



INTRAOPERATIVE MARGIN ASSESSMENT OF EARLY ORAL SQUAMOUS CELL CARCINOMA – A SINGLE-CENTRE STUDY

Surgery

Dr Shivayak Mishra

Surgical Oncologist Superspeciality hospital Pvt limited Rohtak, Haryana

Dr Sabita Dwivedi Eye Spl, Joshi Hospital New Delhi

Dr Surjeet Dwivedi*

Dept Of Surgery Command Hospital Air Force Bangalore *Corresponding Author

ABSTRACT

Oral cancer is a major health issue, especially in India. It is one of the most common malignancies. Tobacco and alcohol are the most common causes of oral cancer which mostly has the propensity to involve the tongue or buccal mucosa. The present study was conducted to assess the margins of early oral squamous cell carcinoma intraoperatively. Smoking, alcohol and tobacco consumption were found to be high-risk factors for oral carcinoma and synergistically increase the risk manifold. The results of the frozen section and final histopathological report of resected tumor margins were comparable in our study. Margin shrinkage is often overlooked in the head and neck and especially so in oral cancer resection. Often, in vivo adequate margin of resection transforms into close margin of resection upon removal hence it is prudent to excise a healthy cuff tissue measuring 1 cm. The most important predictor for the recurrence of the disease is the involvement of tumour margins of the resected specimen. One major limitation of the frozen section is that the entire margin of the resected tumour cannot be assessed during surgery. Only a few areas of the margin of the tumour is evaluated and the deeper areas cannot be assessed. It can hence lead to 'False negative' results thereby could lead to potentiated chances of local recurrence or treatment failure. To mitigate this inherent issue, surgeons need to be experienced in judging and directing the most obvious regions for Frozen analysis. The role of teamwork along with the pathology team couldn't be underestimated at any cost. To conclude frozen section is a reliable tool for margin assessment intraoperatively especially in early cases. Surgeon and pathologist experience would certainly assist in mitigating the risk of false negatives.

KEYWORDS

Oral cancer, Tobacco, Frozen analysis, Margins status& shrinkage, Targeted frozen , Reliable

INTRODUCTION :

Oral cancer is among the top 10 malignancies worldwide. Cancer of the oral cavity is the second most frequently reported malignancy worldwide¹. The incidence of oral cancer has been increasing in the last six decades in Asian countries. Oral cancer is of major concern in Southeast Asia including India primarily because of the prevalent oral habits of tobacco chewing, smoking, and alcohol consumption². It is predominantly managed by a multidisciplinary team in which surgery plays an important tool^{03,04}.

The main aim of the oncologic surgeon is to obtain clear margins of resection during surgery. The importance of obtaining clear margin judgment action stems from the fact that those patients who have positive final margins of resection have a high rate of local recurrence and subsequently poor prognosis.⁵

The intra-operative frozen section plays an important role to achieve a tumour-free surgical margin in the resection of oral squamous cell carcinoma.⁶. Frozen section analysis has been a gold standard method for intraoperative margin assessment of oral cancer⁷. The use of intraoperative frozen section evaluation of surgical margins is an accepted and frequent practice in oral oncosurgery⁸. Frozen section analysis is a multistep process, beginning with the retrieval of the specimen from the patient by the surgeon followed by preparation of slides, their microscopic examination, and possible specimen triage for further workup, and finally rendering of the frozen section (FS) diagnosis. Frozen section reports enable the surgeon to decide on whether further resections are needed or not⁹. In literature, the accuracy of frozen sections ranges between 96 and -98% for oral cancer dissection^{10,11}. In a study done by Abbas SA et al, the accuracy of the frozen section was 90.9%, which is slightly lower but comparable to the published reports.

The importance of completely resecting a head and neck tumor has been extensively reviewed in the literature with the conclusion that loco-regional recurrence and overall survival are affected by margin status¹². The definition of what constitutes an adequate margin has been debated in the literature. Most authorities accept >5 mm as adequate, 5 mm or less as 'close,' and cut-through tumor and carcinoma in situ as positive¹³.

Here it is noteworthy that margin shrinkage is often overlooked in the head and neck and especially so in the oral cancer resection¹⁴. Johnson

et al. reported on the issue of margin shrink the age in the oral cavity of dogs and found that there was 30.7%- 47.3% shrinkage from the time the specimen was removed from the oral cavity to the time it underwent the microscopic examination. They concluded that in order to get clear margins of resection a healthy cuff of tissue measuring 8-10mm should be removed.¹⁵

The aim of the study was to assess the margins of early oral squamous cell carcinoma intraoperatively with the objective to evaluate the resected tumor margin intraoperatively by surgeon followed by pathologist by frozen section with comparison to the final histopathology report. The study also tried to identify the anatomical areas in the oral cavity where surgical resections of oral cancers are associated with close or positive margins.

METHODOLOGY :

The study is an observational Cross-sectional Study performed at a super speciality centre in north India where the subjects who were biopsy-proven oral squamous cell carcinoma were included. It was conducted from June 2018 to May 2020. Ethical clearance was undertaken and the study was commenced thereafter.

On the basis of previous studies, oral carcinoma is around 20 per 1 lakh. Taking this value as reference, the minimum required sample size with a 0.35% margin of error and 5% level of significance was 100 patients. So total sample size accepted was 100.

The formula used was:-

$$N \geq ((p(1-p))/(ME/za))^2$$

Where Za is the value of Z at the two-sided alpha error of 5%, ME is the margin of error and p is the prevalence rate. The patients who were included were those who were early cases of histopathologically proven cases with no previous history of surgery or have received radiation therapy. Excluded patients were those who had either advanced stage viz T3 and beyond. All recurrent cases were excluded.

Informed written consent was taken from all the patients undergoing the study. The detailed history, examination findings, and relevant investigations were done and were recorded in the preformed proforma.

The margin of 1.5 cm around the tumour was attempted in cases of

carcinoma tongue and 1 cm for the rest of the oral subsites including biopsy from the tumour bed. After removal of the entire specimen with tumour frozen sections were obtained from the region which looked suspicious on gross examination by a pathologist to check for any microscopic invasion. The final assessment was done by comparing the results with the final histopathology report.

All specimens sent for evaluation by frozen section were rendered on Hematoxylin and Eosin-stained section of OCT-embedded, snap-frozen tissue sectioned at 5-micrometer intervals. Permanent sections were reviewed for correlation with frozen section slides along with intraoperative margin assessment by the surgeon. The frozen section was reported by an experienced pathologist. In cases of a positive report on a frozen section by the pathologist, further resection of the suspected tissue was carried out till a negative margin was achieved.

Resection margin which showed dysplasia, carcinoma in situ, or frankly invasive tumour either at the margin or at a distance of less than 1 cm from the margin was labelled as a positive margin. All patients were followed up for a period of 24 months to look for any recurrence.

Categorical variables were presented in number and percentage (%) and continuous variables were presented as mean $\pm$ SD and median. Qualitative variables were correlated by the Chi-square test/Fisher's Exact test. Inter-rater kappa agreement was used to assess the strength of agreement of resected tumor margin between the surgeon, pathologist, and final histopathology report. A diagnostic test was used to find out sensitivity, specificity, PPV, and NPV. The data was entered in the MS EXCEL spreadsheet and analysis was done using Statistical Package for Social Sciences (SPSS) version 21.0.

RESULTS:

The total number of patients who presented to the surgical oncology department with oral carcinoma during the study period was 161, among whom 58 patients (36.02%) were excluded as they were in advanced stages. Out of these 103 patients (69.97%), three patients were lost to follow up and 100 patients were thus included in the study.

The age of the patients varied from 25 to 82 years with a mean age of 49.74 ± 11.58 years. The majority of patients were in the age group of 41-50 years (41.0%). Most of the patients were males and belonged to the lower-middle socioeconomic group. (Table no 01) Tobacco consumption was present in 15% of patients. Alcohol and cigarette smoking were present in 22% and 21% of the patients. (Table no 01)

The tongue was the most common location of the primary tumor in our study seen in 43% of cases followed by gingiva in 30 % of cases while buccal mucosa involvement was in 18% of cases (18.0%). (Table no 01) Out of 100 patients, 44 patients (44.0%) had T1 stage of oral carcinoma and 56 patients (56.0%) had T2 stage of oral carcinoma. (Table no 01)

A total of 221 margins were obtained from the anterior, posterior, medial, and lateral borders of tumors in 100 patients. The frozen section of 16 patients. (16.0%) were positive of which 6 patients (37.5%) had a recurrence of the tumor. Out of eighty-four patients in whom margins were not involved in the frozen section, 8 patients (9.5%) had a recurrence. On receiving a positive report for a tumor on the frozen section, further resection was performed till a healthy margin was reached. (Table no 02)

Histopathology reports showed involved margins in 15 patients out of which 7 patients had disease recurrence (46.6%). Whereas in 85 patients who had tumour-free margins on histopathology, 7 patients (8.2%) had disease recurrence. (Table no 02)

Fourteen patients (14.0%) had a recurrence of the disease of which 11 patients had T2 lesions while 3 patients had T1 lesions. Among these patients, adjuvant therapy was received by 12 patients, two patients did not receive adjuvant therapy (Table any 02)

In our study, 91 patients survived to date and 9 patients died. The cause of death was disease recurrence in 6 patients and chemo-radiotherapy-associated complications in 2 patients. One patient expired due to a chronic medical disease that was not related to oral carcinoma. Eight patients with disease recurrence survived to date. (Table no 02)

The sensitivity of the frozen section in our study was 73.3% (95% CI:

44.9%, 92.2%) and specificity was 94.1% (95% CI: 86.8%, 98.0%). The positive predictive value (PPV) of the technique for predicting involved margins intraoperatively was 68.7% and the negative predictive value (NPV) was 95.2%. The overall accuracy of the test was 91.0%.

DISCUSSION:

Oral cancer is one of the most common cancers in the world. Early diagnosis and optimal oncological treatment are one of the most important factors affecting survival. In resectable tumors, surgery is superior to all alternative therapies¹⁶

The best chances of cure during surgical excision of oral carcinoma depend on the complete removal of tumor cells from the margins of the excised tumor specimen.

Tumour-free margin yields better results and prevents the recurrence of the disease. Frozen section analysis has been a gold standard method for intraoperative margin assessment of oral cancer¹⁷.

A literature search has also shown that socioeconomic status is inversely related to the incidence of oral carcinoma. In a study done by Saman Warnakulasuriya, it was found that low socioeconomic status has a significant oral cancer risk. He studied that due to poor education, lack of hygiene, lack of access to healthcare, and poor nutrition along with other risk behaviours, the incidence of oral cancer was high in lower socioeconomic status¹⁸.

In the present study, alcohol consumption and smoking were two major high-risk factors present in 22% and 21% of patients respectively. Tobacco consumption was seen in 15 patients (15.0%) Various studies have shown that smoking tobacco is associated with an increased risk of oral and pharyngeal cancer, with risks increasing in a dose-dependent fashion and declining with the duration of cessation of etiological factors¹⁹

Most oral cancer in the present study was encountered in the tongue i.e. in 43% of cases which was in accordance with most previous reports Various studies have also reported the tongue as the most commonly involved area in oral carcinoma. Sayed Akbar Abbas in his study reported the involvement of the tongue in 37.7% and buccal mucosa in 37.7%²⁰. Similar results were shown in another study done by Sandhya Gokavarapu et al²¹ The reasons why the tongue and the buccal mucosa are the predilection sites for oral cancer are that the carcinogens in the oral cavity mixing with saliva have the tendency to pool at the bottom of the mouth and these sites are covered by thin and non-keratinized mucosa. As a consequence, they provide less protection against carcinogen²².

Frozen section assessment of tumor margins is the commonest and most widely used technique to ensure clear margins of resection during surgery²³. In literature, the accuracy of frozen sections ranges between 96-98% for oral cancer resection²⁴. In our study, the accuracy of the frozen section was 91.0%, which is comparable to the published reports. The frozen section was able to pick up 11 patients correctly with positive margins and hence further excision was carried out. Five patients had false-positive interpretations of the frozen section which lead to extra removal of tissue from the surroundings of the tumor. None of these 5 patients required flap reconstruction as a result of excessive removal of tissue. Four patients had false-negative reporting. These 4 patients had dysplasia on the final paraffin-embedded sections and were therefore labelled as positive margins.

The finding of dysplasia in the frozen section needs special attention as it is generally believed to increase the chance of local recurrence. The problem with the interpretation of the dysplasia may be compounded especially when reporting on the frozen section. Our results also showed various interpretations of dysplasia in the frozen section²⁵. Overall, 16 patients had recurrence after surgical excision of oral cancer. Patients with clear margins of resection on frozen sections had a 9.5% recurrence rate while patients with involved margins of resection had a 37.5% recurrence rate. This is consistent with the reports published in literature where the local recurrence rate is 3-35% in patients with negative margins, while for positive margins recurrence rate may approach 100%²⁶

Here it is noteworthy that margin shrinkage is often overlooked in the head and neck and especially so in oral cancer resection. Often, in vivo

adequate margin of resection transforms into a close margin of resection upon removal. Johnson et al. reported on the issue of margin shrinkage in the oral cavity of dogs and found that there was 30.7%-47.3% shrinkage from the time the specimen was removed from the oral cavity to the time it underwent the microscopic examination. They concluded that in order to get clear margins of resection (>5mm) a healthy cuff tissue measuring 8-10mm should be removed²⁷

Strengths of the study:

1. The use of a frozen section does not increase the overall time of the surgery.
2. The frozen section report helps the surgeon intraoperatively to remove adequate tumor specimens thereby achieving a tumour-free margin.
3. This technique helps in the prevention of the unnecessary removal of healthy tissues surrounding the tumor.

Limitations of the study:

1. Difficulty in revisiting the site of positive margins decreases the efficacy of the use of frozen sections.
2. The number of margins that can be sampled in a short period of time is a limiting factor.
3. Further studies with a larger sample size are required to evaluate and compare the results of the frozen section and final histopathological report.

CONCLUSION:

The present study was conducted to assess the margins of early oral squamous cell carcinoma intraoperatively. Smoking, alcohol, and tobacco consumption are high-risk factors for oral carcinoma and combined consumption of all these three has a cumulative effect in causing oral cancer. The most important predictor for the recurrence of the disease is the involvement of tumor margins of the resected specimen. If the margins are involved then the chances of tumor recurrence increase despite giving adjuvant therapy.

The results of the frozen section and final histopathological report of resected tumor margins were comparable in our study. In patients whose margins were not involved in the frozen section, the chances of recurrence were very less. Margin shrinkage is often overlooked in the head and neck and especially so in oral cancer resection. Often, in vivo, adequate margin of resection transforms into a close margin of resection upon removal so in order to get clear margins of resection, a healthy cuff tissue measuring 1 cm should be removed.

One major limitation of the frozen section is that the entire margin of the resected tumor cannot be assessed during surgery. Only a few areas of the margin of the tumor are evaluated and the deeper areas cannot be assessed thereby giving 'False negative' results and thus leading to local recurrence.

A frozen section is a reliable tool for margin assessment intraoperatively. However, a tumour-free margin does not exclude the risks of local recurrence. The expertise of the surgeon and the pathologist and their combined approach during tumor resection intraoperatively is the key to providing better results, preventing local recurrence, and avoiding false reports. We recommend the use of a frozen section for margin assessment intraoperatively in early oral squamous cell carcinoma and to ensure tumour-free margin in oral cancer resection.

Table No 02: Clinico Pathological Profile

Frozen section report	N Number N=100 (%)		
Positive	16	(16.0)	
Negative	84	(84.0)	
Final Histopathology report			
Positive	15	(15.0)	
Negative	85	(85.0)	
Frozen section report	Final histopathological report		
	Positive	Negative	Total
Positive	11	05	16
Negative	04	80	84
Total	23	77	100
Patients who received Adjuvant therapy			

Received Adjuvant therapy	81	(81.0)
Did not receive Adjuvant therapy	19	(19.0)

Table no 01 :Demographic and clinical profile of the patients

Disease recurrence		
Present	14	(14.0)
Local recurrence	06	(06.0)
Loco-regional recurrence	03	(03.0)
Regional recurrence	05	(05.0)
Absent	84	(86.0)

Age (years)	Number N=100 (%)	
21-30	04	(04.0)
31-40	11	(11.0)
41-50	41	(41.0)
51-60	23	(23.0)
>60	21	(21.0)
Mean age (years) (mean±SD)	49.74 ±11.58	

Risk Factor		
Smoking	21	(21.0)
Alcohol	22	(22.0)
Tobacco	15	(15.0)

Location of the primary tumour		
Tongue	43	(43.0)
Gingiva	30	(30.0)
Buccal mucosa	18	(18.0)
Floor of mouth	09	(09.0)

Stage of oral carcinoma		
T1	44	(44.0)
T2	56	(56.0)