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Treatment-Related Toxicities in Older Adults with Head and Neck Cancer: A Population-Based Analysis

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Abstract

Background—Despite advantages in terms of cancer control and organ preservation, the benefits of chemoradiation (CTRT) may be offset by potentially severe, treatment-related toxicities particularly in older patients. Our objectives were to assess the type and frequency of toxicities in older adults with locally or regionally advanced, head and neck squamous cell carcinoma of the (HNSCC) receiving either primary CTRT or RT alone.

Methods—Using SEER cancer registry data linked with Medicare claims, we identified patients aged 66 years or older with locally advanced HNSCC, diagnosed 2001–2009, who received CTRT or RT alone. We examined differences in the frequency of toxicity-related hospital admissions and emergency room (ER) visits as well as feeding tube use and estimated the impact of chemotherapy on the likelihood of toxicity, controlling for demographic and disease characteristics.

Results—Of patients who received CTRT (N=1,502), 62% had a treatment-related toxicity, compared with 46% of patients who received RT alone (N=775). Controlling for demographic and disease characteristics, CTRT patients were twice as likely to experience an acute toxicity compared with their RT only peers. Fifty-five percent of CTRT patients had a feeding tube placed during or after treatment compared with 28% of the RT-only group.

Conclusions—In this population-based cohort of older adults with HNSCC, the rate of acute toxicities and feeding tube use in patients receiving CTRT was considerable. It is possible that for certain older patients, the potential benefit of adding CT to RT does not outweigh the harms of this combined modality therapy.

Keywords

head and neck cancer; toxicity; radiotherapy; chemoradiation; SEER; Medicare

BACKGROUND

Head and neck cancer is the fifth most common cancer worldwide with an estimated annual global incidence of more than 533,000 cases.¹ In the US, almost 53,000 people are diagnosed each year and 30–40% of patients will die of their disease.^{2, 3} The majority of patients (60%) present with locally or regionally advanced disease and squamous cell carcinoma is the most common histology. Forty-three percent of incident cases and 57% of deaths occur in patients aged 65 years and older.⁴

Over the past two decades, combined-modality treatment with chemotherapy and radiation therapy (CTRT) has gained widespread acceptance as numerous studies have demonstrated improved locoregional control and survival compared with radiation therapy (RT) alone.^{5–15} Despite these advantages, the benefit of CTRT may be offset by acute, often severe, treatment-related toxicities, particularly among older patients and those with comorbid medical conditions or poor performance status.^{4, 16–19} As a result, 40–50% of patients who receive CTRT do not receive the planned number of chemotherapy cycles, inevitably reducing dose intensity and the delivery of optimal regimens.²⁰ This is of particular concern in patients aged 70 and older, where there may be little benefit of adding chemotherapy to RT.²¹ Furthermore, the development of chronic and late toxic effects such as speech impairment, dysphagia and feeding-tube dependence can have a long-term detrimental effect on a patient's quality of life.^{4, 19, 22}

While cisplatin-based chemotherapy is the best studied and most established chemotherapeutic agent, newer, targeted radiation-sensitizing regimens may offer similar benefits with less toxicity.^{23, 24} Cetuximab, an epidermal growth factor receptor antibody, was approved for concurrent use with RT after its efficacy, compared with RT alone, was demonstrated in a large, randomised trial.²⁵ That study found no increase in common RT-associated toxic effects, and a subsequent analysis found no difference in quality of life scores between the treatment arms.²⁶ As a result, the use of cetuximab combined with RT may be replacing RT alone in older, sicker patients.²⁷ To date, most studies comparing CTRT and RT alone have focused on oncologic outcomes. Less attention has been paid to the early and late adverse effects of these treatment approaches. Our objectives were to evaluate the nature and frequency of early toxicities and feeding tube use in a cohort of older adults with locally or regionally advanced HNSCC who received primary CTRT or RT alone.

METHODS

Data source

The primary data source was Surveillance Epidemiology and End Results (SEER) cancer registry program records linked with Medicare claims. SEER, sponsored by the National Cancer Institute (NCI), is a consortium of population-based cancer registries covering approximately 28% of Americans in selected states and geographic areas. SEER collects information about site and extent of disease, first course of cancer-directed therapy and sociodemographic characteristics for all newly diagnosed cancers, which are actively followed for date and cause of death.²⁸ 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).²⁸ 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 reviewed by the Institutional Review Board at Memorial Sloan-Kettering Cancer Center and deemed exempt from informed consent requirements.

Study cohort

We identified Medicare beneficiaries aged 66 years or older with a pathologically confirmed primary diagnosis of locally advanced HNSCC arising in the oropharynx, hypopharynx, or larynx between January 1st, 2001 and December 31st, 2009. The cohort was limited to patients with stage III or IV, M0 disease, as defined by American Joint Commission on Cancer criteria (AJCC).²⁹ Patients were classified as receiving primary CTRT if they had any claim for RT, at least one claim for chemotherapy, and no cancer-directed surgery within 6 months of diagnosis. Patients who had at least one claim for RT and no claims for chemotherapy or cancer-directed surgery were categorized as receiving primary RT. We excluded patients enrolled in a Medicare managed care plan (HMO) and those who did not have continuous, complete Medicare coverage from one year prior to diagnosis through death or end of follow-up. Patients diagnosed only at the time of death, who had a history of another malignancy or who had metastatic disease at diagnosis were also excluded.

Outcomes

The primary endpoint was defined as any hospitalization or emergency room (ER) visit for a diagnosis suggestive of an adverse effect of chemotherapy or RT. Acute toxicities included oral complications, hematological complications, gastrointestinal complications, dehydration, deep venous thrombosis or pulmonary embolus, infection, fever, cardiac complications and constitutional symptoms or non-specific complications of treatment. Acute toxicities in these categories were identified by relevant diagnosis and procedure codes in the 6 months following the date of first treatment. Feeding tube placements were evaluated prior to and following treatment initiation. Long-term feeding tube use was based on claims for nutritional support in the Durable Medical Equipment (DME) file or a claim for subsequent feeding tube insertion at 1 and 2 years following initial tube insertion.

Covariates

Demographic characteristics included patient age, sex, race, geographic location, marital status and residence in a metropolitan versus non-metropolitan county. Median income in the census tract of residence was used as a marker of socioeconomic status. Disease characteristics included tumor site, clinical tumor stage, lymph node involvement and year of diagnosis. Comorbidity was estimated using a modification of the Charlson comorbidity index based on inpatient, outpatient and physician claims in the year prior to HNSCC diagnosis.^{33, 34}

Statistical analysis

Unadjusted associations between type of treatment and patient characteristics were examined using chi-square statistics. We estimated the frequency of hospital admissions and ER visits for acute toxicity-related events and characterized the proportion of patients who had a feeding tube placed before or after treatment initiation. Differences between groups in early treatment complications and feeding tube use were assessed using chi-square statistics or Fisher's exact test. Multivariable logistic regression was used to estimate the impact of chemotherapy on the likelihood of a hospitalization or ER visit associated with acute toxicity, controlling for demographic and disease characteristics. The Cochran-Armitage trend test was used to evaluate changes over time in the proportion of all patients receiving CTRT vs. RT and the proportion of patients with a hospitalization or ER visit for an acute toxicity. All analyses were performed in SAS version 9.2 (SAS Institute, Cary, NC).

RESULTS

Characteristics of cohort

We identified 2,277 patients with locally advanced HNSCC, of whom 66% received CTRT and 34% received RT alone (Table 1). The CTRT group was younger, more likely to be white, married, and have a comorbidity score of zero. A greater proportion of the RT group had laryngeal cancer (55%) compared with the CTRT group (39%), while a greater proportion of CTRT patients had oropharyngeal cancer (47% vs. 33%). Over the study period, the proportion of patients diagnosed with oropharyngeal cancers increased from 34% to 49% while the proportion diagnosed laryngeal cancer decreased from 52% to 42%. A greater proportion of patients were diagnosed with T3 compared with T4 disease (36% vs. 24%) and this was relatively consistent across treatment groups (Table 1). There was a decline in the percentage of patients diagnosed with T4 disease over the study period (26% to 17%) but the proportion of patients diagnosed with T3 disease increased (32% to 39%). The proportion of patients receiving RT only decreased significantly, from 51% in 2001 to 18% in 2009 ($p<0.0001$, Figure 1).

Hospitalizations and ER visits for early toxicities

Sixty-two percent of patients receiving CTRT had a hospitalization or ER visit for one or more diagnoses suggestive of an acute adverse effect compared with 46% of patients who received RT alone (Table 2). Some diagnoses had greater specificity for chemotherapy use than others. In particular, patients who received CTRT were more likely to have a hospitalization or ER visit for gastrointestinal and hematological toxicities compared with their peers who had RT only.

Controlling for important demographic and disease characteristics, CTRT patients were twice as likely to experience any toxicity (Table 3). The CTRT group was three times more likely to have a hospitalization or ER visit for a gastrointestinal toxicity or hematological toxicity and twice as likely to experience fever, dehydration and oral complications. An examination the impact of treatment (CTRT vs. RT) on the odds of any toxicity-related hospitalization or ER visit, showed an increased risk with older age at diagnosis ($p=0.02$) and greater comorbidity ($p<0.0001$).

The proportion of patients in the RT only group who experienced acute treatment-related toxicities increased from 40% to 49% over the study period while the proportion of patients with acute toxicity in the CTRT group decreased from 71% to 61%.

Feeding tube use

Seventy-four percent of the CTRT group had a feeding tube placed at any time after diagnosis compared with 50% of RT only patients (Table 4). Following the initiation of cancer-directed therapy, 54% of CTRT patients had a feeding tube compared with 32% of RT patients, and 40% of CTRT patients had claims for enteral nutritional support compared with 19% of RT only patients. Fifteen percent of CTRT patients and 6% of RT only patients had a claim for nutritional one year after tube placement. Of those who had protracted feeding tubes, a greater proportion of RT only patients had a Skilled Nursing Facility (SNF) claim, which is indicative of post-treatment rehabilitation, compared with CTRT only patients (44% vs. 33%, $p<0.002$).

DISCUSSION

The treatment of HNSCC has evolved over the past two decades, with increasing emphasis on organ preservation and multimodality management. Although the benefit of CTRT compared with RT alone is supported by evidence from numerous studies, the combined therapy approach has been associated with poor treatment tolerance and reduced compliance with prescribed dose intensities in certain settings.^{21, 23, 35} The type and severity of treatment-associated toxicity depends on the scope and intensity of the treatment modality, but evidence suggests that older patients are more susceptible to both early and late adverse events.^{4, 19}

In our population-based study, patients who received CTRT were more than twice as likely to experience a hospital admission or ER visit for a diagnosis suggestive of an adverse event compared with patients who received RT alone. Moreover, patients in the older age groups and patients with greater comorbidities were significantly more likely to experience a toxicity compared with younger healthier patients. This is concerning given the increasing use of CTRT, compared with RT, in older, sicker patients.²⁷ In fact, it has been reported that prior to 2006, both age and comorbidity were significant predictors of CTRT use, with younger healthier patients more likely to receive CTRT. In recent years, however, these factors are no longer predictors.²⁷ While it is thought that this could be due to the approval of the less toxic monoclonal antibody, cetuximab in 2006, our results suggest that older, less healthy patients are still predisposed to concerning treatment-related toxicities.

While hematologic complications are chemotherapy-specific, oral complications are common to both chemotherapy and RT and are often enhanced by their combination.³⁶ Mucositis is one of the most significant and dose-limiting acute toxicities associated with RT, and patients may develop oral pain, dysphagia, weight loss and the need for feeding tubes as a result of this complication.^{16, 19} A systematic review found that the incidence of severe mucositis was 34% in patients who received RT alone and 43% in patients who received concurrent CTRT.¹⁶ In the current study, patients who received CTRT were significantly more susceptible to oral complications compared with those who had RT only

(30% vs. 18%), and the proportion of patients with severe mucositis was notably different (12% vs. 3%). Our results are similar to at least one other study in which mucositis severe enough to warrant a hospital admission was present in 10% of patients receiving CTRT.¹⁸ Rates of mucositis-related hospitalizations were similar in younger and older patients receiving CTRT.⁴ In addition, it is widely appreciated that the oral complications seen among patients receiving CTRT lead to phlegm accumulation and increased gagging. This may explain the notable proportion of CTRT patients who experienced gastrointestinal complications compared with RT-only patients (10% vs. 3%). Nausea and vomiting are also common side effects of many chemotherapy regimens, particularly those containing cisplatin.

Following the initial treatment period, poor swallowing function can remain a persistent problem for a non-negligible fraction of patients who receive CTRT and those who receive RT only.¹⁹ In our population-based cohort of older patients, 56% of those who received CTRT had a feeding tube inserted during or after treatment, versus 33% of those who had RT alone. At 1 and 2 years from initial tube placement, the proportion of CTRT patients dependent on a feeding tube was almost three times that of the RT-only group. Although we could not measure the impact of feeding tube use on quality of life, these patients likely had poor functional outcomes related to the inability to eat by mouth. Despite these findings, a significantly greater proportion of patients in the RT only group had post-treatment rehabilitation. CTRT patients are at high risk for acute and late-effect dysphagia, one of the critical sequela of this being aspiration. Available data would indicate that swallowing rehabilitation can improve outcomes and although the data are limited, early intervention appears to be superior to any delays in treatment.³⁷

Between 2003 and 2007 we observed a notable increase in the proportion of patients in the RT only group who had an acute toxicity. It was during this time period that CTRT use, which had remained relatively stable previously, began to increase, and there was a corresponding decline in the use of RT alone. If treatment with RT only was increasingly reserved for the frailest patients, then this group would represent those most susceptible to the toxicities of treatment, and hence most likely to have hospital admissions or ER visits for an adverse events very.²⁵ Alternatively, RT techniques, dosing and schedules may have evolved during the specified time period, resulting in a greater risk of treatment-associated toxicity.³⁸

Several limitations of our analysis should be noted. First, in the absence of detailed clinical information, we were unable to define chemotherapy and RT dosages or to determine whether patients received a full course of therapy.^{39, 40} Second, we identified only patients with acute complications severe enough to warrant a hospital admission or ER visit. Thus our analysis likely underestimates the total incidence of most toxicities.⁴¹ Third, we could not accurately distinguish induction chemotherapy from the typical course of concurrent CTRT. While we were able to control for important patient and tumor characteristics, there may have been residual confounding by unmeasured factors, such as pre-treatment functional status, other risk factors for chemotherapy-related adverse effects and patient and physician preferences. Finally, it was not possible to determine the location of treatment which may have impacted the degree of on-treatment supportive care that was received.

CONCLUSIONS

In this population-based cohort of older adults with HNSCC, the rate of acute toxicities and feeding tube use in patients receiving CTRT was considerable. While the survival benefit associated with CTRT is well established in younger patients, it is not clear whether the benefit adding chemotherapy to RT exceeds the risk of toxicity associated with this therapy in older adults. In the absence of a clear survival advantage, some HNSCC patients may be just as well off with RT only. Risk-stratified approaches may improve overall outcomes in HNSCC, by directing more aggressive treatment modalities to patients with a greater likelihood of benefit and a greater ability to tolerate side effects. Such strategies would reduce the use of combined modality therapy in those who are least likely to benefit from it and least able to tolerate it, sparing them unnecessary toxicity and reducing costs to the patient, payer and society at large.

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Figure 1. Trends in use of CTRT and RT only

Figure shows the proportion of all patients with locally or regionally advanced HNSCC who received CTRT vs. RT only

Abbreviations: CTRT, chemoradiation; RT, radiation therapy

Table 1

Characteristics of Cohort

	All patients		CTRT		RT		p-value
	No.	%	No.	%	No.	%	
Total	2,277	-	1,502	66%	775	34%	
Age at diagnosis							
66-69	636	28%	478	32%	158	20%	<0.0001
70-74	661	29%	474	32%	187	24%	
75-59	486	21%	314	21%	172	22%	
80-84	315	14%	169	11%	146	19%	
85+	179	8%	67	4%	112	14%	
Sex							
Male	1,713	75%	1,152	77%	561	72%	0.0240
Female	564	25%	350	23%	214	28%	
Race							
White	1,915	84%	1,286	86%	629	81%	0.0223
Black	244	11%	146	10%	98	13%	
Other	118	5%	70	5%	48	6%	
Census tract median income							
1st quartile	568	25%	353	24%	215	28%	0.0545
2nd quartile	562	25%	365	24%	197	25%	
3rd quartile	575	25%	386	26%	189	24%	
4th quartile	572	25%	398	26%	174	22%	
Urban-rural residence							
Metropolitan	1,885	83%	1,263	84%	622	80%	0.0218
Non-metropolitan	392	17%	239	16%	153	20%	
Region							
Northeast	480	21%	335	22%	145	19%	0.0136

	All patients		CTRT		RT		p-value
	No.	%	No.	%	No.	%	
South	716	31%	442	29%	274	35%	
Midwest	218	10%	151	10%	67	9%	
West	863	38%	574	38%	289	37%	
Married							
Yes	1,191	52%	845	56%	346	45%	<0.0001
No	1,030	45%	624	42%	406	52%	
Unknown	56	2%	33	2%	23	3%	
Site							
Oropharynx	966	42%	707	47%	259	33%	<0.0001
Hypopharynx	293	13%	205	14%	88	11%	
Larynx	1,018	45%	590	39%	428	55%	
Clinical T-stage							
T1	258	11%	180	12%	78	10%	0.2997
T2	660	29%	427	28%	233	30%	
T3	813	36%	546	36%	267	34%	
T4	546	24%	349	23%	197	25%	
Lymph node involvement							
Negative	801	35%	432	29%	369	48%	<0.0001
Positive	1,477	65%	1,070	71%	407	53%	
Charlson comorbidity score							
0	1,223	54%	849	57%	374	48%	0.0001
1	611	27%	393	26%	218	28%	
2+	443	19%	260	17%	183	24%	
Year of diagnosis							
2001	245	11%	118	8%	127	16%	<0.0001
2002	271	12%	141	9%	130	17%	
2003	265	12%	133	9%	132	17%	

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	All patients		CTRT		RT		p-value
	No.	%	No.	%	No.	%	
2004	223	10%	138	9%	85	11%	
2005	242	11%	160	11%	82	11%	
2006	248	11%	183	12%	65	8%	
2007	236	10%	187	12%	49	6%	
2008	271	12%	217	14%	54	7%	
2009	276	12%	225	15%	51	7%	

Abbreviations: CTRT, chemoradiation; RT, radiation therapy

Table 2

Hospitalization or ER visit for acute toxicity

Toxicity	CTRT	RT Only	p-value
	No. (%)	No. (%)	
Any toxicity	934 (62)	358 (46)	<0.0001
By diagnostic category			
Oral	447 (30)	142 (18)	<0.0001
Dysphagia	301 (20)	121 (16)	0.0100
Mucositis	182 (12)	21 (3)	<0.0001
Esophagitis	73 (5)	17 (2)	0.0020
Gastrointestinal	149 (10)	23 (3)	<0.0001
Nausea, vomiting	106 (7)	17 (2)	<0.0001
Diarrhea	59 (4)	<11	<0.0001
Dehydration	240 (16)	41 (5)	<0.0001
Hematologic	469 (31)	108 (14)	<0.0001
Neutropenia	162 (11)	<11	<0.0001
Thrombocytopenia	63 (4)	<11	0.0002
Anemia	353 (24)	98 (13)	<0.0001
Infection	372 (25)	169 (22)	NS
Infection	318 (21)	135 (17)	0.0336
Aspiration pneumonia	126 (8)	66 (8)	NS
Fever	93 (6)	14 (2)	<0.0001
Acute renal failure	139 (9)	37 (5)	0.0001
Cardiac	247 (16)	127 (16)	NS
PE/DVT	64 (4)	16 (2)	0.0070
Other	116 (8)	16 (2)	<0.0001
Delirium/drug psychoses	87 (6)	16 (2)	<0.0001
Non-specific	35 (2)	0 (0)	<0.0001

Notes: Table shows percent of patients in each group who had a hospitalization or ER visit within each diagnostic category. Cell counts <11 not shown in accordance with SEER-Medicare Data Use Agreement

Abbreviations: CTRT, chemoradiation; RT, radiation; PE/DVT, pulmonary embolism/deep vein thrombosis; NS: Not statistically significant at $p < 0.05$

Table 3

Likelihood of acute toxicity in patients receiving CTRT vs. RT

Toxicity	Adjusted Odds Ratio (95% CI)	p-value
Any toxicity	2.10 (1.72, 2.56)	<0.0001
By diagnostic category		
Oral	1.84 (1.46, 2.32)	<0.0001
Gastrointestinal	3.47 (2.16, 5.58)	<0.0001
Dehydration	2.40 (1.64, 3.51)	<0.0001
Hematologic	3.11 (2.41, 4.01)	<0.0001
Infection	1.32 (1.05, 1.67)	0.0171
Fever	2.70 (1.48, 4.94)	0.0012
Acute renal failure	1.95 (1.29, 2.96)	0.0016
Cardiac	0.99 (0.76, 1.28)	NS
PE/DVT	2.65 (1.45, 4.85)	0.0015
Other	3.76 (2.14, 6.62)	<0.0001

Notes: Odds ratios adjusted for age, sex, race, median income, urban residence, geographic region, marital status, SEER historical stage, Charlson comorbidity index and year of diagnosis.

Acute toxicity was defined as any hospitalization or ER visit for a primary or secondary diagnosis within the specified category suggestive of an adverse effect of chemotherapy or RT within 6 months of a patient's first treatment claim.

Examining the impact of treatment (CTRT vs. RT) on the odds of any toxicity-related hospitalization or ER visit, showed an increased risk with older age at diagnosis ($p=0.02$) and greater comorbidity ($p<0.0001$).

Abbreviations: CTRT, chemoradiation; RT, radiation; GI, gastrointestinal; PE/DVT, pulmonary embolism/deep vein thrombosis; CI, confidence interval; OR, odds ratio; NS: Not statistically significant at $p<0.05$.

Table 4

Feeding tube use

Outcome	CTRT	RT Only	p-value
	No. (%)	No. (%)	
Feeding tube at any time after diagnosis	1,115 (74)	384 (50)	<0.0001
Nutritional support	833 (55)	218 (28)	<0.0001
Long-term feeding tube use			
+1 year from initial claim	324 (22)	75 (10)	<0.0001
+2 years from initial claim	146 (10)	37 (5)	<0.0001
Feeding tube post-treatment only	816 (54)	251 (32)	<0.0001
Nutritional support	600 (40)	145 (19)	<0.0001
Long-term feeding tube use			
+1 year from initial claim	225 (15)	50 (6)	<0.0001
+2 years from initial claim	103 (7)	24 (3)	0.0002
Post-treatment rehabilitation	268 (33)	110(44)	<0.002

Abbreviations: CTRT, chemoradiation; RT, radiation therapy

Notes: P-values from unadjusted Fisher's exact test or chi-square test of association between treatment modality and feeding tube use. Claims for nutritional support identified only patients with a post-treatment claim for feeding tube placement. A Skilled Nursing Facility claim following the placement of the feeding tube was used as a proxy for post-treatment rehabilitation.