

Intraoperative Mandible Bone-Marrow Frozen Sections Are an Effective Predictor of Final Bone Margins: A 10-Year Study

Mohamad Z. Saltagi, MD^{1,2}; Christine Yang, MS¹; Morgan Sandelski, MD¹; Jessica A. Yesensky, MD^{1,2}; Avinash V. Mantravadi, MD^{1,2}; Michael G. Moore, MD^{1,2}; Michael W. Sim, MD^{1,2}

¹Indiana University School of Medicine
²Department of Otolaryngology—Head and Neck Surgery
Indiana University School of Medicine, Indianapolis, IN, USA

Abstract

Importance: Margin status is an essential prognosticator for patients undergoing surgical resection of head and neck squamous cell carcinoma (HNSCC). Intraoperative analysis of mandibular bone margins historically has entailed inconsistent methods of collection and interpretation. Determining an accurate and consistent method of intraoperative mandible bone margin assessment is imperative.

Objective: To determine the feasibility of intraoperative bone-marrow frozen sections (IBMFS) as a predictor of final mandible bone margins, and to evaluate its impact on patient outcomes who undergo mandibulectomy.

Design: Retrospective Chart Review

Setting: A tertiary level academic medical center.

Participants: 133 consecutive patients who underwent mandibulectomy for resection of oral cavity HNSCC from June 2009 to June 2019.

Intervention(s): Mandibulectomy performed with or without intraoperative bone-marrow frozen section analysis of the mandibular bone margins.

Main Outcome(s) and Measure(s): Primary outcome was correlation of intraoperative bone-marrow frozen sections with final histologic mandible bone margin status. Secondary outcomes included other histopathologic findings (perineural spread, lymphovascular invasion), overall survival, disease-free survival, recurrence rates, frequencies and modalities of adjuvant therapy, and postoperative complication rates (fistula, wound dehiscence, free flap failure).

Results: In the study period, 133 patients underwent mandibulectomy for resection of HNSCC. Of these, 91 had documented intraoperative frozen sections performed to assess the bone marrow at the margins of the resection defect, and 90 of 91 (98.9%) had IBMFS margins that correlated with bone margins on final histologic analysis (89 negative margins, 1 positive margin). The remaining 1 patient had negative IBMFS, but final histologic analysis showed a positive bone margin. Forty-two patients had no bone-marrow frozen sections performed intraoperatively; 2 of 42 had positive margins on final pathology. A distance to closest margin ≤ 2 mm was associated with increased recurrence rates (Odds ratio, OR=8, 95% CI = 2.25 to 28.5). Postoperative complication rates and postoperative adjuvant therapy utilization did not significantly differ between patient groups.

Conclusions and Relevance: Intraoperative frozen sections of the mandibular bone-marrow are an accurate, feasible, and consistent method of assessing bone margins. These are predictive of final bone margins and should be highly considered in guiding the extent of surgical resection intraoperatively for patients undergoing mandibulectomy.

Introduction

- Oral cavity squamous cell carcinoma (OCSCC)
 - Most common malignancy in the H/N
 - 350,000 new cases & 175,000 new deaths every year^{1,2}
 - 5-year survival slightly higher than 50-55%¹⁻³
- Margin status
 - Impacts prognosis
 - Impacts morbidity (re-resection vs adjuvant chemo and/or radiation)
- Assessing mandibular bone intraoperative is difficult
 - Cannot send frozen sections
 - Preop imaging can over or underestimate bony invasion³⁻⁵
 - No gold standard for intraoperative assessment
- Study goals:
 - Determine correlation of mandibular intraoperative bone-marrow frozen sections (IBMFS) with final bone margin pathology
 - Report Mandibular OCSCC patient data over past decade

Methods

- Patients
 - 133 patients who underwent mandibulectomy for resection of OCSCCC from June 2009 to June 2019 (relevant CPT codes were searched)
 - At least 2 months follow up
 - Complete records (pathology report)
- Primary Outcome
 - Correlation of intraoperative bone-marrow frozen sections with final histologic mandible bone margin status.
- Secondary Outcomes
 - Included other histopathologic findings (perineural spread, lymphovascular invasion), recurrence rates, margin status, overall survival, disease-free survival, recurrence rates, frequencies and modalities of adjuvant therapy, and postoperative complication rates (fistula, wound dehiscence, free flap failure).

Table 1 Legend
Abbreviations: N = number of patients; No. = number; y, years; SD, standard deviation; ACE-27, Adult Comorbidity Evaluation 27 score; TNM, tumor (T), nodes (N), metastasis (M) status; CT, computed tomography; MRI, magnetic resonance imaging; mm = millimeters. The two-tailed student T-test and multivariate analysis were used for the comparison of continuous variables (age, tobacco use, time to surgery, distance to closest margin, length of follow-up). All other variables were categorical and were compared by two-tailed Chi-squared test. Data are presented as the number (N), unless otherwise stated. *P value is reported for values that were not statistically significantly different. Where applicable, cohen's d is reported for statistically significant or nearly statistically significant comparisons, to help inform effect size, whereby d = 0.2 is a small effect, d = 0.5 is a moderate effect and d ≥ 0.8 is a large effect. P<0.05 is considered statistically significant, where applicable. Cohen's d, when comparing proportions, was calculated using the "Practical Meta-Analysis Effect Size Calculator" from George Mason University (<https://www.campbellcollaboration.org/escalc/html/EffectSizeCalculator-SMD10.php>). **This bone margin status calculation takes into account 2 patients who had re-resections for a presumed positive bone margin, where the final pathology of the re-resected specimen showed no tumor present.

Table 1: Patient Data: IBMFS vs no IBMFS

	IBMFS Taken N = 91	IBMFS Not Taken N = 42	Mean Difference	95% CI	Cohen's d or P value*
Age, y, mean (SD)	59.2 (12.7)	56.0 (18.2)	-3.2	-9.5 to 2.9	P=0.30
Race, No. (%)					
White	79 (86.8)	41 (97.6)	10.8%	-0.6% to 19.5%	P>0.05
Non-White	12 (13.2)	1 (2.4)			
Gender, No. (%)					
Male	66 (72.5)	32 (76.2)	3.7%	-13.1% to 18.0%	P=0.66
Female	25 (27.5)	10 (23.8)			
Tobacco use, packyears; mean (SD)	29.4 (26.3)	22.6 (24.9)	-6.8	-16.3 to 2.7	P=0.16
Time to surgery, days; mean (SD)	53.6 (55.0)	47.0 (43.9)	-6.6	-25.7 to 12.5	P=0.5
Preoperative Therapy, No. (%)					
Radiation	17 (18.7)	10 (23.8)	5.1%	-8.7% to 21.3%	P=0.5
Chemotherapy	11 (12.1)	11 (26.2)	14.1%	0.4% to 29.9%	P=0.043 d = 0.57
Radiation and chemotherapy	8 (8.8)	10 (23.8)	15%	2.2% to 30.3%	P=0.02 d = 0.71
None	71 (78)	31 (73.8)	4.2%	-10.3% to 20.8%	P=0.6
Preoperative imaging, No. (%)					
CT	87 (95.6)	40 (95.2)	0.4%	-6.9% to 11.8%	P=0.92
MRI	18 (19.8)	8 (19.0)	0.8%	-15% to 13.8%	P=0.91
Both	16 (17.6)	6 (14.3)	3.3%	-11.7% to 15.1%	P=0.64
None	2 (2.2)	0 (0)	n/a		
Comorbidity (ACE-27), No. (%)					
None or Mild	42 (46.2)	19 (45.2)	1%	-16.8% to 18.3%	P=0.92
Moderate or Severe	49 (53.8)	23 (54.8)			
Pathologic TNM Stage, No. (%)					
Stage I/II	10 (11.0)	5 (11.9)	0.9%	-9.6% to 14.9%	P=0.88
Stage III/IV	81 (89.0)	37 (88.1)			
Soft tissue Margin status, No. (%)					
Negative	37 (88.1)	86 (94.5)	6.4%	-6.0% to 15.5%	P=0.25
Positive	5 (5.5)	5 (11.9)			
Bone Margin status, No. (%)					
Negative	89** (97.8)	40 (95.2)	2.6%	-3.9% to 13.8%	P=0.42
Positive	2** (2.2)	2 (4.8)			
Perineural invasion, No. (%)					
Negative	39 (42.9)	22 (52.4)			
Positive	50 (54.9)	17 (40.5)	14.4%	-3.8% to 31.0%	P=0.12
Unknown	2 (2.2)	3 (7.1)			
Lymphovascular Invasion, No. (%)					
Negative	43 (47.3)	20 (47.6)			
Positive	47 (51.6)	17 (40.5)	11.1%	-7.0% to 27.8%	P=0.24
Unknown	1 (1.1)	5 (11.9)			
Distance to Closest Margin (mm), mean (SD)	3.3 (3.3)	2.4 (2.4)	-0.9	-2.02 to 0.22	P=0.11 d = 0.37

	IBMFS Taken N = 91	IBMFS Not Taken N = 42	Mean Difference	95% CI	Cohen's d or P value*
Postoperative Complications, No. (%)					
Oral-cutaneous or Pharyngo-cutaneous fistula	16 (17.6)	6 (14.3)	3.3%	-11.7% to 15.1%	P=0.64
Wound dehiscence or infection	13 (14.3)	11 (26.2)	11.9%	-2% to 27.8%	P=0.10
Free flap compromise requiring return to OR	10 (11)	2 (4.8)	6.2%	-5.9% to 14.9%	P=0.25
None	61 (67)	28 (66.7)	0.3%	-15.7% to 17.8%	P=0.97
Postoperative Therapy, No. (%)					
Radiation	59 (64.8)	21 (50)	14.8%	-2.9% to 31.9%	P=0.11
Chemotherapy	31 (34.1)	13 (31)	3.1%	-14.4% to 18.8%	P=0.73
Radiation and chemotherapy	28 (30.8)	10 (23.8)	7.0%	-10.0% to 21.4%	P=0.41
None	29 (31.9)	18 (42.9)	11.0%	-6.1% to 28.3%	P=0.22
Persistent and/or Recurrent Disease, No. (%)					
Recurrence	12 (13.2)	11 (26.2)	13%	-0.8% to 28.9%	P=0.06 d = 0.51
New Primary Tumor	4 (4.4)	3 (7.1)	2.7%	-5.2% to 14.9%	P=0.52
Distant Metastasis	5 (5.5)	2 (4.8)	0.7%	-10.8% to 8.3%	P=0.87
None	61 (67)	28 (66.7)	0.3%	-15.7% to 17.8%	P=0.97
Length of Follow-up, months; mean (SD)	19.0 (16.4)	22.6 (22.5)	3.6	-4.3 to 11.6	P=0.37
Alive, No. (%)					
Alive	62 (68.1)	24 (57.1)	11%	-6.1% to 28.3%	P=0.22
Dead	29 (31.9)	18 (42.9)			

Figure 1: Odds Ratio

	No Recurrence	
	a	b
Distance to Closest Margin ≤ 2.0 mm	20	50
	Recurrence	
	c	d
Distance to Closest Margin ≥ 2.0 mm	3	60

$$OR = (a/c) / (b/d)$$
$$OR = 8.0$$

An odds ratio was calculated to determine the association of recurrence rates with distance to closest margin; odds of having a distance to closest margin ≤ 2 mm were higher in those with recurrence compared to those without recurrence (OR=8, 95% CI = 2.25 to 28.5).

IBMFS & Final Margin Status: Correlations

	IBMFS Negative	IBMFS Positive	Specificity	100%
			Sensitivity	50%
Final margins negative	89	0	PPV	100%
			NPV	98.9
Final margins positive	1*	1	Negative likelihood ratio	50%
			Accuracy	98.9%

- 89 patients had negative IBMFS margins corresponding with negative final margins
- 1 patient had positive IBMFS and positive margins
- 1 patient had negative IBMFS, but had positive final margins
- *2 patients had negative IBMFS and initially had positive final margins, but re-resection revealed no tumor in the re-resected specimen. These patients thus had negative final bone margins corresponding with negative IBMFS.
- The correlation between IBMFS and final bone margins is demonstrated above (right)

Conclusions

- IBMFS is an accurate, feasible, and consistent method of assessing bone margins
- Distance to closest margin is lower in non-IBMFS group
- Recurrence rates trend higher in non-IBMFS group
- Survival rates trend higher in IBMFS group
- Further prospective analysis is needed to further evaluate this method

Contact Information

Michael W. Sim, MD
Assistant Professor
Department of Otolaryngology—Head and Neck Surgery,
Indiana University Health Physicians, Indiana University School of Medicine
1130 W. Michigan Street, Suite 400, Indianapolis, IN 46202
mwsim@iu.edu

Select References

- Ferlay J, Colombet M, Soerjomataram I, et al. Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. *International Journal of Cancer*. 2019;144(8):1941-1953.
- Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: A Cancer Journal for Clinicians*. 2018;68(6):394-424.
- Nieberler M, Stimmer H, Rasthofer D, Weirich G, Wolff KD. Defining secure surgical bone margins in head and neck squamous cell carcinomas: The diagnostic impact of intraoperative cytological assessment of bone resection margins compared with preoperative imaging. *Oral Oncol*. 2020;102:104579.
- Li MM, Puram SV, Silverman DA, Old MO, Rocco JW, Kang SY. Margin Analysis in Head and Neck Cancer: State of the Art and Future Directions. *Ann Surg Oncol*. 2019;26(12):4070-4080.
- Zeng B, Yang L, Liang YJ, Lao XM, Mei XY, Liao GQ. Diagnostic value of intraoperative bone marrow assessment for bone margins in patients with head and neck squamous cell carcinoma: a systematic review and meta-analysis. *Int J Oral Maxillofac Surg*. 2020;49(9):1128-1134.
- Ravasz LA, Slootweg PJ, Hordijk GJ, Smit F, van der Tweel I. The status of the resection margin as a prognostic factor in the treatment of head and neck carcinoma. *J Craniomaxillofac Surg*. 1991;19(7):314-318.
- Patel RS, Dirven R, Clark JR, Swinson BD, Gao K, O'Brien CJ. The prognostic impact of extent of bone invasion and extent of bone resection in oral carcinoma. *Laryngoscope*. 2008;118(5):780-785.
- Loree TR, Strong EW. Significance of positive margins in oral cavity squamous carcinoma. *Am J Surg*. 1990;160(4):410-414.
- Binahmed A, Nason RW, Abdoh AA. The clinical significance of the positive surgical margin in oral cancer. *Oral Oncol*. 2007;43(8):780-784.
- Layfield EM, Schmidt RL, Esebua M, Layfield LJ. Frozen Section Evaluation of Margin Status in Primary Squamous Cell Carcinomas of the Head and Neck: A Correlation Study of Frozen Section and Final Diagnoses. *Head Neck Pathol*. 2018;12(2):175-180.
- Piccirillo JF. Importance of comorbidity in head and neck cancer. *Laryngoscope*. 2000;110(4):593-602.