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Original Article

Role of Intraoperative Frozen Section in Assessment of Final Tumor Margin Status in Surgery of Squamous Cell Carcinoma of Head and Neck

Junaid Akram, Kamran Zamurrad, Muhammad Ali, Usman Afzal Malik, Imran Ul Haq*, Aqsa Akram**

Department of ENT, Combined Military Hospital Quetta/National University of Medical Sciences (NUMS) Pakistan,
*Department of ENT, Combined Military Hospital/National University of Medical Sciences (NUMS), Rawalpindi Pakistan,
**Department of Dental Surgery, AFID/National University of Medical Sciences (NUMS), Rawalpindi Pakistan

ABSTRACT

Objective: To evaluate the diagnostic utility of intraoperative frozen section analysis in assessing final tumor margin status in surgeries for squamous cell carcinoma of the head and neck.
Study Design: Cross-sectional study.
Place and Duration of Study: Department of ENT, Tertiary Care Hospital, Rawalpindi and Quetta Pakistan, from Sep 2022 to Nov 2024.
Methodology: A total of 192 patients aged between 18 to 85 years, with histologically confirmed squamous cell carcinoma of the head and neck and undergoing surgical resection with curative intent were analyzed. During surgery, the primary tumor was resected with a margin of normal tissue as per standard oncologic principles. IFS analysis was performed on the resected margins by a pathologist experienced in head and neck pathology. The results of the IFS were compared with the final margin status.
Results: In a total of 192 patients, 137(71.4%) were male. The mean age was 50.60±20.69 years, ranging between 18-84 years. The most common tumor location was tongue, 56(29.2%). The mean tumor size was 4.52±1.97 cm. Tumor evaluation revealed moderately, poorly, and well differentiated in 59(30.7%), 69(35.9%), and 64(33.3%) patients, respectively. The diagnostic performance of IFS margin status showed that sensitivity, specificity, PPV, NPV, and overall diagnostic accuracy was 89.9%, 80.4%, 61.1%, 95.8%, and 82.8%.
Conclusion: Intraoperative frozen section analysis demonstrates high sensitivity and diagnostic accuracy in assessing surgical margins for squamous cell carcinoma of the head and neck. While its performance is influenced by patient demographics, tumor location, and differentiation, IFS remains a critical tool for optimizing surgical outcomes.
Keywords: Head, Neck, Sensitivity, Specificity, Squamous Cell Carcinoma, Tumor.

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INTRODUCTION

Head and neck cancers account for nearly 4% of all cancers in the USA, with a higher prevalence among males, and individuals above 50 years of age.[1] Squamous cell carcinoma (SCC) of the head and neck encompasses malignancies originating from the squamous epithelium lining the oral cavity, pharynx, and larynx.[2] These cancers represent a significant portion of global cancer incidence, showing approximately 890000 new cases every year, and death among 450000 annually.[3] Tobacco use, alcohol consumption, and infection with oncogenic viruses are some of the most common risk factors.[4]

Surgical resection is considered to be the best approach for managing head and neck SCC.[5] Achieving clear surgical margins is crucial for reducing local recurrence and improving overall survival rates.[6] Positive surgical margins have been found in 15-30% of head and neck SCC surgeries and linked with a 2-fold rise in local recurrences.[7] The prognosis of head and neck SCC is closely related to the completeness of tumor excision. Positive surgical margins are linked with higher rates of local recurrences and reduced survival rates.[8]

Intraoperative frozen section (IFS) analysis is utilized during surgery to evaluate the status of margins in real-time, that may guide immediate re-excision if needed. IFS analysis can also provide immediate feedback on margin status, that may facilitate intraoperative decisions achieving negative margins.[9] Despite the widespread use of IFS, the accuracy and reliability of IFS in assessing final tumor margins have been a subject of debate.[10] Discrepancies between IFS and final pathology can lead to either unnecessary additional resections or missed residual tumor tissue, impacting outcomes. This study was

Correspondence: Dr Junaid Akram, Department of ENT, Combined Military Hospital Quetta Pakistan
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planned to evaluate the diagnostic utility of IFS analysis in assessing final tumor margin status in surgeries for SCC of the head and neck.

METHODOLOGY

This cross-sectional study was planned at the department of ENT, Tertiary Care Hospital Rawalpindi and Quetta, Pakistan during September 2022 to November 2024. Considering the sensitivity of intraoperative frozen section histopathology as 76.5%,[11] with 95% confidence level and 6% margin of error, the sample size was calculated to be 192 using WHO sample size calculator. Approval for this study was taken from Institutional ethical review board (vide certificate number CMH QTA-IERB/61/2024). Informed and written consents were obtained from all study participants after explaining them the aims and protocol of this research.

Inclusion Criteria: Patients aged between 18 to 85 years, with histologically confirmed SCC of the head and neck, and undergoing surgical resection with curative intent were included.

Exclusion Criteria: Patients with history of head and neck malignancies, or those who had received neoadjuvant chemotherapy or radiotherapy. Patients with distant metastases at the time of diagnosis were excluded. Patients unwilling to be part of this research were not included.

Demographic characteristics including gender, age, along with tumor characteristics (size, location, stage) were documented. During surgery, the primary tumor was resected with a margin of normal tissue as per standard oncologic principles. IFS analysis was performed on the resected margins by a pathologist experienced in head and neck pathology. The results of the IFS were communicated to the surgical team intraoperatively. If the IFS indicated positive or close margins, additional tissue was resected as deemed appropriate by the surgical team. All resected specimens, including any additional tissues removed based on IFS findings, underwent formalin fixation and paraffin embedding. Permanent section was prepared and evaluated by a pathologist blinded to the IFS results. The final margin status was classified as positive (tumor at the margin), or negative (no tumor within 5 mm of the margin). IFS results, and final permanent section margin status were noted.

Data analysis was performed using "International Business Machines- Statistical Package for the Social Sciences (IBM-SPSS), version 26.0". Frequency and percentages were shown for qualitative variables. Mean and standard deviation were calculated for continuous variables. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and overall diagnostic accuracy of IFS in detecting positive margins were calculated using the final permanent section analysis as the gold standard. Subgroup analyses were performed to evaluate the impact of gender, age, location, and differentiation of tumor on the accuracy of IFS. For all inferential statistics, $p \leq 0.05$ was taken as significant.

RESULTS

In a total of 192 patients, 137(71.4%) were male. The mean age was 50.60±20.69 years, ranging between 18-84 years. The most common tumor location was tongue, 56(29.2%). The mean tumor size was 4.52±1.97 cm. Tumor evaluation revealed moderately, poorly, and well differentiated in 59(30.7%), 69(35.9%), and 64(33.3%) patients, respectively (Table-I).

Table-I: Characteristics of Patients (n=192)

Characteristics		Frequency (%)
Gender	Male	137(71.4%)
	Female	55(28.6%)
Age (years)	18-45	81(42.2%)
	46-60	38(19.8%)
	61-85	73(38.0%)
Tumor location	Tongue	56(29.2%)
	Buccal mucosa	48(25.0%)
	Alveolus	40(20.8%)
	Maxilla	25(13.0%)
	Larynx	15(7.8%)
	Floor of mouth	8(4.2%)
Tumor differentiation	Moderately differentiated	59(30.7%)
	Poorly differentiated	69(35.9%)
	Well differentiated	64(33.3%)

The diagnostic performance of IFS margin status showed that sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and overall diagnostic accuracy was 89.9%, 80.4%, 61.1%, 95.8%, and 82.8% (Table-II).

Table-II: Diagnostic performance of intraoperative frozen section in assessing final tumor margin status (n=192)

Intraoperative Frozen section margin status	Final tumor margin status		Sensitivity	Specificity	PPV	NPV	Diagnostic accuracy
	Positive	Negative					
Positive	44(22.9%)	28(14.5%)	89.9%	80.4%	61.1%	95.8%	82.8%
Negative	5(2.6%)	115(59.8%)					

positive predictive value (PPV), negative predictive value (NPV)

Males exhibited a sensitivity of 91.4%, specificity of 79.4%, and diagnostic accuracy of 82.3%, while

females showed a sensitivity of 85.7%, specificity of 82.9%, and accuracy of 83.6%. Age evaluation showed that the highest diagnostic accuracy was in patients aged 18-45 years (91.3%) with sensitivity of 95.8%. Accuracy decreased with age, being 84.2% in the 46-60 years' group and 72.6% in those 61-85 years. Carcinoma tongue had the highest diagnostic accuracy (90.0%), followed by carcinoma buccal mucosa, and maxilla (82.9% each). Moderately differentiated tumors had the diagnostic accuracy of 86.4% and sensitivity 92.3%. Poorly differentiated had 84.1% accuracy and 94.7% sensitivity. Well-differentiated tumors showed slightly lower accuracy (78.1%) and sensitivity (82.4%). Table-III is showing details about the stratification of various characteristics of patients with respect to IFS margin status diagnostic utility.

Table-III: Comparison of characteristics of patients with regards to IFS margin status taking final tumor margin status as the gold standard (n=192)

Characteristics		Sensitivity	Specificity	PPV	NPV	Diagnostic accuracy
Gender	Male	91.4%	79.4%	60.4%	96.4%	82.3%
	Female	85.7%	82.95	63.2%	94.4%	83.6%
Age (years)	18-45	95.8%	89.5%	79.3%	98.1%	91.3%
	46-60	83.3%	84.6%	71.4%	100%	84.2%
	61-85	84.6%	70.0%	37.9%	100%	72.6%
Tumor location	Tongue	90.9%	89.5%	83.3%	94.4%	90.0%
	Buccal mucosa	90.0%	80.6%	60.0%	96.2%	82.9%
	Alveolus	85.7%	80.5%	42.9%	97.1%	81.3%
	Maxilla	91.7%	79.3%	64.7%	95.8%	82.9%
	Larynx	88.9%	73.9%	57.1%	94.4%	78.1%
	Floor of mouth	89.2%	74.9%	62.8%	93.8%	82.8%
Tumor differentiation	Moderately differentiated	92.3%	84.8%	63.2%	97.5%	86.4%
	Poorly differentiated	94.7%	80.0%	64.3%	97.6%	84.1%
	Well differentiated	82.4%	76.6%	56.0%	92.3%	78.1%

DISCUSSION

This study demonstrated that IFS exhibited high sensitivity (89.9%) and NPV (95.8%), with a diagnostic accuracy of 82.8%. This underscores its utility as an effective intraoperative tool for ensuring clear surgical margins and minimizing the risk of residual disease. Layfield *et al.,* reported concordance rates of 97% between IFS and permanent section analysis.[12] While our study achieved slightly lower specificity (80.4% vs. 94.8%), the sensitivity (89.9%) was comparable. The observed differences may be attributable to the larger sample size in Layfield *et al.,* study, which involved 1796 pairs of IFS and permanent section diagnoses, allowing greater refinement in identifying false-positive and false-negative cases.[12] Ali *et al.,* evaluating 251 cases of oral SCC reported a sensitivity of 88.8% and diagnostic accuracy of 91.6%.[13] These values align closely with our findings. However, our specificity was slightly lower, potentially due to variations in the inclusion of cases across tumor locations and stages. Differences in pathology expertise and techniques for sampling tumor margins during surgery could also explain this discrepancy. Long *et al.,* reported significantly lower sensitivity (76.5%) for IFS compared with FTSH.[11] Their findings suggested that IFS might have limitations in assessing three-dimensional tumor margins, particularly in accounting for the periphery of the specimen. This contrasts with our study, which utilized a rigorous sampling strategy and pathologist collaboration, leading to improved sensitivity. The broader range of tumor locations and the exclusion of neoadjuvant-treated patients in our study likely enhanced the reliability of IFS results.

This research showed that male gender exhibited slightly higher sensitivity (91.4%) than females (85.7%), and this could be attributed to gender-related disparities in tumor biology and resectability.[14] The diagnostic accuracy was found to be higher in 18-45 years (91.3%) age group, and gradually declining with the increase in age. This pattern is somewhat similar to what Ali *et al.,* which may suggest that younger patients may have better-defined tumor margins due to lower rates of tissue fibrosis or anatomical distortion.[13] Conversely, older patients (61-85 years) in our study showed the lowest accuracy (72.6%), likely influenced by comorbid conditions and more advanced disease stages complicating surgical resections. Tumor location is also expected to significantly impact the diagnostic performance of IFS. Tumor differentiation influenced IFS performance, with moderately and poorly differentiated tumors achieving higher diagnostic accuracy (86.4% and 84.1%, respectively) than well-differentiated tumors (78.1%). This finding may be attributed to the clearer delineation of poorly differentiated tumor margins compared to the gradual transitions seen in well-differentiated tumors.[15]

The high sensitivity and NPV of IFS in this research exhibited the critical role of IFS evaluation in intraoperative decision-making. By accurately identifying negative margins, IFS minimizes the need for unnecessary additional resections, preserving healthy tissue and reducing surgical morbidity.[16,17] The relatively lower specificity and PPV suggest that some cases may result in over-resection, underscoring the need for careful interpretation of IFS results and

adjunctive measures, such as advanced imaging or molecular diagnostics.[18] The superior performance of IFS in younger patients suggests its particular value in this demographic, potentially contributing to better postoperative outcomes. For challenging tumor locations, enhanced sampling protocols and close collaboration between surgeons and pathologists could improve diagnostic accuracy. Addressing the limitations in older patients through preoperative optimization and advanced imaging could further refine the reliability of IFS.

While our study provides valuable insights, several limitations must be acknowledged. The relatively small sample size may have constrained subgroup analyses, particularly for less common tumor locations. The exclusion of patients with prior malignancies or neoadjuvant therapy might have limited the applicability of results to more complex cases. Our reliance on conventional IFS methods without adjunctive techniques, such as fluorescence-guided surgery or molecular margin analysis, may have constrained diagnostic accuracy in certain scenarios.

CONCLUSION

It is concluded that intraoperative frozen section analysis demonstrates high sensitivity and diagnostic accuracy in assessing surgical margins for squamous cell carcinoma of the head and neck. While its performance is influenced by patient demographics, tumor location, and differentiation, IFS remains a critical tool for optimizing surgical outcomes. Further studies incorporating advanced diagnostic modalities and larger, more diverse populations are warranted to refine its application and address its limitations in challenging cases.

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Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

JA & KZ: Data acquisition, data analysis, critical review, approval of the final version to be published.

MA & UAM: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

IUH & AA: Conception, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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