [7].

We evaluated the prognostic value of frozen section to see whether it is justified to routinely perform frozen section analysis for every patient and if it has an impact on survival of T1 and T2 cancers of oral cavity.

Materials and Methods

Patients with oral cancer operated between January 2010 and December 2011 from a tertiary cancer hospital were retrospectively evaluated (For this type of study formal consent is not required), the institute practices routine use of frozen section for margin assessment intra operatively, this involves orientation of the resection specimen by surgeon and sampling of 4–5 margins for frozen section in all dimensions by the pathologist. Margins are revised until frozen section confirms negative, revised tissue is inked by the surgeon for proper orientation. Patients operated under the guidance of a single consultant surgeon are reviewed and cases with pT1 and pT2 status according to UICC TNM staging are filtered for the study; Cases with primary squamous cell carcinoma on histology were only included. 90 patients were obtained on applying the above mentioned criteria; the sample was analyzed by Log-rank and cox regression model, SPSS version 17.0 for Windows (SPSS,

Chicago, IL, USA) was used for statistical analysis. A two-tailed *p* value of less than 0.05 was considered statistically significant. Variables associated with death (*p* < 0.10) are further tested in a multivariable Cox regression model adjusting for potential risk factors and confounders. The Kaplan-Meier graphs are drawn to indicate the survival probability. The tested variables are age, gender, site, pT stage, pN stage, lymphovascular infiltration, perineural invasion and margin status (UK Royal College of Pathologists for head and neck carcinoma in 1998) [8], local recurrence and neck recurrence.

Results

Status of Locoregional recurrence free status and overall survival (LRFS) by log rank test was derived for testing frozen section result (Table 1). A total of 63 (70 %) patients were male and 27 (30 %) were female, age ranged from 29 years to 63 years, mean—47.8 years, a median period of follow up was 24 months (Table 2). Histology showed 36(40 %) with pT1 and 54 (60 %) with pT2 status. Neck staging —60 (66.6 %) were N0, 18 (20 %) were N1 and 12 (13.3 %) patients were N2b. 15 (16.6 %) patients reported involved margin in frozen sections that were revised until negative. Adjuvant treatment was given in 50 (55.5 %) patients.

Among 90 patients 80 (88.8 %) survived to date. Ten patients died, of which six patients died of disease recurrence and four of unknown causes without evidence of locoregional recurrence. Six patients are alive with recurrence (4 local recurrence and 2 neck recurrence). Total 12 patients had recurrence (local, regional or loco-regional) and five (5.5 %) patients reported local recurrence, two (2.2 %) with local and regional recurrence and five (5.5 %) with only regional recurrence.

A total of 15 patients reported involved margin in frozen section of which four (26.6 %) patients had locoregional recurrence. Frozen section was negative in 75 patients of which eight (10.6 %) patients reported with locoregional recurrence (Table 1).

Final histopathology showed 11 patients with margin positive of which four (36.6 %) patients reported with locoregional recurrence. 79 patients reported clear margin in histopathology of which eight (10.1 %) patients had locoregional recurrence (Table 1).

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Table 1 Status of locoregional recurrence free status (LRFS) and overall survival(OS)

	No. of patients	LRRFS	%	<i>p</i> value for LRFS (Log-rank test)	Patients survived	OS (%)	<i>p</i> value for OS (Log-rank test)
FS +ve	15	11	73.3	0.028	11	73.3	0.037
FS –ve	75	67	89.3		69	92	
HPE +ve	11	7	63.6	0.005	7	63.6	0.004
HPE –ve	79	71	89.8		73	92.4	

FS +ve Frozen Section positive for tumor in the margin, FS –ve Frozen Section negative for tumor in the margin, HPE +ve Final histopathology positive for tumor in the margin, HPE –ve Final histopathology negative for tumor in the margin, LRRFS Locoregional recurrence free status, OS Overall survival

Table 2 Demographic data of patients

	No. of patients
<i>Gender</i>	
Male	63
Female	27
<i>Site</i>	
Tongue	47
Buccal mucosa	33
<i>Grade</i>	
Well differentiated	63
Moderate + poorly differentiated	27
<i>Lymphovascular invasion</i>	
Negative	85
Positive	5
<i>Perineural Spread</i>	
Negative	83
Positive	7
<i>Frozen section report: margin status</i>	
Negative	75
Involved	15
<i>Histopathology: marginal status</i>	
Negative	79
Involved	11
<i>Recurrence</i>	12
Local + neck recurrence	2
Local recurrence	5
Neck recurrence (only)	5
Absent	78

local and regional recurrence and five (5.5 %) with only regional recurrence.

The overall survival (OS) of patients with involved margin in frozen section was 73.3 % and negative for tumor was 92 % trend for good survival was seen in the group of frozen negative in the margin (*p* value 0.037, Fig. 1).

Overall survival was statistically significant (*p* value 0.004, Fig. 2) and dependent on histopathology margin

status. Survival was 63.6 and 92.4 % respectively in histopathological involved margin and uninvolved margin.

Locoregional disease control was 73.3 % for patients with involved margin in frozen section, and 89.3 % if margin was uninvolved in frozen section. Better loco regional control was seen in the group of patients with frozen section negative for margin. Whereas, LRFS was highly significant (*p* value 0.005) for uninvolved margin to involved margin on histopathology (Table 1).

Involved margin in frozen section was borderline significantly associated with the higher risk of death, crude hazard ratio (HR) 3.52 (95 % CI:0.99, 12.47). Involved margin in histopathology and recurrence of local as well as neck were significantly associated with increased risk of death. However, multivariable cox-regression model revealed recurrence of neck disease as the only significant factor associated with increased risk of death, adjusted HR, 11.55 (95 % CI:2.91, 45.79) (*p* < 0.0001) but not the local recurrence and involved margin in histopathology.

Discussion

Surgeon aims to gain clear negative margins on an initial attempt but close margins are inevitable due to anatomical and pathological constraints. Close margin on initial resection was reported about 42 % by various authors [9, 10]. Byers et al [11] found that the surgeon was able to obtain clear margins in 67 % cases only. Pathak et al [12] found that the accuracy rate of frozen in predicting clear margin status was 70.4 %, while the rate of clinical judgment was 67.4 % in achieving clear margins. Kerawala et al [13] reported an error of more than a centimeter in relocating possible site for revision of margin in 32 % of cases. Lee et al [14] recommended frozen section and intra operative re-excision of involved and close margins, however; he found only 50 % of re-excision samples contained tumor. These studies indicate the frequency of inadequate margins and difficulties encountered on re excision. Clear margins were obtained in 39 (43.33 %) cases by sole judgment of surgeon in the current study.

Fig. 1 Overall survival—frozen section

Fig. 2 Overall survival—histopathology

Also 39 (43.33 %) of patients were left with close margins, 12 (13.3 %) patients had involved margins which were later revised. Among 12 patients who underwent excision of involved margin under frozen section control 11 (12.2 %) patients were identified in frozen section and one patient was revised by clinical judgment immediately after excision, four patients were revised due to false interpretation of margin as “involved” in frozen section.

Chen et al [15] reported 100 % local recurrence in positive margins and 17 % in negative margins. The outcome of positive margins on further therapy reported by Binahmed et al [10] suggests that the patients with positive margins did not significantly benefit from radiotherapy alone and recurrences among them were greater than the patients with initial clear margins, Kovacs et al has reported better survival rates with chemo radiotherapy in such

instances [16]. Combined analysis of RTOG and EROTC trials suggests improved outcome of patients with involved margin and perinodal spread on delivery of adjuvant concurrent chemo radiation [17].

In the current study, locoregional recurrence was 7.6 % ($n = 3$) patients in clear margins, 12.8 % ($n = 5$) in close margins, and 33.33 % ($n = 4$) in patients with involved margins despite revisions.

Three of four false positive results in frozen section had their posterior margin in retromolar trigone. The possibility of ambiguity with juxtaoral organ of Chievitz is considerable in these cases. Juxtaoral organ of Chievitz is located in the RMT. Histologically it is easily misinterpreted as well-differentiated squamous cell carcinoma with perineural invasion, mucoepidermoid carcinoma, or metastatic deposits from a visceral organ [18–21].

The final outcome of the patients in our study was not influenced by frozen section, recurrences were always higher in the patients who underwent revision. However; histopathology status was significant for survival. Possibly the focus of remaining disease in such cases contribute to metastasis and redistribution of lymphatics post surgery might have significance in this regard.

In the study by Margaret Brandwein-Gensler et al [6], it is emphasized that margin status alone had no association with local recurrence or OS. 25 % of their patients developed local and/or locoregional recurrences who were treated by adequate marginal clearance. The study showed the importance of adjuvant radiotherapy in patients with high risk to improve local disease free survival, however; intermediate and low risk group had no benefit of radiotherapy.

Spiro et al [22]. Reported that the presence of positive margins increased the likelihood of local recurrence but did not impact on survival since subsequent surgery and/or irradiation controlled tumor recurrence in some of their patients.

The authors emphasize the importance of multiparameter prognostic histological assessments which include nuclear pleomorphism, and mitotic rate, degree of keratinization, pattern of invasion, lymphocytic response, perineural, lymphovascular invasion, nodal status including extracapsular invasion in addition to margin status. Two patients with initial clear adequate margins developed locoregional recurrence and subsequently died of disease. One of them patient had 16 positive nodes in neck, and other two had positive nodes in neck.

Despite great accuracy of frozen sections, difficulty in revisiting the site of positive margins decreases the efficacy of use of frozen section, the number of margins that can be sampled in short period of time is a limiting factor as well, possible false negative results can mislead the surgeon when used routinely.

Conclusion

Frozen section assessment is accurate but their use in the surgery of oral cavity cancer might not improve loco regional disease control or survival when used routinely.

Margin status is an important factor under clinician's control, however; revision on frozen control may not benefit the patient.

Limitations of study: Being a retrospective study, all of the prognostic parameters of carcinoma oral cavity could not be interpreted.

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Conflict of interest None.

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