Evaluating the impact of patient, tumor, and treatment characteristics on the development of jaw complications in patients treated for oral cancers: A SEER–Medicare analysis

Beth M. Beadle, MD, PhD,[1]* Kai-Ping Liao, PhD,[2] Mark S. Chambers, DMD, MS,[3] Linda S. Elting, DrPH,[2] Thomas A. Buchholz, MD,[1] K. Kian Ang, MD, PhD,[1] Adam S. Garden, MD,[1] B. Ashleigh Guadagnolo, MD, MPH[1]

[1]Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, Texas, [2]Department of Biostatistics, The University of Texas MD Anderson Cancer Center, Houston, Texas, [3]Department of Head and Neck Surgery, The University of Texas MD Anderson Cancer Center, Houston, Texas.

Accepted 18 September 2012
Published online 14 November 2012 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/hed.23205

ABSTRACT: *Background.* Jaw complications, including osteoradionecrosis, are significant sequelae of radiation therapy (RT) for oral cancers. This study identifies the impact of patient, tumor, and treatment characteristics on the development of jaw complications in patients treated with RT.

Methods. The Surveillance, Epidemiology, and End Results (SEER)–Medicare database was used to identify patients treated with RT for oral cancers from 1999 to 2007. Jaw complications were identified by International Classification of Diseases 9th revision (ICD-9) diagnosis codes and/or related procedures using Current Procedural Terminology (CPT) and ICD-9 codes.

Results. A total of 1848 patients were identified. With a median follow-up of 2.5 years, 297 patients (16.1%) developed jaw complications: 226 patients had a diagnosis, 41 patients had a procedure, and 30 patients had both. On multivariate analysis, female sex, lack of chemotherapy use, and fewer comorbidities were associated with a statistically significant increase in jaw complications.

Conclusions. Even with modern techniques, jaw complications are a notable and potentially devastating side effect of RT for oral cancers.

Head Neck **35:** 1599–1605, 2013

KEY WORDS: osteoradionecrosis, head and neck radiation, IMRT, jaw complications, SEER–Medicare

INTRODUCTION

Approximately 55,000 patients were diagnosed with, and approximately 12,000 patients died of, cancers of the head and neck in 2011.[1] Although the treatment for head and neck cancers is highly dependent on the site of origin and stage of the disease at presentation, radiation therapy (RT) is a crucial treatment modality for the majority of tumors arising from the oral cavity and oropharynx, either in a definitive or postoperative setting. Although providing durable locoregional control, radiation can also cause significant long-term sequelae for survivors. These include dysphagia, xerostomia, jaw complications, osteoradionecrosis (ORN), and dental caries, all of which can significantly influence the quality of life and can require expensive medical interventions.[2–6] Jaw complications comprise a spectrum of side effects, ranging from exposed bone, which can heal with conservative medical management, to nonhealing wounds requiring hyperbaric oxygen therapy (HBO). The most serious of the jaw complications from radiation arises in manifest ORN requiring mandibulectomy and reconstruction. All of these potential jaw complications of radiation therapy can have significant lifetime medical, economic, and quality of life implications for affected patients.

Advances in technology, most notably the development of intensity-modulated radiation therapy (IMRT), have sought to minimize the dose of radiation given to critical normal tissues, including the salivary glands and the mandible, with the goal of minimizing the chronic toxicities of radiation therapy.[7–13] IMRT has been widely accepted as a standard of care for head and neck cancer treatment; multiple Surveillance, Epidemiology, and End Results (SEER)–Medicare analyses have demonstrated significant increases in the use of IMRT for head and neck cancer from 2000 to 2005.[14,15] Despite widespread adoption of IMRT for head and neck cancer, there is a dearth of published data specifically reporting on patient outcomes with respect to long-term complications for patients treated with IMRT.

The goal of this study was to identify the rates of jaw complications, of all degrees of severity, in patients treated with radiation therapy using modern techniques (ie, IMRT) for oral cavity and oropharynx cancers and identify the patient, tumor, and treatment characteristics associated with these complications.

METHODS AND MATERIALS

Data source

We used the SEER–Medicare linked database to identify the cohort and outcomes of interest. The SEER program (a National Cancer Institute–supported database)

*Corresponding author: B. M. Beadle, The University of Texas MD Anderson Cancer Center, Department of Radiation Oncology, Houston, TX. 77030. Tel: 713-563-2300 Fax: 713-563-2366; E-mail: bbeadle@mdanderson.org

Ehab Y. Hanna, MD, was recused from consideration of this manuscript.

Presented at the 2012 Multidisciplinary Head and Neck Cancer Symposium, Phoenix, AZ, January 26–28, 2012.

includes tumor registries in 17 geographic areas: Greater California, San Francisco–Oakland, Los Angeles, San Jose, Connecticut, Detroit, Seattle–Puget Sound, Atlanta/Rural Georgia, Iowa, Louisiana, New Mexico, Utah, Hawaii, Kentucky, Louisiana, and New Jersey, comprising approximately 25% of the U.S. population.[16] These registry data are linked by encrypted patient identifiers to Medicare claims files. The Medicare program provides payments for hospital, physician, and outpatient medical services for 97% of the U.S. citizens who are ≥65 years of age.[17,18] The Patient Entitlement and Diagnosis Summary File (PEDSF), as well as Medicare claims files including the Medicare Provider Analysis and Review (MEDPAR), Outpatient (OUTPAT), and National Claims History (NCH), were used to identify diagnoses and procedures for each patient.

Cohort identification

We queried the database for patients treated between 1999 and 2007 for oral cavity and oropharyngeal cancers, as defined by SEER and International Classification of Diseases 9th revision (ICD-9) codes, who had radiation therapy as one component of their care. This query captured patients who had both definitive and adjuvant radiation therapy. For inclusion, patients needed to complete treatment within 3 months of the date of diagnosis. The SEER major tumor site codes of interest were: cancers of the lip (01), tongue (02), floor of mouth (04), gum and other mouth (05), tonsil (07), oropharynx (08), and other oral cavity and pharynx (10). The ICD-9 diagnosis codes of interest were: cancers of the lip (140.x), tongue (141.x), floor of mouth (144.x), gum (143.x), oropharynx (146.x), mouth (145.x), and ill-defined sites of the oral cavity, lip, and pharynx (149.x). For inclusion, the tumor needed to be pathologically confirmed, not diagnosed at death or autopsy, with a stage indicated, and no evidence of distant disease. Table 1 shows the algorithm for development of this cohort.

TABLE 1. Algorithm for cohort identification from the primary SEER–Medicare database.

Criterion	No. of patients	Excluded	
		No. of patients, *n*	%
Entire head and neck cancer cohort	172,708	0	0.0%
Head and neck cancer is only cancer or first of more than 1 cancer	87,381	85,327	49.4%
Diagnosis between 1999 and 2007	43,788	43,593	49.9%
Age at diagnosis (y) ≥66 and ≤80	19,205	24,583	56.1%
Parts A and B coverage and no HMO 1 y prior to and after diagnosis	9,657	9,548	49.7%
In Medicare for age only (not end-stage renal disease or disability)	9,617	40	0.4%
Microscopically confirmed	9,558	59	0.6%
Stage nonmissing and nonmetastatic disease	7,728	1,830	19.1%
Limited to oral cancer sites (SEER primary codes 01, 02, 04, 05, 07, 08, 10)	4,159	3,569	46.2%
Must receive definitive or adjuvant radiation therapy	1,860	2,299	55.3%
With household income information	1,848	12	0.6%

Outcome identification

The primary outcome analyzed in this study was the development of jaw complications following the delivery of radiation therapy for oral cavity and oropharyngeal cancers. The database was queried for ICD-9 codes for the diagnosis of jaw complications or the Current Procedural Terminology (CPT) codes and ICD-9 codes for procedures used to manage jaw complications. Because we were specifically interested in the influence that IMRT may have on reducing late effects associated with radiation therapy, our study window for identifying late jaw complications began at least 90 days following the last radiation treatment. For the diagnosis of a jaw complication, ICD-9 codes were included for osteonecrosis of the jaw (733.45), osteomyelitis or diseases of the jaws (526.4), including inflammatory conditions of the jaws (526.4), alveolitis of the jaw (526.5), periradicular pathology associated with previous endodontic treatment (526.89), and other diseases of the jaws (526.9). For procedures indicating a jaw complication, CPT codes and ICD-9 procedure codes were included for drainage of abscess (41800), alveolectomy including curettage of osteitis or sequestrectomy (41830), and hyperbaric oxygen therapy (99183). In addition, for patients with a concurrent diagnosis code for a jaw complication, the ICD-9 procedure code for operations on facial bones and joints (76.x) was included. Patients who underwent procedures coded as operations on facial bones and joints but who did not also have a concurrent diagnosis of a jaw complication were not identified as having a jaw complication procedure since it was not possible to exclude the possibility of this procedure for recurrent disease. For patients who underwent all other procedures, the diagnosis of a jaw complication was implied by the specific procedure code; thus, patients with recurrent disease were not included.

Definition of explanatory variables

Potential explanatory variables in our study included age at diagnosis, sex, race, marital status, urban versus rural residence, SEER geographic region, neighborhood income level, neighborhood educational level, and stage at diagnosis. We also evaluated comorbidities using the comorbidity index as constructed by Klabunde's algorithm calculating a modified comorbidity score using inpatient and outpatient claims within a 6-month window prior to the date of diagnosis.[19–22]

Detailed radiation treatment-related characteristics were identified from Medicare claims data through the ICD-9 procedure codes or CPT codes for radiation treatment planning and delivery. The cohort was further categorized as having received IMRT if any IMRT delivery or planning CPT codes were present (77418, 77301, GO174-IMRT, GO178-IMRT). If patients did not have an IMRT planning

or delivery code as part of their RT claims, they were then assumed to have received conventional 2-dimensional (2-D) or 3-dimensional (3-D) radiation therapy techniques. In addition to radiation therapy delivery, we identified treatment with surgery and chemotherapy using the SEER coding for receipt of these modalities as part of primary management for a patient's disease at the time of diagnosis.

Statistical analysis

Statistical analyses were conducted using SAS statistical software (version 9.2; SAS Institute, Cary, NC). The unadjusted association of each potential explanatory variable with the outcome of jaw complication was assessed using the chi-square statistic for binary and categorical variables. Multivariate analyses were performed using the stratified Cox regression model to derive hazard ratios (HRs) and 95% confidence intervals (CI). Models were constructed using stepwise forward selection with $p = .2$ for significance as entry criteria into the model and with $p < .05$ for significance as stay criteria in the model. The model was built using all patients, and then it was stratified by the use of IMRT or non-IMRT to account for nonproportional hazards.

RESULTS

Study cohort characteristics and development of jaw complications

We identified 1848 patients that met our criteria for inclusion. The median follow-up time for the cohort was 2.5 years. The mean age at diagnosis was 72.2 years (range, 66–80 years). Table 2 summarizes the demographic and treatment characteristics of the cohort. The most common site of cancer was tongue (38.6%) followed by gum and other mouth (21.4%) and tonsil (21.5%). Of the entire cohort, 745 patients (59.7%) had surgery and 636 patients (34.4%) had chemotherapy (154 with adjuvant radiation and 482 with definitive radiation). A total of 679 patients were treated with IMRT; 1169 patients were treated with conventional radiation therapy (either 2-D or 3-D techniques). Using all diagnosis and procedure codes, a total of 297 patients developed the outcome of interest, comprising 16.1% of the total population. Of these 297 patients, 226 patients (a total of 12.2% of the cohort) had only a diagnosis of a jaw complication without a concurrent procedure for treatment, 41 patients (2.2%) had a procedure for a jaw complication without a noted diagnosis, and 30 patients (1.6%) had both a diagnosis and a procedure for the jaw complication. As noted earlier, patients who had an unspecified procedure without a concurrent diagnosis code were omitted since recurrent disease could not be excluded; patients with a specific procedure code were included, even in the absence of a diagnosis code, since the diagnosis is implied by the procedure (for instance, hyperbaric oxygen therapy would be used only for a jaw complication and not a recurrence). Thus, a total of 71 patients (3.8%) had a procedure for a jaw complication following radiation therapy for oral cavity and oropharyngeal cancers.

On univariate analysis, female sex ($p = .002$), non-Black race ($p = .023$), lower Charlson comorbidity index ($p = .001$), early stage at diagnosis ($p = .011$), adjuvant radiation ($p = .013$), and lack of chemotherapy use ($p = .001$) were all statistically significant in the increased development of jaw complications (Table 3).

TABLE 2. Demographics and characteristics of the entire cohort of patients with oral cancers and statistical significance of these factors on the development of jaw complications.

		Jaw complications		
Characteristic	Total	No. of patients, *n* (%)		*p* value
Age at diagnosis, y				
66–69	636	113	(17.8)	.303
70–74	721	113	(15.7)	
75–80	491	71	(14.5)	
Sex				
Female	641	126	(19.7)	.002
Male	1027	171	(16.7)	
Race				
Black	134	11	(08.2)	.023
White	1609	272	(16.9)	
Other	105	14	(13.3)	
Marital status				
Married	1035	171	(16.5)	.053
Unmarried	716	103	(14.4)	
Unknown	97	23	(23.7)	
Charlson comorbidity index				
0	1097	204	(18.6)	.001
1	486	64	(13.2)	
2+	265	29	(10.9)	
Urban vs rural				
Urban	1678	266	(15.9)	.420
Rural	170	31	(18.2)	
SEER region				
West/Hawaii	856	143	(16.7)	.739
Northeast	386	63	(16.3)	
Midwest	200	33	(16.5)	
South	406	58	(14.3)	
Income quartile				
1st quartile	462	69	(14.9)	.846
2nd quartile	462	74	(16.0)	
3rd quartile	462	75	(16.2)	
4th quartile	462	79	(17.1)	
Education quartile				
1st quartile	437	73	(16.7)	.217
2nd quartile	436	81	(18.6)	
3rd quartile	433	66	(15.2)	
4th quartile	435	57	(13.1)	
Unknown	107	20	(18.7)	
Stage at diagnosis				
Early	493	97	(19.7)	.011
Advanced	1355	200	(14.8)	
Radiation role				
Definitive	1103	158	(14.3)	.013
Adjuvant	745	139	(18.7)	
Type of radiation*				
IMRT	679	95	(14.0)	.064
Non-IMRT	1169	202	(17.3)	
Chemotherapy use				
Chemotherapy	636	76	(11.9)	.001
No chemotherapy	1212	221	(18.2)	

Abbreviations: SEER, Surveillance, Epidemiology, and End Results; IMRT, intensity-modulated radiation therapy.
* Note: The use of IMRT is a time-sensitive variable, with different follow-up times as a consequence of its increasing use in the later years of this analysis.

TABLE 3. Comparison of patients treated with IMRT and those treated with non-IMRT.

Characteristic	Total	IMRT		Non-IMRT		Chi-square *p* value
		n	(%)	*n*	(%)	
Age at diagnosis, y						
66–69	636	**265**	(**41.7**)	371	(58.3)	.004
70–74	721	255	(35.4)	466	(64.6)	
75–80	491	159	(32.4)	332	(67.6)	
Sex						
Male	1207	**469**	(**38.9**)	738	(61.1)	.010
Female	641	210	(32.8)	431	(67.2)	
Marital status						
Married	1035	**410**	(**39.6**)	625	(60.4)	.010
Unmarried	716	241	(33.7)	475	(66.3)	
Unknown	97	28	(28.9)	69	(71.1)	
Charlson comorbidity index						
0	1097	**413**	(**37.6**)	684	(62.4)	.078
1	486	185	(38.1)	301	(61.9)	
2+	265	81	(30.6)	184	(69.4)	
Urban vs rural						
Urban	1678	**633**	(**37.7**)	1045	(62.3)	.006
Rural	170	46	(27.1)	124	(72.9)	
SEER region						
West/Hawaii	856	**358**	(**41.8**)	498	(58.2)	<.001
Northeast	386	127	(32.9)	259	(67.1)	
Midwest	200	56	(28.0)	144	(72.0)	
South	406	138	(34.0)	268	(66.0)	
Income quartile						
1st quartile	462	140	(30.3)	322	(69.7)	.002
2nd quartile	462	167	(36.1)	295	(63.9)	
3rd quartile	462	177	(38.3)	285	(61.7)	
4th quartile	462	195	(42.2)	267	(57.8)	
Education quartile*						
1st quartile	437	**191**	(**43.7**)	246	(56.3)	.001
2nd quartile	436	171	(39.2)	265	(60.8)	
3rd quartile	433	136	(31.4)	297	(68.6)	
4th quartile	435	141	(32.4)	294	(67.6)	
Unknown	107	40	(37.4)	67	(62.6)	
Stage at diagnosis						
Early stage	493	158	(32.0)	335	(68.0)	.012
Advanced stage	1355	**521**	(**38.5**)	834	(61.5)	
Radiation role						
Definitive	1103	**426**	(**38.6**)	677	(61.4)	.041
Adjuvant	745	253	(34.0)	492	(66.0)	
Chemotherapy use						
Chemotherapy	636	**331**	(**52.0**)	305	(48.0)	<.001
No chemotherapy	1212	348	(28.7)	864	(71.3)	
Year of treatment						
1999–2003	934	111	(11.9)	823	(88.1)	<.001
2004–2007	914	**568**	(**62.1**)	346	(37.9)	

Abbreviations: IMRT, intensity-modulated radiation therapy; SEER, Surveillance, Epidemiology, and End Results.
* Note: Education level is defined as the percentage of people over the age of 25 years who had at least 12 years education within a given area. Boldface entries indicate statistically significant in the increased use of IMRT vs. non-IMRT.

On multivariate analysis, female sex, lack of chemotherapy use, and a low comorbidity score were the 3 factors that were statistically significant in predicting the development of all jaw complications. Male patients were less likely than female patients to develop jaw complications (HR = 0.71; 95% CI 0.56–0.89). Patients treated without chemotherapy were more likely to develop jaw complications than those who did receive chemotherapy (HR = 1.44; 95% CI 1.10–1.88), and patients with higher comorbidity scores were less likely to develop jaw complications than those with no comorbidities (HR = 0.73; 95% CI 0.55–0.96 for comorbidity score of 1 and HR = 0.67, 95% CI 0.45-0.99 for comorbidity score of 2 or more).

Impact of IMRT vs. non-IMRT techniques on the development of jaw complications

On univariate analysis, the use of IMRT demonstrated a trend to reduced development of jaw complications compared with non-IMRT ($p = 0.064$). The rate of jaw complications in patients treated with IMRT was 14.0% compared with 17.3% for patients treated with non-IMRT; however, the population treated with IMRT varied considerably from those treated with non-IMRT (Table 3). In addition, the use of IMRT itself was time sensitive, with increased use during the later years of analysis; 62% of patients treated from 2004 to 2007 were treated with IMRT compared with 11.9% of patients treated from 1999 to 2003.

We explored the time to development of jaw complications stratified by those treated with IMRT versus those treated with non-IMRT techniques. Among the 297 patients who developed jaw complications after radiation therapy, the median time to development of these complications was 462 days for the IMRT treatment group compared with 386 days for the non-IMRT treatment group. The stratified Cox regression model shows that the development of jaw complications over time between the IMRT and non-IMRT treatment groups has a nonproportional hazard. Specifically, the patients treated with IMRT may have a longer latency until the development of jaw complications within the first 3 years (see Figure 1). However, after 3 years, the risks of development of jaw complications appear to be similar between the 2 groups.

DISCUSSION

Severe jaw complications, particularly osteoradionecrosis requiring surgical intervention, are among the most debilitating and expensive chronic side effects of

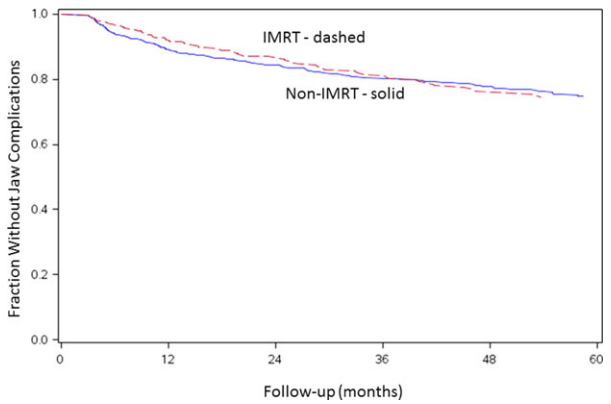

FIGURE 1. Adjusted Cox regression analysis depicting the development of jaw complications with time for patients treated with IMRT (dashed) compared with those treated with non-IMRT (solid). All jaw complications were included, regardless of the time of development; however, the graph is truncated at 5 years, which is twice the median follow-up time of 2.5 years. IMRT, intensity-modulated radiation therapy. [Color figure can be viewed in the online edition, which is available at wileyonlinelibrary.com.]

radiation therapy for oral cancers. In this analysis of a large population-based cohort, which is reflective of community-based practice, we demonstrated that the rates of severe jaw complications are consistent with published reports. However, the rates of lower-grade complications are much higher than expected from the reported literature.

Osteoradionecrosis itself represents a spectrum of diseases. Studer and colleagues[12] established a grading system: grade 1 was defined as exposed bone without radiographic evidence of necrosis that healed with conservative treatment, grade 2 as exposure and necrosis of superficial cortical bone which healed without surgery, grade 3 as diffuse bone necrosis requiring resection, and grade 4 as recurrent/residual necrosis despite prior surgery. Clayman[23] reviewed the literature to determine the rates of ORN after head and neck radiation and found crude rates of postextraction ORN of 11.8% from 1938 to 1968 and 5.4% from 1968 to 1992. This trend for reduction in the rates of ORN continued in the modern era; Wahl[24] reviewed the literature and described a rate of 3.0% from 1997 to 2004. It was hypothesized that the reduction in rates of ORN was due to several technological advances in the delivery of radiation therapy, including high-energy photons, CT planning, as well as improved dental prophylaxis and improved awareness of the risks of dental interventions after treatment.[23,24] Of note, these prior literature reviews are limited by the detail of the data originally published. It can be deduced from these studies that most reports of ORN reflect grade 3–4 disease, or in some cases grade 2, which are those that require intervention with surgery and/or hyperbaric oxygen; rates of less severe, but still bothersome, cases of jaw complications are less well documented.

Overall, this analysis suggests that a much larger proportion of patients than is predicted have low-grade jaw complications, such as exposed bone that require conservative treatment, including antibiotics. In some patients, these cases progress to more advanced disease requiring procedures and more invasive treatment. Arguments could be made that both the early and more advanced jaw complications should be considered clinically meaningful. Even conservative treatment is inconvenient for patients, may be expensive, and have an impact on quality of life.

Evaluating the other contributing factors, we found female sex, lack of chemotherapy use, and low Charlson comorbidity index to be significantly associated with development of jaw complications. Females were more likely to develop jaw complications than males. This may be due to higher rates of osteoporosis in females contributing to bone complications, potential concurrent use of bisphosphonates, or possibly better dental care and follow-up in females,[25,26] leading to increased diagnosis rates. Patients who did not receive chemotherapy were more likely to develop jaw complications; the mechanism for this is unclear. One potential hypothesis is that patients who did not receive chemotherapy may have been less healthy at the onset of treatment, with reduced functional capacity and physiologic reserve; these patients may have had a shorter life expectancy and thus less time to develop jaw complications. Finally, patients with fewer comorbidities were more likely to develop jaw complications; this is likely due to improved follow-up and longer survival in this group. Indeed, patients with more comorbidities (Charlson comorbidity score of 2 or more) had a median survival of only 35 months compared with 81 months in patients with a Charlson comorbidity score of 0; as a result, patients with higher Charlson comorbidity scores were less likely to live long enough to develop jaw complications. Further study is warranted to investigate the factors contributing to jaw complications after radiation and providing effective early interventions.

In this analysis, we found that IMRT does not result in a significantly different rate of development of jaw complications (of all grades) compared with non-IMRT. When first adopted for the treatment of head and neck cancer, the principal goals of IMRT were to provide improved tumor coverage and to minimize postradiation xerostomia. Phase II and III trials have demonstrated that IMRT can accomplish both of these goals.[27–29] What is less clear is whether IMRT is useful in reducing other complications of radiation, including dysphagia and ORN. In the Radiation Therapy Oncology Group (RTOG) multiinstitutional study of IMRT for early-stage oropharyngeal cancer (RTOG 0022), a rate of 6% ORN was reported.[27] The guidelines of that study were that 1 cubic centimeter of the mandible not receive greater than 106% of the prescribed dose; thus, mandibular sparing was not prioritized. The phase III PARSPORT trial demonstrated that IMRT can reduce xerostomia, but other late effects were not impacted; dose constraints on the mandible were not defined in the manuscript.[29] It is interesting that the reduction in xerostomia afforded by IMRT has not resulted in a decrease in ORN; it could be hypothesized that improved salivary function would have resulted in better postradiation dental health and fewer jaw complications.

Some recent series from academic settings have reviewed the rates of ORN in patients treated with IMRT. Nguyen et al[30] retrospectively reviewed a series of 83 patients treated with IMRT for locally advanced head and neck cancers of all subsites; their mean mandibular dose was less than 44 Gy, and with a median follow-up of 28 months, they had only a single case of ORN requiring a procedure (HBO). Ben-David and colleagues[13] reviewed the experience with IMRT at the University of Michigan. In this series, all patients treated with parotid-sparing IMRT on prospective trials with pretreatment dental intervention were evaluated. With 176 patients and a median follow-up of 34 months, they reported no cases of ORN. These 2 series largely limit their complication definition to more severe jaw complications necessitating procedures and may not capture early complications that respond to conservative management.

This analysis and conclusions drawn as a result should be considered hypothesis-generating. As with all observational studies using claims data, this study does have inherent limitations. Claims data in the Medicare data set were not collected for research purposes; thus, there is some uncertainty regarding their completeness and accuracy. The data also do not reflect patient and provider preferences. In addition, the data source used in these analyses captures patients only over 65 years of age; given that the population of head and neck cancer patients is getting younger due to human papillomavirus–associated

cancers, this emerging subpopulation was not captured in this analysis.[31] Also, the data source does not capture complete data on roughly 15% of patients with managed care coverage. With regard to this analysis in particular, patients who develop osteoradionecrosis often have had recent dental work, which prompts the complication; it is not possible to capture dental extractions from the SEER–Medicare database, so the number of patients who had an antecedent extraction or surgery is not evaluated in this analysis. Furthermore, patients who have had mandibular surgery (compared with tonsillectomy or glossectomy) could be expected to be at increased risk for the development of jaw complications. Due to limitations in accurately capturing the full extent of surgery from claims data, we did not attempt to control for the specific surgeries such as glossectomy or mandibulectomy, because claims data may only reflect "resection of tumor" rather than itemize anatomy removed in en bloc resections. In addition, the incidence of osteoradionecrosis has been reported to correlate with the dose of radiation therapy received.[32–34] Although it would be interesting to evaluate the impact of dose on our outcomes, dose is not available in the SEER–Medicare database. Although we can determine the number of fractions delivered, the diversity of fractionation schema used for treatment of head and neck cancer precluded our ability to derive conclusions about the actual dose delivered to patients in this analysis. Despite these limitations, this data source provides a comprehensive population-based resource for studying patterns of care and outcomes across the country.

The results of this analysis should motivate future study of the rates and impact of jaw complications on patients with head and neck cancers, specifically as it relates to the role of IMRT on development of jaw complications. Although rates of severe complications are approximately 3% to 4%, a notably larger proportion of this cohort had low-grade complications that may have an impact on them from a quality of life, medical, and socioeconomic standpoint. Further study of the economic burden of jaw complications, as well as further follow-up on later term complications, is crucial to adequately counsel these patients, design their care, schedule follow-up, and effectively treat their cancer and possible side effects of treatment.

Acknowledgements

We acknowledge that this study used the linked SEER–Medicare database. The interpretation and reporting of these data are the sole responsibility of the authors. The authors acknowledge the efforts of the Applied Research Program, NCI; the Office of Research, Development and Information, CMS; Information Management Services (IMS), Inc.; and the Surveillance, Epidemiology, and End Results (SEER) Program tumor registries in the creation of the SEER–Medicare database.

REFERENCES

1. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun MJ. Cancer statistics, 2009. *CA Cancer J Clin* 2009;59:225–249.
2. Chambers MS, Garden AS, Kies MS, Martin JW. Radiation-induced xerostomia in patients with head and neck cancer: pathogenesis, impact on quality of life, and management. *Head Neck* 2004;26:796–807.
3. Chambers MS, Rosenthal DI, Weber RS. Radiation-induced xerostomia. *Head Neck* 2007;29:58–63.
4. Eisbruch A, Kim HM, Terrell JE, Marsh LH, Dawson LA, Ship JA. Xerostomia and its predictors following parotid-sparing irradiation of head-and-neck cancer. *Int J Radiat Oncol Biol Phys* 2001;50:695–704.
5. Epstein JB, Robertson M, Emerton S, Phillips N, Stevenson-Moore P. Quality of life and oral function in patients treated with radiation therapy for head and neck cancer. *Head Neck* 2001;23:389–398.
6. Langendijk JA, Doornaert P, Verdonck-de Leeuw IM, Leemans CR, Aaronson NK, Slotman BJ. Impact of late treatment-related toxicity on quality of life among patients with head and neck cancer treated with radiotherapy. *J Clin Oncol* 2008;26:3770–3776.
7. Puri DR, Chou W, Lee N. Intensity-modulated radiation therapy in head and neck cancers: dosimetric advantages and update of clinical results. *Am J Clin Oncol* 2005;28:415–423.
8. Chou WW, Puri DR, Lee NY. Intensity-modulated radiation therapy for head and neck cancer. *Expert Rev Anticancer Ther* 2005;5:515–521.
9. Kam MK, Leung SF, Zee B, et al. Prospective randomized study of intensity-modulated radiotherapy on salivary gland function in early-stage nasopharyngeal carcinoma patients. *J Clin Oncol* 2007;25:4873–4879.
10. Eisbruch A, Ship JA, Dawson LA, et al. Salivary gland sparing and improved target irradiation by conformal and intensity modulated irradiation of head and neck cancer. *World J Surg* 2003;27:832–837.
11. Eisbruch A, Ten Haken RK, Kim HM, Marsh LH, Ship JA. Dose, volume, and function relationships in parotid salivary glands following conformal and intensity-modulated irradiation of head and neck cancer. *Int J Radiat Oncol Biol Phys* 1999;45:577–587.
12. Studer G, Studer SP, Zwahlen RA, et al. Osteoradionecrosis of the mandible: minimized risk profile following intensity-modulated radiation therapy (IMRT). *Strahlenther Onkol* 2006;182:283–288.
13. Ben-David MA, Diamante M, Radawski JD, et al. Lack of osteoradionecrosis of the mandible after intensity-modulated radiotherapy for head and neck cancer: likely contributions of both dental care and improved dose distributions. *Int J Radiat Oncol Biol Phys* 2007;68:396–402.
14. Guadagnolo BA, Liu CC, Cormier JN, Du XL. Evaluation of trends in the use of intensity-modulated radiotherapy for head and neck cancer from 2000 through 2005: socioeconomic disparity and geographic variation in a large population-based cohort. *Cancer* 2010;116:3505–3512.
15. Sher DJ, Neville BA, Chen AB, Schrag D. Predictors of IMRT and conformal radiotherapy use in head and neck squamous cell carcinoma: a SEER-Medicare analysis. *Int J Radiat Oncol Biol Phys* 2011;81:e197–e206.
16. National Cancer Institute (NCI). Surveillance, Epidemiology, and End Results (SEER) program research data (1973–2008). In: Schottenfeld D, Fraumeni JF Jr, editors. Bethesda, MD: Surveillance Research Program, 2010 edition. Cancer Statistics Branch; Released April, 2011 based on November 2010 submission. Available at www.seer.cancer.gov. Accessed September 28, 2011.
17. Potosky AL, Riley GF, Lubitz JD, Mentnech RM, Kessler LG. Potential for cancer related health services research using a linked Medicare-tumor registry database. *Med Care* 1993;31:732–748.
18. Warren JL, Klabunde CN, Schrag D, Bach PB, Riley GF. Overview of the SEER-Medicare data: content, research applications, and generalizability to the United States elderly population. *Med Care* 2002;40 (Suppl 8): IV3–IV18.
19. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987;40:373–383.
20. Klabunde CN, Potosky AL, Legler JM, Warren JL. Development of a comorbidity index using physician claims data. *J Clin Epidemiol* 2000;53: 1258–1267.
21. Klabunde CN, Harlan LC, Warren JL. Data sources for measuring comorbidity: a comparison of hospital records and medicare claims for cancer patients. *Med Care* 2006;44:921–928.
22. Klabunde CN, Legler JM, Warren JL, Baldwin LM, Schrag D. A refined comorbidity measurement algorithm for claims-based studies of breast, prostate, colorectal, and lung cancer patients. *Ann Epidemiol* 2007;17: 584–590.
23. Clayman L. Management of dental extractions in irradiated jaws: a protocol without hyperbaric oxygen therapy. *J Oral Maxillofac Surg* 1997;55: 275–281.
24. Wahl MJ. Osteoradionecrosis prevention myths. *Int J Radiat Oncol Biol Phys* 2006;64:661–669.
25. Swank ME, Vernon SW, Lairson DR. Patterns of preventive dental behavior. *Public Health Rep* 1986;101:175–184.
26. Moeller JF, Chen H, Manski RJ. Investing in preventive dental care for the Medicare population: a preliminary analysis. *Am J Public Health* 2010;100:2262–2269.
27. Eisbruch A, Harris J, Garden AS, et al. Multi-institutional trial of accelerated hypofractionated intensity-modulated radiation therapy for early-stage oropharyngeal cancer (RTOG 00–22). *Int J Radiat Oncol Biol Phys* 2010;76:1333–1338.
28. Lee N, Harris J, Garden AS, et al. Intensity-modulated radiation therapy with or without chemotherapy for nasopharyngeal carcinoma: radiation therapy oncology group phase II trial 0225. *J Clin Oncol* 2009;27: 3684–3690.
29. Nutting CM, Morden JP, Harrington KJ, et al. Parotid-sparing intensity modulated versus conventional radiotherapy in head and neck cancer

(PARSPORT): a phase 3 multicentre randomised controlled trial. *Lancet Oncol* 2011;12:127–136.
30. Nguyen NP, Vock J, Chi A, et al. Effectiveness of intensity-modulated and image-guided radiotherapy to spare the mandible from excessive radiation. *Oral Oncol* 2012;48:653–657.
31. Chaturvedi AK, Engels EA, Anderson WF, Gillison ML. Incidence trends for human papillomavirus-related and -unrelated oral squamous cell carcinomas in the United States. *J Clin Oncol* 2008;26:612–619.
32. Lee IJ, Koom WS, Lee CG, et al. Risk factors and dose-effect relationship for mandibular osteoradionecrosis in oral and oropharyngeal cancer patients. *Int J Radiat Oncol Biol Phys* 2009;75:1084–1091.
33. Chopra S, Kamdar D, Ugur OE, et al. Factors predictive of severity of osteoradionecrosis of the mandible. *Head Neck* 2011;33:1600–1605.
34. Nabil S, Samman N. Incidence and prevention of osteoradionecrosis after dental extraction in irradiated patients: a systematic review. *Int J Oral Maxillofac Surg* 2011;40:229–243.