Published in final edited form as:

Laryngoscope. 2021 February ; 131(2): E466–E472. doi:10.1002/lary.28725.

Surgical Resection is Justifiable for Oral T4b Squamous Cell Cancers With Masticator Space Invasion

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Abstract

Objectives: To examine survival endpoints in patients with tumor (T)4b oral cavity squamous cell carcinoma (OCSCC) with pathologically proven masticator space invasion treated with primary surgery followed by adjuvant therapy.

Study Design: Retrospective review at an academic cancer center.

Methods: Twenty-five patients with T4b OCSCC with pathologic masticator space invasion were treated with primary surgery from May 2012 to December 2016. Only patients with ≥ 2 years follow-up from date of surgery were included. Sixteen patients received adjuvant chemoradiation.

Results: Median follow-up time was 39 months from date of surgery. Overall survival (OS), disease-specific survival (DSS), and recurrence-free survival at 24 months were 44.0%, 63.2%, and 52.6%, respectively. On univariate analyses, adjuvant chemoradiation was associated with improved OS. Advanced age and prolonged length of hospital stay was associated with worse OS.

Conclusion: For pT4b OCSCCA involving the masticator space, primary surgical resection followed by adjuvant chemoradiation demonstrates 24-month DSS of > 50% and OS of 44%.

Keywords

Oral cavity squamous cell carcinoma; oral cancer; T4b tumor; masticator space

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Level of Evidence: 4

INTRODUCTION

The 8th edition of the American Joint Committee on Cancer (AJCC) staging system defines tumor (T)4b oral cavity cancer as very advanced local disease, which invades the masticator space, pterygoid plates, or skull base and/or encases the internal carotid artery.¹ The 2018 National Comprehensive Cancer Network (NCCN) guidelines suggest clinical trials or nonsurgical therapies for T4b oral cavity cancer due to an inability to achieve clear surgical margins.² Liao et al. have reported favorable outcomes for a certain subset of surgically resected T4b oral cavity squamous cell carcinoma (OCSCC) involving the masticator space.^{3–5} Masticator space invasion is the most common subset of T4b OCSCC compared to disease invasion of the pterygoid plates, skull base, and/or encasement of the internal carotid artery.⁴ The masticator space contains the ramus and body of the mandible, the muscles of mastication (medial and lateral pterygoids, masseter and temporalis), and the mandibular nerve.⁶ Radical, compartmental, en bloc resection of the entire masticator space contents for improved margin control has been proposed in the Indian population by Trivedi et al. This can include en bloc resection of the mandible, maxilla, pterygoid plates, and all of the muscles of mastication from origin to insertion.⁷ Unlike T4b OCSCC invading the pterygoid plates, skull base, and/or encasing the internal carotid artery, masticator space resectability may be more feasible given less morbid constraints on margin clearance (e.g., masseter muscle resection vs. internal carotid artery resection). Thus, T4b OCSCC with masticator space invasion warrants further evaluation with clear OUTCOME measures after radical surgery and adjuvant therapies.

The primary objective of the current study was to examine 2-year survival outcomes for patients with T4b OCSCC treated with primary surgical extirpation with and without adjuvant therapy. Additionally, demographic and clinical factors were analyzed to determine prognostic significance.

MATERIALS AND METHODS

Patient Characteristics

This study was approved by the Emory University Institutional Review Board and included only patients treated at Winship Cancer Institute (Emory University, Atlanta, GA). Patient inclusion criteria included pT4b OCSCC cases that had undergone primary surgical treatment between 2012 and 2016 and had 24 months of follow-up from time of definitive surgery. Twenty-five cases were included. All cases met criteria for T4b staging (AJCC Eighth Edition) based on pathologic evidence of masticator space invasion. No cases with pterygoid plate involvement, skull base involvement, or internal carotid artery encasement underwent curative, primary surgery. Median follow-up time was 39 months from date of surgery.

Treatment Characteristics

All patients received primary surgical treatment with attempted margin clearance of > 1 cm (mucosal and soft tissue). A specimen-driven margin approach was utilized for all cases. Intraoperative frozen pathologic analysis was performed, and superceding margins were

excised as indicated to achieve margin control. All patients underwent ipsilateral modified radical neck dissection for both clinically negative and positive nodal disease. Patients underwent contralateral modified radical neck dissection for clinically positive nodal disease. Reconstruction was performed in the same setting with free tissue transfer or regional flap reconstruction.

In accordance with the NCCN guidelines, all patients were recommended to undergo postoperative adjuvant external beam radiation therapy (EBRT) for pT4b disease and adjuvant chemoradiation for close margins (≤ 5 mm) and/or extranodal extension.

Statistical Analysis

The primary outcome measure from the study was overall survival (OS). Additional survival endpoints from the date of surgery included disease-specific survival (DSS), recurrence-free survival (RFS), local recurrence-free survival (LRFS), regional recurrence-free survival (RRFS), and distant recurrence-free survival (DRFS). Survival endpoints were estimated using the Kaplan-Meier method and were compared using log-rank tests. Median, 6-month, 12-month, and 24-month survival rates from the date of surgery were reported. Additional outcomes included medical complications, surgical complications, 30-day readmissions, tracheostomy dependence, gastrostomy tube dependence, and length of hospital stay. Medical complications included myocardial infarction, cardiopulmonary arrest, arrhythmia, cerebrovascular accident, respiratory failure, pneumonia, delirium, alcohol withdrawal, deep vein thrombosis, hyperglycemia, gastrointestinal bleed, acute kidney injury, sepsis, anemia requiring transfusion intraoperatively, and anemia requiring transfusion postoperatively. Surgical complications included free flap takeback, free flap failure, donor site breakdown, orocutaneous fistula, postoperative hematoma, chyle leak, and cervical wound dehiscence.

Descriptive statistics are reported as frequencies for the categorical variables and as means and standard deviations for the continuous variables. Demographic and clinical variables were analyzed using univariable Cox proportional hazards models to determine prognostic significance. Model assumptions were checked and verified. Statistical significance was assessed at the 0.05 level, and statistical analysis was performed using SAS 9.4 (SAS Institute Inc., Cary, NC).

RESULTS

Median follow-up time was 39 months from date of surgery. The mean age was 64.7 years (range, 36–91 years), and 13 patients (52.0%) were female. Regarding risk factors, nine patients (36.0%) had a > 10 pack-year smoking history; six patients (24.0%) had chronic alcohol abuse; four patients (16.0%) used smokeless tobacco; and one patient (4.0%) chewed Betel nut. The mean Charlson comorbidity index (CCI) was 7.4. Additional baseline demographic and clinical variables of the cohort are included in Table I.

Staging and Site of Origin

There were three predominant subsites of origin: buccal mucosa ($n = 7$, 28%), retromolar trigone ($n = 7$, 28%), and mandibular gingiva ($n = 5$, 20%). The vast majority of patients were clinically staged as T4b ($n = 24$, 96%), and 68% ($n = 17$) were radiographically +N.

There were no patients suspected to have distant metastasis at the time of surgery. Eighteen patients (75%) had radiographic masticator space invasion below the coronoid notch. Table I includes additional clinical staging data. Using specimen-driven margin analyses, the mean margin clearance was 1.79 mm. One patient had an indeterminate final margin status and was excluded from margin analyses. There were 23 patients (96%) having at least one final surgical margin ≥ 5 mm, and 20 patients (83%) having at least one final surgical margin ≥ 3 mm.

Sixteen patients (64%) underwent adjuvant chemoradiation therapy. Two patients (8%) underwent adjuvant EBRT only. Seven patients (28%) underwent no additional therapy, either due to patient refusal, poor performance status, or death prior to initiation of adjuvant therapy. Intensity-modulated radiation therapy was administered to the primary tumor bed and regional lymphatics based on postoperative computed tomography simulator imaging. The prescribed dose was typically 2 Gray (Gy) per fraction per day, given 5 days per week, with a total radiation dose between 60 and 66 Gy. With regard to adjuvant chemotherapy, six patients (24%) were treated with cisplatin; six patients (24%) were treated with a combination of carboplatin and taxol; two patients (8%) were treated with a combination of docetaxel and cetuximab; and two patients (8%) were treated at an outside facility with an unknown regimen of chemotherapy.

Complications and Clinical Outcomes

The mean length of hospital stay was 15.3 days. Eighteen patients (72%) and 12 patients (48%) experienced perioperative medical and surgical complications, respectively. The two most common medical complications were postoperative delirium ($n = 7$, 28%) and postoperative anemia requiring transfusion ($n = 12$, 48%). The most common surgical complication was orocutaneous fistula ($n = 3$, 12%). Twenty-three patients (92%) underwent a tracheostomy, and 39.1% of those patients were tracheostomy-dependent > 30 days postoperatively. Likewise, the vast majority of patients required gastrostomy tubes (84%), with 89% of those patients continuing to require enteral access > 6 months out from surgery. Seven patients (28%) were readmitted within 30 days of their initial discharge from the hospital.

Survival Outcomes

At 24 months, the OS was 44.0%, and DSS was 63.2% (Figs. 1 and 2). Recurrence-free survival at 24 months was 52.6%, with LRFS, RRFS, and DRFS rates at 65.6%, 78.2%, and 72.3%, respectively (Fig. 3A–D). On univariate analyses, adjuvant chemoradiation versus no adjuvant therapy was associated with improved OS (hazard ratio [HR], 0.16; 95% CI, 0.05–0.48) and LRFS (HR, 0.15; 95% CI, 0.02–0.88). Advanced age as a continuous variable was associated with worse OS (HR, 1.11; 95% CI, 1.04–1.19), DSS (HR, 1.12; 95% CI, 1.01–1.23), and RFS (HR, 1.14; 95% CI, 1.03–1.27). Using our median age to dichotomize the data, patients ≥ 65 years old had far better overall survival (Fig. 4) (log rank $P = .02$) and the median survival for those ≥ 65 years old was 6.7 months, whereas the median survival for the younger patients has not been reached. Prolonged length of hospital stay was associated with a somewhat decreased OS (HR, 1.05; 95% CI, 1.01–1.11). There was no difference in

DSS for masticator space involvement above the coronoid notch compared to below (HR, 1.17; 95% CI, 0.23–5.88) (Fig. 5).

DISCUSSION

There is a growing body of evidence to suggest that primary surgical management of T4b OCSCC involving the masticator space is feasible with comparable outcomes to T4a OCSCC treated in a similar manner. In the Taiwanese population, Liao et al. demonstrated that 48 patients with T4b OCSCC tumors involving the masticator space below the mandibular notch (i.e., infranotch) treated with primary surgery had comparable outcomes to 133 patients with T4a OCSCC treated in an identical fashion at 5-year follow-up: local control, 80.0% vs. 78.0%, $P = .728$; neck control, 87.0% vs. 82.0%, $P = .480$; DFS, 63.0% vs. 55.0%, $P = .281$; DSS, 68.0% vs. 60.0%, $P = .353$; and OS, 62% vs. 44%, $P = .264$, respectively.⁴ Mair et al. compared 135 T4a and 75 infranotch T4b OCSCC Indian patients treated similarly with primary surgical resection followed by adjuvant treatment. On comparison between all T4a and infranotch T4b cases, a significant difference was observed with regard to 3-year local control (49.6% vs. 41.1%; $P = .025$) and DFS (65.3% vs. 42%; $P = .035$). However, no significant difference was observed in 3-year locoregional control (71.1% vs. 61.8%; $P = .107$) and OS (49.6% vs. 41.1%; $P = .518$).⁸ Trivedi et al. has demonstrated similar early survival outcomes in the Indian population as well with 38 of 45 patients alive without disease at 21-month median follow-up.⁷

Adjuvant chemoradiation versus no adjuvant therapy was associated with improved OS (hazard ratio [HR], 0.16; 95% CI, 0.05–0.48) and LRFS (HR, 0.15; 95% CI, 0.02–0.88). Liao et al. demonstrated similar survival benefits with adjuvant therapy for T4b OCSCC demonstrating 5-year OS comparable to resected pT4a disease followed by adjuvant therapy (45% vs. 49%; $P = .776$).³

As we have seen with our study of oropharyngeal cancer patients, age mattered.⁹ We do not have the statistical power to ferret out the relationship between age and CCI on overall survival. Prolonged length of stay was also associated with a barely statistically significant decreased OS (HR, 1.05; 95% CI, 1.01–1.11), which has also been demonstrated in the literature for surgical treatment of OCSCC.¹⁰ There was no survival advantage detected in our study for infranotch versus supranotch tumors; however this may be the result of our small sample size.

To our knowledge, the current study represents the largest U.S. cohort of patients with T4b OCSCC treated with primary surgery in the current literature. OS, DSS, and RFS at 24-month follow-up were 44.0%, 63.2%, and 52.6%, respectively.

Although the primary objective of the current study was to examine oncologic outcomes, notable perioperative outcomes can be discussed. Postoperative delirium and anemia were the two most common medical complications. Orocutaneous fistula was the most common surgical complication. The 30-day readmission rate was 28%, which is considerable. Additionally, 39% of patients who underwent tracheostomy were tracheostomy-dependent > 30 days postoperatively; of those who required a gastrostomy tube, 89% continued to need

their enteral access > 6 months out from surgery. In light of these secondary outcomes, preoperative counseling should include a discussion regarding morbidity and quality of life associated with treatment of T4b OCSCC.

Limitations of this study include its single institution experience, small sample size, and generalizability beyond very advanced OCSCC treated with surgery and adjuvant therapy. Winship Cancer Institute is part of a large academic hospital system, with possible selection bias for challenging OCSCC referrals. This should be considered a pilot study demonstrating early oncologic outcomes following primary surgical treatment for T4b OCSCC. An additional limitation that must be addressed is margin clearance. The mean margin clearance in the current series was 1.79 mm. There were 23 patients (92.0%) having at least one final surgical margin ≥ 5 mm. Reported inadequate margin clearance rates (< 5 mm) for infranotch T4b OCSCC in the existing literature are ~12% to 13%.^{5,8} The existing literature, however, does not specify whether a specimen-driven or tumor bed-driven approach was utilized. A specimen-driven margin approach is utilized at our institution, which may partially account for the discrepancy between margin clearance reported herein and clearance rates reported elsewhere in the literature. In regard to technique of surgical extirpation, we have recently adopted the radical compartment resection for T4b OCSCC as described by Trivedi et al. This technique involves removing the entire contents of the masticator space en bloc irrespective of the extent of tumor spread into this area (both pterygoid muscles and masseter muscle are removed from origin to insertion).¹¹ Anecdotally, we have observed improved margin clearance since adopting this technique.

CONCLUSION

For pT4b OCSCC involving the masticator space, primary surgical resection followed by adjuvant chemoradiation demonstrates 24-month DSS of > 50% and OS of 44%. Despite suboptimal margins, modern surgical techniques have improved our ability to resect and potentially cure patients with tumors with masticator space involvement. This study represents the first report of this treatment methodology in the U.S. population.

ACKNOWLEDGMENT

Research reported in this publication was supported in part by the Biostatistics and Bioinformatics Shared Resource of Winship Cancer Institute of Emory University and NIH/NCI under award number P30CA138292. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

The authors have no funding, financial relationships, or conflicts of interest to disclose.

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No. of Subject	Event	Censored	Median Survival (95% CI)	6 Mo Survival	12 Mo Survival	24 Mo Survival
25	15 (60%)	10 (40%)	12.3 (6.2, NA)	72.0% (50.1%, 85.5%)	52.0% (31.2%, 69.2%)	44.0% (24.5%, 61.9%)

Fig. 1.
Overall survival (months from surgery).

Fig. 2.
Disease-specific survival (months from surgery).

Fig. 3.
(A–D) RFS at 6, 12, and 24 months. (A) Overall RFS, (B) local RFS, (C) regional RFS, (D) distant RFS. RFS = recurrence-free survival.

Age at surgery	No. of Subject	Event	Censored	Median Survival (95% CI)	6 Mo Survival	12 Mo Survival	24 Mo Survival
≤65	12	4 (33%)	8 (67%)	NA (2, NA)	83.3% (48.2%, 95.6%)	66.7% (33.7%, 86.0%)	66.7% (33.7%, 86.0%)
>65	13	11 (85%)	2 (15%)	6.7 (2, 15.7)	61.5% (30.8%, 81.8%)	38.5% (14.1%, 62.8%)	23.1% (5.6%, 47.5%)

Fig. 4.

Overall survival (months from surgery) stratified by median age. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

Masticator involvement	No. of Subject	Event	Censored	Median Survival (95% CI)	6 Mo Survival	12 Mo Survival	24 Mo Survival
Above coronoid notch	6	2 (33%)	4 (67%)	NA (6.7, NA)	100.0% (NA, NA)	50.0% (5.8%, 84.5%)	50.0% (5.8%, 84.5%)
Below coronoid notch	18	6 (33%)	12 (67%)	43 (8.2, NA)	92.9% (59.1%, 99.0%)	71.4% (40.6%, 88.2%)	64.3% (34.3%, 83.3%)

Fig. 5. Disease-specific survival (months from surgery) for infra-versus supranotch tumors. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

TABLE I.

Demographic and Clinical Characteristics of T4b OCSCC Population.

Variable	Level	N = 25	%
Age at surgery (years)	Mean	64.7	-
Sex	Male	12	48
	Female	13	52
Race	White	15	60
	Black	6	24
	Hispanic	1	4
	Indian	2	8
	Other	1	4
Charlson Comorbidity Index	< 6	5	20
	6	20	80
Smoking pack-years	Never	14	56
	10	2	8
	>10	9	36
ETOH	No	19	76
	Yes	6	24
BMI	< 25	10	40
	25.0–29.9	9	36
	= 30	6	24
Clinical T stage	T4a	1	4
	T4b	24	96
Radiologic masticator space involvement	Above coronoid notch	6	24
	Below coronoid notch	18	72
	Missing data	1	4
Clinical N stage	N0	8	32
	N1	1	4
	N2b	13	52
	N2c	3	12
Pathologic tumor subsite	Buccal mucosa	7	28
	Oral tongue	1	4
	Floor of mouth	2	8
	Mandibular gingiva	5	20
	Retromolar trigone	7	28
	Maxillary gingiva	2	8
	Hard palate	1	4
Adjuvant treatment	None	7	28
	XRT	2	8
	XRT/Chemo	16	64
Tracheostomy dependence	< 30 days	14	61
	>30 days	9	39

Variable	Level	N = 25	%
Gastrostomy tube dependence	Missing	2	-
	< 6 months	2	8
	> 6 months	16	64
	Missing	7	28
30-day mortality	No	22	88
	Yes	3	12
LOS (days)	Mean	15	-

BMI = body mass index; Chemo = chemotherapy; LOS = length of stay; N = nodal; OSCC = oral cavity squamous cell carcinoma; T = tumor; XRT = radiotherapy; ETOH = alcohol abuse.