Original Article

# Increase in Primary Surgical Treatment of T1 and T2 Oropharyngeal Squamous Cell Carcinoma and Rates of Adverse Pathologic Features: National Cancer Data Base

Jennifer R. Cracchiolo, MD[1]; Shrujal S. Baxi, MD, MPH[2]; Luc G. Morris, MD, MSc[1]; Ian Ganly, MD, MSc, PhD[1]; Snehal G. Patel, MD[1]; Marc A. Cohen, MD, MPH[1,3]; and Benjamin R. Roman, MD, MSH[1]

**BACKGROUND:** There has been increasing interest in the primary surgical treatment of patients with early T classification (T1-T2) oropharyngeal squamous cell carcinoma (OPSCC), with the stated goal of de-escalating or avoiding adjuvant treatment. Herein, the authors sought to determine the degree to which this interest has translated into changes in practice patterns, and the rates of adverse postoperative pathologic features. **METHODS:** Patients with T1 to T2 OPSCC in the National Cancer Data Base who were treated from 2004 through 2013 were categorized as receiving primary surgical or primary radiation-based treatment. Trends in treatment selection and factors related to the selection of primary surgery were examined. The rates of adverse pathologic features including positive surgical margins, extracapsular spread (ECS), and advanced T and N classifications after surgery were analyzed. **RESULTS:** Of 8768 patients with T1 to T2 OPSCC, 68% underwent primary surgical treatment, increasing from 56% in 2004 to 82% in 2013 ($P<.0001$). The highest versus lowest volume hospitals treated 78% versus 59% of patients with primary surgery (odds ratio, 2.23; 95% confidence interval, 1.55-3.22 [$P<.0001$]). Higher lymph node classification was found to be predictive of lower rates of primary surgery, but the majority of patients with clinical N2/N3 disease underwent primary surgery. Among patients treated with surgery, positive surgical margins were present in 24% and ECS in 25% of patients. The rate of positive surgical margins decreased over time ($P<.0001$) and was observed less often at high-volume centers ($P<.0001$). Among candidates for single-modality therapy (those with clinical T1-T2/N0-N1 disease), 33% had positive surgical margins and/or ECS and 47% had at least 1 adverse feature (T3-T4 disease, N2-N3 disease, positive surgical margins, and/or ECS). **CONCLUSIONS:** Primary surgical treatment among patients with early T classification OPSCC has become more widespread. ***Cancer*** **2016;122:1523-32**. *© 2016 American Cancer Society.*

**KEYWORDS:** extracapsular spread (ECS), human papillomavirus-related oropharyngeal squamous cell carcinoma (OPSCC), positive surgical margins, transoral robotic surgery (TORS), treatment selection.

## INTRODUCTION

The incidence of oropharyngeal squamous cell carcinoma (OPSCC) in the United States is rising, and is projected to double by 2030 to >15,000 diagnoses per year.[1] In addition to the classic risk factors of chronic tobacco and alcohol exposure, the human papillomavirus (HPV) has emerged as the leading causative agent for OPSCC in the United States and other countries.[2,3] Compared with patients with tobacco-associated OPSCC, patients with HPV-associated OPSCC are on average younger at the time of diagnosis, have fewer comorbid illnesses, and have a superior prognosis.[4-6] At the time of presentation, patients with HPV-associated OPSCC tumors commonly present with low T classification (T1-T2) but advanced stage of disease (AJCC stage III-IV) because of lymph node metastases.[7,8]

To our knowledge, uncertainty persists regarding the most appropriate treatment strategies for patients with OPSCC. Before the 1990s, primary surgery and primary radiotherapy (RT) were the most commonly used strategies. In the late 1990s, organ preservation trials demonstrated the survival benefits of chemoradiotherapy over RT alone,[9] leading to the increased use of chemoradiotherapy in the early 2000s.[10,11] However, there has recently been renewed enthusiasm for primary surgical approaches for the treatment of OPSCC.[12-14] This has been driven by technologic advances such as transoral robotic surgery (TORS) that enhance the feasibility of surgery for patients with OPSCC of low T classification and offer the potential of avoiding or de-escalating adjuvant treatments. TORS was approved by the US Food and Drug Administration (FDA) in 2009.

**Corresponding author:** Benjamin R. Roman, MD, MSH, Head and Neck Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, 1275 York Ave, Rm C-1075, New York, NY 10065; romanb@mskcc.org

[1]Head and Neck Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, New York; [2]Department of Medical Oncology, Memorial Sloan Kettering Cancer Center, New York, New York; [3]Department of Otolaryngology-Head and Neck Surgery, Joan and Sanford I. Weill Medical College of Cornell University, New York, New York

**DOI:** 10.1002/cncr.29938, **Received:** December 18, 2015; **Revised:** January 21, 2016; **Accepted:** January 26, 2016, **Published online** March 11, 2016 in Wiley Online Library (wileyonlinelibrary.com)

To achieve the goal of minimizing the extent of postoperative therapy for patients with early T classification OPSCC, it is important to select patients appropriately for 1 of 2 current standard initial treatment strategies: primary surgery or primary RT with or without chemotherapy. Specifically, surgical patients should ideally be those for whom the likelihood of adverse pathologic risk factors is low. According to National Comprehensive Cancer Center guidelines, the adverse risk factors that prompt the escalation of adjuvant therapy include N2 to N3 lymph node status, advanced pathologic T classification, positive surgical margins, the presence of lymph nodes with extracapsular spread (ECS), and tumor perineural invasion or lymphovascular invasion.[15] Conversely, if patients have none of these adverse features, they may be treated with surgery alone.

Although recent work has examined variables associated with patients treated with TORS since its approval by the FDA,[16] to our knowledge there is limited knowledge of national trends in the primary treatment strategy for patients with OPSCC of early T classification before and during the TORS era, particularly those factors associated with the decision to triage patients to primary surgical therapy, and the success of physicians in selecting patients for surgery in whom adverse pathologic features are not present. The goal of the current study was to use a large, high-quality US cancer registry to examine these questions at a national level.

## MATERIALS AND METHODS

### Data Source

The data source for this study was the National Cancer Data Base (NCDB), a joint program of the Commission on Cancer and the American College of Surgeons that collects hospital-based registry data regarding >80% of cases of malignancies of the oral cavity and pharynx in the United States.[17] The source files were used in accordance with the NCDB Participant Use Data File data use agreement. The current study was given an Institutional Review Board waiver by the Memorial Sloan Kettering Cancer Center.

### Study Cohort

We identified all patients with clinically staged T1 and T2 OPSCC who were diagnosed between 2004 and 2013 and who were aged ≥18 years. We included *International Classification of Diseases for Oncology* (ICD-O) codes for the oropharynx (codes C019, C090, C091, C098, C099, C100, C101, C102, C103, C104, C108, C109, and C142). We included only those patients with histologically proven SCC tissue examined by microscope rather than cytology alone; the tissue could be examined from biopsy or surgical pathology specimens. We excluded those patients who had received part or all of their treatment outside of the NCDB-reporting facility to be certain that the various possible primary treatments were in fact delivered, and in what order. Patients for whom information regarding treatment was missing or those for whom the sequence of treatments was not clear, as well as those whose staging information was inconsistent with treatment information or could not be assessed, were excluded (Fig. 1). The total cohort with complete data was 8768 patients.

### Outcomes

The main outcome of the current study was the choice of primary treatment modality. Patients were categorized as receiving "primary radiation" or "primary surgical" treatment. The primary treatment modality was determined to be RT if the patient did not receive primary surgery but had undergone RT. The primary modality was surgery if the patient underwent surgery before any RT or chemotherapy. A "local tumor excision" such as excisional biopsy was not considered primary surgery. For the tonsil and other oropharynx, all categories of "pharyngectomy" were used; 91% of cases were classified as "limited/partial pharyngectomy," which includes tonsillectomy; 4% were "pharyngectomy not otherwise specified"; 2% were "total pharyngectomy"; 1% were "radical pharyngectomy"; and the remaining cases were classified as other subclassifications of pharyngectomy. Tumors of the base of the tongue (ICD-O code C019) were listed with other tongue tumors; patients treated with primary surgery were those who underwent at least "glossectomy" and not "local tumor excision."

A secondary outcome was the presence of adverse pathologic features among those patients who underwent primary surgical treatment. For the current analysis, we included only those patients undergoing primary surgery who had complete information regarding surgical margin status and ECS (Fig. 1).

### Tumor Characteristics

Clinical T and N classifications were used for the analysis of predictors of primary treatment modality because patients who did not undergo surgery did not have pathologic information available. For the secondary analysis of pathologic factors among those undergoing primary surgery, the T and N classifications were each described according to both clinical and pathologic staging. ECS is

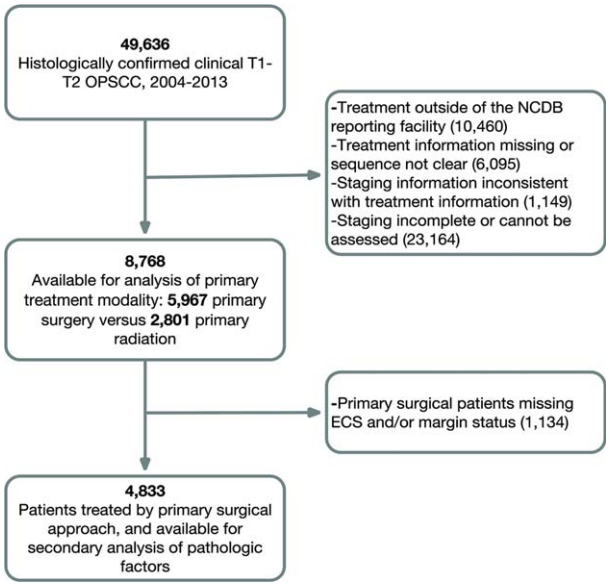


**Figure 1.** Flow diagram of patient inclusion and exclusion. ECS indicates extracapsular spread; NCDB, National Cancer Data Base; OPSCC, oropharyngeal squamous cell carcinoma.

defined in the NCDB as either negative, microscopic, macroscopic, or unknown; for the current analysis, ECS was determined to be positive if microscopically or macroscopically positive. Surgical margins were defined as positive if there was microscopic or macroscopic "residual tumor." Close surgical margins are not recorded in the NCDB and would be considered negative by coding rules.

### *Covariates*

Patient sociodemographic factors included age, sex, race, insurance status (grouped as private, uninsured, or government insurance including Medicare and Medicaid), and comorbidities (Charlson-Deyo comorbidity index[18]). Hospital volume was defined as the total new number of OPSCC cases seen over all years from 2004 through 2013, with hospitals divided into quartiles by volume for analysis. Hospital type was defined as either "academic," which included academic/research programs as well as National Cancer Institute (NCI)-designated comprehensive cancer centers, or "community," which included community cancer programs, comprehensive community cancer programs, integrated network cancer programs, and other specified types of programs.

### *Statistical Analysis*

We used descriptive and chi-square statistics to compare tumor, patient sociodemographic, and hospital factors among patients who underwent primary surgery versus those who received primary RT. The Cochran-Armitage trend test was used to determine whether the percentage of patients treated with a primary surgical approach (vs primary RT approach) changed over time. For multivariable analysis, we used hierarchical generalized linear models with a logit link to account for clustering of patients within hospitals while evaluating the influence of tumor, patient sociodemographic, and hospital factors on the binary choice of primary treatment modality. The large sample size allowed us to include all variables of interest in the multivariable model and no model selection was necessary. For the secondary analysis of pathologic factors among those undergoing primary surgery, we used descriptive statistics as well as the Cochran-Armitage trend test to examine how these pathologic features changed over time. As a sensitivity analysis for one of these pathologic features (surgical margin positivity), we also performed logistic regression of year on surgical margin positivity to ensure that the trend over time was in a downward direction. $P$ values $<.05$ were considered statistically significant. Analyses were conducted using Stata statistical software (release 12.1; StataCorp LP, College Station, Tex).

## RESULTS

### *Characteristics of the Cohort*

We identified 8768 patients who presented with T1 and T2 OPSCC between 2004 and 2013 (Table 1). The majority were male (79%), aged 50 to 64 years (55%), and white (92%). The majority had private insurance (68%) and no comorbidities (82%). Slightly less than one-half of the patients (49%) were treated at community cancer programs. Although 26% of patients were treated at higher volume hospitals that saw >50 patients with OPSCC, another 34% were treated at low-volume hospitals in which only ≤10 patients with OPSCC were treated between 2004 and 2013. With regard to tumor factors, 47% of patients presented with clinically classified T1 tumors and 53% presented with T2 tumors, whereas 26% of patients had clinically or radiographically classified N0 disease, 23% had N1 disease, 47% had N2 disease, and 3% of patients had N3 disease at the time of presentation.

### *Primary Treatment Selection*

Overall, 68% of patients (5967 patients) underwent primary surgical treatment. From 2004 through 2013, the use of the primary surgical approach increased over time from 56% of patients in 2004 to 82% in 2013 ($P<.0001$) (Fig. 2). Patients selected for primary surgical treatment tended to have lower lymph node disease status at the time of presentation (81% of patients with N0 disease,

**TABLE 1.** Primary Treatment Modality in Patients With T1 to T2 OPSCC

| Characteristic | Overall No. (Column %) | Primary Surgical Treatment (Versus Primary XRT) No. (Row % Compared With Primary XRT [Not Shown]) | $P$[a] | Multivariable Analysis of Primary Surgical Treatment Adjusted OR (95% CI) | $P$[a] |
|---|---|---|---|---|---|
| Patients | 8768 | 5967 (68.1%) | | | |
| Age at diagnosis, y | | | .265 | | |
| <50 | 1732 (19.8%) | 1210 (69.9%) | | 1 (reference) | |
| 50–64 | 4843 (55.2%) | 3287 (67.9%) | | 0.78 (0.68–0.89) | **<.0001** |
| 65–79 | 1940 (22.1%) | 1297 (66.9%) | | 0.68 (0.55–0.83) | **<0.0001** |
| ≥80 | 253 (2.9%) | 173 (68.4%) | | 0.70 (0.49–0.99) | **.046** |
| Sex | | | **.001** | | |
| Male | 6911 (78.8%) | 4644 (67.2%) | | 0.93 (0.81–1.06) | .251 |
| Female | 1857 (21.2%) | 1323 (71.2%) | | 1 (reference) | |
| Race | | | .688 | | |
| White | 8032 (91.6%) | 5463 (68%) | | 1 (reference) | |
| Black | 492 (5.6%) | 332 (67.5%) | | 0.85 (0.67–1.06) | .152 |
| Other | 244 (2.8%) | 172 (70.5%) | | 1.10 (0.80–1.51) | .556 |
| Clinical N classification[b] | | | **<.0001** | | |
| N0 | 2304 (26.3%) | 1856 (80.6%) | | 1 (reference) | |
| N1 | 2030 (23.2%) | 1357 (66.8%) | | 0.44 (0.37–0.51) | **<.0001** |
| N2 | 4151 (47.3%) | 2602 (62.7%) | | 0.33 (0.28–0.38) | **<.0001** |
| N3 | 283 (3.2%) | 152 (53.7%) | | 0.26 (0.20–0.35) | **<.0001** |
| Clinical T classification[b] | | | .245 | | |
| T1 | 4155 (47.4%) | 2853 (68.7%) | | 1 (reference) | |
| T2 | 4613 (52.6%) | 3114 (67.5%) | | 0.93 (0.84–1.03) | .142 |
| Insurance status | | | **.007** | | |
| Private | 5942 (67.8%) | 4091 (68.8%) | | 1.19 (1.01–1.39) | **.036** |
| Uninsured | 358 (4.1%) | 220 (61.5%) | | 0.93 (0.70–1.25) | .639 |
| Government[c] | 2468 (28.1%) | 1656 (67.1%) | | 1 (reference) | |
| Charlson-Deyo Comorbidity Index | | | **.029** | | |
| 0 | 7194 (82%) | 4854 (67.5%) | | 1 (reference) | |
| 1 | 1279 (14.6%) | 911 (71.2%) | | 1.13 (0.97–1.30) | .122 |
| ≥2 | 295 (3.4%) | 202 (68.5%) | | 0.95 (0.71–1.26) | .705 |
| Year diagnosed | | | **<.0001** | | |
| 2004 | 568 (6.5%) | 319 (56.2%) | | 1 (reference) | |
| 2005 | 644 (7.3%) | 354 (55%) | | 0.98 (0.76–1.27) | .913 |
| 2006 | 674 (7.7%) | 400 (59.3%) | | 1.09 (0.84–1.41) | .484 |
| 2007 | 747 (8.5%) | 431 (57.7%) | | 1.14 (0.89–1.46) | .294 |
| 2008 | 1052 (12%) | 674 (64.1%) | | 1.50 (1.18–1.89) | **.001** |
| 2009 | 1174 (13.4%) | 792 (67.5%) | | 1.78 (1.41–2.25) | **<.0001** |
| 2010 | 939 (10.7%) | 651 (69.3%) | | 1.86 (1.46–2.39) | **<.0001** |
| 2011 | 979 (11.2%) | 724 (74%) | | 2.28 (1.78–2.92) | **<.0001** |
| 2012 | 970 (11.1%) | 784 (80.8%) | | 3.37 (2.60–4.37) | **<.0001** |
| 2013 | 1021 (11.6%) | 838 (82.1%) | | 3.82 (2.95–4.96) | **<.0001** |
| Facility type | | | **<.0001** | | |
| Academic/ NCI CCC | 4496 (51.3%) | 3306 (73.5%) | | 1 (reference) | |
| Community | 4272 (48.7%) | 2661 (62.3%) | | 0.91 (0.75–1.10) | .334 |
| Hospital volume | | | **<.0001** | | |
| 1–10 patients | 3018 (34.4%) | 1791 (59.3%) | | 1 (reference) | |
| 11–20 patients | 1576 (18%) | 1057 (67.1%) | | 1.41 (1.13–1.75) | **.002** |
| 21–50 patients | 1883 (21.5%) | 1336 (71%) | | 1.52 (1.17–1.97) | **.002** |
| >50 patients | 2291 (26.1%) | 1783 (77.8%) | | 2.23 (1.55–3.22) | **<.0001** |

Abbreviations: 95% CI, 95% confidence interval; NCI CCC, National Cancer Institute comprehensive cancer center; OPSCC, oropharyngeal squamous cell carcinoma; OR, odds ratio; XRT, external radiotherapy.

[a] $P$ values in bold type are <.05.

[b] Both the N and T classifications are defined as clinical staging because this was the only information available before selection of the primary treatment modality.

[c] Medicare and Medicaid.

67% of patients with N1 disease, 63% of patients with N2 disease, and 54% of patients with N3 disease selected for surgery; $P<.0001$) (column 2 in Table 1). Patients undergoing primary surgery tended to have private insurance compared with no insurance or government insurance (69% vs 62% and 67%, respectively; $P = .007$). Patients treated at academic hospitals were treated with a primary surgical approach more often than those treated at community hospitals (74% vs 62%; $P<.0001$), and patients treated at the highest volume hospitals were

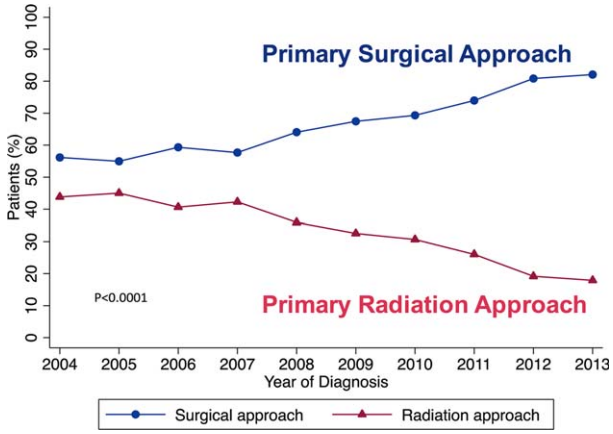


**Figure 2.** Primary treatment approach for patients with T1 to T2 oropharyngeal squamous cell carcinoma. The total number of patients was 8768, including 2801 patients (31.9%) who were undergoing a primary radiotherapy approach and 5967 patients (68.1%) who were being treated with a primary surgical approach. There were a total of 568 patients in 2004, which increased to a total of 1021 patients in 2013 ($P<.0001$ for differences in the primary treatment approach over time).

treated with a primary surgical approach more often than those treated at the lowest volume hospitals (78% vs 59%; $P<.0001$) (column 2 in Table 1).

### *Factors Associated With Primary Surgery*

On multivariable analysis, in addition to the year of diagnosis, several tumor and nontumor factors were found to be associated with the use of a primary surgical approach (column 3 in Table 1). Clinical N0 classification was found to be associated with a higher likelihood of a primary surgical approach (N1 vs N0 disease: odds ratio [OR], 0.44 [95% confidence interval (95% CI), 0.37-0.51; $P<.0001$]; N2 vs N0 disease: OR, 0.33 [95% CI, 0.28-0.38; $P<.0001$]; and N3 vs N0 disease: OR, 0.26 [95% CI, 0.20-0.35; $P<.0001$]). Younger patients were more likely to undergo a primary surgical approach (aged 50-64 years vs aged <50 years: OR, 0.78 [95% CI, 0.68-0.89; $P<.0001$]; aged 65-79 years vs aged <50 years: OR, 0.68 [95% CI, 0.55-0.83; $P<.0001$]). Higher volume hospitals were significantly more likely to use a primary surgical approach compared with the lowest volume hospitals (>50 patients vs 1-10 patients: OR, 2.23; 95% CI, 1.55-3.22 [$P<.0001$]). On the multivariable analysis, hospital type was not found to be associated with the primary treatment approach.

### *Pathologic Factors in Patients Treated With a Primary Surgical Approach*

Of the 5967 patients treated with a primary surgical approach, 4833 had complete pathologic information

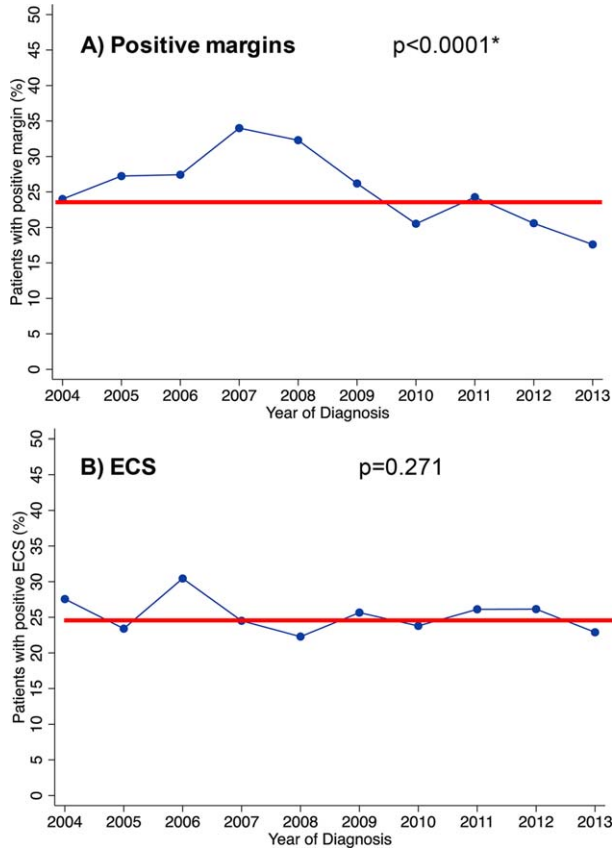


**Figure 3.** Change in pathologic factors over time. (A) Positive surgical margin (24% overall). (B) Extracapsular spread (ECS) (25% overall). *P* values were determined via the Cochran-Armitage trend test. *For surgical margin status, the *P* value was the same when using logistic regression to ensure the trend was in a downward direction.

available regarding T classification, N classification, surgical margins, and ECS. In this group, 24% had positive surgical margins, 25% had ECS, and 43% had either positive surgical margins and/or ECS. There was a significant decrease over time in the rate of positive surgical margins ($P<.0001$) (Fig. 3A). Surgical margin positivity was highest in 2007 at 34% and dropped to 18% in 2013. Patients treated at community and low-volume hospitals were more likely to have positive surgical margins on final pathology (positive surgical margin rate at community hospitals of 33% vs 17% at academic medical centers [$P<.0001$]; positive surgical margin rate at lowest volume hospitals of 33% vs 17% at highest volume hospitals [$P<.0001$]) (Fig. 4). There was no change in rates of ECS over time ($P = .271$) (Fig. 3B). A higher pathologic lymph node classification was associated with increased rates of ECS (17% of patients with N1 disease, 38% of patients with N2 disease, and 51% of patients with N3 disease [$P<.0001$]; data not shown).

Overall, 56% of patients undergoing a primary surgical approach had a pathologic N2 or N3 lymph node classification. Pathologic N-upstaging occurred in 24% of patients with cN0 disease, 39% of patients with cN1 disease, and 3% of patients with cN2a/N2b disease (Table 2). Pathologic T-upstaging occurred in 17% of patients with cT1 disease and 11% of patients with cT2 disease (Table 3).

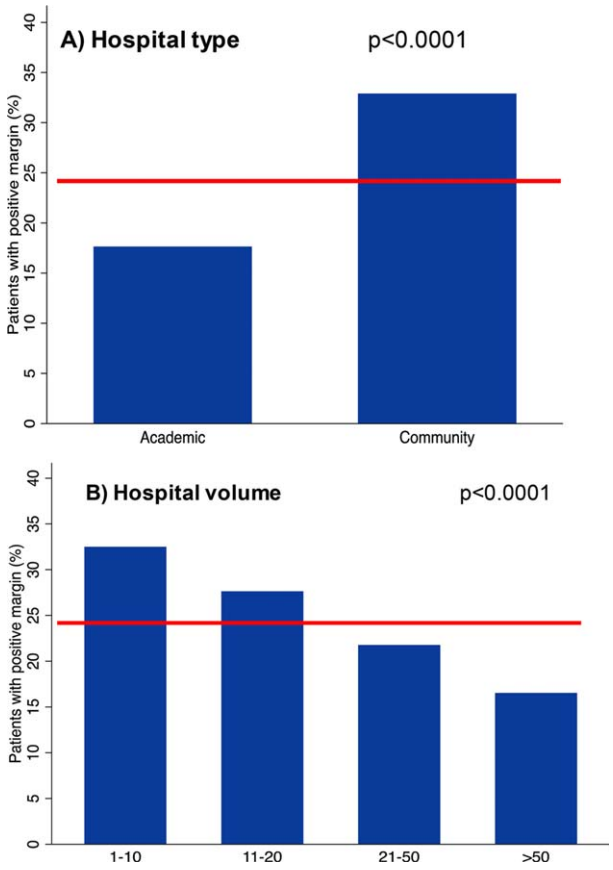


**Figure 4.** Surgical margin positivity by hospital characteristics. (A) Positive surgical margins by hospital type. (B) Positive surgical margins by hospital volume. The line represents the overall positive surgical margin percentage. *P* values were determined via the chi-square statistic.

### *Adverse Pathologic Factors Among Candidates for Single-Modality Therapy*

Among patients treated with primary surgery for whom complete pathologic information was available, 2570 (53%) were clinically classified as having T1 to T2/N0 to N1 disease and therefore were candidates for single-modality therapy with surgery. Of these, 723 patients (28%) were pathologically upstaged out of single-modality therapy to T3 to T4 and/or N2 to N3 disease. In addition, 842 patients (33%) had positive surgical margins and/or ECS. In total, 1200 of the patients originally classified with T1 to T2/N0 to N1 disease (47%) had at least 1 adverse feature (T3-T4 disease, N2-N3 disease, positive surgical margins, or ECS).

## DISCUSSION

The incidence of OPSCC is rapidly increasing in the United States due to HPV-associated disease. Many of these patients have low T classification (T1-T2) tumors that are amenable to primary surgical treatment. The potential advantage of this approach is the possibility of avoiding or de-escalating postoperative therapies. To our knowledge to date there has been limited information regarding trends in the primary treatment of patients with OPSCC of early T classification, or rates of adverse pathologic features in surgically treated patients.

We observed a significant increase in the use of primary surgery and a decrease in the use of a primary RT approach to treating patients with T1-T2 OPSCC between 2004 and 2013. Although a lower clinical lymph node stage was associated with a primary surgical approach, primary surgery was nonetheless chosen for nearly two-thirds of patients with clinical N2/N3 disease.

**TABLE 2.** Clinical N Compared with Pathologic N Classification Among Patients Treated with Primary Surgery[a]

| | | Pathologic N Classification, No. (Row %) | | | | |
|---|---|---|---|---|---|---|
| Patients | N = 4833 | N0<br>1230 (25.5) | N1<br>921 (19.1) | N2a/N2b<br>2380 (49.2) | N2c/N3<br>302 (6.3) | |
| Clinical N classification, no. (column %) | | | | | | |
| N0 | **1427 (29.5)** | 1085 (76.0) | 172 (12.1) | 158 (11.1) | 12 (0.8) | →24% upstaged |
| N1 | **1143 (23.7)** | 77 (6.74) | 625 (54.7) | 415 (36.3) | 26 (2.3) | →39% upstaged |
| N2a/N2b | **2000 (41.4)** | 54 (2.7) | 115 (5.8) | 1763 (88.2) | 68 (3.4) | →3% upstaged |
| N2c/N3 | **263 (5.4)** | 14 (5.32) | 9 (3.4) | 44 (16.7) | 196 (74.5) | |

[a] Clinical stage row totals do not match those in column 2 in Table 1 because of the exclusion of surgical patients with incomplete pathologic information.

**TABLE 3.** Clinical T Compared with Pathologic T Classification Among Patients Treated with Primary Surgery[a]

| | | Pathologic T Classification, No. (Row %) | | | | |
|---|---|---|---|---|---|---|
| | | T1 | T2 | T3 | T4 | |
| Patients | N = 4833 | 2287 (47.3) | 2227 (46.1) | 208 (4.3) | 111 (2.3) | |
| Clinical T classification, no. (column %) | | | | | | |
| T1 | **2345 (48.5)** | 1948 (83.1) | 358 (15.3) | 24 (1.0) | 15 (0.6) | →17% upstaged |
| T2 | **2488 (51.5)** | 339 (13.6) | 1869 (75.1) | 184 (7.4) | 96 (3.9) | →11% upstaged |

[a] Clinical stage row totals do not match those in column 2 in Table 1 because of the exclusion of surgical patients with incomplete pathologic information.

Nontumor factors including receiving treatment at a high-volume hospital also were found to be associated with the selection of a primary surgical approach.

Among the subgroup of patients who underwent primary surgery, 25% had a positive surgical margin. This rate improved over time and there was a lower rate noted at high-volume and academic institutions. One in 4 patients receiving a primary surgical approach also had ECS. Nearly one-half of patients (47%) treated with primary surgery who by clinical staging might have been candidates for surgical treatment alone (T1-T2/N0-N1 disease) had at least 1 adverse feature requiring adjuvant RT or chemoradiation.

The findings presented herein have to be considered within the context of important limitations. First, there were a significant number of exclusions due to incomplete staging information, a basic oncologic reporting requirement that should in theory be better represented. The strength of the NCDB for inquiry into practice patterns in head and neck oncology might be examined in separate dedicated analyses given the large amount of missing data. Second, in determining the cohort who received primary surgical therapy, we included those patients coded as having a "tonsillectomy" who were listed as a subcategory of "pharyngectomy not otherwise specified." Although we cannot be certain that such patients underwent an oncologic surgical resection, we did exclude from our primary surgical cohort any patient who underwent a "local tumor excision" or "excisional biopsy," which would help to exclude the simple tonsillectomies performed explicitly for biopsy purposes. We also noted that all patients in the current study who were classified as having received primary surgical therapy had both their pathologic T and pathologic N classification recorded, suggesting primary tumor resection and neck dissection; pathologic N classification especially would not be likely to be noted among patients receiving primary RT. The issue of the classification of tonsillectomy as primary surgery or not is important because simple tonsillectomy confers no benefit to these patients and may lead to overtreatment if there are resulting positive surgical margins. Third, HPV status was only routinely recorded in the NCDB after 2010 and therefore was not accounted for in the current analysis. This is important because the relevance of ECS and its relation to N-upstaging may be different between HPV-related and non-HPV-related disease. Nonetheless, decisions regarding primary treatment selection over much of the study were most likely made without information concerning HPV status because it was not routinely tested in clinical practice during many of these years. In addition, the NCBD does not record information regarding preoperative or postoperative radiologic workup and reoperations for positive surgical margin status, factors that may influence treatment decision making. Finally, information regarding the pathologic features of perineural invasion and lymphovascular invasion are not available in the NCDB, and therefore there may be an underestimation of the rates of adverse features among surgically treated patients.

The steepest rise in primary surgical therapy has been observed toward the end of the study period, correlating with FDA approval of TORS in 2009 as well as increasing interest in other methods of transoral endoscopic head and neck surgery including transoral laser microsurgery.[19] Hospital volume also was found to be predictive of a primary surgical approach. High-volume hospitals were the innovators and early adopters of transoral approaches, resulting in a surgical bias. This most likely was necessary because the diffusion of any technology requires innovators who push it forward.[20]

An important goal in primary treatment selection, especially for patients with HPV-related OPSCC, is to avoid the increased toxicity associated with multimodal adjuvant therapy that would obviate the desired goal (de-escalation) of surgical therapy.[4] In National Comprehensive Cancer Center guidelines over the study period,

indications for postoperative adjuvant therapy (RT alone or chemoradiation) included adverse features of advanced pathologic T classification (T3/T4), advanced N classification (N2/N3), positive surgical margins, ECS, perineural invasion, and lymphovascular invasion.[15] It should be noted that some data suggest that ECS may not be as important in patients with HPV-related OPSCC,[21] and a future prospective trial may negate this as a recommendation for adjuvant chemoradiation.[22] Nevertheless, during the years of the current study and as of this publication, positive surgical margins and ECS are considered to be indications for adjuvant chemoradiation (triple-modality therapy) as a category 1 recommendation based on Radiation Therapy Oncology Group and European Organization for Research and Treatment of Cancer data demonstrating benefit in these patients.[23-25] In some patients, primary surgical treatment results in none of these features, and the patient therefore is able to avoid any adjuvant treatment with RT or chemoradiation. To the degree that any of these pathologic factors might be anticipated before treatment selection, there may be opportunities to improve the treatment selection process in an attempt to avoid escalated modalities of adjuvant therapy.

Positive surgical margin status is a factor that should be anticipated before choosing primary surgery. Although there is some debate regarding the significance of close or positive surgical margins in patients with HPV-related OPSCC, the majority of surgeons nonetheless strive to minimize this adverse factor.[26] Reported rates of positive surgical margins in the literature for TORS are as high as 33%.[27] The decrease in positive surgical margin status observed over time may be related to improvements in patient selection combined with advancements in surgical skills as experience increased. Consistent with this observation is the finding that positive surgical margins were more commonly observed in low-volume hospitals. Although continued overall progress in technique might be expected, a ceiling effect of technical improvement may exist when a rate of positive margins persists.

ECS is another pathologic risk factor that should be better anticipated before treatment selection. In this cohort, 1 in 4 patients undergoing primary surgery had ECS. One recent study found that greater than one-half of patients with HPV-related regional metastases were found to have ECS and that computed tomography was not a reliable method for determining the presence of ECS in patients with HPV-related OPSCC.[24] In the future, ECS may be considered to be less important for HPV-associated disease.[21,22] Until that time, better ways to predict ECS will lead to fewer patients being selected for primary surgical treatment who end up receiving escalated postoperative therapy.

In the current study, >67% of patients with clinically advanced lymph node disease underwent surgery. These patients are more likely to receive escalated adjuvant therapy secondary to advanced lymph node disease and the increased probability of having ECS. However, it is important to note that patients treated with primary surgery have pathologically staged lymph node information, whereas in patients treated with primary RT, only clinical staging is used to determine the need for adjuvant therapy. Pathologic staging occasionally may reveal a lack of lymph node metastases noted on preoperative imaging, leading to less unnecessary adjuvant treatment in this group than if they were treated with primary RT based on imaging staging alone. Conversely, pathologic staging may lead to important upstaging, identifying those patients who might otherwise be undertreated with adjuvant therapies. Specifically, patients with advanced lymph node disease (eg, HPV-negative oropharyngeal cancer) may have improved outcomes with primary surgery followed by chemoradiation, but one prospective trial attempting to answer this question was recently closed due to insufficient accrual.[28] Alternatively, functional outcomes may be superior in patients with an advanced lymph node stage undergoing primary surgery followed by a lower dose of RT compared with standard concurrent chemoradiation without compromising oncologic outcomes, a question that is currently being examined in an ongoing trial.[29] Until such data have matured, and with higher rates of HPV-positive disease, the high volume of primary surgery in this cohort theoretically requiring escalated adjuvant therapy should be examined.

Patients with cT1 to cT2 and cN0 to cN1 tumors are potential candidates for single-modality therapy with surgery alone. In this cohort, >25% of these patients were T- or N-upstaged enough to require adjuvant therapy and 33% of patients had positive surgical margins and/or ECS theoretically requiring adjuvant chemoradiation, whereas slightly more than one-half of patients had no adverse features requiring adjuvant therapy. Although a full clinical assessment of the submucosal extent of tumors involving the base of the tongue and tonsil may be difficult, T-upstaging in general would suggest radiographic evaluation underrepresented the extent of tumor at the time of pretreatment evaluation. N-upstaging also suggests lymph node disease that was more advanced than was observed on pretreatment radiologic imaging. Improvements in pretreatment radiologic staging could help to better select

patients for primary surgery who do not need adjuvant therapy.

Although there is great enthusiasm for the primary surgical approach to treating patients with T1 to T2 OPSCC because of the possibility of limiting treatment-related morbidity, we have demonstrated elements of suboptimal treatment selection that may ultimately be leading to escalation of adjuvant therapy. The findings of the current study shed light on areas in which improvements are needed in treatment selection and treatment provision.

## FUNDING SUPPORT

Funded in part through the National Institutes of Health/National Cancer Institute Cancer Center Support Grant P30 CA008748 and through the National Institutes of Health/National Cancer Institute Training Grant T32 CA009685.

## CONFLICT OF INTEREST DISCLOSURES

Shrujal S. Baxi has acted as a paid consultant for Bristol-Myers Squibb and received nonfinancial support from AstraZeneca for work performed outside of the current study.

## AUTHOR CONTRIBUTIONS

**Jennifer R. Cracchiolo:** Conceptualization, methodology, writing–original draft, writing–review and editing, visualization, and project administration. **Shrujal S. Baxi:** Conceptualization, methodology, formal analysis, and writing–review and editing. **Luc G. Morris:** Conceptualization, formal analysis, investigation, data curation, writing–original draft, writing–review and editing, and supervision. **Ian Ganly:** Writing–original draft, writing–review and editing, and visualization. **Snehal G. Patel:** Conceptualization and writing–review and editing. **Marc A. Cohen:** Conceptualization, methodology, formal analysis, investigation, resources, writing–original draft, writing–review and editing, visualization, supervision, and project administration. **Benjamin R. Roman:** Conceptualization, methodology, software, validation, formal analysis, investigation, resources, data curation, writing–original draft, writing–review and editing, visualization, supervision, project administration, and funding acquisition.

## REFERENCES

1. Chaturvedi AK, Engels EA, Pfeiffer RM, et al. Human papillomavirus and rising oropharyngeal cancer incidence in the United States. *J Clin Oncol.* 2011;29:4294–4301.
2. D'Souza G, Kreimer AR, Viscidi R, et al. Case-control study of human papillomavirus and oropharyngeal cancer. *N Engl J Med.* 2007;356:1944–1956.
3. Chaturvedi AK, Engels EA, Anderson WF, Gillison ML. Incidence trends for human papillomavirus-related and -unrelated oral squamous cell carcinomas in the United States. *J Clin Oncol.* 2008;26: 612–619.
4. Ang KK, Harris J, Wheeler R, et al. Human papillomavirus and survival of patients with oropharyngeal cancer. *N Engl J Med.* 2010; 363:24–35.
5. Sedaghat AR, Zhang Z, Begum S, et al. Prognostic significance of human papillomavirus in oropharyngeal squamous cell carcinomas. *Laryngoscope.* 2009;119:1542–1549.
6. Fakhry C, Westra WH, Li S, et al. Improved survival of patients with human papillomavirus-positive head and neck squamous cell carcinoma in a prospective clinical trial. *J Natl Cancer Inst.* 2008; 100:261–269.
7. Huang SH, Perez-Ordonez B, Liu FF, et al. Atypical clinical behavior of p16-confirmed HPV-related oropharyngeal squamous cell carcinoma treated with radical radiotherapy. *Int J Radiat Oncol Biol Phys.* 2012;82:276–283.
8. Goldenberg D, Begum S, Westra WH, et al. Cystic lymph node metastasis in patients with head and neck cancer: an HPV-associated phenomenon. *Head Neck.* 2008;30:898–903.
9. Calais G, Alfonsi M, Bardet E, et al. Randomized trial of radiation therapy versus concomitant chemotherapy and radiation therapy for advanced-stage oropharynx carcinoma. *J Natl Cancer Inst.* 1999;91: 2081–2086.
10. Chen AY, Zhu J, Fedewa S. Temporal trends in oropharyngeal cancer treatment and survival: 1998–2009. *Laryngoscope.* 2014;124: 131–138.
11. Liederbach E, Lewis CM, Yao K, et al. A contemporary analysis of surgical trends in the treatment of squamous cell carcinoma of the oropharynx from 1998 to 2012: a report from the National Cancer Database. *Ann Surg Oncol.* 2015;22:4422–4431.
12. Lorincz BB, Jowett N, Knecht R. Decision management in transoral robotic surgery: indications, individual patient selection, and role in the multidisciplinary treatment for head and neck cancer from a European perspective [published online ahead of print March 31, 2015]. *Head Neck.* doi: 10.1002/hed.24059.
13. Mydlarz WK, Chan JY, Richmon JD. The role of surgery for HPV-associated head and neck cancer. *Oral Oncol.* 2015;51:305–313.
14. Chen AY. A shifting paradigm for patients with head and neck cancer: transoral robotic surgery (TORS). *Oncology (Williston Park).* 2010;24:1030, 1032.
15. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology, Head and Neck Cancers, Version 1.2015. http://www.nccn.org/professionals/physician_gls/pdf/head-and-neck.pdf. Accessed January 12, 2016.
16. Chen MM, Roman SA, Kraus DH, Sosa JA, Judson BL. Transoral robotic surgery: a population-level analysis. *Otolaryngol Head Neck Surg.* 2014;150:968–975.
17. Bilimoria KY, Stewart AK, Winchester DP, Ko CY. The National Cancer Data Base: a powerful initiative to improve cancer care in the United States. *Ann Surg Oncol.* 2008;15:683–690.
18. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *J Clin Epidemiol.* 1992;45:613–619.
19. Holsinger FC. New approaches: robotics and endoscopic head and neck surgery. In: Harrison LB, Sessions RB, Kies M, eds. Head and Neck Cancer: A Multidisciplinary Approach. 4th ed. Philadelphia: Lippincott Williams and Wilkins; 2013.
20. Rogers EM. Diffusion of Innovations. 5th ed. New York, NY: Free Press; 2003.
21. Sinha P, Lewis JS Jr, Piccirillo JF, Kallogjeri D, Haughey BH. Extracapsular spread and adjuvant therapy in human papillomavirus-related, p16-positive oropharyngeal carcinoma. *Cancer.* 2012;118: 3519–3530.
22. ClinicalTrials.gov. Post operative adjuvant therapy de-intensification trial for human papillomavirus-related, p16+ oropharynx cancer (ADEPT) [ClinicalTrials.gov: NCT01687413]. https://clinicaltrials.gov/ct2/show/NCT01687413. Accessed August 25, 2015.
23. Bernier J, Domenge C, Ozsahin M, et al. Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. *N Engl J Med.* 2004;350:1945–1952.
24. Cooper JS, Pajak TF, Forastiere AA, et al; Radiation Therapy Oncology Group 9501/Intergroup. Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. *N Engl J Med.* 2004;350:1937–1944.
25. Bernier J, Cooper JS, Pajak TF, et al. Defining risk levels in locally advanced head and neck cancers: a comparative analysis of concurrent postoperative radiation plus chemotherapy trials of the

EORTC (#22931) and RTOG (#9501). *Head Neck.* 2005;27: 843–850.
26. Weinstein GS, O'Malley BW Jr, Rinaldo A, Silver CE, Werner JA, Ferlito A. Understanding contraindications for transoral robotic surgery (TORS) for oropharyngeal cancer. *Eur Arch Otorhinolaryngol.* 2015;272:1551–1552.
27. Genden EM, Kotz T, Tong CC, et al. Transoral robotic resection and reconstruction for head and neck cancer. *Laryngoscope.* 2011;121:1668–1674.
28. Radiation Therapy Oncology Group. RTOG 1221 protocol information. http://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=1221. Accessed May 26, 2015.
29. ClinicalTrials.gov. Transoral surgery followed by low-dose or standard-dose radiation therapy with or without chemotherapy in treating patients with HPV positive stage III-IVA oropharyngeal cancer [ClinicalTrials.gov: NCT01898494]. https://clinicaltrials.gov/ct2/show/NCT01898494. Accessed January 12, 2016.