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Comparative effectiveness of primary radiotherapy versus surgery in elderly patients with locally advanced oropharyngeal squamous cell carcinoma

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ABSTRACT

Objectives: To determine the comparative effectiveness of primary radiotherapy (RT) and primary surgery (PS) for locally advanced oropharyngeal squamous cell carcinoma (OPSCC).
Materials and methods: Eligible individuals were patients in the SEER-Medicare registry diagnosed with locally advanced OPSCC between 2000 and 2011. Patients were categorized as receiving either primary RT ± chemotherapy, or PS ± adjuvant RT or chemoradiotherapy (CRT). Overall survival (OS) was analyzed using Cox multivariable analysis (MVA). Risks of gastrostomy dependence (GD), esophageal stricture (ES), and osteoradionecrosis (ORN) were analyzed using logistic regression.
Results: A total of 2754 patients (69% RT, 31% PS) were included in this cohort, with a median age of 72 years. Patients treated with RT, CRT and PS experienced 3-year OS outcomes of 36.1%, 52.8%, and 54.9%, respectively ($p < 0.001$). Increasing age, unmarried status, increasing comorbidity, lower income, base of tongue (BOT) site, higher stage, no prior PET, and RT alone (but not CRT) were associated with inferior OS. Independent predictors of GD at 6 months included black race, BOT site, advanced stage, and CRT. The risks of ORN and stricture were not associated with treatment modality. Concurrent chemotherapy improved OS with definitive RT but had no impact in adjuvant RT. Only cisplatin- and taxane-containing regimens improved OS, but all concurrent agents, including cetuximab, significantly worsened GD.
Conclusion: Local therapy decisions for locally advanced OPSCC must be individualized, with CRT increasing acute and chronic GD. The differential survival impact of concurrent chemotherapy in the definitive and adjuvant setting may be a consideration in decision-making.

Introduction

The prevalence of oropharyngeal squamous cell carcinoma (OPSCC) has increased dramatically, and it is now the most commonly diagnosed head and neck malignancy in the United States [1]. This increase, driven by human papillomavirus (HPV) infection, has been seen in elderly populations as well [2]. As radiotherapy and surgical techniques have improved, primary surgical therapy and radiation therapy are both viable treatment approaches for this disease. The opportunity to spare patients the toxicity of concurrent chemoradiotherapy (CRT) or even any adjuvant radiotherapy (RT) is the main benefit of surgery, whereas eliminating any immediate surgical risk or delayed surgical complication are strengths of definitive RT or CRT.

Outcome comparisons between upfront surgery and radiotherapy are generally small and all retrospective, as two prospective trials will not be completed for several years [3]. The general consensus from these studies is that survival outcomes are not significantly different [4,5], but the potential to minimize the exposure of patients to CRT and its complications may favor an initial surgical approach [6,7]. Yet there is a gap in comparing these two locoregional modalities in the elderly, which comprises a significant percentage of the afflicted population [8]. Given the well-known toxicities in delivering concurrent chemotherapy to older patients, the therapeutic ratios of these two treatments take on added importance.

In this study, we have used the Surveillance, Epidemiology, and End Results (SEER)-Medicare database to compare survival and toxicity

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outcomes in elderly patients with locally advanced OPC treated with upfront surgery versus definitive RT or CRT. We compared overall survival outcomes, as well as gastrostomy use and dependence, esophageal stricture, and osteonecrosis, in order to understand the therapeutic ratios of these two competing treatments. Moreover, we analyzed the differential importance of concurrent chemotherapy in the definitive and postoperative settings, including a focus on the impact of alternative chemotherapy regimens.

Methods

Data sources

This cohort was created from the Surveillance, Epidemiology and End Results (SEER)-Medicare database, which links health care claims for fee-for-service Medicare enrollees with patient demographic and tumor-specific data recorded by SEER cancer registries. The Medicare program provides health care benefits to 97% of the U.S. population aged 65 years or older, and approximately 94% of SEER patients 65 years or older have been successfully linked with their Medicare claims [9].

Cohort definition

Fig. 1 details the inclusion and exclusion characteristics that defined the cohort composition. Patients were aged 66 years or older and diagnosed with "regional" or "distant" squamous cell carcinoma of the oropharynx (Table 1) between the years 2000 and 2011, and Part A/B coverage was mandatory for 1 year prior diagnosis to 1 year following diagnosis. Because some locally advanced primary tumors were coded as "distant" historical stage in the SEER registry (e.g. extension to larynx/hypopharynx, mandible, extrinsic tongue musculature, other bone or hard palate), patients with this stage were included in the analysis. The first treatment (either surgery, RT, or chemotherapy) was required to have started within 6 months of diagnosis. Patients needed to receive either definitive surgery or definitive RT for inclusion.

Treatment assignments

Claims for at least 20 RT fractions were required for patients to have been coded as receiving curative-intent radiotherapy, within 12 weeks of starting treatment; shorter regimens may have been palliative in intent. Concurrent chemoradiotherapy was defined by a chemotherapy claim between 3 weeks prior to starting RT and the end of RT. Chemotherapy delivered prior to 3 weeks before RT was considered induction therapy, and these patients were excluded, since subsequent radiotherapy selects for favorable responders. Adjuvant RT was assigned after surgery if the first RT claim was present within 90 days of surgery, and adjuvant CRT was assigned if chemotherapy was administered between 3 weeks before RT to the last RT claim.

Patients who underwent a diagnostic tonsillectomy without neck dissection were classified as receiving primary RT. Diagnostic lymph node excisions were not considered as a primary surgery; only neck dissections were considered a curative-intent operation.

Chemotherapy agents were categorized as cisplatin, carboplatin-only, taxane-containing (including doublets with a platinum), cetuximab-only, and other.

Outcomes

Overall survival was calculated from the date of diagnosis to the date of death. All patients were analyzed for toxicity endpoints, with stage serving as a covariate. Gastrostomy use was evaluated at 3 time points: any, 6 months or longer, and 12 months or longer. Gastrostomy use required a claim for enteral nutrition from diagnosis to 3 months from the last treatment; patients who first used enteral feedings after that time may have had dysphagia from disease progression. The date of last use was the last claim for nutrition. The presence of a clinically relevant early esophageal stricture was defined as a dilation code within the first year of surviving patients. The presence of a clinically relevant bone complication was coded using the methodology of Beadle et al. [10] One year was chosen as the primary analysis for these latter two toxicities since subsequent procedures may be more likely due to disease progression. For gastrostomy dependence analyses at 6 and 12 months, the denominators were patients alive at 6 and 12 months, respectively.

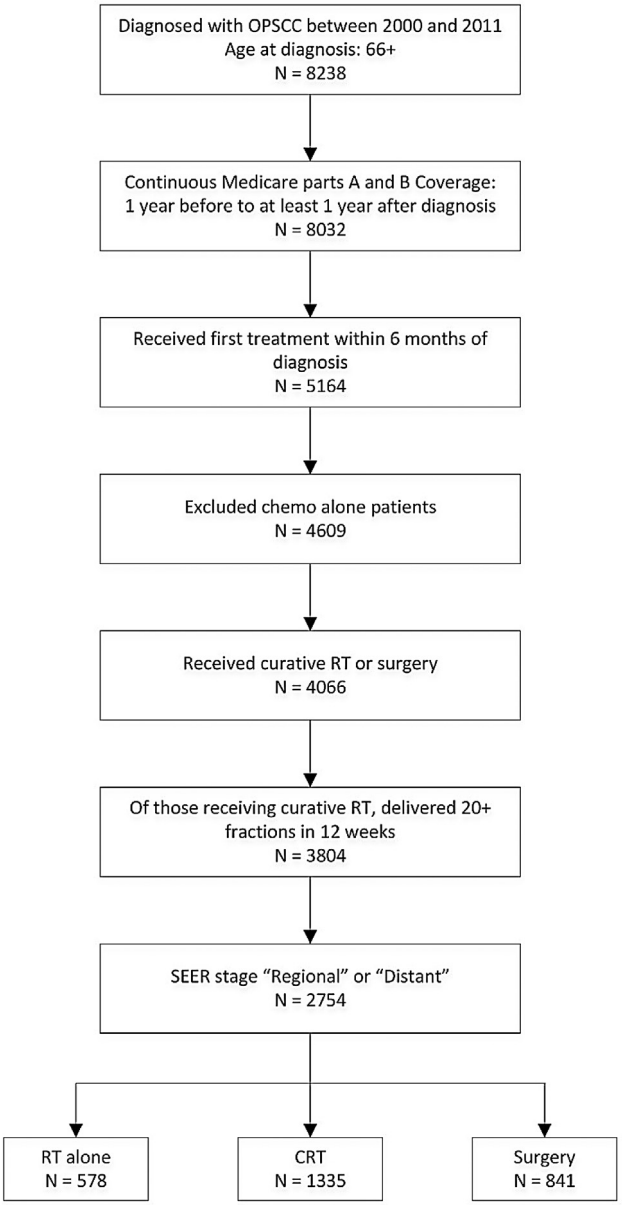


Fig. 1. Cohort definition.

Chemotherapy analyses

We performed several sensitivity analyses on the relative benefits and harms of chemotherapy in these two cohorts. First, an interaction term was placed in the multivariable model for overall survival to assess whether the primary therapy modality (i.e. RT or surgery) was an effect modifier of the impact of chemotherapy. Subset analyses were then performed in primary radiotherapy patients and in surgical patients

Table 1
Patient characteristics. Abbreviations: SE = standard error; CI = confidence interval; HS = high school; RT = radiotherapy; CRT = chemoradiotherapy; IMRT = intensity modulated radiation therapy. PET = positron emission tomography.

Characteristic	Entire cohort (n = 2754)	Primary radiotherapy (n = 1913)	Primary surgery (n = 841)	P value
Patient characteristics				
Age (median, IQR)	72, 69–77	73, 69–78	71, 68–76	< 0.001
Age (quartile)				< 0.001
≤68	665 (24%)	434 (23%)	231 (27%)	
69–72	750 (27%)	511 (27%)	239 (28%)	
73–77	678 (25%)	470 (25%)	208 (25%)	
≥78	661 (24%)	498 (26%)	163 (19%)	
Gender				0.522
Female	776 (28%)	546 (29%)	230 (27%)	
Male	1978 (72%)	1367 (71%)	611 (73%)	
Race				0.107
White	2429 (88%)	1682 (88%)	747 (89%)	
Black	214 (8%)	160 (8%)	54 (6%)	
Other	111 (4%)	71 (4%)	40 (5%)	
Marital status				0.184
Married	1490 (54%)	1019 (53%)	471 (56%)	
Other	1264 (46%)	894 (47%)	370 (44%)	
Charlson-Deyo comorbidity				0.113
0	1392 (51%)	965 (50%)	427 (51%)	
1	655 (24%)	474 (25%)	181 (22%)	
2	244 (9%)	185 (10%)	59 (7%)	
3–7	198 (7%)	146 (8%)	52 (6%)	
Tobacco exposure				0.821
Yes	1669 (61%)	1162 (61%)	507 (60%)	
No	1085 (39%)	751 (39%)	334 (40%)	
SEER region				< 0.001
Northeast	499 (18%)	321 (17%)	178 (21%)	
South	779 (28%)	585 (31%)	194 (23%)	
Midwest	279 (10%)	181 (9%)	98 (12%)	
West	1197 (43%)	826 (43%)	371 (44%)	
Median census tract income				0.826
≤25%	217 (8%)	156 (8%)	61(7%)	
25–50%	1404 (51%)	978 (51%)	426 (51%)	
50–75%	750 (27%)	518 (27%)	232 (28%)	
≥75%	360 (14%)	246 (13%)	114 (14%)	
Area of residence				0.119
Metropolitan	2292 (83%)	1578 (82%)	714 (85%)	
Non-metropolitan	462 (17%)	335 (18%)	127 (15%)	
% HS diploma				0.023
≤70%	562 (20%)	405 (21%)	157 (19%)	
70–85%	902 (33%)	643 (34%)	259 (31%)	
85–90%	475 (17%)	305 (16%)	170 (20%)	
≥90%	792 (29%)	545 (28%)	247 (29%)	
Disease characteristics				
Primary site				0.391
Tonsil	933 (34%)	633 (33%)	300 (36%)	
Base of tongue	1297 (47%)	915 (48%)	382 (45%)	
Other	524 (19%)	365 (19%)	159 (19%)	
Historic stage				0.807
Regional	2285 (83%)	1585 (83%)	700 (83%)	
Distant	469 (17%)	328 (17%)	141 (17%)	
Grade				< 0.001
I	140 (5%)	96 (5%)	44 (5%)	
II	955 (35%)	642 (34%)	313 (37%)	
III	1047 (38%)	681 (36%)	366 (44%)	
Other	612 (22%)	494 (26%)	118 (14%)	
Treatment characteristics				
Primary RT				
RT alone	578 (30%)	578 (30%)	0	
Concurrent CRT	1335 (70%)	1335 (70%)	0	
Primary surgery				
Surgery only	390 (47%)	0	390 (46%)	
Adjuvant RT	254 (30%)	0	254 (30%)	
Adjuvant CRT	197 (23%)	0	197 (23%)	
Chemotherapy				< 0.001
Cisplatin	596 (39%)	515 (39%)	81 (41%)	
Carboplatin-only	108 (7%)	95 (7%)	13 (12%)	
Taxane-containing	322 (21%)	286 (21%)	36 (11%)	
Cetuximab-only	365 (24%)	331 (25%)	34 (17%)	
Other	141 (9%)	108 (8%)	33 (17%)	
RT modality				0.068
2D/3D	1689 (71%)	1351 (71%)	338 (75%)	
IMRT	675 (29%)	562 (29%)	113 (25%)	
PET use				< 0.001
Yes	1583 (57%)	1207 (63%)	376 (45%)	
No	1171 (43%)	706 (37%)	465 (55%)	

who received adjuvant radiotherapy.

Statistical methods

Summary statistics for patient characteristics were reported using medians and interquartile ranges (IQR) for continuous variables, and using counts and percentages for categorical variables. Patient characteristics, disease characteristics, and treatment characteristics were compared between primary radiotherapy and primary surgery using the χ^2-test. The overall survival was estimated using the Kaplan-Meier method. Median survival time and 95% confidence intervals (CI) were reported. Univariable and multivariable Cox regression analyses were used to assess the association between the overall survival and patient, disease, treatment characteristics. Variables with a univariable p-value of 0.2 or less were entered in a backward selection algorithm to yield the parsimonious multivariable regression model. The assumption for proportional hazards was evaluated by using scaled Schoenfeld residuals. Hazard ratios and 95% confidence intervals (CI) were reported. Univariable logistic regression and multivariable logistic regression with the backward selection algorithm were used to identify the predictors for toxicity endpoints at 1 and 3 years. Odds ratios and 95% confidence intervals (CI) were reported. Two-sided p-values were reported and a p-value less than 0.05 was considered statistically significant. All analyses were conducted using SAS version 9.4 (Cary, NC).

Results

Patient and treatment characteristics

Patient characteristics (n = 2754) are shown in Table 1. The median age of the cohort was 72 years, and the majority (72%) of patients were male. Nearly 88% of the individuals were white. There was a smoking-related claim in 61% of all patients. The historic stage was regional and distant in 83%, and 17%, respectively.

Primary radiotherapy was used in 69% of all patients; out of these individuals, radiation alone and concurrent chemotherapy were implemented in 30% and 70% of the group, respectively. Patients treated with radiotherapy alone were slightly but significantly more likely to have higher Charlson-Deyo comorbidities scores (50% vs 56%, 27% vs. 27%, 14% vs 9%, and 9% vs. 8% with scores of 0, 1, 2, and 3–7, for RT vs. CRT, respectively, p = 0.022). These individuals were also older (median 76, IQR 70–81 years) than those treated with CRT (median 71, IQR 68–76 years, p < 0.001). Patients older than 72 years (median) were less likely to receive any concurrent systemic therapy (44% vs. 53%, p < 0.001), and of those patients receiving systemic treatment, older patients were more likely to receive cetuximab (34% vs. 18%, OR

Table 2
Overall survival results. A hazard ratio over 1 means increased mortality. Abbreviations: SE = standard error; CI = confidence interval; HS = high school; RT = radiotherapy; CRT = chemoradiotherapy; IMRT = intensity modulated radiation therapy.

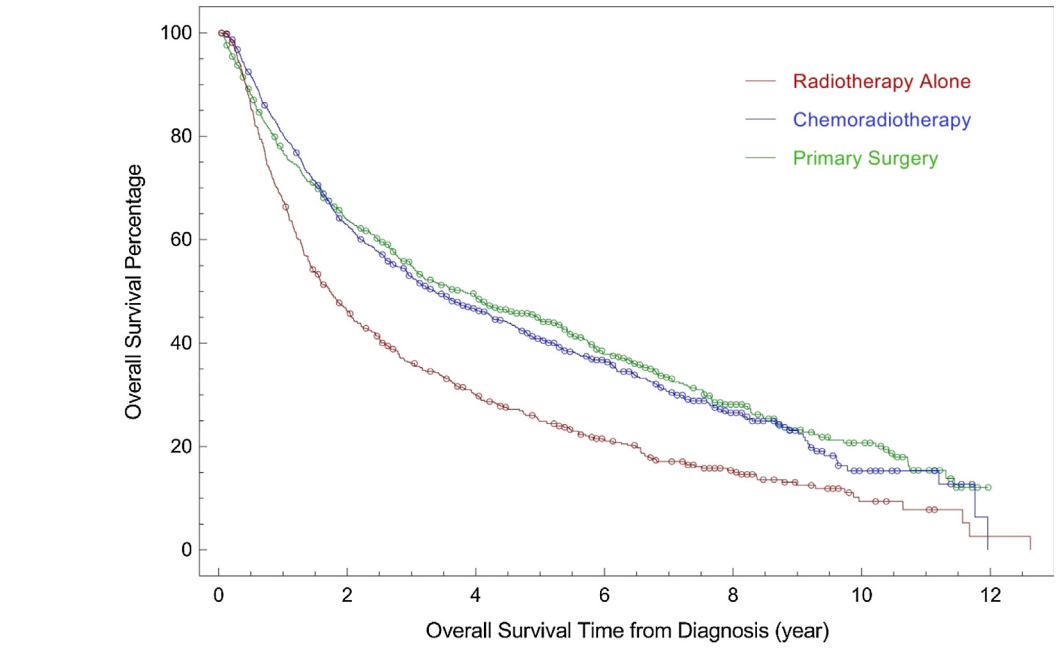
Characteristic	3-year survival % (SE)	Univariable Analysis (95% CI)	Multivariable analysis	P value
Patient characteristics				
Age (quartile)				< 0.001
≤68	62.9 (2.0)	Reference	Reference	
69–72	56.5 (2.0)	1.24 (1.07–1.44)	1.24 (1.06–1.46)	
73–77	48.2 (2.1)	1.56 (1.35–1.80)	1.50 (1.28–1.75)	
≥78	31.3 (1.9)	2.49 (2.16–2.87)	2.03 (1.74–2.38)	
Gender				
Male	51.1 (1.2)	Reference		
Female	46.2 (1.9)	1.21 (1.09–1.34)		
Race				
White	51.3 (1.1)	Reference		
Black	36.0 (3.5)	1.43 (1.21–1.69)		
Other	42.6 (5.2)	1.15 (0.89–1.48)		
Marital status				< 0.001
Married	55.3 (1.4)	Reference	Reference	
Other	43.4 (1.5)	1.47 (1.33–1.61)	1.32 (1.18–1.46)	
Charlson-Deyo comorbidity				< 0.001
0	56.8 (1.4)	Reference	Reference	
1	44.7 (2.1)	1.54 (1.37–1.73)	1.51 (1.34–1.71)	
2	35.0 (3.4)	1.81 (1.53–2.14)	1.63 (1.37–1.93)	
3–7	25.6 (3.5)	2.34 (1.96–2.79)	1.93 (1.61–2.31)	
Tobacco exposure				
No	50.0 (1.6)	Reference		
Yes	50.5 (1.3)	0.99 (0.90–1.10)		
SEER region				
West	51.0 (1.6)	Reference		
Northeast	50.6 (2.4)	1.07 (0.93–1.22)		
South	48.5 (1.9)	1.08 (0.96–1.21)		
Midwest	45.8 (3.2)	1.15 (0.98–1.36)		
Median census tract income				0.018
≥75%	58.8 (2.8)	Reference	Reference	
50–75%	51.5 (2.0)	1.24 (1.04–1.47)	1.02 (0.86–1.22)	
25–50%	48.5 (1.4)	1.27 (1.08–1.48)	1.10 (0.94–1.30)	
≤25%	35.8 (3.4)	1.75 (1.42–2.16)	1.37 (1.09–1.72)	
Area of residence				
Metropolitan	49.6 (1.1)	Reference		
Non-metropolitan	50.2 (2.5)	0.97 (0.85–1.11)		
% HS diploma				
≥90%	53.8 (1.9)	Reference		
85–90%	51.8 (2.5)	1.07 (0.92–1.24)		
70–85%	47.6 (1.8)	1.12 (0.99–1.27)		
≤70%	45.1 (2.2)	1.26 (1.10–1.45)		
Disease characteristics				
Primary site				< 0.001
Tonsil	55.6 (1.8)	Reference	Reference	
Base of tongue	50.3 (1.5)	1.16 (1.04–1.29)	1.19 (1.06–1.34)	
Other	38.0 (2.3)	1.60 (1.40–1.82)	1.43 (1.24–1.65)	
Grade				
I	44.4 (4.4)	Reference		
II	46.7 (1.7)	0.95 (0.77–1.18)		
III	51.1 (1.7)	0.81 (0.66–1.01)		
Historic stage				< 0.001
Regional	53.1 (1.1)	Reference	Reference	
Distant	33.4 (2.4)	1.70 (1.50–1.92)	1.77 (1.55–2.02)	
Treatment characteristics				
Treatment				0.008
Surgery + C/RT	54.9 (1.8)	Reference	Reference	
RT alone	36.1 (2.1)	1.59 (1.40–1.80)	1.24 (1.08–1.42)	
CRT	52.8 (1.5)	1.03 (0.92–1.15)	1.06 (0.94–1.20)	
RT modality				
2D/3D	48.7 (1.3)	Reference		
IMRT	55.9 (2.2)	0.82 (0.72–0.93)		
PET use				< 0.001
Yes	59.5 (1.4)	Reference	Reference	
No	37.8 (1.5)	1.68 (1.52–1.85)	1.62 (1.46–1.81)	

2.41 (95% CI 1.87–3.11, p < 0.001). Of the patients treated with initial surgery, 47%, 30%, and 23% received no adjuvant therapy, adjuvant radiotherapy, and adjuvant chemoradiotherapy, respectively.

Of the 841 patients who underwent surgery, 371 (44%) underwent primary site surgery plus neck dissection, 297 (35%) received primary site surgery only, and 173 (21%) underwent neck dissection only.

Overall survival

The median follow-up duration for surviving patients was 3.3 years.



Number at risk

Year	0	1	2	3	4	5
Radiotherapy Alone	578	375	248	183	143	109
Chemoradiotherapy	1335	963	650	473	351	253
Primary Surgery	841	587	448	351	281	219

Fig. 2. Overall survival.

Table 2 shows the univariable and adjusted predictors of overall survival. Younger age, married status, lower comorbidity score, higher census tract income, tonsil site, regional (versus distant) stage, PET use, and treatment type ($p < 0.001$) were all associated with improved survival. Using primary surgery as the reference, radiation alone was significantly related to inferior survival (HR 1.24, 95% CI 1.08–1.42), whereas there was no difference between CRT and surgery (HR 1.06, 95% CI 0.94–1.20). Survival curves are shown in Fig. 2.

Sensitivity analyses on survival

In the first sensitivity analysis, we excluded patients from the surgical cohort who underwent a non-transoral surgery (n = 172). The results were essentially identical. We also performed a subset analysis of locally advanced patients treated with RT, CRT or primary site surgery plus neck dissection. In this regression, treatment type was again associated with overall survival ($p = 0.035$), but the distinction was between surgery and RT (HR 1.20, 95% CI 1.01–1.42) and not surgery and CRT (HR 1.02, 95% CI 0.87–1.20).

Gastrostomy dependence

Enteral feeding was evaluated in 3 ways: any enteral feeding, gastrostomy use past 6 months from the end of last treatment, and gastrostomy use past 12 months from the end of last treatment. Table 3 shows the multivariable predictors of any gastrostomy use. Among all patients, 43% (n = 1182) of individuals used enteral feeding at some point in the first year of treatment. Treatment type was associated with any gastrostomy use ($p < 0.0001$), with chemoradiotherapy significantly increasing the risk of enteral feedings (OR 2.44, 95% CI 2.04–2.93) over primary surgery; patients treated with radiotherapy alone were not significantly more likely to require a gastrostomy (OR 0.96, 95% CI 0.76–1.21).

A total of 21% (n = 632) of all patients were gastrostomy-dependent past 6 months (Table 4). The multivariable predictors of medium-term gastrostomy dependence were similar to any dependence, including treatment ($p < 0.001$), except radiation alone was almost significantly improved in comparison to primary surgery (OR 0.76, 95% CI 0.55–1.03).

Finally, 20% (n = 406) of surviving patients were gastrostomy-dependent at least one year from the end of treatment. Multivariable regression disclosed several variables predictive of long-term gastrostomy dependence, including older age, non-married status, base of tongue primary site, and advanced stage. Treatment with CRT (OR 1.66, 95% CI 1.28–2.15) but not RT alone (OR 0.84, 95% CI 0.58–1.22) was strongly associated with gastrostomy-dependence at one year in comparison to surgery.

Esophageal dilation

The crude risk of esophageal dilation within one year of the end of treatment was 4.3% (n = 88) for surviving patients. On multivariable analysis, only region (Northeast, South, and Midwest all significantly greater than West) were associated with increased risk of stricture. Treatment type was not associated with this toxicity. Among 3 year survivors, chemoradiotherapy was actually protective on multivariable analysis, with the OR 0.62 (95% CI 0.43–0.91) in comparison to primary surgery ($p = 0.0042$ for the 3-way comparison).

Bone toxicity

Ninety-seven surviving patients (4.7%) experienced a bone toxicity within the first year of finishing radiotherapy. No patients treated with surgery alone developed a bone toxicity. In restricting the analysis to patients who received radiation therapy, there were no significant predictors of osteonecrosis on multivariable analysis. There was also no relationship between treatment and osteonecrosis when restricting the analysis to 3 years survivors.

Table 3
Use of gastrostomy tube at any point. Abbreviations CI = confidence interval; HS = high school; RT = radiotherapy; CRT = chemoradiotherapy; IMRT = intensity modulated radiation therapy.

Characteristic	Gastrostomy use %	Univariable analysis (95% CI)	Multivariable analysis	P value
Patient characteristics				
Age (quartile)				
≤68	41.5	Reference		
69–72	44.8	1.14 (0.93–1.413)		
73–77	44.5	1.13 (0.91–1.405)		
≥78	40.5	0.96 (0.77–1.196)		
Gender				
Male	43.6	Reference		
Female	41.2	0.91 (0.77–1.075)		
Race				
White	43.3	Reference		
Black	43.5	1.01 (0.76–1.334)		
Other	33.3	0.65 (0.44–0.979)		
Marital status				
Married	45.4	Reference		
Other	40.0	0.80 (0.69–0.936)		
Charlson-Deyo comorbidity				
0	45.2	Reference		
1	46.3	1.04 (0.87–1.258)		
2	43.3	0.93 (0.71–1.226)		
3–7	36.9	0.71 (0.52–0.963)		
Tobacco exposure				< 0.001
No	38.3	Reference	Reference	
Yes	45.9	1.36 (1.17–1.594)	1.34 (1.14–1.57)	
SEER region				
West	42.0	Reference		
Northeast	40.7	0.95 (0.77–1.170)		
South	44.7	1.11 (0.93–1.336)		
Midwest	45.9	1.17 (0.90–1.520)		
Median census tract income				
≥75%	41.1	Reference		
50–75%	42.1	1.04 (0.81–1.346)		
25–50%	43.5	1.10 (0.87–1.396)		
≤25%	46.1	1.22 (0.87–1.719)		
Area of residence				
Metropolitan	42.5	Reference		
Non-metropolitan	45.0	1.11 (0.91–1.355)		
% HS diploma				
≥90%	42.4	Reference		
85–90%	41.9	0.98 (0.78–1.232		
70–85%	44.2	1.08 (0.89–1.305)		
≤70%	42.9	1.02 (0.82–1.268)		
Disease characteristics				
Primary site				< 0.001
Tonsil	37.8	Reference	Reference	
Base of tongue	48.7	1.56 (1.32–1.853)	1.51 (1.26–1.80)	
Other	37.6	0.99 (0.79–1.234)	1.00 (0.80–1.26)	
Grade				
I	42.9	Reference		
II	45.2	1.10 (0.77–1.576)		
III	41.7	0.96 (0.67–1.364)		
Historic stage				
Regional	42.7	Reference		
Distant	44.1	1.06 (0.87–1.297)		
Treatment characteristics				
Treatment				< 0.001
Surgery and RT	32.6	Reference	Reference	
RT alone	30.8	0.92 (0.73–1.157)	0.96 (0.76–1.21)	
CRT	54.7	2.50 (2.09–2.989)	2.44 (2.04–2.93)	
RT modality				
2D/3D	45.5	Reference		
IMRT	48.2	1.11 (0.93–1.329)		
PET use				
Yes	48.4	Reference		
No	35.5	0.59 (0.50–0.686)		

Chemotherapy

In a subset analysis restricted to patients receiving radiotherapy, with concurrent chemotherapy as an independent variable and an interaction term for primary therapy*chemotherapy, the interaction term was significant (HR 0.70, p = 0.03). This result means that the impact of concurrent chemotherapy is significantly different in the definitive and adjuvant setting: it is beneficial in primary RT patients but detrimental in primary surgery patients (adjusted HR 1.28, 95% CI 0.95–1.71). Indeed, when just analyzing patients who received surgery

Table 4
Use of gastrostomy tube at 6 months. Abbreviations CI = confidence interval; HS = high school; RT = radiotherapy; CRT = chemoradiotherapy; IMRT = intensity modulated radiation therapy.

Characteristic	Gastrostomy use %	Univariable analysis (95% CI)	Multivariable analysis	P value
Patient characteristics				
Age (quartile)				0.027
≤68	26.2	Reference	Reference	
69–72	24.7	0.92 (0.71–1.20)	0.92 (0.70–1.20)	
73–77	30.5	1.24 (0.95–1.61)	1.32 (1.01–1.73)	
≥78	27.2	1.05 (0.80–1.39)	1.21 (0.91–1.62)	
Gender				
Male	26.5	Reference		
Female	28.6	1.11 (0.91–1.37)		
Race				0.046
White	26.6	Reference	Reference	
Black	34.7	1.47 (1.05–2.04)	1.48 (1.049–2.08)	
Other	21.4	0.75 (0.44–1.28)	0.77 (0.446–1.32)	
Marital status				
Married	27.4	Reference		
Other	26.6	0.96 (0.80–1.16)		
Charlson-Deyo comorbidity				
0	26.9	Reference		
1	29.8	1.15 (0.92–1.45)		
2	31.7	1.26 (0.90–1.76)		
3–7	26.1	0.96 (0.64–1.43)		
Tobacco exposure				
No	25.4	Reference		
Yes	28.1	1.15 (0.94–1.39)		
SEER region				
West	26.3	Reference		
Northeast	26.6	1.02 (0.78–1.32)		
South	27.2	1.04 (0.83–1.31)		
Midwest	30.5	1.23 (0.90–1.69)		
Median census tract income				
≥75%	24.9	Reference		
50–75%	26.7	1.10 (0.80–1.51)		
25–50%	27.8	1.16 (0.87–1.56)		
≤25%	28.9	1.23 (0.80–1.88)		
Area of residence				
Metropolitan	27.0	Reference		
Non-metropolitan	27.5	1.03 (0.80–1.32)		
% HS diploma				
≥90%	27.5	Reference		
85–90%	26.9	0.97 (0.73–1.29)		
70–85%	26.1	0.93 (0.73–1.18)		
≤70%	29.0	1.08 (0.82–1.41)		
Disease characteristics				
Primary site				< 0.001
Tonsil	22.3	Reference	Reference	
Base of tongue	31.7	1.62 (1.31–2.01)	1.52 (1.22–1.89)	
Other	24.1	1.11 (0.83–1.47)	1.11 (0.83–1.48)	
Grade				
I	27.6	Reference		
II	28.8	1.06 (0.67–1.67)		
III	27.4	0.99 (0.63–1.56)		
Historic stage				0.010
Regional	25.7	Reference	Reference	
Distant	34.3	1.51 (1.18–1.93)	1.39 (1.08–1.80)	
Treatment characteristics				
Treatment				< 0.001
Surgery and RT	21.4	Reference	Reference	
RT alone	17.8	0.80 (0.59–1.08)	0.76 (0.55–1.03)	
CRT	34.2	1.91 (1.53–2.39)	1.83 (1.46–2.30)	
RT modality				
2D/3D	28.4	Reference		
IMRT	29.1	1.04 (0.83–1.29)		
PET use				
Yes	28.5	Reference		
No	24.9	0.83 (0.69–1.01)		

and adjuvant RT or adjuvant CRT, there was no association between chemotherapy and survival (multivariable HR 1.1, 95% CI 0.84–1.52, p = 0.42). In contrast, among patients treated with primary radiotherapy, the use of chemotherapy was clearly associated with improved survival (HR 0.86, 95% CI 0.75–0.98, p = 0.03).

When categorizing chemotherapy into specific agents among patients treated with primary radiotherapy, a significant survival benefit (Table 5) over radiotherapy alone was restricted to treatment with cisplatin (HR 0.78, 95% CI 0.65–0.93) or a taxane-containing regimen (HR 0.77, 95% CI 0.64–0.94) (Table 5). In fact, there was a trend for

Table 5
Impact of chemotherapy agent and outcome for patients receiving chemoradiotherapy. A hazard ratio over 1 means increased mortality. Abbreviations: AHR = adjusted hazard ratio; AOR = adjusted odds ratio.

Chemotherapy	3-Year Overall Survival		Any Gastrostomy		6-Month Gastrostomy		Stricture	
	%	AHR	%	AOR	%	AOR	%	AOR
None	36.1	Reference	30.8	Reference	17.8	Reference	11.9	Reference
Cisplatin	59.8	0.78 (0.65–0.93)	56.5	2.74 (2.13–3.52)	34.3	2.58 (1.86–3.60)	7.4	0.61 (0.40–0.92)
Carboplatin-only	44.7	0.79 (0.59–1.06)	52.6	2.35 (1.51–3.66)	32.1	2.07 (1.20–3.59)	13.7	1.26 (0.66–2.39)
Taxane-containing	59.2	0.77 (0.64–0.94)	57.3	2.86 (2.12–3.84)	37.9	2.89 (2.01–4.16)	6.6	0.50 (0.29–0.85)
Cetuximab-only	39.9	1.16 (0.95–1.40)	51.7	2.27 (1.72–3.01)	30.3	1.95 (1.35–2.82)	7.6	0.63 (0.39–1.02)
Other	48.3	0.82 (0.64–1.06)	50.0	2.16 (1.42–3.29)	37.0	2.96 (1.80–4.87)	11.1	0.89 (0.46–1.71)

increasing mortality with use of cetuximab (HR 1.16, 95% CI 0.95–1.40). On the other hand, all concurrent regimens increased the risk of gastrostomy by over a factor of 2, which was significant at 6 months as well.

Discussion

In this study, we have shown that in elderly individuals with locally advanced OPSCC, initial surgery is superior to RT alone but not CRT. Given that CRT is considered the standard-of-care in higher-stage disease [11], these findings confirm the absence of a significant survival difference between the standardly recommended surgical- and radiotherapy-based treatments for this condition [11,12]. Two literature reviews have suggested similar results [6,7], and the present study adds convincing, additional population-based data supporting this conclusion, despite a significant bias favoring primary operative therapy, including both selection bias for surgical candidacy and stage migration for more accurately staging surgical patients.

In contrast, the late toxicity profiles differed by primary treatment modality. In particular, patients treated with definitive CRT experienced a significantly greater (and clinically meaningful) risk of any, 6-month, and 12-month gastrostomy dependence in comparison to those treated with RT alone or initial surgery. Planning with IMRT has improved dramatically since the time of this study, and modern dysphagia-avoidance based planning may minimize the need for enteral support in patients treated today; of course, such improvements would be expected in the RT alone and postoperative settings as well. Nevertheless, dysphagia and chewing, in addition to xerostomia, dominate the chronic toxicity profile in patients treated for OPC [13]. Thus, while it is critical to recognize that operative patients are often selected for their lower volume, resectable disease as well as their potential for superior functional status and recovery, these data support the contention that avoiding concurrent CRT in this population will substantially improve their dysphagia.

On the other hand, treatment modality was not associated with the need for an additional procedure to treat osteonecrosis, either at 1 or 3 years. This result does strongly suggest that differences in radiation dose with definitive versus adjuvant therapy either do not influence these complications, or the reduced dose is counteracted by the additional risk of surgical intervention. In addition, there was actually an increased risk of esophageal dilation among patients treated with primary surgery in comparison to CRT. Although this result may reflect a decreased interest in dilation among patients chronically PEG dependent, it does highlight a potentially increased late effect of primary surgical therapy. However, since osteonecrosis and esophageal stricture can both develop many years after radiotherapy [14], additional follow-up time may be needed to properly address this question.

In a unique and potentially clinically meaningful finding, we have also shown that the impact of chemotherapy depends on whether the patient is treated with primary versus adjuvant radiotherapy. In the former case, concurrent chemotherapy was associated with a significant survival advantage, consistent with multiple randomized studies [11]. In contrast, postoperative CRT did not add improve survival in comparison to adjuvant radiotherapy alone, suggesting surgery may be preferable in operable patients who may poorly tolerate concurrent chemotherapy. This result is hypothesis-generating, especially since information on margin status and other high-risk features was not available. On one hand, this difference may simply reflect the fact that the randomized data show a more questionable benefit to concurrent chemotherapy in the adjuvant setting [15]; on the other hand, one may argue that the risks of postoperative CRT are particularly pronounced in the elderly population, counterbalancing a smaller potential oncologic gain from the more intensive therapy.

This analysis has also shown that while all concurrent drugs significant increased the risk of gastrostomy-dependence, only cisplatin and taxane-containing regimens led to a survival benefit. Carboplatin was not associated with improved survival, and most notably, cetuximab appeared to impair survival. This latter result confirms a similar finding on the adverse effect of the drug in elderly patients on the original Bonner trial [16], strongly arguing against its use in this population.

Finally, it is also worth mentioning the potent improvement in overall survival (absolute difference over 20%) among patients staged with PET, a result that was maintained on multivariable regression. There are several possible explanations for this result, including the increased detection of occult metastatic disease, thus reducing the risk of local therapy in a patient with disseminated disease; stage migration from PET use has been seen in other disease sites [17]. The imaging information may have also facilitated superior local therapy through better radiotherapy targeting or even surgical planning. Finally, the use of PET may be a general marker of higher quality care, which could have improved survival through mechanisms not otherwise characterized.

Claims-based studies suffer from several well-known limitations, and this analysis is no exception. While the analysis did control for smoking claims, the database does not include information on HPV or p16 status, and therefore an imbalance between treatment modalities may have confounded the results. The study only applies to elderly patients, and whether the same result would be seen in a younger cohort is unknown. This report is a retrospective analysis, and there is significant selection bias in which patients received initial surgical versus radiotherapeutic treatment. Because operative patients tend to be healthier with lower-volume disease, both survival and functional outcomes would be expected to be better. Similarly, the survival decrement seen in patients who received radiotherapy alone may partially relate to comorbid conditions that prevented the patient from receiving concurrent chemotherapy.

In addition, the SEER-Medicare database does not provide information on recurrence patterns, so one cannot know whether locoregional control is superior with one treatment approach. Also, while we determined claims-based toxicities, ultimately patient-reported outcomes are the most important functional metric. Enteral feeding is only one measure of dysphagia, and does not include other aspects of swallowing that may be different in the two primary treatment

modalities. Chronic pain, xerostomia, trismus, and neck fibrosis are late complications of head and neck locoregional therapy that are simply not evaluable in SEER-Medicare.

Ultimately, prospective randomized trials are necessary to formally compare primary surgery with radiotherapy in OPC; two such trials are accruing patients in early T-category disease [3], and hopefully these studies will help draw final conclusions on the efficacy and toxicity of these dueling therapies. In the meantime, this paper represents one of the largest comparisons between surgery and RT in elderly patients treated for OPSCC, and our results support the use of either primary modality in the curative treatment of this disease. Patients should be counseled on the balance between immediate and late surgical morbidities with the acute and chronic toxicities of primary radiotherapy, with chronic gastrostomy use as the most obvious differentiator.

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Conflict of interest

No author has any conflict of interest.

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