Original Investigation

Treatment Outcomes for T4 Oropharyngeal Squamous Cell Carcinoma

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IMPORTANCE Little is known about treatment outcomes for T4 oropharyngeal squamous cell carcinoma (OPSCC), particularly in the era of human papillomavirus (HPV)-related disease.

OBJECTIVE To evaluate oncologic outcomes for T4 OPSCC treated with primary surgical and nonsurgical therapies.

DESIGN, SETTING, AND PARTICIPANTS Retrospective cohort study of 131 patients from a single academic hospital, who were treated for T4a or T4b OPSCC (with any N stage and without distant metastatic disease at presentation) between 1998 and 2012 and had a minimum 2-year follow-up (the median follow-up time was 34.6 months). This study was conducted between January 1, 1998, and November 1, 2012.

INTERVENTIONS Sixty-nine patients underwent nonsurgical therapy, 47 (68%) of whom had p16-positive tumors. Nonsurgical treatment paradigms included induction chemotherapy followed by chemoradiotherapy (n = 36 [54%]), concurrent chemoradiotherapy (n = 29 [43%]), and induction chemotherapy followed by radiation therapy alone (n = 2 [3%]). Sixty-two patients underwent surgical treatment, 50 (81%) of whom had p16-positive tumors. Fifty-seven surgical patients (92%) received adjuvant therapy.

MAIN OUTCOMES AND MEASURES Overall survival (OS) was the primary outcome measure. Secondary outcome measures included disease-specific survival (DSS), disease-free survival (DFS), 2-year gastrostomy and tracheostomy tube rates, and major complication rates.

RESULTS Significant baseline differences between the surgical vs nonsurgical groups included age (mean 59.8 vs 55.4 years [P = .005]), sex (male, 95% vs 84% [P = .04]), body mass index (<18.5 [calculated as weight in kilograms divided by height in meters squared], 3% vs 16% [P = .02]), and smoking history of 10 or more pack-years (48% vs 77% [P = .003]). For p16-positive patients, Kaplan-Meier estimates of OS, DSS, and DFS were significantly higher for surgically treated patients than for the nonsurgical group (χ^2_1 = 7.335 for log-rank P = .007, χ^2_1 = 8.607 for log-rank P = .003, and χ^2_1 = 7.763 for log-rank P = .005, respectively). For p16-negative patients, Kaplan-Meier estimates of OS and DSS were higher for the surgical group but did not reach statistical significance (χ^2_1 = 2.649 for log-rank P = .10 and χ^2_1 = 2.077 for log-rank P = .15, respectively), while estimates of DFS were significantly higher for patients treated with primary surgery (χ^2_1 = 3.869 for log-rank P = .049. In a multivariable Cox survival analysis, p16-positive immunohistochemical status had a significant positive association with OS (hazard ratio [HR], 0.55; 95% CI, 0.32-0.95 [P = .03]), DSS (HR, 0.45; 95% CI, 0.22-0.92 [P = .03]), and DFS (HR, 0.55; 95% CI, 0.32-0.95 [P = .03]), and nonsurgical treatment had a significant negative association with OS (HR, 2.79; 95% CI, 1.51-5.16 [P = .001]), DSS (HR, 3.38; 95% CI, 1.59-7.16 [P = .002]), and DFS (HR, 2.59; 95% CI, 1.51-4.45 [P = .001]).

CONCLUSIONS AND RELEVANCE Primary surgical treatment may be associated with improved outcomes in patients with T4 OPSCC. p16 Immunohistochemical status remains a strong prognostic indicator even in patients with locally advanced disease.

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In recent studies of nonsurgical management for advanced stage oropharyngeal squamous cell carcinoma (OPSCC), 3-year overall survival (OS) rates range from 41% to 87%.[1-3] Similarly, for surgically treated patients in recent reports, 3-year OS rates vary from 38% to 86%.[4-7] These trials are marked by a great degree of variability in treatment paradigms, tumor stages, and reporting of p16 immunohistochemistry (IHC) or human papillomavirus (HPV) status. As a result of such heterogeneity, outcome data for T4 OPSCC specifically are imprecise. Available data for this unique subgroup generally demonstrate decreased survival outcomes over advanced-stage disease as a whole, in both surgical and nonsurgical reports.[8-14] Current comparative effectiveness studies evaluating surgical vs nonsurgical management for advanced stage OPSCC are similarly constrained by heterogeneity and methodological limitations.[15-18]

Evidence to guide treatment decisions for T4 OPSCC in the era of HPV-related tumor biology is sparse. Although it has been proposed that TNM staging poorly defines risk in HPV-related OPSCC,[19] T4 staging has been a significant negative prognostic indicator in numerous studies, both with surgical[12] and nonsurgical[20,21] treatment. For this reason, it is critical to examine outcomes specific to patients with T4 OPSCC in the context of p16 IHC status. Thus, the objective of this study was to analyze our experience treating patients with T4 OPSCC and known p16 status to determine predictors of oncologic and functional outcomes.

Methods

Patients

All data collection was approved by the institutional review board at Washington University, St Louis, Missouri. A retrospective review of several institutional databases was performed to identify patients treated for T4 OPSCC between 1998 and 2012. Inclusion criteria were documented clinical T4a or T4b OPSCC as defined by the AJCC 2010 guidelines,[22] known p16 status, treatment with either primary surgery or a nonsurgical modality including both chemotherapy and radiation therapy, and a minimum follow-up of 2 years. Patients were excluded if they had distant metastatic disease on presentation, had prior treatment for a cancer of the upper aerodigestive tract, or were not treated with curative intent.

Surgical treatment of the primary tumor was performed either by transoral laser microsurgery (TLM) as previously described[12] or by open approaches, which included lip splitmandibulotomy or lateral pharyngotomy. In some cases of TLM, the most inferior portions of the tumor were resected during the neck dissection by way of a small pharyngotomy. Selective neck dissection incorporated levels 2 to 4, including other lymphatic or nonlymphatic structures as indicated. Criteria for adjuvant therapy was determined based on the presence of pathological risk factors, although these changed over time based on evolving data.[23,24]

Data collected included demographics, comorbidities as measured by the Adult Comorbidity Evaluation-27 index (ACE-27),[25] clinical presentations, treatment details, and outcomes. Indications for T4a or T4b diagnosis in each patient were verified according to the AJCC 2010 guidelines[22] by evaluating pretreatment imaging, clinic notes, and operative endoscopy to assess areas of tumor invasion. Body mass index (BMI; calculated as weight in kilograms divided by height in meters squared) was dichotomized above and below 18.5 owing to its known association with treatment-related mortality.[26] The ACE-27 score was dichotomized to no or mild comorbidities (0 or 1) vs moderate or severe comorbidities (2 or 3), given the known negative prognostic value of an ACE-27 score of 2 or more in patients with advanced head and neck cancer.[27] To account for year of treatment in the analysis, groups were dichotomized around 2010. Smoking was dichotomized at 10 pack-years, given its prognostic implications in prior studies.[3] Finally, nodal disease was dichotomized by early (N0-N2a) vs advanced (N2b-N3) nodal stage as this has been shown to be prognostic in previous work.[12]

Study End Points

The primary outcome measure was OS. Secondary outcome measures included disease-specific-survival (DSS), disease-free survival (DFS), 2-year gastrostomy and tracheostomy tube rates, and major adverse events. All end points were measured from time of treatment initiation. Recurrences were classified by the first site of recurrent disease, either biopsy proven or from radiological evidence of treatment failure. The definition of major adverse events was adapted from the classification previously described by Patel et al.[28] For the surgical group these included any unanticipated adverse events that required intervention or prolonged length of hospital stay or complications occurring after discharge until 30 days after completion of adjuvant therapy that required readmission. An analogous set of major complications were defined for the nonsurgical group, which included any unanticipated adverse events during the course of treatment or occurring within 30 days after treatment completion that required hospital admission. Major hemorrhage was defined for the surgical group as any postoperative oropharyngeal, neck, or flap donor site hemorrhage that required operative intervention or embolization during hospitalization or until 30 days after completion of adjuvant therapy. For the nonsurgical group this was defined as any oropharyngeal or neck hemorrhage that required operative intervention or embolization during the course of nonsurgical treatment or occurring within 30 days after treatment completion.

Statistical Analysis

Statistical analysis was performed using SPSS version 22 (IBM) and SAS (SAS Institute Inc) software. Descriptive statistics were used to define the characteristics of the treatment groups. To determine differences between surgical and nonsurgical groups, a univariable analysis was performed with a χ^2 test or Fisher exact test for categorical variables and a *t* test or Mann-Whitney test for continuous data, depending on data normality. Predictive variables with a $P < .20$ were included in a multivariable Cox survival analysis. In addition, a propensity score for receiving surgical treatment was calculated for every patient using a logistic regression model and was added to the

multivariable analysis. Adjustment for propensity score was performed to account for potential bias due to measured confounders.

Results

Demographics

Between 1998 and 2012, 156 patients who underwent treatment for T4 OPSCC for curative intent with either primary surgery with or without adjuvant therapy or a nonsurgical approach with both radiation and systemic therapy were identified. Although 156 patients who fit the inclusion criteria were identified, p16 status could not be obtained for 25. In total, 131 patients were included, of whom 69 (53%) were treated with a nonsurgical modality and 62 (47%) with primary surgery.

Patient and tumor characteristics for surgical and nonsurgical groups are presented in **Table 1**. No significant difference in severity of comorbidities was identified using the ACE-27 index, with only 1 patient (nonsurgical group) having a score of 3. Most patients with early N stage had N0-1 disease (n = 20 [29%] nonsurgical and n = 19 [31%] surgical), and most with advanced N stage had N2b-c disease (n = 39 [57%] nonsurgical and n = 35 [56%] surgical). The overall median follow-up was 34.6 months but was significantly longer for the surgical group (43.9 vs 26.7 months [17.2-month difference; 95% CI, 7.0-27.4 months]; $P = .001$).

Treatment Characteristics

The decision to undergo surgical or nonsurgical primary management was made by the multidisciplinary team in consultation with patients. Treatment details are reported in **Table 2**. Because of toxic effects of nonsurgical therapy during treatment, 4 patients in the induction chemotherapy group were unable to complete the intended treatment, including 2 patients who died of sepsis during induction and 2 who underwent radiation therapy alone after an abbreviated induction regimen. Five surgical patients did not undergo adjuvant therapy, 3 who refused postoperative therapy and 2 who died prior to receiving adjuvant therapy.

Outcomes

Survival by p16 Status

For p16-positive patients, Kaplan-Meier estimates of OS, DSS, and DFS were all significantly higher in the surgical group than in the nonsurgical group ($\chi^2_1 = 7.335$ for log-rank $P = .007$, $\chi^2_1 = 8.607$ for log-rank $P = .003$, and $\chi^2_1 = 7.763$ for log-rank $P = .005$, respectively; **Figure 1**). For p16-negative patients, OS and DSS were higher in the surgical group but did not reach statistical significance ($\chi^2_1 = 2.649$ for log-rank $P = .10$ and $\chi^2_1 = 2.077$ for log-rank $P = .15$, respectively), while DFS was significantly higher in patients treated with primary surgery ($\chi^2_1 = 3.869$ for log-rank $P = .049$).

Univariable Analysis

Results from univariable Cox regression analysis (**Table 3**) showed that p16-positive IHC status was associated with improved OS, DSS, and DFS, while nonsurgical treatment and alcohol abuse at the time of treatment had a negative prognostic impact on all 3 survival metrics.

Multivariable Analysis

Even after controlling for variables found to be significant in univariable analyses, p16-positive IHC status remained significantly associated with better outcomes and nonsurgical treatment significantly associated with worse outcomes for OS, DSS, and DFS (Table 3 and **Figure 2**). The effect of treatment on each of the survival analyses did not change even after controlling for propensity score. Alcohol abuse at the time of treatment remained significantly negatively associated with OS and DSS.

Patterns of Failure

In the surgical group there were 12 recurrences (19%) occurring within 2 years. These were evenly split between locoregional and distant for p16-positive patients (n = 4 [8%] for both locoregional and distant), while locoregional recurrences were more common for p16-negative patients (n = 3 [25%] locoregional and n = 1 [8%] distant). Two of the three patients who refused adjuvant therapy after surgical treatment developed recurrent disease, 1 local and 1 regional. In the nonsurgical group, there were 37 recurrences (54%) occurring within 2 years. Both p16-positive and p16-negative patients had more locoregional recurrences than distant recurrences, but this trend was more pronounced in the p16-negative group (n = 12 [55%] locoregional and n = 4 [18%] distant) than in the p16-positive group (n = 13 [28%] locoregional and n = 8 [17%] distant).

Salvage Rates

Salvage treatment was attempted in 5 of the 7 primary surgical patients who had locoregional recurrence. Four had salvage surgical procedures and 1 patient who had refused postoperative adjuvant therapy underwent definitive chemoradiotherapy. Three of these patients (43%) remained disease free at the last follow-up (2 surgical salvage and 1 chemoradiation salvage). Of the 25 primary nonsurgical patients with locoregional failure, surgical salvage was attempted in 7. Three patients (12%) remained disease free at the last follow-up.

Second Primary Cancers

Five second primary cancers occurred in each treatment group. In the surgical group, there were 2 primary lung cancers, 2 OPSCCs contralateral to the original primary, and 1 case of cholangiocarcinoma. In the nonsurgical group, there were 4 primary lung cancers and 1 papillary thyroid carcinoma.

Functional Outcomes

Tracheostomy rates were significant higher in surgically treated patients in the posttreatment period (n = 40 [65%] vs n = 13 [19%]) but were similar in 2-year survivors (n = 5 [10%] surgical and n = 2 [5%] nonsurgical). Two-year gastrostomy tube rates were higher in the surgical group, but the difference did not reach statistical significance (n = 17 [32%] vs n = 8 [20%] [difference, 12 percentage points; 95% CI, −6 to 30 percentage points [$P = .19$]).

Table 1. T4 Oropharynx Squamous Cell Carcinoma: Demographics and Pretreatment Tumor Characteristics

Variable	No. (%)			Percentage Point Difference (95% CI)	*P* Value
	All Patients (n = 131)	Nonsurgical Treatment (n = 69)	Surgical Treatment (n = 62)		
p16 Status					
Positive	97 (74)	47 (68)	50 (81)	13 (−3 to 29)	.10
Negative	34 (25)	22 (32)	12 (19)		
Age, mean (SD), y	57.5 (9.1)	55.4 (9.7)	59.8 (7.7)	4.4 (0.5 to 8.3)	.005
Sex					
Male	117 (89)	58 (84)	59 (95)	11 (1 to 22)	.04
Female	14 (11)	11 (16)	3 (5)		
Race					
White	111 (85)	55 (80)	56 (90)	10 (−2 to 22)	.09
Other	20 (15)	14 (20)	6 (10)		
BMI					
<18.5	13 (10)	11 (16)	2 (3)	13 (3 to 24)	.02
≥18.5	118 (90)	58 (84)	60 (97)		
ACE-27 score					
0-1	99 (76)	56 (81)	43 (69)	12 (−3 to 27)	.12
2-3	32 (24)	12 (19)	19 (31)		
Alcohol abuse during treatment					
Yes	15 (11)	11 (16)	4 (6)	10 (−2 to 22)	.09
No	116 (89)	58 (84)	58 (94)		
Smoking					
≥10 Pack-years	85 (65)	53 (77)	30 (48)	29 (10 to 48)	.003
Never or <10 pack-years	46 (35)	16 (23)	32 (52)		
Year of treatment					
Before 2010	89 (68)	42 (60)	47 (76)	16 (−1 to 33)	.07
2010-2012	42 (31)	27 (40)	15 (24)		
Oropharyngeal subsite[a]					
Base of tongue	58 (44)	25 (35)	33 (53)	18 (0 to 36)	.054
Tonsil	65 (50)	41 (59)	24 (38)	21 (0 to 42)	
Other	8 (6)	3 (6)	5 (9)	3 (0 to 6)	
T4 substage					
T4a	99 (76)	48 (70)	51 (82)	12 (−2 to 26)	.09
T4b	32 (24)	21 (30)	11 (18)		
Indications for T4a diagnosis					
Invasion of extrinsic tongue musculature	65 (71)	31 (65)	39 (76)	11 (−1 to 23)	.08
Medial pterygoid invasion	43 (47)	25 (49)	18 (35)	14 (−2 to 30)	
Hard palate invasion	0	0	0	0	
Mandible invasion	3 (3)	1 (2)	2 (4)	2 (0 to 4)	
Laryngeal involvement	27 (30)	8 (17)	21 (41)	24 (−3 to 51)	
Indications for T4b diagnosis					
Prevertebral space invasion	7 (24)	5 (26)	2 (22)	4 (−67 to 74)	.91
Pterygoid plate invasion	4 (14)	3 (16)	1 (11)	5 (−84 to 94)	
Lateral nasopharynx involvement	22 (76)	16 (84)	6 (67)	17 (−100 to 100)	
Carotid encasement	6 (21)	5 (26)	1 (11)	15 (−100 to 100)	
Lateral pterygoid invasion	5 (17)	3 (16)	2 (22)	6 (−100 to 100)	
Skull base involvement	2 (7)	2 (11)	0	11 (−100 to 100)	
N stage					
N0-2a	45 (34)	23 (33)	22 (36)	3 (−20 to 26)	.80
N2b-3	86 (66)	46 (67)	40 (65)		

Abbreviations: ACE-27, Adult Comorbidity Evaluation–27 index; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared).

[a] Other subsites included soft palate, posterior pharyngeal wall, and vallecula.

Table 2. T4 Oropharynx Squamous Cell Carcinoma Treatment Details

Group	Total[a]
Nonsurgical (n = 69)	
Nonsurgical treatment	
Induction chemotherapy followed by chemoradiotherapy	36 (54)
Chemoradiation alone	29 (43)
Induction chemotherapy follow by radiation therapy alone	2 (3)
Chemotherapy induction agent	
TPF	15 (38)
TPFC	12 (30)
ACCF	9 (22)
Cisplatin	2 (5)
Carboplatin and paclitaxel	2 (5)
Definitive chemotherapy agent	
Cisplatin	41 (62)
Cetuximab	18 (28)
Carboplatin and paclitaxel	5 (8)
Carboplatin and cetuximab	1 (2)
Radiation dosage, median (range), Gy	70 (60-75)
Major adverse events	57 (83)
Gastrostomy tube placement	35 (51)
Pneumonia	10 (14)
Sepsis	9 (13)
Major hemorrhage	5 (7)
Inability to tolerate gastrostomy tube feeds	5 (7)
Deep venous thrombosis	4 (6)
Neutropenic fever	3 (4)
Cardiac arrest	2 (3)
Dehydration but refused gastrostomy placement	2 (3)
Colitis	2 (3)
Death during induction chemotherapy	2 (3)
Other[b]	7 (10)
Surgical (n = 62)	
Surgical approach	
Open	21 (34)
Transoral laser microsurgery	41 (66)
Major glossectomy[c]	20 (32)
Free flap reconstruction	27 (44)
Perineural invasion	28 (45)
Lymphovascular space invasion	40 (62)
Lymph node extracapsular extension	44 (71)
Final margin positive	6 (10)
Neck dissection	
Radical	12 (19)
Modified radical	11 (18)
Selective	39 (63)
Unilateral	28 (45)
Bilateral	34 (55)
Adjuvant therapy	
Chemoradiotherapy	24 (39)
Radiation therapy	33 (53)
No adjuvant therapy	3 (5)
Died prior to receiving adjuvant therapy	2 (3)
Adjuvant chemotherapy agent	
Cisplatin	21 (88)
Cetuximab	3 (12)
Adjuvant radiation dosage, median (range), Gy	66 (26-70)
Major adverse events	54 (87)
Gastrostomy tube placement	40 (64)
Major hemorrhage	7 (12)
Pneumonia	6 (10)
Wound infection	5 (8)
Pulmonary embolism	4 (6)
Cardiac arrest	2 (3)
Return to OR for re-resection of positive margins	2 (3)
Sepsis	2 (3)
Return to OR for free flap revision	2 (3)
Fistula	2 (3)
Other[d]	8 (13)

Abbreviations: ACCF, paclitaxel (Abraxane; Abraxis), cisplatin, cetuximab, fluorouracil; OR, operating room; TPF, docetaxel, cisplatin, fluorouracil; TPFC, docetaxel, cisplatin, fluorouracil, cetuximab.

[a] Data are given as number (percentage) of patients unless otherwise specified.

[b] Other major adverse events in the nonsurgical group includes 1 of each: stroke, endocarditis, severe diarrhea, gastrointestinal tract bleeding, heparin-induced thrombocytopenia, new-onset arrhythmia, and delirium tremens.

[c] Major glossectomy, 75% or greater glossectomy.

[d] Other major adverse events in the surgical group includes 1 of each: deep venous thrombosis, stroke, return to OR for a retained foreign body, myocardial infarction, chyle leak, delirium tremens, death due to major postoperative hemorrhage, death due to postoperative fall.

Adverse Events

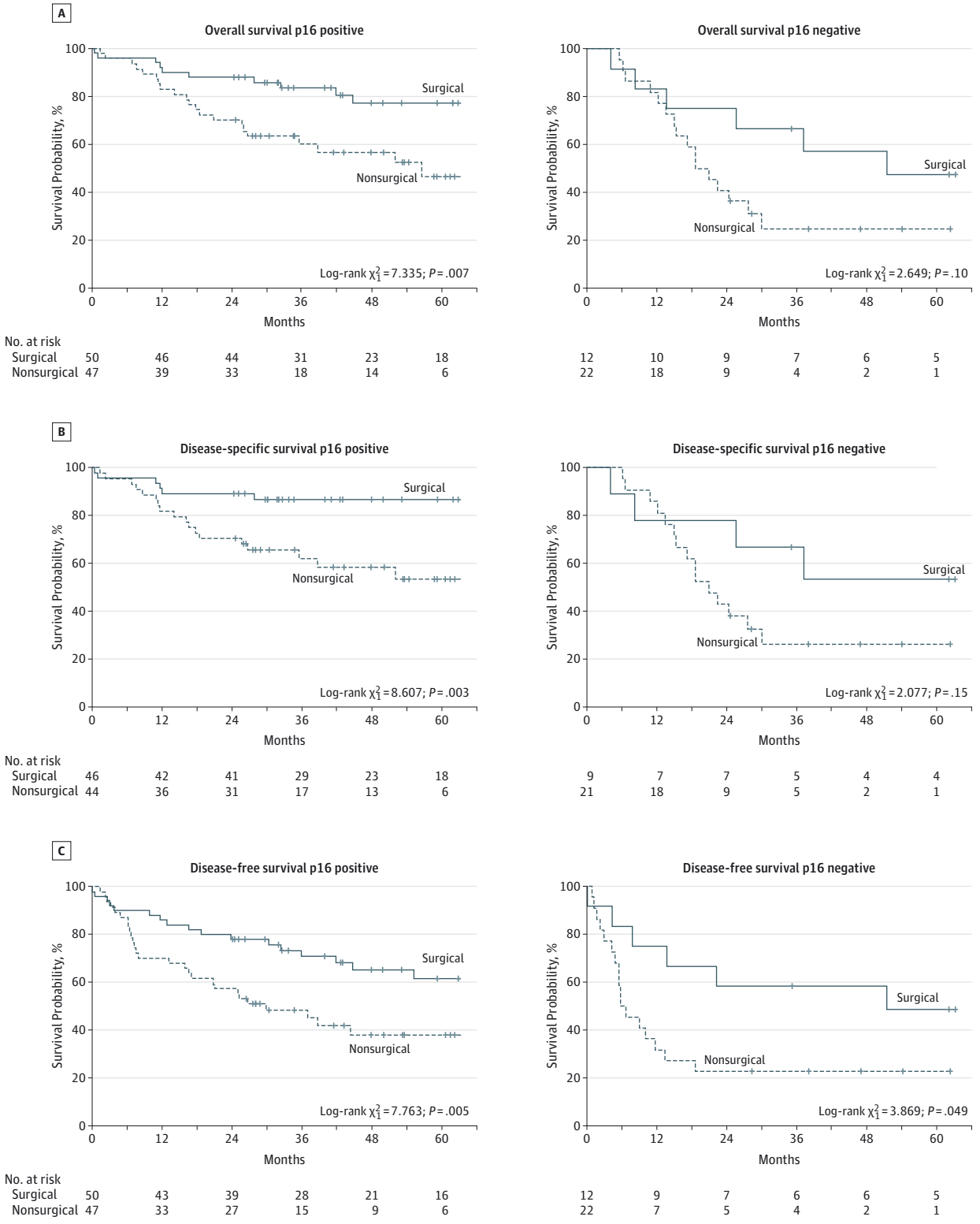
Major adverse events are listed in Table 2 and Table 3. In the surgical group, 2 patients died in the postoperative period, one of a major postoperative oropharyngeal hemorrhage and the other of a postoperative fall after discharge. In the nonsurgical group, 2 patients died during induction chemotherapy, both of sepsis.

Discussion

Oncologic Outcomes

For the cohort of patients with p16-positive T4 OPSCC reported in this study, primary surgical treatment with adjuvant therapy was associated with improved survival over those treated with nonsurgical paradigms. This remained true across all survival metrics, including OS, DSS, and DFS. For p16-negative patients, although improved survival estimates in surgically treated patients did not reach statistical significance for OS and DSS, estimates for DFS were significantly higher in the surgical group. The small sample size for p16-negative patients may have been underpowered to detect a statistically significant difference in OS and DSS. There is little previously published data, however, for this subgroup of patients with T4 OPSCC that would have allowed for calculation of sample size. Estimates from this report will aid in sample size calculations

Figure 1. Kaplan-Meier Survival Estimates



A, Kaplan-Meier estimates of overall survival stratified by p16 status. B, Kaplan-Meier estimates of disease-specific survival stratified by p16 status. C, Kaplan-Meier estimates of disease-free survival stratified by p16 status. Hash marks represent censored data.

Table 3. Cox Univariable and Multivariable Survival Analysis

	OS		DSS		DFS	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Univariable						
Age, continuous	1.00 (0.97-1.03)	.80	0.99 (0.96-1.02)	.49	1.01 (0.98-1.03)	.69
Sex, male vs female	1.15 (0.46-2.88)	.77	1.01 (0.40-2.56)	.99	0.98 (0.45-2.15)	.96
Race, white vs other	0.94 (0.46-1.93)	.87	0.75 (0.36-1.56)	.44	0.93 (0.49-1.78)	.83
BMI, <18.5 vs ≥18.5	1.32 (0.59-2.91)	.50	1.61 (0.72-3.61)	.25	0.99 (0.45-2.17)	.98
ACE-27 score, 0-1 vs 2-3	1.00 (0.53-1.77)	.91	1.02 (0.51-2.01)	.96	1.08 (0.62-1.89)	.79
Alcohol, abuse at the time of treatment vs moderate or no use	3.16 (1.61-6.20)	.001	3.53 (1.72-7.22)	.001	2.71 (1.44-5.10)	.002
Smoking, >10 pack-years vs never or <10 pack-years	1.61 (0.89-2.91)	.12	1.59 (0.82-3.09)	.17	1.35 (0.82-2.24)	.24
Year of treatment, prior to 2010 vs 2010-2012	1.73 (0.88-3.37)	.11	1.60 (0.80-3.18)	.18	1.12 (0.66-1.92)	.67
Oropharyngeal subsite, tonsil vs base of tongue	0.95 (0.55-1.64)	.85	1.11 (0.60-2.04)	.75	1.13 (0.69-1.83)	.63
T4 substage, T4a vs T4b	0.82 (0.45-1.48)	.51	0.75 (0.39-1.43)	.38	0.75 (0.44-1.27)	.28
N stage, N0-2a vs N2b-N3	1.37 (0.80-2.35)	.26	1.33 (0.73-2.45)	.35	1.17 (0.72-1.91)	.53
p16 Status, positive vs negative	0.46 (0.28-0.76)	.002	0.32 (0.18-0.59)	.001	0.46 (0.28-0.76)	.002
Treatment, nonsurgical vs surgical	2.63 (1.47-4.71)	.001	3.29 (1.65-6.57)	.001	2.46 (1.49-4.07)	.001
Multivariable						
Treatment, nonsurgical vs surgical	2.79 (1.51-5.16)	.001	3.38 (1.59-7.16)	.002	2.59 (1.51-4.45)	.001
p16 Status, positive vs negative	0.55 (0.32-0.95)	.03	0.45 (0.22-0.92)	.03	0.55 (0.32-0.95)	.03
Alcohol, abuse at the time of treatment vs moderate or no use	2.13 (1.01-4.50)	.048	2.28 (1.03-5.03)	.04	1.88 (0.94-3.77)	.07
Year of treatment, prior to 2010 vs 2010 and after	1.96 (0.99-3.89)	.053	1.82 (0.90-3.69)	.10	1.34 (0.77-2.33)	.30
Smoking, ≥10 pack-years vs <10 pack-years	0.88 (0.46-1.71)	.71	0.68 (0.31-1.49)	.34	0.84 (0.48-1.46)	.53

Abbreviations: ACE-27, Adult Comorbidity Evaluation–27 index; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); DFS, disease-free survival; DSS, disease-specific survival; HR, hazard ratio; OS, overall survival.

for future studies comparing treatment outcomes for patients with T4 OPSCC. Significantly higher recurrence rates in the nonsurgical group likely account for the observed survival differences.

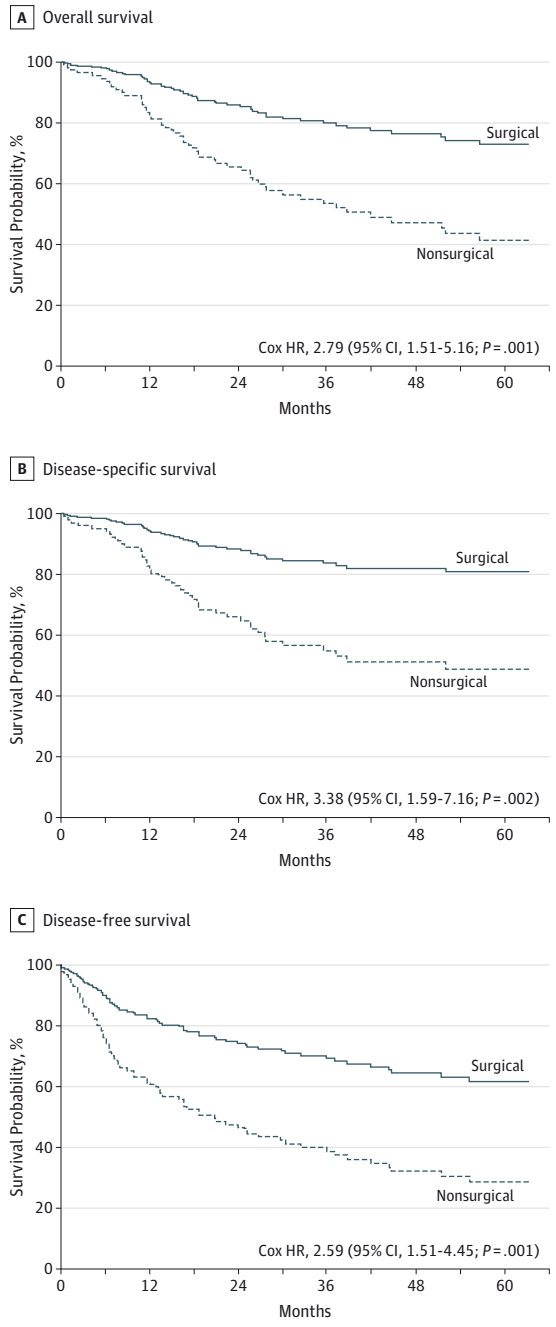
Few studies have directly compared surgical and nonsurgical modalities for the treatment of advanced OPSCC, and the results of these reports are conflicting and limited by methodological constraints.[15-18] Karatzanis et al[18] reported improved survival outcomes for tongue base carcinoma managed surgically vs nonsurgically and included 135 patients with T4 staging. Comorbidity and p16 status were not assessed in this report, however, and T3 and T4 patients were grouped for analysis. Conversely, Bossi et al[15] found significantly improved outcomes for chemoradiotherapy over surgical treatment in a cohort study of 171 patients. The surgical patients were overwhelmingly p16 negative and treated prior to 1999, whereas the nonsurgical group was treated after 2004 with a much larger proportion of p16-positive patients

Although there are few comparative effectiveness studies, numerous reports have evaluated outcomes for single-treatment modalities in advanced OPSCC. Although the high survival estimates for surgical patients in the present study are supported by other recent reports,[12] they are in stark contrast to historical data.[14,29,30] Many of these, however, were performed prior to improvements and standardization of adjuvant therapy,[23] and none were risk-stratified by p16 status. Given the trends in HPV-related disease, older studies are likely to have had a higher proportion of p16 negative patients, at least partially accounting for worse outcomes.[31] In addition, surgical management may have improved by progress up the learning curve,[32] technological advances, and better understanding of margin management.[12,33]

Nonsurgical outcomes in this report, however, are similar to available historical data and several recent studies.[6,11,14,20,34] The difficulty with these comparisons is the wide variation in nonsurgical regimens. Certain nonsurgical paradigms may demonstrate improved results, particularly the use of selected induction agents. With ACCF (paclitaxel [Abraxane; Abraxis], cetuximab, cisplatin, and fluorouracil) induction therapy in a small cohort of advanced T-stage tumors mostly from the oropharynx, Adkins et al[35] reported a 2-year complete response rate of 61% and OS of 80%.

Given the limitations in comparative effectiveness trials and the significant heterogeneity of single modality studies, the literature on management of advanced OPSCC is inconclusive and particularly limited for T4 staging. In this report, surgical treatment for T4 OPSCC remained a significant positive predictive factor, even when adjusting for several other clinically important variables, including p16 status. Comorbidity, however, did not affect outcomes in this study, likely as a result of the high proportion of low-risk patients (ACE-27 score of 0-1), similar distribution between treatment groups, and of the short duration of follow up. T4 substage was also not significantly prognostic. Similar outcomes for T4a and T4b disease have also been demonstrated in a recent large nonsurgical series.[20] For surgical patients, although T4b disease is considered unresectable by National Comprehensive Cancer Network guidelines,[36] this distinction is somewhat arbitrary and resectability is dependent on an individual tumor's pattern of invasion as well as surgeon experience, expertise, and train-

Figure 2. Cox Multivariable Survival Analysis



A, Cox multivariable survival analysis for overall survival by treatment modality adjusted for p16 status, alcohol abuse at the time of treatment, smoking history, and year of treatment. B, Cox multivariable survival analysis for disease-specific survival by treatment modality adjusted for p16 status, alcohol abuse at the time of treatment, smoking history, and year of treatment. C, Cox multivariable survival analysis for disease-free survival by treatment modality adjusted for p16 status, alcohol abuse at the time of treatment, smoking history, and year of treatment. HR indicates hazard ratio.

ing. Smoking history, as well, was not prognostically significant. Although 10 pack-years has been used to risk-stratify patients for nonsurgical therapy,[3] smoking status has been shown to lose prognostic impact in surgically treated p16-positive patients.[12] It is possible that in patients with far-advanced local disease, the impact of smoking on survival is eclipsed by the influence of other variables such as treatment and p16 status. Alcohol abuse at the time of treatment, on the other hand, remained a significant negative prognostic factor in a multivariable model. This is consistent with previous reports demonstrating an independent adverse effect of alcohol abuse on survival for patients with head and neck cancer.[37]

Functional Outcomes

Reported long-term gastrostomy tube rates after treatment for advanced OPSCC vary considerably in recent studies.[38-40] In the present study, 2-year gastrostomy tube rates were substantial, at 32% in the surgical group and 20% in the nonsurgical group. Compared with studies reporting lower long-term gastrostomy tube rates,[38] T4 staging in this study was meticulously verified, and only patients with confirmed T4 staging were included. In addition, several variables essential to functional outcomes were not gathered such as tumor volume[41] or the availability and adherence to speech and swallowing therapy.[42]

Adverse Events

The definition of adverse events used in this study was broad, encompassing all events that either increased hospital stay or required an unanticipated hospital admission. This resulted in an event rate of over 80% for both groups. Adverse event rates for the nonsurgical group, however, appear largely similar to previous reports.[39,43] In contrast, adverse events in the surgical group are significantly higher than generally reported in the literature.[5,28,44,45] Several factors likely account for this discrepancy. First, complications for T4 OPSCC, specifically, are rarely reported. Second, although rates of perioperative surgical complications in this study are similar to previous studies,[5,28,45,46] surgical reports do not often include adverse events occurring during adjuvant radiation therapy or chemoradiotherapy, even though such adjuvant therapy is an integral part of the treatment plan.

Limitations

Several limitations of this study must be recognized. Although this is a large cohort for specifically T4 OPSCC, it has a relatively small sample size. In addition, the retrospective design is subject to the omissions and inaccuracies in the medical records. Several variables that may also have prognostic significance for functional or oncologic outcomes were not available. These include primary tumor volume,[47,48] radiation dosage to the neck and low-risk areas,[49] total treatment time, and number and extent of breaks in nonsurgical and adjuvant treatment.[50] Other variables that were collected in this report were dichotomized for analysis according to previously published work. In particular, N staging was divided between N0-N2a and N2b-N3, which has been shown to be prognostic in p16-positive surgically treated patients, but not in other patients with OPSCC.[12] Although all patients were treated with curative intent, approximately one-third of the nonsurgical patients were treated using cetuximab alone as the chemotherapeutic agent, which may have influenced the survival outcomes in this population.[51,52]

Finally, the differences between the surgical and nonsurgical groups in both measured and unmeasured variables must be acknowledged. Treatment choice may have selection bias, given that some patients treated nonsurgically were not candidates for an operative approach. Many adverse pretreatment risk factors trended toward the nonsurgical patients including p16-negative IHC status, race other than white, smoking, low BMI, alcohol abuse, and T4b staging, and of those staged T4b, more had carotid encasement and skull base involvement. Patients not chosen for surgery may have had more characteristics that predict a higher risk of relapse. Many of these variables were accounted for in multivariable and propensity analyses. Nevertheless, the results of this study should be interpreted in light of these differences.

Conclusions

The results of this study indicate that up-front surgical treatment for patients with T4 OPSCC as part of their management paradigm may be beneficial. However, recognized limitations of this retrospective study require prospective validation of these results. Conventional T4 substaging (T4a vs T4b) was not significantly prognostic. Although swallowing outcomes, as measured by a persistent gastrostomy tube at 2 years, were not significantly different between treatment groups, there was substantial treatment-related morbidity regardless of management strategy.

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