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Trends in Chemoradiation Use in Elderly Patients with Head and Neck Cancer: Changing treatment patterns with cetuximab

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Abstract

Background—Cetuximab was approved for use in chemoradiation (CTRT) for locally-advanced head and neck squamous cell carcinoma (HNSCC) in 2006.

Methods—Among 3,705 patients with locally-advanced HNSCC identified in the linked Surveillance Epidemiology and End Results (SEER)-Medicare database, we assessed treatment trends including surgery, RT, CTRT and specific agents used in CTRT. We examined the influence of demographic and clinical characteristics on the likelihood of receiving CTRT before and after 2006.

Results—Chemoradiation use increased from 29% of patients diagnosed in 2001 to 61% in 2009 ($p < 0.0001$). Compared to prior to 2006, neither age nor comorbidity score was associated with receipt of CTRT after 2006. Platinum combinations were the most commonly used concurrent chemotherapies before 2006, but since then cetuximab has become the most commonly used agent.

Conclusions—The use of CTRT has increased substantially and cetuximab may have increased CTRT use, especially in older and sicker patients.

Keywords

head and neck cancer; chemoradiation; cetuximab; population-based; squamous cell carcinoma

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Introduction

Elderly patients are disproportionately affected by head and neck squamous cell carcinoma (HNSCC), with greater than 40% of incident cases and more than half of deaths from the disease occurring in patients aged 65 years and older.^{1,2} The majority of patients present with either larger primary tumors or have regional lymph node involvement. The curative management of locally or regionally advanced HNSCC includes complete resection of the tumor and regional lymph nodes typically followed by radiation. Definitive radiation commonly incorporating chemotherapy is an organ-preserving alternative to surgical resection, and can also be used in patients with unresectable tumors.³

In patients who are not treated surgically, the addition of chemotherapy to radiation (CTRT) has been shown to improve overall survival by 4.5% at 5 years when compared to radiation alone.⁴⁻⁶ The improved tumor control associated with CTRT may come at the cost of more acute and long-term treatment-related toxicities, which can be severe, particularly among older patients and those with comorbid medical conditions or poor performance status.⁷⁻⁹ This potential for added toxicity is especially relevant since a meta-analysis of more than 17,000 clinical trial participants, showed no clear overall survival benefit of adding chemotherapy to radiation in patients older than 70 years of age.¹⁰

The most recent addition to the drug armamentarium in HNSCC is cetuximab, a monoclonal antibody targeting the epidermal growth factor receptor (EGFR), approved in 2006 for concurrent use with radiation in locally or regionally advanced disease. In the registration trial, adding cetuximab to radiation improved locoregional control from 34% to 47% and improved 5-year overall survival by 5% when compared with radiation alone.¹¹ Unlike more traditional agents, when combined with radiation, there was no increase in common acute radiation-associated toxicity or a decline in patient reported quality of life reported with the addition of cetuximab.¹² Older patients -over the age of 65 in a post hoc subset analysis - did not demonstrate an overall survival benefit from the addition of cetuximab to radiation.¹¹

Our objectives were to assess the impact of the approval of cetuximab on the use of CTRT in older patients with advanced, non-metastatic HNSCC, and to characterize trends in the use of specific chemotherapeutic agents among patients receiving CTRT.

Materials and Methods

Data

The primary data source was the Surveillance Epidemiology and End Results (SEER) cancer registry program records linked with Medicare claims. Sponsored by the National Cancer Institute (NCI), SEER is a consortium of population-based cancer registries covering approximately 28% of the US population. For all incident cancers in their coverage areas, the SEER registries collect information regarding site and extent of disease, the first course of cancer-directed therapy and sociodemographic characteristics, with active follow-up for date and cause of death. Medicare is the primary health insurer for 97% of the US population aged 65 years and older and covers inpatient hospital care (Part A), and outpatient care and physician services (Part B). The SEER-Medicare files were used in

accordance with a data-use agreement between the NCI and the Centers for Medicare and Medicaid Services (CMS). This study was approved by the Institutional Review Board at Memorial Sloan-Kettering Cancer Center.

Study Cohort

We identified all Medicare beneficiaries aged 66 years or older with a pathologically confirmed primary diagnosis of advanced, non-metastatic HNSCC (AJCC stages III, IVa or IVb) arising in the oropharynx, hypopharynx, or larynx between January 1st, 2001 and December 31st, 2009. We included beneficiaries aged 66 or older to ensure a full year of Medicare claims prior to diagnosis for identifying comorbid conditions. We excluded patients enrolled in a Medicare managed care plan (HMO) and those who did not have continuous Medicare coverage from one year prior to six months post diagnosis in order to capture all relevant treatments. Patients who were diagnosed only at the time of death, who had a history of another malignancy or who had metastatic disease at diagnosis were also excluded. Patients who did not have a claim for either radiation or surgery within six months of diagnosis were considered to not have received definitive therapy and were excluded.

Outcomes

The primary endpoint was type of first-line therapy, classified as surgery, CTRT or radiation alone. If a patient had a claim for head and neck cancer-directed surgery prior to any claim for radiation, treatment was classified as surgery. In patients with any claim for radiation and no prior cancer-directed surgery within 6 months of diagnosis, treatment was classified as having had CTRT if there was at least one claim for chemotherapy, or as radiation alone if there were no claims for chemotherapy. Using Common Procedural Terminology (CPT) J codes, patients who received CTRT were also assigned to one of four mutually exclusive treatment groups according to the specific chemotherapy agents they received. The grouping system was hierarchical in that any patient receiving cetuximab, either alone or in combination with any other chemotherapeutic agent was classified as having had cetuximab. The remaining categories were cisplatin therapy alone, any other platinum-containing regimen including carboplatin, or a regimen with no cetuximab or platinum agent.

Covariates

Demographic and disease characteristics included age, sex, race, marital status, urban or rural residence, geographic region, year of diagnosis, primary site of disease, tumor stage and lymph node involvement. In the absence of individual-level information about SES, we used median income in the census tract of residence at the time of diagnosis. Comorbidity was estimated using a modification of the Charlson index based on inpatient, outpatient and physician claims in the year prior to diagnosis.^{13,14}

Statistical Analysis

We used descriptive statistics to compare patients treated with CTRT to those treated with surgery or RT alone. We assessed the trends in the treatment of locally advanced HNSCC. To examine the impact of cetuximab approval in 2006 on the use of CTRT, we divided the study period into pre-cetuximab approval (2001 thru 2005) and post-cetuximab approval

(2006 thru 2009). We used the Cochran-Armitage trend test to evaluate changes over time in the proportion of all patients receiving CTRT versus other (surgery or radiation). We then used a multivariable logistic regression to evaluate the impact of age, comorbidity, and clinical stage on the likelihood of receiving CTRT in each of these time periods. In patients treated with CTRT for whom information on specific chemotherapy was available, we evaluated trends in chemotherapy selection over the entire study period, including the use of cetuximab since 2006. All analyses were performed in SAS version 9.2 (SAS Institute, Cary, NC).

Results

Cohort Characteristics

We identified 3,705 patients treated for advanced, non-metastatic HNSCC (Table 1). The median age was 73 years (range 66–100) and 19% were 80 years or older. The majority of patients were male (75%), white (83%), married (54%) and had a Charlson comorbidity score of 0 (56%). Almost half (47%) of the group had primary tumors arising in the larynx. More than a quarter (26%) had T4 tumors and 64% had lymph node involvement. Overall, 1,143 (31%) patients had surgery, 1,683 (45%) received CTRT, and 879 (24%) were treated with radiation alone.

Patients who received CTRT were similar to patients treated with surgery in terms of age and comorbidity compared to patients treated with radiation only who tended to be older ($p<0.0001$) and have more comorbid illnesses ($p<0.0001$). Oropharynx and hypopharynx were more likely to be treated with CTRT while larynx tumors were more likely to be treated with RT alone or surgery ($p<0.0001$). While there was no significant difference in treatment by sex, race or income quartile, those living in urban regions were slightly more likely to receive CTRT than rural areas. ($p=0.016$).

Trends in Treatment

As presented in Figure 1, the use of surgery declined over the study period from 38% of patients diagnosed in 2001 to 24% of patients diagnosed in 2009 (37% decrease). The use of radiation alone declined by 53%, from 32% of patients diagnosed in 2001 to 15% of patients diagnosed in 2009. The proportion of patients receiving CTRT more than doubled over the study period, from 29% in 2001 to 61% in 2009 ($p<0.0001$, Figure 1).

Before 2006, patients 80 years of age or older with locally advanced HNSCC were half as likely to receive CTRT compared to patients younger than 70 years of age (adjusted odds ratio (OR) 0.50 (95% Confidence Interval (CI) 0.38–0.67)). Similarly, patients with a Charlson comorbidity score ≥ 2 were 30% less likely to receive CTRT than patients with a Charlson comorbidity score of 0. After 2006, Charlson comorbidity score was not associated with receipt of CTRT (Table 2). While patients aged 70–79 were slightly more likely to receive CTRT than younger patients, patients over the age of 80 were as likely as patients younger than 70 years to receive CTRT after 2006. Patients with laryngeal primary tumors were less likely to receive CTRT than patients with pharyngeal primary tumors, and patients

with T1 tumors were less likely to receive CTRT before and after 2006 than patients with larger tumors.

Information about specific chemotherapeutic agents was available for 1503 of the 1683 patients (89%) treated with CTRT. Cetuximab was the most commonly used concurrent agent after 2006 and used in 32%, 47% and 74% of patients aged 66–69, 70–79, and 80 or older, respectively. Cisplatin alone was used for 24% of patients receiving CTRT in 2001. The percentage of patients receiving cisplatin alone increased to a third of patients receiving CTRT in 2004 but then declined with the availability of cetuximab (Figure 2). While other platinum regimens constituted 63% of concurrent chemotherapy prior to 2006, these regimens were only used in 27% of patients diagnosed after cetuximab approval. When looking at chemotherapy use during CTRT by age, other platinum regimens were used in 63% patients under the age of 80 and 66% of patients aged 80 and over treated before 2006. In 2006 and after, the use declined to 31% of patients aged 66–69 years, 27% of patients aged 70–79 years, and 19% of patients aged 80 or older. In patients with a Charlson comorbidity score <2 treated with CTRT after 2006, the choice of chemotherapy was cetuximab (44%), cisplatin alone (27%), another platinum regimen (27%) and other (1%). While in patients with a Charlson comorbidity score ≥ 2, the choice of chemotherapy was cetuximab (54%), other platinum (25%), cisplatin alone (13%) and other (5%). The use of non-cetuximab, non-platinum regimens was modest throughout the study period.

Discussion

We observed an increase in the use of CTRT and a decline in the use of surgery and radiation alone in a population-based cohort of older patients diagnosed with locally advanced HNSCC. For the healthiest patients who are generally considered good surgical candidates, CTRT offers the potential for organ preservation with no detriment to overall survival.⁴ For patients with unresectable disease, CTRT has been shown to improve survival compared with RT alone.^{6,15,16} Although the use of CTRT appeared to be increasing prior to 2006, our analysis suggests that the approval of cetuximab may have further encouraged the use of CTRT in an older and sicker cohort.

Although there is improvement in local tumor control, there is limited evidence on the survival benefit of adding chemotherapy to radiation in elderly patients with locally or regionally advanced HNSCC. The lack of an obvious survival benefit in this subset of patients is likely due, at least in part, to higher rates of death due to non-HNSCC causes, diluting survival benefits.^{17,18} Older patients are also more likely to have both comorbid conditions and age-related pharmacokinetic and pharmacodynamic changes that can increase the risk of treatment-related toxicities associated with incomplete treatment delivery and death.^{19–23} In one study of patients over 65 receiving CTRT, 65% had either an emergency room visit or a hospitalization for an acute treatment-related toxicity within 6 months of starting treatment.²⁴ Similarly, single institution studies have found that while CTRT can be safely administered in older patients without an increased risk of death during treatment, these patients face a greater likelihood of experiencing an acute toxicity compared with their younger counterparts.^{9,25} Further, in patients treated with CTRT on three different Radiation Therapy Oncology Group (RTOG) studies, older age was associated with an increased risk

of experiencing late swallowing dysfunction.²⁶ Yet, age is not a proxy for functional status and may not adequately determine which patients are most likely to tolerate and complete a full course of CTRT. In our study, the oldest and sickest patients were less likely to receive CTRT before 2006, but not after. We found a slightly higher likelihood of CTRT in patients 70–79 year old ($p=0.02$) compared to patient aged 66–69 which may represent an evolving change in practice such as increased use of more advanced surgical techniques but further follow-up will be needed to clarify. Although the availability of cetuximab is one possible cause for the increased use of CTRT, the trends could also reflect increased experience and comfort in administering CTRT and supporting patients through the potentially toxic treatment.^{27–29}

There are currently multiple single agents and doublet chemotherapy regimens for concurrent use with radiation in locally or regionally advanced HNSCC which have not been compared prospectively.³ Often the choice of an appropriate regimen is based on a patient's clinical profile (functional status and comorbid illness) and the toxicity expected from specific chemotherapeutic agents. In our analysis, cetuximab was the most commonly used concurrent agent in elderly patients receiving CTRT after it received FDA approval in 2006. Although cetuximab integrated with definitive radiation improved survival compared to radiation alone in a phase III trial, cetuximab with radiation has not yet been prospectively compared to other concurrent chemoradiotherapy options. In selected retrospective, single-institution studies, the combination of cetuximab and radiation appears less efficacious than cisplatin and radiation.^{30–32} Further, data from prospective trials in the setting of metastatic HNSCC setting suggest that not all tumors respond the same to EGFR inhibitors.

Specifically, recently published and presented data suggests that patients with human papillomavirus (HPV)-related tumors have a lower response rate to EGFR inhibition compared with patients with tumors that are negative for HPV.^{33–35} Yet, Rosenthal et al. recently presented follow-up correlative data from the original phase III trial of radiation alone versus cetuximab plus radiation, and those with p16+ disease, a surrogate for HPV-related disease, had statistically significant longer locoregional control when treated with cetuximab and radiation compared to radiation alone.³⁶ However, the control arm here was radiation alone and not an alternative radiation sensitizer. The results of RTOG 1016, a randomized trial of cetuximab versus cisplatin concurrent with radiation in locally or regionally advanced HPV-related head and neck cancer, are eagerly awaited in this regard. Single-agent cisplatin remains the most studied and the first-line standard agent recommended for radiation-sensitization for locally or regionally advanced HNSCC. But cisplatin is associated with potential significant toxicity, such as renal dysfunction and hearing loss and there is a need for less toxic alternatives.^{37,38} These alternatives, however, must yield improved outcomes to justify any added toxicities and financial costs.

The use of other platinum-based regimens in CTRT declined substantially after 2006. We observed that before 2006, almost two-thirds of patients in this population receiving CTRT were treated with other platinum-based regimens, and this proportion declined to less than a third of patients after 2006 when cetuximab became available. The rapid uptake of cetuximab use in CTRT in elderly patients with locally advanced HNSCC likely reflects the presumed gentler side effect profile for the targeted agent compared with standard chemotherapy regimens, especially in patients who may be considered poor candidates for

cisplatin therapy. However, retrospective studies evaluating cetuximab in clinical practice report that the addition of cetuximab to radiation may be associated with more toxicity than reported in the registration trial.^{39,40} Specifically, patients can experience oral mucositis, skin dermatitis, weight loss and prolonged feeding tube dependence with the combination.

All of the currently recommended chemotherapy agents for locally advanced head and neck cancer, with the exception of cetuximab, are available in generic versions, and many are used off-label when administered with radiation.⁴¹ Despite having greater experience with generic radiation sensitizers, our study shows that in older patients, oncologists are electing to use cetuximab which is associated with significantly greater drug cost than other accepted regimens. As there are unlikely to be a prospective randomized trials comparing alternative chemotherapy regimens to one another, methods of assessing the comparative effectiveness of these options are greatly needed.³⁰

Several limitations of our analysis should be noted. While we could identify receipt of chemotherapy and in many case the specific agents used, Medicare claims lack the detailed clinical information that would describe chemotherapy and radiation dosages and schedule of administration.^{42–44} Also, in the absence of medical records, we could not determine whether patients received induction chemotherapy in addition to concurrent CTRT. We are unable to distinguish between different radiation delivery such as hyperfractionation or accelerated fractionation. Finally, while we were able to control for important patient and disease characteristics, there may have been residual confounding by unmeasured factors, such as pre-treatment functional status, and patient and physician preferences.

CONCLUSIONS

Chemoradiation is increasingly used in patients with locally or regionally advanced HNSCC. Since 2006, cetuximab has replaced platinum-containing regimens to become the most commonly used radiation-sensitizing agent, despite a lack of evidence that cetuximab is associated with superior oncologic outcomes in this population compared to other available agents. In addition, the availability of cetuximab, generally seen as a less toxic alternative to standard chemotherapy, may have also contributed to the use of CTRT in older and sicker patients who might have previously been treated with radiation alone.

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Figure 1.

Treatment trends in locally advanced HNSCC by year of diagnosis

Note: Chemoradiation (CTRT) radiation (RT). The test for trend compares the proportion of patients receiving CTRT versus other (surgery or RT only) over time.

Figure 2.

Chemotherapy Selection in CTRT by year of diagnosis

Note: Cetuximab was only available for use starting in 2006.

Table 1

Characteristics of the Cohort Stratified by Primary Treatment

CTRT (N = 1,683)							RT Only (N = 879)		Surgery (N = 1,143)		p-value ^b
Characteristic	N	%	N	% ^a	N	%					
Age											
66-69	544	32%	197	22%	410	36%	<0.0001				
70-79	887	53%	411	47%	563	49%					
80+	252	15%	271	31%	170	15%					
Sex											
Male	1293	77%	644	73%	845	74%	NS				
Female	390	23%	235	27%	298	26%					
Race											
White	1425	85%	715	81%	949	83%	NS				
Black	176	10%	113	13%	132	12%					
Other	82	5%	51	6%	62	5%					
Married											
Yes	954	57%	414	47%	630	55%	0.0002				
No	692	41%	442	50%	487	43%					
Unknown	37	2%	23	3%	26	2%					
Census tract median income											
1st quartile	390	23%	245	28%	291	25%	NS				
2nd quartile	420	25%	228	26%	279	24%					
3rd quartile	425	25%	204	23%	296	26%					
4th quartile	448	27%	202	23%	277	24%					
Urban/Rural											
Metropolitan	1421	84%	703	80%	939	82%	0.0157				
Non-metropolitan	262	16%	176	20%	204	18%					
Region											

Characteristic	CTRT (N = 1,683)		RT Only (N = 879)		Surgery (N = 1,143)		p-value ^b
	N	%	N	% ^a	N	%	
Northeast	373	22%	169	19%	223	20%	<0.0001
South	499	30%	316	36%	314	27%	
Midwest	172	10%	75	9%	156	14%	
West	639	38%	319	36%	450	39%	
Charlson comorbidity score							
0	964	57%	432	49%	672	59%	<0.0001
1	434	26%	244	28%	269	24%	
2+	285	17%	203	23%	202	18%	
Site							
Hypopharynx	227	13%	99	11%	105	9%	<0.0001
Larynx	655	39%	490	56%	611	53%	
Oropharynx	801	48%	290	33%	427	37%	
T-stage classification							
T1	198	12%	93	11%	181	16%	<0.0001
T2	496	29%	275	31%	295	26%	
T3	605	36%	297	34%	299	26%	
T4	384	23%	214	24%	368	32%	
Lymph node involvement							
No	476	28%	416	47%	427	37%	<0.0001
Yes	1,207	72%	463	53%	716	63%	

^a Percentages may not total 100% because of rounding

^b p-values were based on chi-squared test of treatment received by characteristic

Table 2

Adjusted Odds of CTRT Use Before and After 2006

2001–2005			2006–2009	
Adjusted OR (95% CI)		<i>p</i> -value	Adjusted OR (95% CI)	<i>p</i> -value
Age at diagnosis				
66–69	Reference	<0.0001	Reference	0.0168
70–79	0.91 (0.74–1.11)		1.29 (1.02–1.64)	
80+	0.50 (0.38–0.67)		0.90 (0.66–1.22)	
Charlson comorbidity score				
0	Reference	0.0211	Reference	NS
1	1.01 (0.81–1.26)		1.03 (0.80–1.32)	
2+	0.70 (0.53–0.91)		0.91 (0.69–1.19)	
Site				
Larynx	Reference	<0.0001	Reference	0.0003
Hypopharynx	1.92 (1.43–2.58)		1.81 (1.25–2.64)	
Oropharynx	1.63 (1.32–2.02)		1.57 (1.21–2.02)	
Clinical T-stage				
T1	Reference	<0.0001	Reference	0.0005
T2	1.81 (1.29–2.55)		1.54 (1.10–2.15)	
T3	3.11 (2.21–4.37)		1.59 (1.10–2.30)	
T4	2.00 (1.42–2.81)		0.98 (0.67–1.42)	
Lymph nodes				
No	Reference	<0.0001	Reference	NS
Yes	1.57 (1.27–1.94)		1.27 (0.95–1.68)	

Odds ratio adjusted for sex, race, marital status, income, urban or rural residence, and geographic region.