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Treatment selection in oropharyngeal cancer: a Surveillance, Epidemiology, and End Results (SEER) patterns of care analysis

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Abstract

Purpose—Treatment for oropharyngeal cancer (OPC) has changed over the past two decades under multiple influences. We provide a population-based description of the application of radiotherapy, surgery, and chemotherapy to OPC in 1997, 2004 and 2009.

Methods—The National Cancer Institute’s Patterns of Care study for OPC included multiple variables not available in the public-use dataset. We identified factors correlating with selection of primary surgery versus radiotherapy with or without chemotherapy (RTC) and analyzed predictors of all-cause mortality. We estimated the frequency of human papillomavirus (HPV) testing.

Results—RTC was more common in 2009 than in 1997, and was more commonly applied to Stage IV cases. However, RTC was not an independent risk factor for mortality compared with surgery. HPV status was known in 14% of patients in 2009.

Conclusions—RTC is the most common treatment for OPC, but it may not provide the best outcomes. HPV testing was uncommon in 2009.

Keywords

oropharyngeal neoplasm; radiotherapy; chemoradiotherapy; surgery; human papillomavirus

Introduction

Oropharyngeal cancer (OPC) has changed dramatically over recent years. While alcohol [1] and tobacco [2] remain risk factors of OPC, there has been a significant increase in disease incidence which has been associated with human papillomavirus (HPV) [3, 4]. The increase of HPV-related OPC potentially has significant implications for treatment and selection survival outcomes.

Both surgery, with or without adjuvant radiotherapy (RT), and nonsurgical treatment, RT with or without chemotherapy, have been utilized and advocated [5–7], though to date there

are no high-quality studies providing a direct comparison of these treatment approaches. Previous studies have demonstrated that RT alone [8] and RT plus chemotherapy [9] confer effective locoregional tumor control and survival. For example, Denis et al. reported that RT plus chemotherapy may be more effective than RT alone in the setting of advanced stage tumors. However, both RT alone and RT plus chemotherapy have been associated with long-term complications such as dysphagia and pharyngeal strictures [10, 11]. The more recent introduction of transoral surgical strategies has been temporally associated with an upswing in the proportion of patients receiving primary surgery [12].

These recent countercurrents have not been measured with population-based data. The details of treatment selection are not described with population basis for patients at all ages. The purpose of this study was to examine trends in OPC treatment selection for surgery vs. RT with or without chemotherapy (RTC), and differences by treatment setting across the US population using Surveillance, Epidemiology, and End Results (SEER) Patterns of Care (POC) data. We also describe patients with known HPV status in order to determine which characteristics are associated with receipt of HPV testing.

Methods

This study is based on the National Cancer Institute's SEER POC data for head and neck cancer. Those data were collected for cases incident in 1997, 2004 and 2009. SEER is a population-based cancer registry program which collects demographic, tumor and some treatment information and is generally representative of the U.S. cancer patient population [13]. SEER POC studies entail the collection of additional information not contained in public-use SEER records on a sample of patients with select cancers from participating SEER registries such as systemic therapy regimens, co-morbidities, physician residency training status and information about the facility where patient received treatment. Non-Hispanic blacks, Hispanics, Asian/Pacific Islanders and American Indians/Native Alaskans are over-sampled to provide more stable estimates for analyses examining race/ethnicity. American Joint Committee on Cancer (AJCC) 6th Ed. [14] staging data were available for the 2004 and 2009 cohorts. For the 1997 cohort, SEER extent-of-disease variables describing tumor size, extension, and nodal status were used to derive AJCC 6th Ed. [14] stage by an algorithm composed with consultation from SEER and AJCC cancer registrars (B. Matt and D. Gress, personal communications). Extent of disease coding rules in use during 1988–2003 by cancer registries, including SEER, classified supraclavicular nodes as sites of distant metastasis rather than as regional nodal disease as they would be considered by AJCC 6th Ed. [14] rules. Our algorithm was consistent with the latter. Cases were followed actively by the SEER program until death, loss to follow up, or December 31, 2011.

Treatment variables included receipt of surgical treatment, RT, and chemotherapy. Those who received surgery alone or surgery and RT (with or without chemotherapy) were classified as having “primary surgery,” whereas patients who had RT only (with or without chemotherapy) were classified as having “RTC.”

OPC cases were identified using the International Classification of Diseases of Oncology, Third Edition (ICD-O-3) primary site codes 19, 24, 51-52, 90-91, 98-103, 108-109, 140, 142 and 148 and malignant squamous neoplasms with histology codes between 8050 and 8089. A total of 872 OPC patients were retrieved from SEER POC data. Patients whose treatment status was unknown (n=37) were excluded from the analysis. Furthermore, patients who received either no cancer-directed therapy or chemotherapy only (n =48) were excluded from the bivariate analysis and multivariable models because these approaches are primarily used in the palliative setting for oropharyngeal cancer, and the focus in this study was on selection of curative treatments.

Statistical analyses were performed using SAS statistical software (version 9.4). Sample weights were used to account for oversampling in all the analyses using PROC SURVEY. The sample weights were derived from the inverse of the sampling proportion in each sample strata; sample strata were characterized by age, race, cancer stage and SEER registry. Bivariate analyses were done to determine the association between demographic, tumor and hospital characteristics with treatment selection. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using multivariable logistic regression to predict receiving primary surgery versus RTC. Multivariable Cox proportional hazards regression was used to determine factors associated with all cause survival. In both multivariable models, purposeful selection by backward elimination was used to select variables to include in the model with a p-value of 0.2 or less required to stay in the model[15]; the base model for logistic regression included age, race, gender, marital status and Charlson comorbidity index (a broad measure of multisystem comorbidity which has been validated as a predictor of survival outcome, including for head and neck cancer[16, 17]) while the base model for the Cox proportional model included age, race, gender and hospital size (measured by number of inpatient beds). Given current treatment controversies related to primary treatment of advanced stage OPC, we also analyzed the subset of patients with T4 stage OPC to examine the specific patterns of care and survival in that select population.

Results

We identified 872 patients in the cohort, of whom 37 were excluded due to unknown treatment status (Figure 1). There were 125 patients in 1997, 375 in 2004, and 335 in 2009 (Table 1). There were no statistically significant differences in age at diagnosis, sex, marital status, or insurance status between the three cohorts; there were fewer non-white patients in 1997 (12% vs 14% in 2004 and 2009; Rao-Scott chi-square $p<.0001$). Treatment selection varied significantly with time for all cases and for T4 stage only OPC cases. The percentage of cases receiving primary surgery decreased from 46% in 1997 to 35% in 2004 and 28% in 2009. Conversely, there was an increase in the proportion of cases receiving RTC from 47% in 1997 to 61% in 2004 and 65% in 2009. The same trends were present within the subset of patients with T4 class. Patients receiving no cancer-directed therapy or chemotherapy only consisted of 8%, 4% and 7% in 1997, 2004 and 2009, respectively. The most commonly used chemotherapy agents were cisplatin/carboplatin, followed by methotrexate, 5-fluorouracil, and taxanes.

There were 284 and 503 OPC cases that received primary surgery and RTC, respectively (Table 2). The mean age was 56 years for primary surgery patients and 58 years for RTC patients ($p < 0.0001$). While treatment selection was not distributed differently by sex, race, marital status, insurance status, or Charlson score, there was an association with tumor stage: patients with stages I/II/III OPC cancer had similar proportions of patients receiving surgery or RTC, but a significantly greater proportion of those with IVA/IVB/IVC received RTC. When specifically examining T class, a significantly greater proportion of those with T1 tumors received surgery, whereas RTC became more prevalent as T class increased ($p < 0.0001$). Similar patterns were observed when examining N class among all cases but did not reach statistical significance ($p = 0.06$). Treatment did not differ significantly by metastasis status. Hospital residency training status and bed size were not significantly associated with treatment selection among all cases.

In a subgroup analysis of the T4 class cases, the use of primary surgery changed over time – from 36% in 1997 to 24% in 2004 and 14% in 2009. In 1997, 2004 and 2009, 6%, 5% and 7%, respectively, of T4 stage only OPC cases received no cancer-directed therapy or chemotherapy only (Table 1). After excluding patients with either no cancer-directed therapy or chemotherapy only, age distribution was similar between primary surgery and RTC groups ($p = 0.51$). N class ($p = 0.0045$) and hospital size ($p = 0.0055$) were significantly associated with receipt of primary surgery among T4 cases (Table 2).

Multivariate models involving all OPC cases demonstrated that earlier year of diagnosis and earlier stage independently predicted receipt of primary surgery versus RTC after adjusting for age at diagnosis, race, sex, marital status at diagnosis, Charlson score, AJCC stage and hospital size (Table 3). The adjusted odds ratio for receiving primary surgery versus RTC was 0.29 (95% CI; 0.15, 0.55) in 2004 and 0.17 (95% CI; 0.09, 0.33) in 2009, with 1997 as the reference group. The adjusted odds of receiving primary surgery versus RTC were higher for early stage versus late stage with I/II/III as the reference [0.36 (95% CI; 0.18, 0.70) for stage IVA and IVB cases and 0.28 (95% CI; 0.08, 0.97) for IVC cases].

Similar to the analysis of all OPC patients, T4 cases diagnosed with OPC in earlier years had higher odds of receiving primary surgery versus RTC (Table 3) on multivariate analysis. Unlike with the all-stages cohort, the odds of receiving surgery increased with increasing bed size in T4 cases; the odds ratio was 3.33 (95% CI; 1.67, 6.66) for patients treated at hospitals with bed size greater than or equal to 300 with bed size less than 300 as the reference group.

Each additional year of age at diagnosis (HR= 1.03: 95% CI; 1.02, 1.05), being unmarried (HR= 2.10: 95% CI; 1.51, 2.91), and having a Charlson score of at least one or more (HR= 1.77: 95% CI; 1.20, 2.62) were also significantly associated with increased hazard of death (Table 4). Diagnosis in 2009 (versus 1997) (HR= 0.51: 95% CI; 0.33, 0.78) was significantly related to lower risk of death. Compared to stages I-III cases, stage IVC patients had a significantly greater hazard of death (HR 2.22: 95% CI; 1.16, 4.26). RTC versus primary surgery was not significantly associated with increased hazard of death from all causes (HR= 1.42: 95% CI; 0.93, 2.17). Neither hospital size (Table 4) nor residency training status (results not shown) was significantly associated with risk of death when included in

multivariable models. Among T4 cases, only stage remained significant in multivariate models (Table 4). Those with Stage IVC disease had a hazard 5.64 (95% CI; 3.00, 10.58) times higher than stage IVA/ IVB patients.

HPV status was only collected for OPC cases diagnosed in 2009. HPV status was known in 14% of 2009 cases (Figure 2). The rate of HPV testing was greatest among cases with OPC located on the tongue base (16%) and on the tonsils (12%); other oropharynx sites combined had a testing rate of 11%. For the OPC cases with known HPV status, 43% of tongue base cancers and 52% of tonsil cancers were HPV-positive. HPV status was not significantly associated with the type of therapy received, $p=0.79$. (Table 5).

Discussion

Evaluating population-level data, our results show a clear trend away from primary surgery for management of OPC from over half of patients diagnosed in 1997 to fewer than one quarter of those diagnosed in 2009. Although no high-quality studies directly compared surgery to RTC, previous research describing the addition of chemotherapy to radiotherapy for locally advanced oropharyngeal cancer [9, 18, 19] provided evidence that there was an alternative to surgery, with its evident detriments related to tumor exposure and reconstruction. There were additional studies of patients with unresectable cancer [20, 21] that provided a basis for RTC in the setting of Stage IVB disease as well. Forastiere and Trotti stated in 1999 [22] that RTC should be considered standard of care on the basis of studies published at that time, and our results suggest that there was general agreement with their perspective.

Our data show a similar trend to that reported by Goldenberg et al, [23] who found that about 60% of patients received RTC and that chemoradiation or radiation alone were the most common treatment selections based on 2,192 Medicare recipients between 1997 and 2005. Our findings in a representative sample of younger and older adults in the U.S. population were concordant, which is noteworthy because that study included only patients age 66 and older, a group representing 23% of the population. Chen et al. [24] also reported similar trends in a 1985-2001 National Cancer Data Base cohort derived mainly from patients treated at larger hospitals. Our data in fact indicate that at larger hospitals, patients with T4 cancers were more likely to undergo primary surgery, probably related to availability of subspecialist multidisciplinary treatment teams at larger hospitals, including oncologic and reconstructive surgeons. Our study includes populations not covered by prior studies.

Survival analysis identified year of diagnosis as a predictor of mortality. Patients diagnosed in 2009 had a lower hazard of death than those in 1997. The prevalence of HPV may explain a large portion of that variation. The proportion of OPCs associated with HPV has risen steadily over the past 20 years, and with the improved prognosis of HPV-associated OPC [3], substantial differences would be expected over the years we studied. Unfortunately, information on HPV was available only in 2009 for our cohort, so we could not account for its confounding effect. As shown in prior studies [25–27], age, unmarried status, and Charlson score +1 were independent predictors of mortality. However, RTC was not

associated with greater hazard of all-cause mortality for either the entire cohort or the T4 subgroup.

The management of OPC has changed substantially over the past decade, with two major reasons being the identification of HPV as an etiologic factor in a large subgroup of patients and the introduction of transoral surgical techniques that obviate many difficulties with tumor exposure and reconstruction. The latter is not well-represented in our data. Transoral laser techniques have been adapted to the oropharynx over the past decade [28], and although a small number of centers have described good results over a large number of cases, [29] these techniques have not been widely applied across the population. Robotic surgery has become more common recently [30], but was much less common until FDA approval in 2010. Analysis of those trends would require more recent data than was available to us.

This study reports the frequency of HPV testing in patients with oropharyngeal cancer across the population. The clinical importance of HPV was first recognized about 10 years ago.[31] In 2009, 14% of OPC cases in our dataset had known HPV status. Of the cases with known status, 35% were HPV-positive. The only other population-based estimate for the frequency of HPV testing was reported by Polednak and Phillips,[32] who reported known HPV status in 46% of Connecticut registry patients in 2010 rising to 66% in 2012. As understanding of the prognostic value of HPV becomes more widespread, we would expect more cases to be tested. Our calculated proportion, measured relatively early in the HPV era, should serve as a comparison for future studies.

Despite adjustment for a number of sociodemographic and clinical factors, including Charlson score, a limitation of this study is the unavailability of factors that may be key to the clinical decision-making process, such as functional status, treatment options offered to patients, and patient preferences, potentially leading to residual confounding. However, a strength of the study is that the use of SEER POC data represents diverse geographical regions of the US population. Furthermore, detailed information about cancer treatment and other variables that would otherwise not be available allows for increased classification of treatment and the control of potential confounders. Another advantage of this study is the use of AJCC staging, which is more clinically relevant than SEER-coded stage and provides the ability to delineate between stage IVA, IVB and IVC.

Given the absence of high level evidence to inform decisions about initial treatment of OPC cancer, this analysis provides useful information about how decisions are made across the population. Future research should analyze the impact of treatment on cancer outcomes such as quality of life and incorporate newer treatment modalities as they are developed and incorporated into clinical practice.

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Figure 1.
Flow chart of study inclusion and exclusion criteria in analyses.

Figure 2. Weighted percentages of HPV Status for OPC Patients Diagnosed in 2009
HPV=human papillomavirus; OPC=oropharyngeal cancer

Table 1

Treatment approaches for OPC patients for all stages and T4 stage only cases by year of diagnosis, weighted column %).

Treatment	All Stages (n=835)				T4 Stage Only (n=194)			
	1997 (n=125)	2004 (n=375)	2009 (n=335)	1997 (n=33)	2004 (n=79)	2009 (n=82)	2009 (n=82)	2009 (n=82)
No cancer-directed therapy [‡]	8%	4%	7%	6%	5%	7%	7%	7%
Primary surgery								
Surgery only [‡]	6%	6%	5%	6%	1%	4%	4%	4%
Surgery and RT [§]	40%	29%	23%	30%	23%	10%	10%	10%
RTC								
RT only	21%	15%	9%	27%	16%	15%	15%	15%
RT & Chemotherapy	26%	46%	56%	30%	54%	65%	65%	65%
P-value	< 0.0001[*]				< 0.0001[*]			

OPC=oropharyngeal cancer; RTC= radiotherapy with or without chemotherapy; RT =radiotherapy

^{*} Significant at $\alpha = 0.05$

[‡] Includes patients who received chemotherapy only

[§] Includes patients who received both surgery and chemotherapy (chemotherapy received after surgery).

^{||} Includes patients who received both Surgery and RT with or without chemotherapy.

^{||} Pearson Chi-Square P-value. P-value compares patients who had primary surgery versus those who had RTC. This excludes patients who did not receive cancer-directed therapy or chemotherapy only.

Table 2

[‡]. Demographic, tumor and hospital characteristics by treatment and stage, (weighted row %).

Characteristics	All Stages, (n=787)					T4 Stage Only, (n=182)				
	Surgery (n=284)	RTC (n=503)	Row total, n	P value [§]		Surgery (n=42)	RTC (n=140)	Row total, n	P value [§]	
Year										
1997	59%	41%	115			43%	57%	31		
2004	38%	62%	359			18%	82%	75		
2009	28%	72%	313	0.0006*		15%	85%	76	0.0442*	
Age										
20-49	44%	56%	162			20%	80%	39		
50-64	35%	65%	421			17%	83%	98		
65+	34%	66%	204	0.40		28%	72%	45	0.51	
Sex										
Female	45%	55%	249			23%	67%	61		
Male	35%	65%	538	0.08		20%	80%	121	0.76	
Race										
Non-white	31%	69%	339			21%	79%	100		
White	37%	63%	448	0.13		21%	79%	82	0.97	
Marital status										
Married	39%	61%	385			28%	72%	72		
Unmarried	33%	67%	402	0.40		17%	83%	110	0.23	
Health										
Yes	36%	63%	718			20%	80%	162		
Insurance										
No/Unknown	37%	63%	69	0.93		29%	61%	20	0.47	
Charlson										
0	38%	62%	581			22%	78%	135		
Score										
1	32%	68%	206	0.42		18%	82%	47	0.70	
Stage Group										
I, II & III	53%	47%	197			-	-			
(AJCC 6 th Ed.)										
IVA & IVB	29%	71%	374			21%	79%	161		
IVC	29%	71%	49			7%	93%	12		
Unknown	30%	70%	167	0.0012*		16%	84%	9	0.18	
T Class										
(2 missing)										
T1	64%	36%	139			-	-	-		
T2	39%	61%	192			-	-	-		

Characteristics	All Stages, (n=787)			T4 Stage Only, (n=182)		
	Surgery (n=284)	RTC (n=503)	Row total, n	P value ^{//}	Surgery (n=42)	RTC (n=140)
T3	16%	84%	83	–	–	–
T4	21%	79%	182	–	21%	79%
Unknown	25%	75%	189	<0.0001 [*]	–	–
N Class						
N0	51%	49%	167	45%	55%	29
N1	34%	66%	171	4%	96%	32
N2	30%	70%	338	22%	78%	90
N3	23%	77%	32	9%	91%	16
Unknown	43%	57%	79	0.06	26%	74%
						0.0045 [*]
M Class						
M0	38%	62%	686	21%	79%	161
M1	29%	71%	49	7%	93%	12
Unknown	25%	75%	52	0.17	16%	84%
						0.18
Residency						
Yes	36%	64%	494	24%	76%	123
No/ Unknown	38%	62%	293	0.75	13%	87%
						59
Program						
1–299/Unknown	37%	63%	318	12%	88%	69
300	35%	65%	469	0.76	26%	74%
						0.0055 [*]

RTC= radiotherapy with or without chemotherapy

[†] Excluded patients who either received chemotherapy or no cancer directed therapy

^{//} Weighted Rao-Scott Chi-Square P-value

^{*} Significant at $\alpha = 0.05$

Table 3

Multivariate logistic model predicting primary surgery versus RTC for all stages and T4 stage only patients diagnosed in 1997, 2004 and 2009 using SEER POC (weighted data).

		Surgery versus RTC Odds Ratio (95% CI)	
Characteristics		All Stages n= (787)	T4 Stage Only n= (182)
Year of diagnosis	1997	1.00 (Referent)	1.00 (Referent)
	2004	0.29 (0.15, 0.55) *	0.19 (0.07, 0.52) *
	2009	0.17 (0.09, 0.33) *	0.15 (0.04, 0.51) *
Age continuous)		0.98 (0.95, 1.01)	1.04 (0.99, 1.10)
Race	Non-white	1.00 (Referent)	1.00 (Referent)
	White	0.80 (0.59, 1.37)	1.23 (0.52, 2.93)
Sex	Female	1.00 (Referent)	1.00 (Referent)
	Male	1.47 (0.88, 2.47)	1.08 (0.40, 2.89)
Marital status	Married	1.00 (Referent)	1.00 (Referent)
	Unmarried	1.26 (0.74, 2.17)	1.46 (0.58, 3.70)
Charlson Score	0	1.00 (Referent)	1.00 (Referent)
	1	0.95 (0.50, 1.78)	0.57 (0.16, 2.08)
Stage Group (AJCC 6 th Ed.)	I, II & III	1.00 (Referent)	–
	IVA & IVB	0.36 (0.18, 0.70) *	1.00 (Referent)
	IVC	0.28 (0.08, 0.97) *	0.35 (0.04, 3.22)
	Unknown	0.25 (0.12, 0.52) *	0.36 (0.13, 0.95) *
Hospital Beds	1–299/Unknown	1.00 (Referent)	1.00 (Referent)
	300	0.95 (0.55, 1.65)	3.33 (1.67, 6.66) *

OPC=oropharyngeal cancer; RTC= radiotherapy with or without chemotherapy

* Significant at $\alpha = 0.05$

Table 4

Hazard ratios and 95% CI for all stages and T4 stage only OPC patients diagnosed in 1997, 2004 and 2009 using SEER POC (weighted data).

		Hazard Ratio 95 CI)	
Characteristics		All Stages n= (787)	T4 Stage Only n= (182)
Year of diagnosis	1997	1.00 (Referent)	1.00 (Referent)
	2004	0.69 (0.47, 1.01)	0.87 (0.50, 1.52)
	2009	0.51 (0.33, 0.78) *	1.00 (0.55, 1.83)
Age continuous)		1.03 (1.02, 1.05) *	1.02 (0.99, 1.04)
Race	Non-white	1.00 (Referent)	1.00 (Referent)
	White	0.74 (0.54, 1.00)	1.04 (0.72, 1.49)
Sex	Female	1.00 (Referent)	1.00 (Referent)
	Male	0.94 (0.64, 1.38)	0.82 (0.57, 1.18)
Marital status	Married	1.00 (Referent)	1.00 (Referent)
	Unmarried	2.10 (1.51, 2.91) *	1.85 (0.96, 3.55)
Charlson Score	0	1.00 (Referent)	1.00 (Referent)
	1	1.77 (1.20, 2.62) *	1.61 (0.88, 2.96)
Stage Group (AJCC 6 th Ed.)	I, II & III	1.00 (Referent)	–
	IVA & IVB	1.37 (0.83, 2.26)	1.00 (Referent)
	IVC	2.22 (1.16, 4.26) *	5.64 (3.00, 10.58) *
	Unknown	1.25 (0.72, 2.17)	0.19 (0.13, 1.06)
Type of Therapy	Surgery	1.00 (Referent)	1.00 (Referent)
	RTC	1.42 (0.93, 2.17)	0.71 (0.37, 1.38)
Hospital Beds	1–299 /Unknown	1.00 (Referent)	1.00 (Referent)
	300	1.24 (0.90, 1.71)	1.38 (0.77, 2.48)

* Significant at $\alpha = 0.05$

OPC=oropharyngeal cancer

Table 5

Treatment selection by HPV status, all patients diagnosed in 2009.

HPV status	Treatment	
	Surgery (n=94)	RTC (n=219)
Positive	8%	5%
Negative	6%	9%
Unknown	86%	86%

Chi-square p=0.79.