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Scientific Article

The impact of radiation treatment planning technique on unplanned hospital admissions

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Abstract

Purpose: Treatment burdens and toxicities related to palliative radiation therapy (RT) may lead to unplanned hospital admissions (UHAs). The likelihood for these toxicities may be related to treatment technique. We compared rates of UHA between patients receiving nonconformal (2-dimensional) and conformal (3-dimensional or higher) radiation treatments to bone metastases involving the vertebral column.

Methods and materials: We retrospectively analyzed patients treated with RT for bone metastases at a single tertiary care center between 2010 and 2017. We compared rates of RT-related UHA within 90 days of receiving radiation using Cox competing risk regression models.

Results: We identified 326 patients with bone metastases involving the vertebral column, 139 of whom received radiation by nonconformal technique and 187 by conformal technique. On multivariable analysis, conformal techniques were associated with a reduced risk of 90-day UHA (hazard ratio [HR]: 0.35; 95% confidence interval [CI], 0.14-0.88). Other significant factors include hematologic cancer (HR: 0.17; 95% CI, 0.03-0.82) and baseline Eastern Cooperative Oncology Group score ≥ 2 (HR: 3.02; 95% CI, 1.05-8.69).

Conclusions: The utilization of conformal (non-2-dimensional) radiation treatment plans may help reduce treatment-related toxicities and consequently UHAs after palliation of bone metastases.
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Introduction

Radiation therapy (RT) is a highly effective form of symptom palliation for patients with bone metastases. At the same time, patients who receive palliative RT for bone metastases are particularly vulnerable to treatment-related burdens and toxicities that sometimes lead to unplanned hospitalizations.[1] Unplanned hospital admission (UHA) is a result of treatment-related burdens that overwhelm patients to such an extent that hospitalization is required. UHAs are costly and have a negative impact on the wellbeing of patients with cancer in many ways.[2,3] Adverse reactions to chemotherapy agents and surgical interventions are known to result in UHAs and, consequently, greater morbidity and/or mortality.[4,5] The consequences of RT, in particular palliative RT (ie, interventions meant to ease the burden of tumor-related symptoms for patients with cancer), on UHAs has not yet been as well established.

The vertebral column is a very common site of metastatic bone involvement and among the most frequently irradiated regions for the purpose of palliation.[6,7] Because of its central location within the body, radiation beams targeting the vertebral column cross sensitive normal structures including the bowel, bladder, and esophagus and can cause significant complications including nausea, diarrhea, cystitis, odynophagia, and esophagitis. These complications can be so severe that they result in UHAs for dehydration, inability to take in adequate nutrition, or uncontrolled pain.[8]

In theory, radiation treatment planning technique may be a mediator for the development of treatment-related toxicity. For instance, if a radiation treatment plan is able to spare dose to normal organ structures, then side effects caused by inflammatory responses within these organs may be averted.[8] The dose to surrounding normal structures is often higher with conventional nonconformal (2-dimensional) techniques compared with more conformal planning techniques.[9-11] Yet, given the scarcity of compelling data supporting the advantages of 3-dimensional or other highly conformal planning for limiting toxicity during treatment of bone metastases,[12] conformal planning is often not reimbursed by payers.

We hypothesized that patients with bone metastases involving the spine were less likely to experience a UHA for a treatment-related toxicity if radiation were delivered using conformal (3-dimensional or higher) RT. We examined the impact of radiation planning technique on toxicity-related hospital admissions among patients with advanced cancer who received palliative RT treatment to vertebral metastases.

Methods and materials

Setting and study design

A retrospective observational cohort analysis was conducted on patients with advanced cancer who were treated at Mount Sinai Hospital, New York, New York. Mount Sinai Hospital is a high-volume quaternary care center that treats patients from widely diverse socioeconomic backgrounds. Our study was approved by the institutional review board.

Subjects

Patients with advanced cancer with bone metastases were identified through electronic medical records and review of International Classification of Diseases 9 and 10 codes (198.3 and C79.51, respectively). Patients ages 18 to 95 years with confirmed pathologic or radiographic evidence of osseous metastases in the spine who had their first palliative RT course to a bone metastasis between January 2010 and February 2017 were included.

We defined a treatment course as a group of RTs prescribed by the radiation oncologist in 1 consult encounter. These treatments were typically given within 1 week of each other and may have targeted different anatomic sites but included at least 1 spine site. We included the first treatment course given to a patient that comprised palliative RT to a spinal region (cervical, thoracic, lumbar, sacral). Patients were placed in the first cohort if they received nonconformal (2-dimensional) radiation and in the second cohort if they received conformal (3-dimensional, intensity modulated radiation RT, stereotactic body RT) radiation. Patients who received both nonconformal and conformal treatments during 1 course or within a week of finishing their first course were excluded from our analysis.

Radiation technique

Our department utilized computed tomography simulation for all treatments, conformal and nonconformal

Table 1 Treatment-related toxicities from radiation therapy (adapted from Needham and Hokin[8])

Region	Vertebrae[a]	Toxicity
Head, neck	C1 to T2	Otitis, dysphagia, odynophagia, mucositis, esophagitis, xerostomia, musculoskeletal pain
Chest	T3 to T8	Dyspnea, cough, esophagitis, cardiomyopathy, musculoskeletal pain
Abdomen	T9 to L4	Esophagitis, gastritis, colitis, diarrhea, nausea, vomiting, musculoskeletal pain
Pelvis	L5 to S5	Bladder retention, dysuria, diarrhea, abdominal cramping, musculoskeletal pain
Skin	Any	Dermatitis, erythema, desquamation
General	Any	Changes in mental status, anemia, immunocompromised (increased risk of infection)

a Vertebrae levels corresponding to body region.

alike. Conformal was defined as using ≥ 3 static beam angles and varying beam weightings to achieve a 100% dose cloud around the radiation target. Nonconformal was defined as 2 beam angles, parallel-opposed and with equal weighting. For nonconformal treatments, no normal structures with the exception of kidneys were taken into consideration when drawing multileaf collimators on the parallel opposed anteroposterior/posteroanterior fields. In conformal treatment plans, at least 1 organ (most frequently the gastrointestinal [GI] tract [small or large bowel, stomach, esophagus]) was contoured and treated as an organ at risk during planning. Dose distributions in the form of a dose-volume histogram, or dose clouds depicted on the plans themselves, were reviewed to ensure that the dose to organs at risk was as low as reasonably achievable. Often, this minimal dose was kept less than the standard accepted normal tissue constraints because the total (palliative) prescription dose was less than normal tissue constraints.

Outcomes of interest

Our primary outcome of interest was a UHA for RT-related toxicities within 90 days (the standard window for acute toxicity) of RT. The chief complaint and admission diagnoses were used to determine whether a hospitalization was RT related (eg, admission for severe noninfectious diarrhea within a week of lumbar spine RT would be considered an RT-related admission). Table 1 groups the vertebrae levels with their corresponding body region and relevant toxicities. The determination of RT-related admissions was made by a team consisting of an attending radiation oncologist, radiation oncology resident, and medical student. Stays in the emergency department that did not result in an eventual hospital admission were excluded. Only admissions related to the first RT were considered; all other admissions for reasons unrelated to RT (eg, chemotherapy, procedures) were omitted from our analysis for simplification.

Other predictors

We included patient-related predictors that could have an impact on treatment burden: age, sex, race, medical insurance, primary cancer type, Charlson comorbidity index,[13] baseline Eastern Cooperative Oncology Group (ECOG) performance status, and outpatient/inpatient status during RT. In addition, we included predictors related to the RT plan: spinal treatment volume, radiation total dose, and radiation fractional dose. Spine treatment volume was determined by the number of vertebrae treated with radiation. The fractional radiation dose was calculated by dividing total dose by number of fractions.

Data sources

Demographic information and hospitalization courses were collected from electronic medical records from Epic (Epic Systems Corporation, Verona, WI). RT plans were acquired from MOSAIQ version 2.64 software (Elekta AB, Stockholm, Sweden). Medical insurance status was extracted from the hospital's cost accounting system (Allscripts TSI).

Statistical analysis

Continuous and categorical variables were summarized by median and range and by proportion, respectively. The balance between cohorts was assessed by the standardized difference of means (for continuous variables) and percentage (for categorical variables). Although there is no standard threshold to determine an acceptable balance, a standardized difference below 0.1 usually indicates negligible differences between groups.[14] Cumulative incidence functions (CIFs) were used to estimate time from RT to first UHA in a competing risk setting. The first UHA within 90 days of RT was the defining event, and death within the 90-day window was the competing event. CIFs were compared between 2 types of RT techniques using Gray's test to test the null hypotheses of equality of CIFs across groups.[15,16] In a supplementary analysis, hospice admission was also included as a competing event.

Univariable Cox competing risk regression models for admission were built for all demographic and clinical variables using Fine and Gray's extension of Cox regression.[17] Only a limited number of variables could be included in the multivariable analysis to ensure adequate
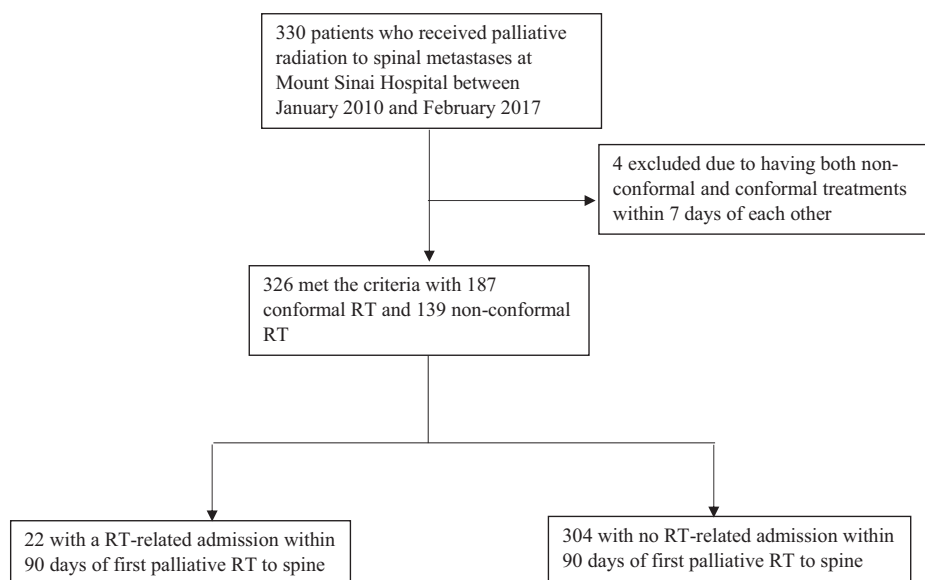
Figure 1 Patient consort diagram. Inclusion criteria: (1) Age 18-95 years, (2) confirmed pathologic or radiologic evidence of spinal metastases, (3) receipt of first palliative radiation therapy to bone metastases between January 2010 and February 2017, and (4) no receipt of both nonconformal (2-dimensional) and conformal treatments (3-dimensional or higher) within a course or within a week of finishing the first course.

statistical power because of the small number of events. Therefore, backward stepwise selection based on Akaike information criterion using R packages (crrstep and cmprsk) was performed. Primary cancer type, baseline ECOG status, inpatient status during RT, spinal treatment volume, and RT techniques were chosen for the final model.

Hazard ratios (HRs) for the time to UHA and corresponding 95% confidence intervals (CIs) were calculated in both univariable and multivariable analyses to assess the associations between variables and risk of admissions. All hypothesis testing was 2-sided and conducted at the 5% level of significance. Statistical analyses were performed with the SAS version 9.4 (SAS Institute Inc., Cary, NC) software package and R Statistical Software (R-3.4.1, Foundation for Statistical Computing, Vienna, Austria). All results were reported following the SAMPL guidelines.

Results

Patient demographic and clinical information

A total of 326 patients met our inclusion criteria for analysis; 139 (42.6%) received nonconformal (2-dimensional) radiation and 187 (57.4%) received conformal (non-2-dimensional) radiation. Four patients were excluded because they had both nonconformal and conformal RT within 7 days of each other. The patient consort diagram is presented in Fig 1.

Notable differences between the cohorts were baseline ECOG scores, inpatient status, spine treatment volume, total radiation dose, and fractional dose of radiation (Table 2). Patients with hematological cancers can be further broken down into subgroups with multiple myeloma (n = 92), lymphoma (n = 2), and leukemia (n = 1).

Comparisons of CIFs between RT planning technique groups

A total of 22 patients had a UHA within 90 days of the start of their first RT to the spine: 15 received nonconformal RT, and 7 received conformal RT. A total of 304 patients had no UHA. Among patients who received conformal RT, UHAs did not appear to be affected by year of RT (Suppl. Fig 1). From the entire study group, 102 patients died (all-cause) within 90 days of RT. Death was considered a competing risk. None of the 22 patients with a UHA experienced death. Hospitalization details are summarized in Table 3.

The median follow-up for patients was 201 days (95% CI, 143-267). Gray's test of equality between the nonconformal and conformal RT groups showed a significant difference in both 90-day admissions (P = .0111) and death as competing events (P = .0151l; Fig 2).

Table 2 Patient characteristics and demographics

n	Overall	Nonconformal RT	Conformal RT	SMD
	326	139	187	
Age, y (median [range])	62 [23-95]	60 [23-95]	64 [31-93]	0.187
Sex (%)				
Female	135 (41.4)	54 (38.8)	81 (43.3)	0.091
Male	191 (58.6)	85 (61.2)	106 (56.7)	
Race (%)				
White	132 (40.5)	56 (40.3)	76 (40.6)	0.131
Black	85 (26.1)	36 (25.9)	49 (26.2)	
Hispanic	58 (17.8)	22 (15.8)	36 (19.3)	
Other	51 (15.6)	25 (18.0)	26 (13.9)	
Primary cancer (%)				
Gastrointestinal	48 (14.7)	23 (16.5)	25 (13.4)	0.199
Breast	39 (12.0)	14 (10.1)	25 (13.4)	
Genitourinary	45 (13.8)	18 (12.9)	27 (14.4)	
Hematologic	86 (26.4)	40 (28.8)	46 (24.6)	
Lung	65 (19.9)	29 (20.9)	36 (19.3)	
Other	43 (13.2)	15 (10.8)	28 (15.0)	
Insurance type (%)				
Medicaid	62 (19.0)	26 (18.7)	36 (19.3)	0.205
Medicare	156 (47.9)	61 (43.9)	95 (50.8)	
Private	101 (31.0)	50 (36.0)	51 (27.3)	
None/Other	7 (2.1)	2 (1.4)	5 (2.7)	
CCI (median [range])	6 [1-15]	6 [1-15]	6 [2-15]	0.169
Baseline ECOG (%)				
0/1	157 (48.2)	47 (33.8)	110 (58.8)	0.518
2/3/4	169 (51.8)	92 (66.2)	77 (41.2)	
Inpatient status during RT (%)				
No	195 (59.8)	61 (43.9)	134 (71.7)	0.586
Yes	131 (40.2)	78 (56.1)	53 (28.3)	
Spine volume (median [range])	4 [0.5-20]	5 [1-16]	3 [0.5-20]	0.653
RT total dose (median [range])	2000 [800-4680]	3000 [800-3750]	2000 [800-4680]	0.503
Fractional dose (median [range])	300 [180-1800]	300 [200-800]	400 [180-1800]	0.921

CCI, Charlson comorbidity index; ECOG, Eastern Cooperative Oncology Group; RT, radiation therapy; SMD, standardized mean difference.

Univariable and multivariable analyses for rates of UHA are summarized in Table 4. On univariable analysis, patients treated with conformal techniques were less likely to experience a UHA within 90 days of RT (HR: 0.33; 95% CI, 0.14-0.81). Additionally, patients with hematologic cancers (HR: 0.18; 95% CI, 0.04-0.88) were less likely to experience a UHA. An ECOG score of ≥ 2 (HR: 2.55; 95% CI, 1.00-6.51) put patients at a higher risk of a UHA.

On multivariable analysis, conformal techniques remained with reduced risk of 90-day admission (HR: 0.35; 95% CI, 0.14-0.88). Other significant variables included hematologic cancer (HR: 0.17; 95% CI, 0.03-0.82) and baseline ECOG score ≥ 2 (HR: 3.02; 95% CI, 1.05-8.69). Inpatient status during RT was also associated with a lower risk of a subsequent RT-related admission (HR: 0.34; 95% CI, 0.13-0.91).

Supplementary analysis using hospice admission and death as competing risk events also showed that conformal RT was significantly associated with a reduced risk of 90-day admission (HR: 0.29; 95% CI, 0.11-0.75). These results are presented in Supplementary Table 1.

Discussion

Our investigation shows that patients who receive radiation with conformal planning techniques (3-dimensional or higher) had an associated 65% reduced risk of experiencing a radiation-related UHA within the acute toxicity window of 90 days of RT. Notably, those with a baseline ECOG score of ≥ 2 were 2 times more likely to be admitted to the hospital for management of an RT-related toxicity compared with those with an ECOG score of 0 to 1. These results held true when hospice status was considered a competing event in our multivariable analysis.

Table 3   Reasons of RT-related admissions within 90 days of initiating palliative RT to the spine

Irradiated regions	Reason for admission	Total (n = 22)	Nonconformal RT (n = 15)	Conformal RT (n = 7)
Head, neck, chest, abdomen, pelvis, general	Gastrointestinal symptoms (abdominal pain, diarrhea, constipation, nausea & vomiting, dysphagia, GERD, jaundice, pancreatitis)[a]	16 (72.7%)	11	5
Head, neck, chest, abdomen, pelvis, general	Constitutional symptoms (appetite and weight loss, dehydration, fatigue, cachexia, failure to thrive, pallor)	11 (50.0%)	7	4
Head, neck, chest, abdomen, pelvis, general	Musculoskeletal symptoms (pain of the back, hips, or extremities)	12 (54.6%)	7	5
General, skin	Infection	4 (18.2%)	4	0
Chest	Dyspnea	4 (18.2%)	3	1
General	Anemia	2 (9.1%)	1	1

GERD, gastroesophageal reflux disease; RT, radiation therapy.

[a] Gastrointestinal symptoms can also lead to dehydration, appetite and weight loss, renal failure, altered mental status, dizziness, and weakness.

RT planning techniques for palliative spine cases, especially if the diagnosis is consistent with a bone metastasis, are often restricted by third-party payers to those that are least costly. Most often, these are simple 2-dimensional treatment plans utilizing 2 equally weighted opposing beams. Using ≥3 static beams can create a more conformal treatment plan with less high dose going to the surrounding normal tissues. This consequently results in less treatment toxicity, in theory (as shown dosimetrically in previously published literature) and in clinical practice as discussed here.

The difference in volume of irradiated tissue between a typical 2- versus 3-dimensional D plan is shown in Fig 3. This dosimetric difference is particularly meaningful when

Figure 2   Estimated cumulative incidence curves with radiation therapy–related admissions and death as competing events for nonconformal and conformal radiation therapy. Gray's test of equality showed significant differences in 90-day admissions (P = .0111) and death (P = .0151).

the target site is located behind sensitive organs such as the GI tract, as is the case with a spine metastasis.[18] The higher incidence of UHAs associated with nonconformal treatment modalities could be explained by the greater amount of normal tissues included in the irradiated volume, causing clinically significant normal tissue toxicity.[19,20] This dosimetric advantage of radiation delivery has been demonstrated in the 3-dimensional palliation of thoracic and lumbar metastases, where less dose is delivered to the heart and kidneys, respectively.[9,10] Nonconformal (2-dimensional) treatment planning may still be preferable in some circumstances given its availability, simplicity in planning, and lower cost. When utilized in anatomic areas where sensitive tissues are not nearby (eg, during palliation of metastases involving extremities), nonconformal treatment planning is particularly useful.

GI-related toxicities (eg, nausea, vomiting, diarrhea, and dehydration) are major contributors to UHA after cancer treatment in general and after radiation treatment (palliative or curative, and for any cancer).[21] We also observed a significant proportion of GI-related toxicities from palliative spine RT (Table 3), which suggests that the GI tract is highly vulnerable and acutely affected during RT. The downstream effects of GI toxicities can amplify other non-GI symptoms such as dehydration and renal failure, and thereby potentiate UHAs.

Functional status is an important determinant in a patient's ability to tolerate and recover from RT effects, especially during palliation of incurable cancers.[22] Studies have found correlations between poor functional status with interruptions in RT treatments, treatment adverse effects, and mortality.[23-25] We did not find a correlation between ECOG performance status and treatment technique. ECOG was a significant predictor of UHA.

There are several limitations in our study. First, our study is an observational cohort analysis from a single center; thus, our results may not be completely
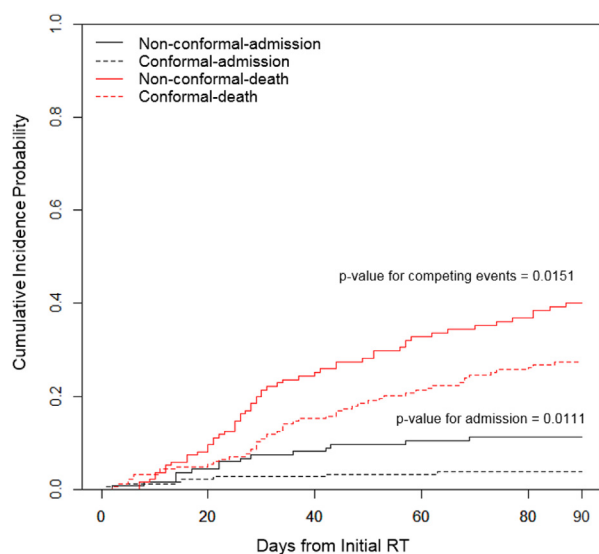
Table 4 Univariable and multivariable Cox competing risk regression analyses on admission rate within 90 days of palliative RT to the spine

	Univariable analysis		Multivariable analysis	
	Hazard ratio	P-value[a]	Hazard ratio	P-value[a]
RT technique		**.0158**		**.0260**
Nonconformal	Ref		Ref	
Conformal	0.33 (0.14-0.81)	**.0158**	0.35 (0.14-0.88)	**.0260**
Age	1.00 (0.96-1.04)	.9444		
Sex		.6698		
Female	Ref			
Male	1.21 (0.51-2.88)	.6698		
Race		.7100		
White	Ref			
Black	1.09 (0.41-2.85)	.8666		
Hispanic	0.66 (0.18-2.39)	.5296		
Other	0.49 (0.11-2.23)	.3573		
Primary cancer		.1293		.1500
Gastrointestinal	Ref		Ref	
Breast	0.20 (0.02-1.71)	.1429	0.23 (0.03-1.96)	.1806
Genitourinary	0.91 (0.28-2.94)	.8706	0.87 (0.26-2.94)	.8235
Hematologic	0.18 (0.04-0.88)	**.0342**	0.17 (0.03-0.82)	**.0273**
Lung	0.88 (0.30-2.59)	.8209	0.77 (0.27-2.17)	.6203
Other	0.18 (0.02-1.51)	.1141	0.18 (0.02-1.49)	.1112
Insurance		.5710		
Medicaid	Ref			
Medicare	1.34 (0.44-4.10)	.6103		
Private	0.78 (0.21-2.91)	.7112		
None/Other	(excluded in univariable analysis)			
CCI	1.12 (0.98-1.28)	.0929		
Baseline ECOG		.0513		**.0410**
0/1	Ref		Ref	
2/3/4	2.55 (1.00-6.51)	.0513	3.02 (1.05-8.69)	**.0410**
Inpatient status during RT		.6940		.0326
No	Ref		Ref	
Yes	0.84 (0.36-1.99)	.6940	0.34 (0.13-0.91)	**.0326**
Spine volume	1.08 (0.99-1.19)	.0942	1.07 (0.95-1.21)	.2803
RT total dose (Unit = 200)	1.10 (0.97-1.25)	.1442		
Fractional dose[b] (Unit = 200)	0.74 (0.35-1.55)	.4212		

CCI, Charlson comorbidity index; ECOG, Eastern Cooperative Oncology Group; Ref, reference; RT, radiation therapy.

  [a] P-value < .05 in bold.

  [b] Fraction dose only limited to dosage <800 because high dosage was usually from stereotactic technique.
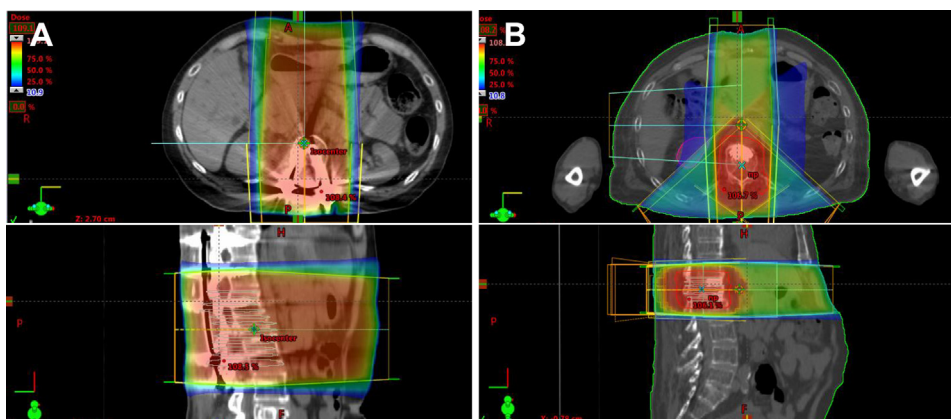

Figure 3 Comparison of a typical 2-dimensional nonconformal treatment plan with 2 equally weighted opposed fields (A) and a 3-dimensional conformal treatment plan with 4 fields (B).

generalizable. A large number of patients at our institution had multiple myeloma, which may not reflect the distribution of malignancies seen in other hospitals and community settings. Nevertheless, the distribution of primary cancer types was not significantly different between nonconformal and conformal cohorts and thus did not confound our multivariable analysis. Second, the number of analyzable events was small; thus only a small group of covariates could be employed in our model. Third, although unplanned admissions were a primary outcome of our study, we did not take into account other downstream services, such as emergency department visits that last <24 hours and re-treatment rates.

Conclusions

Our study adds to the current literature by demonstrating that treatment technique may have a clinically significant impact on acute treatment-related toxicities to such an extent that hospitalization may be necessary to overcome symptom burden. Moreover, hospitalization occurs more often in patients with poorer baseline functional status. Overall, unplanned admissions were the result of multiple factors, including functional status, primary cancer type, and also socioeconomic support.[21]

The primary goal of palliative RT is to relieve suffering and reduce symptom burden. UHAs are directly antithetical to this goal and have a negative impact on patients with advanced cancer.[26] Therefore, authorization by payers should allow for the use of more conformal radiation treatment planning methods and thus the least toxic treatment option possible in the setting of palliation for patients with bone metastases.

Supplementary data

Supplementary material for this article (https://doi.org/10.1016/j.adro.2018.06.006) can be found at www.advanceradonc.org.

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