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A comparison of intra-operative diagnostic tools and its correlation with the histopathological diagnosis in squamous cell carcinoma of the oral cavity

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ABSTRACT

Background and Objective: To compare the results between touch imprint cytology and frozen section and to assess its accuracy in relation to the histopathological diagnosis in oral squamous cell carcinoma of the oral cavity. The present study emphasizes the correlation of touch imprint cytology and frozen section for the evaluation of surgical margins, considering histopathological diagnosis as the gold standard.

Methodology: This study takes into account patients of all ages and gender systemically fit and healthy enough to undergo surgical procedures under general anesthesia, presenting with massive lesions or ulcerations in the oral cavity with pre-determined confirmation as oral squamous cell carcinoma of varying grades who have been admitted as inpatients at the Department of Cranio-Maxillofacial Surgery unit, at College of Dental Sciences, Davangere, Karnataka, India. The results were assessed, and the data accrued was subjected to statistical analysis.

Results: The result of imprint cytology showed that it was highly significant at $p<0.001$ and significant at $p<0.005$. Using the spearman test in calculating the correlation between imprint cytology and frozen section, it was evident that both imprint cytology and frozen section are valuable adjunct intraoperative diagnostic guides for the management of malignancies as they help make a prompt therapeutic decision that may prevent surgical re-intervention.

Conclusion: this study demonstrates that both imprint cytology and frozen section provide relatively accurate assessment of surgical margin clearance and can be used as a reliable adjunct to histopathological diagnosis. However, surgical margin clearance cannot solely depend on these intraoperative tools. More research needs to be done for the assessment of the utility of these lesions as these procedures can only be used to assess the presence or absence of atypia.

Key words: oral squamous cell carcinoma, touch imprint cytology, frozen section, histopathology, biopsy

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INTRODUCTION

Oral Squamous Cell Carcinoma (OSCC) is a common cancer and a leading cause of death. Although accounting for 2% - 4% of malignancies in the West, this carcinoma accounts for nearly 40% of all cancers on the Indian subcontinent. An important factor in the poor prognosis of OSCC is the fact that many at times it goes undiagnosed or untreated until it is advanced. The prognosis for patients with OSCC that are treated early is better; the 5-year survival rates are as high as 80%. Histopathology is the gold standard for the diagnosis even though it is time-consuming. Therefore, new diagnostic methods for early identification of oral neoplastic diseases are needed [1-11].

The best chance of surgical cure in OSCC is complete removal of all malignant cells. Unfortunately, it is not possible to identify the microscopic extent of the tumour invasion by inspection and palpation. To ensure complete tumour removal, the surgeon excises "safe" margin around the tumour and uses Frozen Section (FS) or Imprint Cytology (IC) to confirm that the margins of resection do not contain cancerous tissue [2,3].

Intraoperative diagnosis includes FS and IC, both of which provide rapid intraoperative pathologic consultation [11].

Intraoperative consultation examinations are required by surgeons from pathologists for immediate important decisions regarding the optimal extent of surgery. Surgeons particularly want to know regarding the clearance of the tumour margins. Both FS and IC serve this purpose well. Both provide accurate results in minutes while the patient is under anaesthesia. Although FS analysis is a preferred method of intraoperative consultations, in underdeveloped countries where resources are limited this facility may not be available in many institutions. Therefore, we aim to compare the diagnostic efficacy of IC versus FS for OSCC. IC has proven its accuracy in diagnosing surgical specimens belonging to thyroid, parathyroid, and breast cancer and prostrate. These techniques play an important role in evaluating resection margins of OSCC, however, its added benefits are still under investigation.

METHODS AND MATERIALS

The present study is a prospective comparative study which evaluated 12 patients admitted in the inpatient department of Oral and Maxillofacial Surgery at the College of Dental Sciences, Davangere, Karnataka, India requiring surgery for OSCC at various sites in the oral cavity.

Armamentarium used

- Frosted micro slides
- Bio fix spray
- Sample collecting bottles
- Normal saline
- 10% formalin
- Tumour specimen

Inclusion criteria were patients of all age groups; both male and female patients, systemically fit and healthy enough to undergo surgery, presenting with massive lesions or ulcerations with a pre-determined diagnosis of OSCC conducted by biopsy.

Exclusion criteria were patients diagnosed with any other organ malignancies, systemically unfit for surgery and patients who were unwilling or unable to give consent to be a part of this study.

Operative technique

A thorough clinical examination of all the patients was carried out, which included examining the oral cavity of the patients for findings such as blanching of the oral mucosa, bleeding and ulcerations present at various sites as well as tongue movements. The inter-incisal mouth opening of the patients was also measured and recorded in millimetres.

Clinical diagnosis was pre-determined by histopathological diagnosis with the help of incisional biopsy with tissue samples of adequate width and depth taken from the affected area of oral mucosa.

The sample for IC was taken by carefully imprinting the apparent clear margins of the raw cut surface of the donor site on to the slide which was then sprayed using a bio fix spray and was sent to the Department of Oral Pathology, College of Dental Sciences, Davangere, Karnataka, India for analysis.

A sample from the same specimen which was used for IC was transported in normal saline for FS studies to the Department of General Pathology, JJM Medical College, Davangere. Later, the tumour specimen was grossed according to the standard protocols and was received by the same department for obtaining permanent histopathological sections.

Clinical criteria

- Positive: isolated cells or clusters of malignant cells showing keratinization. The cells have distinct cell borders, vesicular nuclei and prominent nucleoli.
- Questionable: suggestive of malignancy but uncertain due to limited number of cells or degree of atypia.
- Negative: no evidence of malignancy like high N/C ratio, pleomorphism, coarse chromatin, or irregular nuclear outlines.

Statistical analysis was done using inferential statistics using the Kolmogrov-smirnoff test and the Shapiro Wilk test. Software used in the analysis was SPSS version 23.0

RESULTS

12 participants were enrolled in this study, with a pre-requisite diagnosis of established OSCC through previously conducted biopsy. A minimum of 4 sections each for IC and FS were obtained from each patient, which totalled up to 48 margins that were included in the study.

Among the subjects, 50% were found to be male and 50% were found to be female, establishing a ratio of about 1:1.

The age group varied from 20-60 years, among which the mean age was found to be 43.5 with a standard deviation of 10.9.

OSCC can be classified based on histopathological variation as:

- Well-differentiated squamous cell carcinoma (WDSCC)
- Moderately- differentiated squamous cell carcinoma (MDSCC)
- Poorly differentiated squamous cell carcinoma (PDSCC)

It was observed that among the study group, around 75% of the patients were established as MDSCC, 16.7% were found to be classified under PDSCC and around 8.3% were categorized as WDSCC (Figure 1 and 2).

The data was collected, and a normality distribution table was established. The statistical tests were applied. The table shows that the data collected is highly significant at $p<0.01$ and is significant at $p<0.05$ (Table 1).

GRAPH 1: GENDER DISRTIBUTION

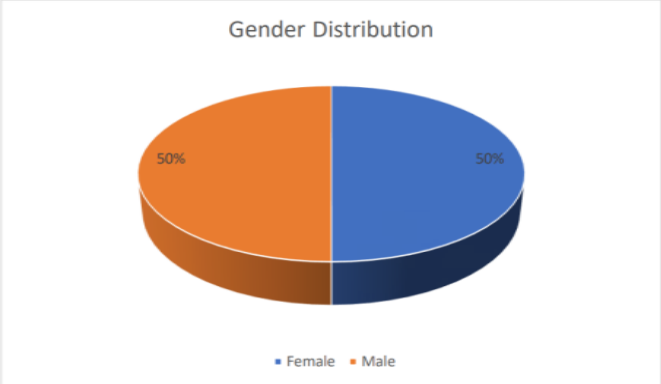

Fig. 1. Gender distribution

GRAPH 2: OSCC GRADING

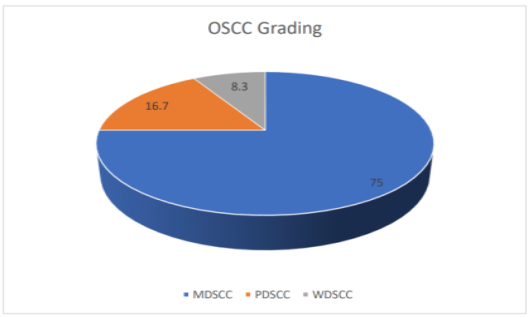

Fig. 2. Grading of Oral Squamous Cell Carcinoma

Tab. 1: Normality Distribution Table

		Kolmogorov-Smimov			Shapiro-Wilk		
	Group	**Statistic**	**Df**	**Sig.**	**Statistic**	**df**	**Sig.**
Positive	Imprint cytology	442	12	.000 HS	554	12	.000 HS
	Frozen section	442	12	.000 HS	.554	12	.000 HS
Negative	Imprint cytology	399	12	.000 HS	680	12	.001 HS
	Frozen section	399	12	.000 HS	.680	12	.001 HS
Questionable	Imprint cytology	299	12	.004 HS	856	12	.044 S
	Frozen section	299	12	.004 HS	856	12	.044 S

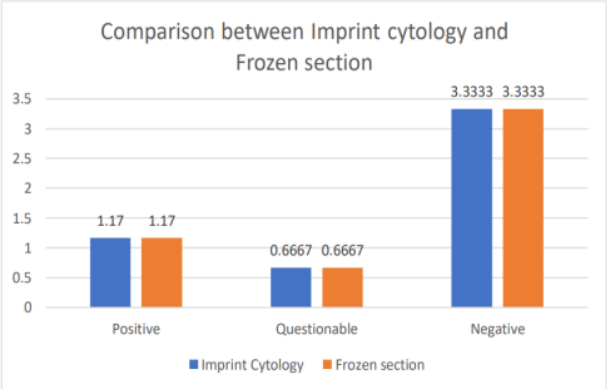

Fig. 3. Comparison between Frozen Section and Imprint cytology

The statistical test applied is the Spearman correlation test which gives a comparison in the results between IC AND HP followed by a comparison between the results of FS and HP in accordance with the above- mentioned clinical criteria.

- For positive margins: A positive correlation was observed in both IC and FS (p- 0.39) when compared with the HP which was used as the gold standard.
- For negative margins: A positive correlation was observed in both IC and FS (0.19) when compared with the HP which was used as the gold standard.
- For questionable margins: A weak negative correlation was observed in comparison of IC and FS with the HP (p- 0.33).

Following this, the data between IC and FS were compared. The statistical test applied is the Mann- Whitney U test (Figure 3).

DISCUSSION

The surgical margin is the adjacent mucosal or connective tissue surface removed by the surgeon during operative procedures in cases of malignancies. The term "surgical clearance" and "surgical margins" are used interchangeably. Margin clearance is important, as positive surgical margins can often lead to local recurrence. The present study highlights the importance of intraoperative diagnostic techniques such as FS and IC for surgical margin clearance.

The best chance of surgical cure in OSCC is complete removal of all malignant cells. Unfortunately, it is not possible to identify the microscopic extent of the tumour invasion by inspection and palpation. To ensure complete tumour removal, the surgeon "excises" safe margins around the tumour and uses FS or IC to confirm that the margins of the resection do not contain cancerous tissue [12-20].

IC is a well- known rapid histopathological method of intra-operative analysis of biopsy specimens along with FS. Different studies have analysed the importance of both procedures; However, FS have shown interpretational difficulties in the form of freezing artefacts, cost-effectiveness, and expertise in operating the cryostat machine etc., IC on the other hand is a very simple, cheap and easy to perform procedure requiring pathologist's expertise in the cytology interpretation [2,3].

Intra-operative diagnosis includes FS and IC, both of which provide rapid intra-operative pathologic consultation. FS

procedure involves a rapid microscopic analysis of a specimen by thin slicing of tissue cut from a fresh specimen. FS has several limitations, often making the interpretation difficult. The most important limitations that interfere with the results are the technical problems which include freezing artefacts, poor quality sections, bloated cell morphology and poorly stained sections.

Although it is generally believed that the conventional FS is the best technique for intra-operative consultation, IC has also emerged as an accurate, simple, economically reasonable and rapid diagnostic tool. Different studies carried out in different regions of the world have proved its diagnostic accuracy [21,6].

The current study enrolled a total of 12 cases, with at least 4 margins each, over a period of 12-18 months all of whom were inpatients at the Department of Oral and Maxillofacial Surgery. The chief complaints of these patients ranged from increase in the growth of the lesion, non-healing ulcers, and difficulty in mastication or deglutition to burning sensation of the respective region among many others.

The aim of this study is to compare the accuracy of IC and FS with the histopathological diagnosis and to establish their efficacy as intra-operative diagnostic tools to facilitate margin clearance, in patients previously affirmed as OSCC of varying grades.

The patients enrolled in this study were in the age range of 20-60 years, with an equal gender predilection. Among the study group, 75% were graded as MDSCC, 16.7% as PDSCC and 8.3% as WDSCC respectively, presenting variations of symptoms.

SK Dutta et al, in their study concluded that IC is an accurate, simple, rapid and cost-effective method of diagnosis. It does not alter the resected specimen which can later be fixed and sectioned. The accuracy of IC for the diagnosis of both benign and malignant tumours was found to be 75%. Having enlisted the probable reasons for inaccurate specific diagnosis of IC, they mentioned that the most benign tumours have low cellular yield and paucity of cells which sometimes leads to erroneous diagnosis. The cytological picture of some inflammatory lesions closely mimics certain benign or borderline soft tissue tumours, for example, granulation tissue was found to mimic nodular fasciitis, fibroblasts of granuloma were perceived as spindle cells of fibromatosis. Low-grade sarcomas have little cellularity and mild pleomorphism, and they are commonly diagnosed as benign lesions on IC. Conversely, schwannoma is highly pleomorphic and imprint smears are inadvertently but unavoidably reported as malignant [21,6].

Even though FS is the most widely used method for intra-operative evaluation of margin status, comparative studies between IC and FS have highlighted that the latter is not a practical modality in many situations. This is because FS requires expensive instruments, skilled technicians and histopathologists. Even though architectural orientation is better appreciated in the case of FS, artefacts are more commonly encountered. Morphological details are more vivid in imprint smears. The turnaround time is also less in case of imprints [22-34].

Neduvancherry S et al, prove in their study the specificity of FS in the evaluation of neck nodes in head and neck cancer is close to 100% whereas sensitivity varies from 43% to 93%. Although multiple studies compare IC and FS in other sites like breast and prostate, only four studies (three based on sentinel nodes) have looked into the accuracy of IC for detecting lymph node metastasis in head and neck cancer. In other studies, the sensitivity of IC in the evaluation of neck nodes in head and neck cancer varies from 50% to 87.5%, whereas specificity varies between 95.4% to 100%. In their experience and opinion, the pattern of obtaining the imprint may also affect the sensitivity of IC. The tissue surfaces to be imprinted should be flat without any bevelling or irregularity which may lead to an inadequate imprint smear. Excess tissue fluid and blood in the imprint may also lead to misinterpretation. The imprint smear should ne monolayered, which can be obtained by touching the cut surface on the slide once and firmly. Repeated touching the slide surface may lead to overlap of cells and questionable interpretation [13, 35].

On the other hand, in our study both IC and FS proved to be highly accurate and positively correlated to the histological diagnosis.

According to literature, the mean time duration for reporting FS results is 41.18 ± 3.62 minutes, whereas for IC, it is found to be 18.12 ± 2.01 minutes. The longer turnaround time for intraoperative reporting could be due to the operation theatre and pathology lab being in separate buildings. In a study carried out by Asthana et al, the average time taken for reporting the IC for lymph nodal metastasis in head and neck cancer was 15 minutes [3].

In the present study, the total estimate of time taken was approximately 30-40 minutes due to the aforementioned reason i.e., the laboratory being in a distant different building

In the study done by Neduvanchery et al, the authors also elaborate on the cost-effectiveness of IC over FS. While FS requires expensive equipment such as the cryostat (5000-25,000 USD), cytomatrix and expert technicians to perform, cytology requires just two frosted slides and ethyl alcohol fixative. Hence proving that IC is a reliable alternative for FS in situations where resources as well as technical expertise are limited. Another drawback of FS includes the freezing artefacts, which highly influences the tissue section interpretation [35,13].

The conclusion of their study showed concordance to that of our study, in which the total cost of FS rounded up to 1500-2000 INR as compared to that of IC at an effective cost of 500-800 INR. Thereby, proving that IC is far more economically feasible than FS.

In their study, Ord RA and Seena A raised several questions while evaluating the significance of surgical margins such as, how helpful is FS in guiding the surgeon? What is a positive margin? What treatment is indicated for a positive margin? How confident can the operating surgeon be that the negative margin ensures that the entire tumour has been removed? In such cases FS has been used both in diagnosis and to evaluate margins. In most publications, the accuracy for such a diagnosis is 96.8%-98% [2, 3].

Intra-operative molecular diagnosis may therefore eventually be developed as the "state of art" method for oncologic surgery. Although, local recurrence has been observed with increasing frequency in tumours even with negative margins as the size of the tumour increases.

Irrespective of the status of nodes, this validates the use of adjuvant radiation therapy for all T3 and T4 lesions despite the negative

margins to remain on a safer side, as well as for T1 and T2 lesions with positive margins where further excision is not feasible.

The current study was designed to compare the accuracy of IC and FS as an intra-operative diagnostic tool and its correlation with the histopathological diagnosis in squamous cell carcinoma of the oral cavity.

According to this study, both IC and FS are equally effective in determining safe margins for the excision of the lesion.

In conclusion, both FS and IC provide effective results. It is especially accurate in distinguishing between benign and malignant lesions. Since IC shows only cytological features, architectural changes in the form of basement membrane invasion cannot be commented upon. This is a drawback of IC that invasion cannot be identified. Although, it can facilitate the detection of dysplastic cytological changes.

It is well recognized that the freezing and sectioning techniques of frozen section results in unavoidable distortions and artifacts, rendering diagnosis difficult in many instances. IC reveals crisper cytological details and further has the advantage of being inexpensive, simple, and more time efficient than FS. The greatest advantage of cytology examination is of not having such artifacts, resulting in superior nuclear and cytological details. Minimal tissue is required for cytological examination. Also, certain tissues cannot be studied by FS, i.e.; bone, necrotic tissue, and fat etc., which give excellent results on IC.

To summarize, it would be fair to say that this study shows an extent of positive correlation between both IC and FS and the final HP and high accuracy between the results of both the diagnostic modules.

CONCLUSION

Both FS and IC provide accurate diagnosis. The accuracy of IC is quite high in particular, in differentiating benign from malignant lesions. Since IC shows only cytological features, architectural changes in the form of the basement membrane, depth of invasion cannot be commented upon. This is a drawback of IC. Although, it does, however, facilitate the detection of dysplastic cytological changes.

FS is the most widely used method for intra-operative evaluation of margin status. Comparative studies between IC and FS have highlighted that the latter is not a practical modality in many situations. This is because FS requires expensive instruments, skilled technicians and histopathologists. Even though architectural orientation is better appreciated in the case of FS, artifacts are more commonly encountered.

The cost-effectiveness of IC over the FS is also proven here. While FS requires expensive equipment and expert technician to perform, cytology requires minimal tools. Thus, IC is a reliable alternative for FS in situations with limited resources and technical expertise. Another issue with FS is the freezing artifacts that are commonly encountered which may affect the tissue section's interpretation.

In summation, this study demonstrates that both FS and IC provide reliable diagnosis and can be used as an adjunct to histopathology, however surgical clearance cannot solely depend on these intra-operative diagnostic tools. These procedures can only be used to assess the presence or absence of atypia. More research needs to be done for the assessment of the utility of these modalities, as the sample size in current study is considerably low.

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Nil

CONFLICTS OF INTEREST

There are no conflicts of interest

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