

Variables That Impact Recurrence in Oropharyngeal Carcinoma Treated with TORS

Madia C Russillo, MD; Aditi Katwala, BS; Alex Michael, MD; Zaid Al-Qurayshi, MBBS; Marisa Buchakjian, MD, PhD; Nitin Pagedar, MD; Rodrigo Bayon, MD
University of Iowa Hospitals and Clinics, Dept of Otolaryngology.

Introduction

- The incidence of oropharyngeal squamous cell carcinoma (OPSCC) has risen within the last two decades, with HPV related OPSCC (p16 positive) making up the greatest percentage of this increase.
- P16 positive OPSCC (p16+OPSCC) tends to have a favorable prognosis with better treatment response rates and overall survival for patients compared to p16 negative OPSCC. However, the treatment paradigm for both remain the same.
- For surgically resectable disease, Transoral Robotic Surgery (TORS) has greatly improved access for an operation in a narrow space such as the oropharynx.
- The concept of clearance of surgical margins is integral to an operation performed for cancer.
- There remains a lack of consensus on ideal margin dimensions in TORS for OPSCC.
- It is important to delineate whether intraoperative frozen section assessment would accurately identify a true positive margin.
- It also remains unclear whether the results of having clear, close or positive surgical margins are implicated in the risk of local recurrence and overall survival for p16+OPSCC.

Objectives

- Does margin status of intraoperative frozen sections and final resection correlate with disease recurrence?
- What other independent variables are associated with disease recurrence and overall survival in patients with p16+OPSCC?

Methods

- This is a single institution, retrospective study that evaluated patients with p16 positive and p16 negative OPSCC undergoing TORS.
- 142 patients from October 2012 to October 2020 were included, of which 127 patients had p16+ OPSCC.
- Variables evaluated included: age, sex, racial background, tobacco and alcohol use, tumor subsite, stage of tumor, lymphovascular invasion (LVI), perineural invasion (PNI), intraoperative frozen margin status, final pathology status, recurrence, and mortality.
- Exclusion Criteria:
 - Diagnosis other than squamous cell carcinoma (SCC).
 - Salvage surgery following neoadjuvant therapy.
 - Unknown p16 status.
 - Cases where intraoperative frozen margins were not obtained.

Results

	Study sample (N=127)		Initial frozen section margin status		P ^a	Permanent pathology margin status		P ^a	
	n	%	Uninvolved ^b (n=88)	Involved ^b (n=39)		Uninvolved (n=89)	Involved ^b (n=38)		
Initial frozen section margin status									
Negative	88	69.29	88	100.00		74	83.15	14	36.84
Severe dysplasia/Carcinoma in situ	10	7.87	0	0.00		5	5.62	5	13.16
Positive	29	22.83	0	0.00	NA ^c	10	11.24	19	50.00
Margins re-excision									
Not performed	74	59.20	72	83.72		66	75.00	8	21.62
Performed	51	40.80	14	16.28	<0.001	22	25.00	29	78.38
Final frozen section margin status									
Negative	119	93.70	86	97.73		89	100.00	30	78.95
Severe dysplasia/Carcinoma in situ	2	1.57	0	0.00		0	0.00	2	5.26
Positive	6	4.72	2	2.27	0.010	0	0.00	6	15.79
Final permanent pathology margin status									
Negative	39	30.71	31	35.23		39	43.82	0	0.00
Close (1-5 mm)	50	39.37	43	48.86		50	56.18	0	0.00
Very close (<1mm)	5	3.94	5	5.68		0	0.00	5	13.16
Severe dysplasia/Carcinoma in situ	6	4.72	0	0.00		0	0.00	6	15.79
Positive	27	21.26	9	10.23	<0.001	0	0.00	27	71.05
Neck dissection									
Not performed	11	9.02	3	3.57		6	7.06	5	13.51
Performed	111	90.98	81	96.43	0.004	79	92.94	32	86.49
Lymph node(s) involvement									
Negative	19	16.24	17	19.77		15	17.86	4	12.12
Positive	98	83.76	69	80.23	0.10	69	82.14	29	87.88
Adjuvant radiotherapy									
Not received	30	23.62	22	25.00		24	26.97	6	15.79
Received	97	76.38	66	75.00	0.66	65	73.03	32	84.21
Adjuvant chemotherapy									
Not received	92	72.44	65	73.86		64	71.91	28	73.68
Received	35	27.56	23	26.14	0.67	25	28.09	10	26.32
Recurrence on follow-up									
No	113	88.98	82	93.18		82	92.13	31	81.58
Yes	14	11.02	6	6.82	0.032	7	7.87	7	18.42
Mortality on follow-up									
No	115	90.55	82	93.18		79	88.76	36	94.74
Yes	12	9.45	6	6.82	0.19	10	11.24	2	5.26

Table 1. Descriptive statistics of the study population in p16+ OPSCC cases only.

- p16- disease was more prevalent to have positive or severe dysplasia/CIS on margins compared to p16+ cases.
- For p16+ cases, initial frozen marginal status was positively correlated with final frozen margin status and final permanent pathology margin status.
- Initial frozen status was also correlated with recurrence but not with mortality.

Margin status	Patients No. (N=127)	Local recurrence %	Unadjusted odds ratio (95% CI).
Initial frozen section margin status			
Negative	88	6.82	Reference
Severe dysplasia/Carcinoma in situ	10	30.00	5.86(1.20, 28.62)
Positive	29	17.24	2.85(0.80, 10.15)
Final frozen section margin status			
Negative	119	10.92	Reference
Severe dysplasia/Carcinoma in situ	2	50.00	8.15(0.48, 138.31)
Positive	6	0.00	NA ^a
Final permanent pathology margin status			
Negative	39	5.13	Reference
Close (1-5 mm)	50	10.00	2.06(0.38, 11.21)
Very close (<1mm)	5	0	NA ^a
Severe dysplasia/Carcinoma in situ	6	50.00	18.50(2.17, 157.46)
Positive	27	14.81	3.22(0.55, 18.99)

^a Not applicable because of event of recurrence was identified.

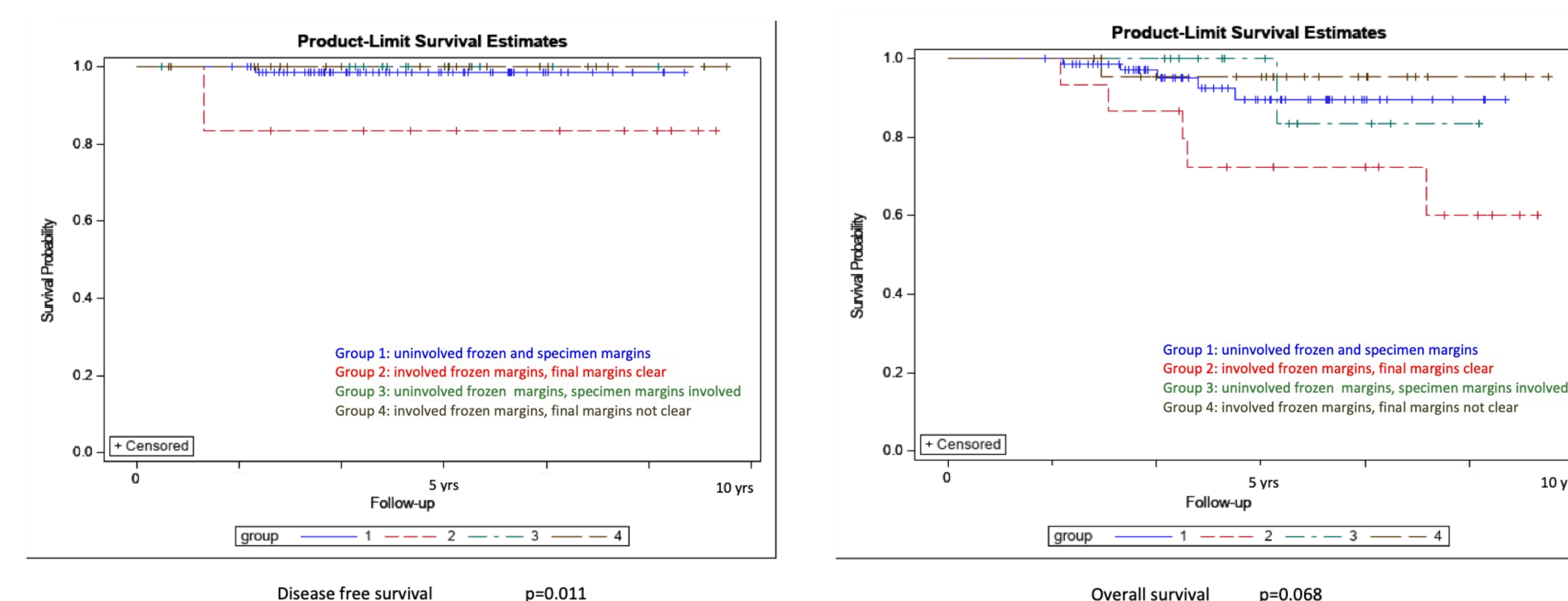


Table 2. Local recurrence rates based on margin status.

Figure 1. Disease free survival and Figure 2. Overall survival in patients with p16+ OPSCC over 10-year period.

- We found higher recurrence rates when initial frozen margin status was positive or showed carcinoma in situ (which was more likely to occur in a p16- cancer).
- In our 14 cases of recurrence, final resection margin and final pathology were not statistically significant.
- Even though it was not statistically significant, carcinoma in situ on the final frozen status was associated with a 50% chance of local recurrence on the final frozen margin status and the final permanent pathology margin status.

Results cont.

- The only variable significantly associated with recurrence was p16 status, with **p16+ cases having decreased recurrence compared to p16- cases**. 92% of patients with p16+ cancer had no recurrence and no mortality.
- P16+ OPSCC was more likely to be found at stage 1, compared to stages 1, 2 and 4 for p16- cancer. Perineural invasion was mostly absent in p16+ cases, and lymphovascular invasion was not significantly different.
- Males were far more likely to be diagnosed with p16+ OPSCC, and the predominant subsite for this cancer was the tonsil and tongue base.
- Recurrence was **5x** more likely when the patient had involved frozen margins and **3x** more likely when frozen margins were clear but final specimen margins were involved.
- The lowest disease-free survival was in patients with involved frozen margins and subsequently cleared final margins, but with our smaller sample size in groups B, C, and D, we may not be able to generalize this finding to the overall population.
- We additionally found higher rates of disease-free survival in the group with involved initial margins and uncleared final margins

Conclusions

- P16- OPSCC cases are more likely to have CIS or positive margins on final resection. This is also more likely to be associated with disease recurrence.
- For p16+ OPSCC, there is a likely association with close or positive margins on final resection with risk of recurrence.
- It is possible that the status of final resection margin may not be negatively implicated in disease free and overall survival.

References

- Persky MJ, Albergoti WG, Rath TJ, Kubik MW, Abberbock S, Geltzeiler M, Kim S, Duvvuri U, Ferris RL. Positive Margins by Oropharyngeal Subsite in Transoral Robotic Surgery for T1/T2 Squamous Cell Carcinoma. Otolaryngol Head Neck Surg. 2018 Apr;158(4):660-666. doi: 10.1177/0194599817742852. Epub 2017 Nov 28. PMID: 29182490; PMCID: PMC5880728.
- Buchakjian MR, Tasche KK, Robinson RA, Pagedar NA, Sperry SM. Association of main specimen and tumor bed margin status with local recurrence and survival in oral cancer surgery. JAMA Oto Head Neck Surg. 2016; 142(12):1191-1198.
- Holcomb AJ, Herberg M, Strohl M, Ochoa E, Feng A, Abt NB, Mokhtari TE, Suresh K, McHugh CI, Parikh AS, Sadow P, Faquin W, Faden D, Deschler DG, Varvares MA, Lin DT, Fakhry C, Ryan WR, Richmon JD. Impact of surgical margins on local control in patients undergoing single modality transoral robotic surgery for HPV related oropharyngeal squamous cell carcinoma. Head Neck. 2021; 43(8): 2434-2444.
- Buchakjian MR, Ginader T, Tasche KK, Pagedar NA, Smith BJ, Sperry SM. Independent predictors of prognosis based on oral cavity squamous cell carcinoma surgical margins. Oto Head Neck Surg. 2018; 159(4):675-682
- Warner L, O'Hara JT, Lin DJ, Oozeer N, Fox H, Meikle D, Hamilton D, Iqbal MS, Robinson M, Paleri V. Transoral robotic surgery and neck dissection alone for head and neck squamous cell carcinoma: Influence of resection margins on oncological outcomes. Oral Oncology. 130 (2022) 105909.
- Llerena P, Wang K, Puram S, Pipkorn P, Jackson R, Bollig C. National analysis of positive surgical margins in oropharyngeal salivary gland malignancies. Amer Jour of Oto-Head and Neck Medicine and Surgery 43(2022) 103527.