

## Scientific Article

# Impact of Performance Status and Comorbidity on Palliative Radiation Treatment Tolerance and End-Of-Life Decision-Making



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## Abstract

**Purpose:** Previous studies have indicated a relationship between functional status and comorbidity on overall survival when treating patients with bone and brain metastases. However, the degree to which these findings have been integrated into modern-day practice remains unknown. This study examines the impact of performance measures, including Karnofsky Performance Status (KPS) and comorbidity, on palliative radiation therapy treatment tolerance and fractionation schedule. The relationship between a shorter fractionation schedule (SFx) and pending mortality is examined.

**Methods and materials:** This study included patients who were treated with palliative intent to the brain or bone between January 1, 2016 and June 30, 2016. Demographic and medical characteristics collected included KPS score (stratified as good [90-100], fair [70-80], and poor ( $\leq 60$ )), socioeconomic status, comorbidity (binary measure using the Adult Comorbidity Evaluation-27 scale), site of metastatic disease, and treatment facility. Univariable analyses were performed using the Cox proportional hazards regression model to assess the impact of the variables on the prescribed number of fractions (binary measure,  $\geq 10$  [long fractionation schedule], and  $< 10$  [SFx]), and major treatment interruptions (MTIs; defined as missing  $\geq 3$  radiation therapy treatment days or ending treatment prematurely).

**Results:** A total of 145 patients were eligible for study inclusion, including 95 patients who were treated for bony metastatic disease and 50 patients for brain metastases. High comorbidity ( $P = .029$ ) and both fair ( $P = .051$ ) and poor ( $P = .065$ ) functional status were associated with more frequent MTIs. However, high comorbidity and low KPS score were not associated with

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shorter treatment plans. In addition, patients with an earlier time to death were not more likely to receive an SFx ( $P = .871$ ).

**Conclusions:** Low KPS and elevated comorbidity scores predict for a poorer prognosis and more frequent MTIs; however, there was no indication that physicians incorporated this information in the fractionation scheduling.

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## Introduction

Performance status is a useful measure for patients who receive palliative radiation therapy (RT), and the Karnofsky performance status (KPS) is a positive predictor of overall survival in this patient population.<sup>1,2</sup> Multiple studies suggest that radiation oncologists should use shorter fractionation schedules (SFx) for patients who near the end of life.<sup>3–6</sup> KPS in combination with comorbidity can be tools to assist in the fractionation scheduling for this cohort. Performance status also has the potential to gauge treatment tolerance for patients who receive palliative RT because KPS has already been shown to predict for treatment interruptions in the definitive setting.<sup>7</sup> Nonetheless, this has yet to be examined in patients who receive RT with palliative intent.

Furthermore, the degree to which performance status and comorbidity are integrated into a palliative radiation treatment algorithm remains unknown. Specifically, the influence of both KPS and comorbidity on palliative RT fractionation decision-making has not been studied. In addition, the magnitude of any shift toward an SFx for patients with a poor prognosis (ie, estimable measure using comorbidity and KPS) is unknown.

This study examines the impact of functional status and comorbidity on the fractionation schedule used and major treatment interruptions (MTIs) while simultaneously assessing the relationship between the fractions prescribed and time to mortality, with an overarching goal of optimizing treatment in this cohort.

## Methods and materials

This retrospective study was approved by our institutional review board. Eligible patients were age  $\geq 18$  years and treated with palliative RT between January 1, 2016 and June 30, 2016. Patients were treated at a private academic hospital or safety-net hospital within a single hospital system. Diagnostic workup and radiation treatment for each patient were required to have been within this hospital system. Patients were included if they were treated with palliative RT to the brain or bone (including the spinal column).

Palliative RT that targeted other sites of metastatic disease and superior vena cava syndrome were not included in these analyses because of the limited number of patients and to ensure a homogenous population for our study. Patients who received Gamma Knife or stereotactic body RT were excluded from this study. There is less variability in the fractionation prescription for Gamma Knife and stereotactic body RT among radiation oncology providers at our institution. Therefore, an analysis of the variation of these techniques by comorbidity, functional status, or other variables would be difficult. In addition, these techniques are only offered to patients with an excellent performance status and few comorbidities; thus, any analysis using these variables would be futile.

Demographic, medical, and treatment-related information was collected retrospectively from electronic medical records. Demographic variables included sex, age, race, preferred language, socioeconomic status (SES), and treatment location. Medical variables included comorbidity and KPS at the time of consultation. Treatment variables included prescribed fractions before treatment initiation and MTIs.

## Socioeconomic status

To characterize SES, 3 census tract variables were collected: Educational level, poverty level, and median income. These 3 variables were equally weighted and used to develop an SES score based on previously published methodologies.<sup>8</sup> In this study, SES was binary, and the upper 50% of scores in our state were categorized as high SES and the lower 50% as low SES.

## Comorbidity classification

The Adult Comorbidity Evaluation-27 model is an effective scale used to assess patients with cancer who are treated with RT and can predict overall survival.<sup>9–11</sup> In this model, comorbidity is classified on a scale of 0 to 3: 0 indicates no comorbid conditions and 3 severe comorbid conditions.<sup>9</sup> Our study categorized patients with a score of 0 to 1 as having low comorbidity and 2 to 3 as high comorbidity, using clinical documentation before the initiation of palliative RT treatment.

## Karnofsky performance status

KPS and Eastern Cooperative Oncology Group performance status are 2 common and strongly correlated scales that can be used as prognostic tools for patients with advanced, life-limiting illnesses.<sup>12–16</sup> KPS is the most frequently used performance measure at our institution, and therefore used in this study. KPS was not estimated retrospectively, and only included if a physician documented a score in the electronic medical record during the consultation visit. A score of 90 to 100 was classified as a good KPS score, 70 to 80 as fair, and  $\leq 60$  as poor.

## Prescribed fractions

The prescribed, rather than the delivered, number of fractions was used to document fractionation because prescribed fractions document the clinical decision-making process of treating physicians better. Patients were divided into 2 groups:  $<10$  fractions (ie, short fractionation schedule [SFx]) and  $\geq 10$  fractions (ie, long fractionation schedule [LFx]).

## Major treatment interruptions

MTIs were used to document treatment tolerance for patients who received palliative RT. In our study, a patient was defined as having an MTI if  $\geq 3$  RT treatment days were missed, or if treatment ended prematurely.

## Time to death

Time to death and survival were determined after documenting the date of the last palliative RT treatment, the date of death (if applicable), and date of last medical follow-up visit for each patient.

## Statistical methods

Demographic, medical, and treatment-related characteristics were compared between the 2 treatment sites (brain and bone) using the  $\chi^2$  test. Univariable analyses were performed using the logistic regression model to assess the impact of the variables on projected fractions, MTIs, and time to death.

Because of sample size limitations, multivariable analyses were unable to be performed. All tests were 2-sided, and a  $P$  value of  $< .05$  was considered statistically significant. Odds ratios (OR) and corresponding 95% confidence interval (CI) and  $P$  value were estimated. All statistical analyses were performed using the statistical software SAS, version 9.4.

## Results

A total of 145 patients were eligible for study inclusion, including 95 patients who were treated for bone metastases and 50 patients with brain metastases (Table 1). The majority of patients were male (55.9%), and 71.0% of patients were age  $< 65$  years. Language preference included English (60.0%), Spanish (37.2%), and Creole (2.8%), and 80% of patients were treated at the private academic hospital and 20% at the safety-net hospital. There were more patients classified as having low comorbidity (72.4%).

Of the patients with bony metastatic disease, 82.1% were projected to receive at least 10 fractions compared to 98.0% of patients with brain metastases ( $P = .006$ ). There were no baseline differences between treating hospital, age, language preference, comorbidity, SES, KPS, and MTIs when comparing brain and bone palliative patients.

## Impact of baseline characteristics on major treatment interruptions

Overall, 22.8% of patients experienced MTIs with no significant difference when comparing the site treated. On univariate analysis (Table 2), high comorbidity was a predictor of MTIs in this population of patients (OR: 3.32;  $P = .029$ ). Poor and fair versus good functional status had some association with MTIs, but this was not statistically significant (OR: 8.44;  $P = .051$  and OR: 8.04;  $P = .065$ , respectively). Location of metastasis, treating hospital, SES, sex, and age had no impact on the frequency of MTIs.

## Impact of baseline characteristics on fractionation technique used

On univariate analysis (Table 3), bone versus brain palliative radiation treatment (OR: 9.42;  $P = .034$ ) was associated with SFx. Comorbidity, KPS, treating hospital, sex, and age were not associated with SFx versus LFx.

## Impact of end-of-life state on fractionation choice used

In this study, no relationship was found between the planned number of fractions and time to death with fractions as a continuous variable (hazard ratio [HR]: 0.995;  $P = .871$ ) and categorized variable (10 vs 1-5: HR: 1.252;  $P = .610$  and  $> 10$  vs 1-5: HR: 1.133;  $P = .813$ ).

## Discussion

This study was designed to assess the impact of functional status and comorbidity on radiation planning

**Table 1** Patient demographics and clinical treatment characteristics

Category	All (n = 145)	Brain (n = 50)	Bone (n = 95)	P-value
Treating hospital, no. (%)				.662
Safety-net hospital	29 (20.0)	11 (22.0)	18 (18.9)	
Private hospital	116 (80.0)	39 (78.0)	77 (81.1)	
Sex, no. (%)				.015
Male	81 (55.9)	21 (42.0)	60 (63.2)	
Female	64 (44.1)	29 (58.0)	35 (36.8)	
Age, no. (%)				.180
<65 years	103 (71.0)	39 (78.0)	64 (67.4)	
65+ years	42 (29.0)	11 (22.0)	31 (32.6)	
Race, no. (%)				.264
Non-Hispanic white	47 (32.4)	11 (22.0)	36 (37.9)	
Non-Hispanic black	27 (18.6)	10 (20.0)	17 (17.9)	
Hispanic	68 (46.9)	28 (56.0)	40 (42.1)	
Other	3 (2.1)	1 (2.0)	2 (2.1)	
Preferred language, no. (%)				.460
English	87 (60.0)	27 (54.0)	60 (63.2)	
Spanish	54 (37.2)	22 (44.0)	32 (33.7)	
Creole	4 (2.8)	1 (2.0)	3 (3.2)	
Comorbidity, no. (%)				.757
Low	105 (72.4)	37 (74.0)	68 (71.6)	
High	40 (27.6)	13 (26.0)	27 (28.4)	
SES, no. (%)				.671
Low	71 (49.0)	27 (54.0)	44 (46.3)	
High	65 (44.8)	20 (40.0)	45 (47.4)	
Unknown	9 (6.2)	3 (6.0)	6 (6.3)	
KPS, no. (%)				.246
Good	39 (31.5)	17 (39.5)	22 (27.2)	
Fair	63 (50.8)	21 (48.8)	42 (51.9)	
Poor	22 (17.7)	5 (11.6)	17 (21.0)	
Unknown	21 (14.5)	7 (14.0)	14 (14.7)	
Projected fractions, no. (%)				.006
<10	18 (12.4)	1 (2.0)	17 (17.9)	
≥10	127 (87.6)	49 (98.0)	78 (82.1)	
Treatment interruption, no. (%)				.499
No	112 (77.2)	37 (74.0)	75 (78.9)	
Yes	33 (22.8)	13 (26.0)	20 (21.1)	

Abbreviations: KPS = Karnofsky performance status; no. = number; SES = socioeconomic status.

and treatment tolerance for patients who receive palliative RT. Within this cohort, high comorbidity was predictive of increased frequency of MTIs. Lower KPS also showed a correlation with MTIs. Neither high comorbidity nor low KPS correlated with receiving shorter treatment regimens. In addition, there was no correlation between projected fractions and time to death.

Many studies have correlated performance status and comorbid medical conditions with overall survival in patients who are treated with palliative radiation. However, studies that demonstrate a correlation between these factors and treatment tolerance are lacking. In a comprehensive analysis of treatment interruptions involving all cancer sites, one study found that the most common reason for treatment interruption was adverse tissue reactions.<sup>17</sup> For patients with head and neck cancer, KPS

has been previously shown to be predictive of radiation treatment interruptions,<sup>7</sup> and decreased cervical cancer treatment tolerance was associated with genitourinary and gastrointestinal toxicity.<sup>18</sup>

With regard to patients treated with palliative intent, one study demonstrated a correlation between low KPS score, high number of fractions prescribed, and nonbone metastases with early discontinuation of treatment.<sup>19</sup> In our study, comorbidity was significantly associated with MTIs, but KPS showed a strong correlation. MTIs were uniquely classified in our study to encompass both missed RT days and early treatment termination, which makes our methodology more comprehensive than those previously reported.

Although performance status and comorbidity are widely accepted prognostic indicators for patients with

**Table 2** Univariable analysis demonstrating factors associated with major treatment interruptions

Category	OR (95% CI)	P-value
Treating hospital, no. (%)		
Safety-net hospital	Reference	
Private hospital	0.99 (0.26-3.78)	.982
Sex, no. (%)		
Male	Reference	
Female	0.90 (0.31-2.60)	.849
Age, no. (%)		
<65 years	Reference	
65+ years	0.87 (0.26-2.90)	.816
Comorbidity, no. (%)		
Low	Reference	
High	3.32 (1.13-9.75)	.029
SES, no. (%)		
Low	Reference	
High	0.48 (0.15-1.51)	.209
Unknown	0.83 (0.09-7.70)	.872
KPS, no. (%)		
Good	Reference	
Fair	8.04 (0.995-64.90)	.0506
Poor	8.44 (0.88-81.00)	.065
Location		
Brain	Reference	
Bone	0.87 (0.29-2.58)	.800

Abbreviations: CI = confidence interval; KPS = Kamofsky performance status; no. = number; OR = odds ratio; SES = socioeconomic status.

metastatic disease, other predictive factors including location of metastases, number of metastases, age, sex, and histologic characteristics all play a role.<sup>20</sup> These factors are different when comparing diseases sites. Unique prognostic factors for patients with brain metastases include the presence of extracranial metastases, number of brain metastases, significant weight loss, and specific serum markers.<sup>20–25</sup> Unique prognostic factors for patients with metastases to the spine include primary lesion location, pain, hypercalcemia, and visceral metastases.<sup>26–28</sup>

Clinical measures are also useful. The Glasgow Prognostic Scale uses C-reactive protein and albumin levels to generate a score that can be used in conjunction with KPS to predict patient survival.<sup>29</sup> These measures may also be useful in the radiation planning process; however, we were not able to incorporate all these aspects into this retrospective study. In addition, the ability to integrate KPS and comorbidity into a new patient consultation without ordering additional tests makes them inexpensive and reasonable metrics to evaluate as predictors of treatment tolerance and overall prognosis.

There are many benefits of RT for symptom relief near the end of life, and poor functional status alone should not be considered a contraindication to RT in this setting. However, shifting toward hypofractionated palliative radiation in patients with poor prognoses can be beneficial.

**Table 3** Univariable analysis demonstrating factors associated with receiving a shorter fractionation cycle.

Category	Hypofractionation vs ≥10 fractions	
	OR (95% CI)	P-value
Treating hospital, no. (%)		
Safety-net hospital	Reference	
Private hospital	1.55 (0.33-7.41)	0.582
Sex, no. (%)		
Male	Reference	
Female	2.64 (0.85-8.24)	0.095
Age, no. (%)		
<65 years	Reference	
65+ years	1.38 (0.44-4.38)	0.585
Comorbidity, no. (%)		
Low	Reference	
High	0.66 (0.17-2.50)	0.539
SES, no. (%)		
Low	Reference	
High	2.98 (0.88-10.12)	0.080
KPS, no. (%)		
Good	Reference	
Fair	1.75 (0.43-7.02)	0.433
Poor	2.67 (0.54-13.21)	0.300
Location		
Brain	Reference	
Bone	8.77 (1.11-69.16)	0.039

Abbreviations: CI = confidence interval; KPS = Kamofsky performance status; no. = number; OR = odds ratio; SES = socioeconomic status.

In one institutional study, 6.3% of patients received RT within the last month of life, and 2.3% of patients received RT in their last week of life.<sup>30</sup> These numbers would likely be higher if the study was limited to patients who receive palliative radiation.

In our study, we found documentation that 8.3% of patients received radiation within the last month of life. The actual percentage might be even higher because palliative care patients have inconsistent follow-up, and many patients have no further documentation after RT, which makes a true estimate of overall survival difficult. Single-fraction RT is known to be noninferior for pain relief from uncomplicated bone metastases, and has fewer toxicities.<sup>31–33</sup> Caravatta et al. also demonstrated that short-course accelerated whole brain RT (WBRT) of up to 18 Gy in 4 fractions delivered twice daily may be an alternative to 30 Gy in 10 fractions owing to its effective symptom relief and survival profile.<sup>34</sup> Of note, the use of accelerated WBRT would be considered in the setting of patients with a poor prognosis as outlined by the eligibility of the referenced trial. In the study by Caravatta et al., patients had an Eastern Cooperative Oncology Group performance status score of ≤3.

Another study showed that 2 fractions of 8 Gy hypofractionated WBRT may be beneficial for patients with a



poor performance status and short life expectancy compared with longer fractionation schedules.<sup>35</sup> Although there are consensus guidelines for bone metastasis hypofractionation and no corresponding WBRT hypofractionation guidelines, these 2 studies show the utility of shorter WBRT courses in certain populations. Despite growing acceptance, there are disparities in access to hypofractionated RT at the end of life, including for non-Hispanic white patients, no receipt of hospice care, and treatment at a nonhospital affiliated facility.<sup>36</sup> These risk factors need to be monitored in facilities that transition toward shorter treatment protocols.

Many patients with advanced-stage cancer die before or soon after treatment completion, and in some instances, the treating radiation oncologists may be overly optimistic about patient survival.<sup>37–39</sup> Patients with shorter life expectancies do not benefit from longer, more protracted radiation treatments.<sup>40,41</sup> Instead, these patients are burdened by more treatment visits, increased indirect and direct costs, and more toxicity.<sup>41</sup> In our study, neither high comorbidity nor low KPS were correlated with planned SFx (ie, <10 fractions) regimens. In addition, patients who neared death did not receive fewer planned fractions. These findings suggest that incorporating KPS and comorbidity into palliative radiation treatment guidelines would be beneficial, and ultimately create a better quality of life for patients with a limited life expectancy.

Despite choosing an unselected group of sequential patients who were treated with palliative radiation to the bone or brain, the generalizability of this study may be limited because the patients who were examined were from institutions within a single system. A smaller sample size may have limited the power of our analyses. In some cases, functional status may have been so poor that palliative RT was not recommended. In addition, the role of other clinical factors such as social support on fractionation decision-making was difficult to assess. Individual providers were difficult to assess in this study because each radiation oncologist sees a variable number of palliative RT patients, and the sample size for some physicians may be very small. Many patients did not have documentation in the electronic medical record after completing their last RT treatment; therefore, this study likely underestimated the percentage of patients who received radiation within the last month of life. This also made a fully comprehensive survival analysis more difficult.

One strength of this study is its development of a more comprehensive scale for MTIs, which is a less frequently studied topic in palliative radiation. Our study took place in a warmer climate where weather and transportation issues do not burden the population on a seasonal basis, which allowed for a more refined classification of MTIs. In addition, the use of a comorbidity and functional status scale simultaneously to assess palliative radiation treatment plans is novel to our study.

## Conclusions

In this study, the radiation fractionation choice for patients who receive palliative radiation did not correlate with comorbidity or KPS indices. Specifically, physicians did not adjust the fractionation prescription for patients near the end of life. However, comorbidity and KPS were associated with treatment tolerance, and these measures have previously been shown to correlate with mortality. Using comorbidity and KPS to guide the clinical decision making can help clinicians make informed treatment decisions with regard to palliative care regimens, and the integration of these metrics into palliative radiation guidelines is reasonable. Our data suggest that a shorter fractionation course should be considered in patients with a KPS score <90 or an Adult Comorbidity Evaluation-27 score of 2 to 3. We intend to validate this study with a prospective trial where KPS and comorbidity will influence fractionation regimens.

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