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

Haley K. Perlow BS a,1, Vincent Cassidy BS a,1, Benjamin Farnia MD b,c, Deukwoo Kwon PhD c,d, Adam W. Awerbuch BS a, Stephanie Ciraula BA a, Scott Alford BS a, Jacob Griggs BA a, Joseph A. Quintana BS a, Raphael Yechieli MD c,d, Stuart E. Samuels MD, PhD c,d,*

aMiller School of Medicine, University of Miami, Miami, Florida; bDepartment of Radiation Oncology, Jackson Memorial Hospital, Miami, Florida; cSylvester Comprehensive Cancer Center, University of Miami, Miami, Florida; and dDepartment of Radiation Oncology, University of Miami, Florida

Received 25 June 2018; revised 4 September 2018; accepted 4 September 2018

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 (<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, ≥10 [long fractionation schedule], and <10 [SFx]), and major treatment interruptions (MTIs; defined as missing ≥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

Conflicts of interest: The authors have no conflicts of interest to disclose.

* Corresponding author. University of Miami, Department of Radiation Oncology, 1475 NW 12th Avenue, Suite 1500, Miami, FL 33136.
E-mail address: ssamuels@med.miami.edu (S.E. Samuels).
1 Co-first authors.
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.

© 2018 The Author(s). Published by Elsevier Inc. on behalf of American Society for Radiation Oncology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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. Multiple studies suggest that radiation oncologists should use shorter fractionation schedules (SFx) for patients who near the end of life. 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. 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 ≥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. 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. In this model, comorbidity is classified on a scale of 0 to 3: 0 indicates no comorbid conditions and 3 severe comorbid conditions. 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.\textsuperscript{12–16} 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.
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. For patients with head and neck cancer, KPS has been previously shown to be predictive of radiation treatment interruptions, and decreased cervical cancer treatment tolerance was associated with genitourinary and gastrointestinal toxicity.

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. 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...
metastatic disease, other predictive factors including location of metastases, number of metastases, age, sex, and histologic characteristics all play a role. 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. Unique prognostic factors for patients with metastases to the spine include primary lesion location, pain, hypercalcemia, and visceral metastases.

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. 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.

| Location | Category | OR (95% CI) | P-value |
|----------|----------|-------------|---------|
| Bone     | Reference | 1.00        | 1.00    |
| Brain    | Reference | 1.00        | 1.00    |
| Poor     | 1.23 (0.53-2.84) | 0.62     |
| Fair     | 1.11 (0.37-3.29)  | 0.85     |
| High     | 1.38 (0.62-3.09)  | 0.39     |

Abbreviations: CI = confidence interval; KPS = Karnofsky 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. 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 palliative 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, toxicities. 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. 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. 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. 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. Patients with shorter life expectancies do not benefit from longer, more protracted radiation treatments. Instead, these patients are burdened by more treatment visits, increased indirect and direct costs, and more toxicity. 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.

References

1. Chow E, Fung K, Panzarella T, Bezjak A, Danjoux C, Tannock I. A predictive model for survival in metastatic cancer patients attending an outpatient palliative radiotherapy clinic. Int J Radiat Oncol Biol Phys. 2002;53:1291-1302.

2. Westhoff PG, de Graeff A, Mounninkhof EM, et al. An easy tool to predict survival in patients receiving radiotherapy for painful bone metastases. Int J Radiat Oncol Biol Phys. 2014;90:739-747.

3. Ellsworth SG, Alcom CR, Hales RK, McNutt TR, DeWeese TL, Smith TJ. Patterns of care among patients receiving radiotherapy for bone metastases at a large academic institution. Int J Radiat Oncol Biol Phys. 2014;89:110-1105.

4. Steenland E, Leer JW, van Houwelingen H, et al. The effect of a single fraction compared to multiple fractions on painful bone metastases: A global analysis of the Dutch bone metastasis study. Radiother Oncol. 1999;52:101-109.

5. van der Linden YM, Lok JJ, Steenland E, et al. Single fraction radiotherapy is efficacious: A further analysis of the Dutch bone metastasis study controlling for the influence of retreatment. Int J Radiat Oncol Biol Phys. 2004;59:528-537.

6. Lutz S, Balboni T, Jones J, et al. Palliative radiation therapy for bone metastases: Update of an astro evidence-based guideline. Pract Radiat Oncol. 2017;7:4-12.

7. Sreraman R, Vijaykumar S, Chen A. Correlation of radiation treatment interruptions with psychiatric disease and performance status in head and neck cancer patients. Support Care Cancer. 2013;21:3301-3306.

8. Robert SA, Strombom I, Trenham-Dietz A, et al. Socioeconomic risk factors for breast cancer: Distinguishing individual- and community-level effects. Epidemiology. 2004;15:442-450.

9. Kallogjeri D, Piccirillo JF, Spitznagel EL Jr, Steyerberg EW. Comparison of scoring methods for ACE-27: Simpler is better. J Geriatr Oncol. 2012;3:238-245.

10. Omura G, Ando M, Saito Y, Kobayashi K, Yamasoba T, Asakage T. Comorbidity as predictor poor prognosis for patients with advanced head and neck cancer treated with major surgery. Head Neck. 2016;38:364-369.

11. Rogers SN, Aziz A, Lowe D, Husband DJ. Feasibility study of the retrospective use of the Adult Comorbidity Evaluation index (ACE-
27) in patients with cancer of the head and neck who had radiotherapy. *Br J Oral Maxillofac Surg.* 2006;44:283-288.

12. Verger E, Salamero M, Conill C. Can Karnofsky performance status be transformed to the Eastern Cooperative Oncology Group scoring scale and vice versa? *Eur J Cancer.* 1992;28:1328-1330.

13. Conill C, Verger E, Salamero M. Performance status assessment in cancer patients. *Cancer.* 1990;65:1864-1866.

14. Buccheri G, Ferrigno D, Tamburini M. Karnofsky and ECOG performance status scoring in lung cancer: A prospective, longitudinal study of 536 patients from a single institution. *Eur J Cancer.* 1996;32:1135-1141.

15. Roila F, Dominiello M, Morris R, Miller S. Factors predictive of protracted course of radiation therapy in patients treated with definitive chemoradiation for cervical cancer. *Carcin.* 2016;8:e558.

16. Gazelle GS, Berkey B, Gaspar LE, et al. Intra- and interobserver variability in cancer patients; performance status assessed according to Karnofsky and ECOG scales. *Ann Oncol.* 1991;2:437-439.

17. Lindberg RD, Jones K, Garner HH, Jose B, Spanos WI Jr, Bhatnagar D, et al. Evaluation of unplanned interruptions in radiotherapy treatment schedules. *Int J Radiat Oncol Biol Phys.* 1988;14:811-815.

18. Zaki M, Dominiello M, Morris R, Miller S. Factors predictive of protracted course of radiation therapy in patients treated with definitive chemoradiation for cervical cancer. *Carcin.* 2016;8:e558.

19. Puckett LL, Luitweiler E, Potters L, Teckie S. Preventing discontinuation of radiation therapy: Predictive factors to improve patient selection for palliative treatment. *J Oncol Pract.* 2017;13:e782-e791.

20. Sperduto PW, Berkey B, Gaspar LE, Mehta M, Curran W. A new prognostic index and comparison to three other indices for patients with brain metastases: An analysis of 1,960 patients in the RTOG database. *J J Radiat Oncol Biol Phys.* 2008;70:510.

21. Parti R, Richtig E, Avian A, Berghold A, Kapp KS. Karnofsky performance status and lactate dehydrogenase predict the benefit of palliative whole-brain irradiation in patients with advanced intracranial metastases from malignant melanoma. *Int J Radiat Oncol Biol Phys.* 2013;85:662-666.

22. Gaspar L, Scott C, Rotman M, et al. Recursive partitioning analysis (RPA) of prognostic factors in three radiation therapy oncology group (RTOG) brain metastases trials. *Int J Radiat Oncol Biol Phys.* 1997;37:745-751.

23. Grabowski CM, Unger JA, Potish RA. Factors predictive of completion of treatment and survival after palliative radiation therapy. *Radiology.* 1992;184:329.

24. Gerrard GE, Prestwich RJ, Edwards A, et al. Investigating the palliative efficacy of whole-brain radiotherapy for patients with multiple-brain metastases and poor prognostic features. *Clin Oncol (R Coll Radiol).* 2003;15:422-428.

25. Steinmann D, Paelecke-Habermann Y, Geinitz H, et al. Prospective evaluation of quality of life effects in patients undergoing palliative radiotherapy for brain metastases. *BMC Cancer.* 2012;12:283.

26. Pointillart V, Vital JM, Salmi R, Diallo A, Quan GM. Survival prognostic factors and clinical outcomes in patients with spinal metastases. *J Cancer Res Clin Oncol.* 2011;137:849-856.

27. van der Linden YM, Dijkstra SP, Vonk EJ, Marijnen CA, Leer JW. Dutch Bone Metastasis Study Group. Prediction of survival in patients with metastases in the spinal column. *Cancer.* 2005;103:320-328.

28. Mizumoto M, Harada H, Asakura H, et al. Prognostic factors and a scoring system for survival after radiotherapy for metastases to the spinal column. *Cancer.* 2008;113:2816-2822.

29. McMillan DC. The systemic inflammation-based Glasgow prognostic score: A decade of experience in patients with cancer. *Cancer Treat Rev.* 2013;39:534-540.

30. Patel A, Dunmore-Griffith J, Lutz S, Johnstone PA. Radiation therapy in the last month of life. *Rep Pract Oncol Radiother.* 2013;19:191-194.

31. Chow E, van der Linden YM, Roos D, et al. Single versus multiple fractions of repeat radiation for painful bone metastases: A randomised, controlled, non-inferiority trial. *Lancet Oncol.* 2014;15:164-171.

32. Hartwell WF, Scott CB, Bruner DW, et al. Randomized trial of short-versus long-course radiotherapy for palliation of painful bone metastases. *J Natl Cancer Inst.* 2005;97:798-804.

33. Gutiérrez Bayard L, Salas Buszon Mdel C, Angulo Pain E, de Inguuna Baron L. Radiation therapy for the management of painful bone metastases: Results from a randomized trial. *Rep Pract Oncol Radiother.* 2014;19:405-411.

34. Caravatta L, Deodato F, Ferro M, et al. Results of a phase II study of short-course accelerated radiotherapy (SHARON) for multiple metastases. *Am J Clin Oncol.* 2015;38:395-400.

35. Bolukbasi Y, Yalman D, Akcay C, Ozkok S. Results of hypofractionated radiotherapy (2 × 8 Gy) for patients with brain metastases from lung cancer. *J Thorac Oncol.* 2007;2:S767.

36. Guadagnolo BA, Liao KP, Elting L, Giordano S, Buchholz TA, Shih YC. Use of radiation therapy in the last 30 days of life among a large population-based cohort of elderly patients in the United States. *J Clin Oncol.* 2013;31:80-87.

37. Meese JJ, van der Linden YM, van Tienhoven G, et al. Efficacy of radiotherapy for painful bone metastases during the last 12 weeks of life: Results from the Dutch bone metastasis study. *Cancer.* 2010;116:2716-2725.

38. Park KR, Lee CG, Tseng YD, et al. Palliative radiation therapy in the last 30 days of life: A systematic review. *Radiother Oncol.* 2017;125:193-199.

39. Tseng YD, Krishnan MS, Sullivan AJ, Jones JA, Chow E, Balboni TA. How radiation oncologists evaluate and incorporate life expectancy estimates into the treatment of palliative cancer patients: A survey-based study. *Int J Radiat Oncol Biol Phys.* 2013;87:471-478.

40. Chow E, Zeng L, Salvo N, Dennis K, Tsao M, Lutz S. Update on the systematic review of palliative radiotherapy trials for bone metastases. *Clin Oncol (R Coll Radiol).* 2012;24:112-124.

41. Howell DD, James JL, Hartsell WF, et al. Single-fraction radiotherapy versus multifraction radiotherapy for palliation of painful vertebral bone metastases-equivalent efficacy, less toxicity, more convenient: A subset analysis of radiation therapy oncology group trial 97-14. *Cancer.* 2013;119:888-896.