



Replacing 30 Gy in 10 fractions with stereotactic body radiation therapy for bone metastases: A large multi-site single institution experience 2016–2018



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ABSTRACT

Background: Bone metastases cause significant morbidity in patients with cancer, and radiation therapy (RT) is an effective treatment approach. Indications for more complex ablative techniques are emerging. We sought to evaluate RT trends at a large multi-site tertiary cancer center.

Methods: Patients who received RT for bone metastases at a single institution (including regional outpatient clinics) from 2016 to 2018 were identified. Patients were grouped by RT regimen: single-fraction conventional RT (8 Gy × 1), 30 Gy in 10 fractions, SBRT, and “other”. Multinomial logistic regression was performed to assess trends in regimens over time. Binary logistic regression was performed to evaluate factors associated with receipt of SBRT.

Results: Between 2016 and 2018, 5,952 RT episodes were received by 2,969 patients with bone metastases. Overall, 76% of episodes were ≤ 5 fractions. The median number of fractions planned for SBRT and non-SBRT episodes was 3 (IQR 3–3) and 5 (IQR 5–10), respectively. Use of SBRT increased from 2016 to 2018 (39% to 53%, $p < 0.01$) while use of 30 Gy in 10 fractions decreased (26% to 12%, $p < 0.01$), and 8 Gy × 1 was stable (5.3% to 6.9%, $p = 0.28$). SBRT was associated with higher performance status ($p < 0.01$) and non-radiosensitive histology ($p < 0.01$). Use of SBRT increased in the regional network (19% to 48%, $p < 0.01$) and at the main center (52% to 59%, $p = 0.02$), but did not increase within 30 days of death. More patients treated with 8 Gy × 1 than SBRT died within 30 days of treatment (24% vs 3.8%, respectively, $p < 0.01$).

Conclusions: SBRT is replacing 30 Gy in 10 fractions for bone metastases, especially among patients with high performance status and non-radiosensitive histologies. Better prognostic algorithms could further improve patient-centered treatment selection at the end of life.

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1. Introduction

Bone metastases are common among patients with metastatic cancer, with a cumulative incidence reported as high as 60–70%

Abbreviations: RT, radiation therapy; SBRT, stereotactic body radiation therapy; ASTRO, American Society for Radiation Oncology; KPS, Karnofsky Performance Scale.

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for breast and prostate cancer [1,2]. Bone metastases cause debilitating pain and contribute significantly to morbidity, while radiation therapy (RT) can provide effective palliation [3].

American Society for Radiation Oncology (ASTRO) guidelines recommend the use of single-fraction RT for bone metastases, especially for patients with limited life expectancy [4], and discourage any use of extended-fraction RT (>10 fractions). Nonetheless, single-fraction RT is infrequent (4–9%) and extended-fraction persists across the United States [5–7]. Meanwhile, evidence is emerging from randomized trials suggesting SBRT may improve pain response in the palliative setting [8], and overall survival for oligometastatic disease [9–11], with

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publications as early as 2016. However, ASTRO guidelines (2017 update) still specify using SBRT for bone metastases only within the setting of a clinical trial [12].

Based on institutional data published as early as 2008 [13], our institution has been early adopters of SBRT for bone metastases, with dedicated experts in radiation oncology establishing both Spine (2009) and Metastatic Disease Teams (2016) to formalize internal guidelines integrating experience and best available evidence. Additionally, in 2014, an institutional initiative launched to reduce practice variation across all clinical practice sites.

Using longitudinal data from a large multi-site comprehensive cancer center, we evaluated trends in RT modality and fractionation for bone metastases from 2016 to 2018, with an emphasis on SBRT, 30 Gy in 10 fractions, and 8 Gy in one fraction (8 Gy × 1). We analyzed patient and tumor characteristics associated with treatment selection, including appropriate use at end of life. Importantly, we evaluated changes in practice in our community-based regional outpatient clinics compared to the main hospital-based center.

2. Methods

We identified all patients who received RT for bone metastases at a single institution between January 1, 2016–December 31, 2018. Cases were identified through a radiation oncology treatment database query using the International Classification of Disease version 10 diagnosis code for bone metastases. Review of the electronic medical record was performed to collect each patient’s treatment setting (main hospital or regional clinic), primary tumor histology, Karnofsky Performance Scale (KPS) score, and survival following the start of treatment. The KPS score was obtained from the patient’s initial consultation, and therefore subsequent RT episodes were removed from this multivariable analysis.

Treatment episodes were categorized into the following groups: 1) SBRT (defined as treatments in which the dose was ≥ 6 Gy per fraction in ≤ 5 fractions, except for courses where 8 Gy was delivered in one fraction), 2) all 8 Gy × 1 fraction treatments, (typically conventional technique) 3) 30 Gy in 10 fractions, and 4) all other RT regimens. Primary tumor histology was categorized as either radiosensitive or non-radiosensitive, as previously described [14]. Location of the bone metastasis was categorized as either spine or non-spine, with sacral metastases included in spine, as previously described [15,16].

Descriptive statistics were used to summarize patient characteristics. For continuous variables, we report medians and the interquartile range (IQR). We used a Kruskal-Wallis test to compare continuous variables between the RT regimen groups. A chi-squared test was used to assess rate of death within 30 days of RT by treatment regimen. To determine whether the proportion of RT regimens used over time changed, we calculated the proportion of treatment groups in 1-month bins, and performed multinomial logistic regression modeling to predict the relative proportions by time. A chi-squared test for trend of proportions was used to verify trends in proportions of groups. All planned treatment episodes were included in the assessment of trends in RT regimens and death within 30 days of RT. We performed a binary univariable and multivariable logistic regression with mixed effects to evaluate clinical factors of interest associated with receipt of SBRT. Clinical variables that were thought to meaningfully contribute to the selection of radiation regimen at the time of consultation were included in the model. An interaction term between treatment location and year was included to reflect differences in treatment volume of a growing regional network over time. In addition, we included random terms in the model to account for patients with multiple RT courses. A two-sample test

of proportions was used to assess differences in the proportions of SBRT use by treatment setting as well as rate of death within 30 days of RT by treatment regimen. Statistical calculations were conducted in R (The R Foundation, Vienna, Austria) using a p value < 0.05 for statistical significance. Institutional Review Board approval was obtained for this study.

3. Results

We identified 5,952 RT episodes for bone metastases among 2,969 unique patients. Overall, 53% (n = 1,571) of patients received one treatment episode, 23% (n = 689) received two treatment episodes, and 24% (n = 710) received three or more treatment episodes. Median patient age was 64 years (IQR 55–72 years) (see Table 1 for patient characteristics based on first treatment episode and for all treatments). Fifty-six percent (n = 3,345) of overall treatment episodes were for bone metastases located in the spine while 44% (n = 2,607) were for non-spine bone metastases. Among non-spine bone metastasis treatment episodes, the most common sites were the hip/pelvis (n = 1,050, 40%), ribs (n = 344, 13%), shoulder (n = 293, 11%), and femur (n = 298, 11%). The relative proportion of non-spine bone metastases was 44% in 2016 and 46% in 2018 (p = 0.32). Common RT regimens included SBRT (n = 2,790, 47%) and 30 Gy in 10 (n = 1,113, 19%), while 8 Gy × 1 was infrequent (n = 368, 6.2%). About one-third (n = 1,681, 28%) of RT episodes were classified as “other”, of which most (70%, n = 1,183) were 5-fraction regimens (20 Gy in 5 fractions, n = 949, and 25 Gy in 5

Table 1
Overall characteristics.

Characteristic		Patient (n = 2,969)	Episode (n = 5,952)
Age (years)	median (IQR)	64 (55–72)	63 (54–71)
Radiation type			
SBRT	n (%)	1,384 (46.6%)	2,790 (46.9%)
Other (i.e. 20 Gy in 5)	n (%)	769 (25.9%)	1,681 (28.2%)
30 Gy in 10	n (%)	696 (23.4%)	1,113 (18.7%)
8 Gy × 1	n (%)	120 (4.0%)	368 (6.2%)
Total number of fractions	median (IQR)	5 (3–5)	5 (3–5)
Primary tumor histology			
Radiosensitive			
Breast	n (%)	492 (16.6%)	830 (13.9%)
Prostate	n (%)	459 (15.5%)	1,002 (16.8%)
Myeloma/Lymphoma	n (%)	90 (3.0%)	187 (3.1%)
SCLC	n (%)	39 (1.3%)	71 (1.2%)
Non-radiosensitive			
NSCLC	n (%)	404 (13.6%)	853 (14.3%)
Renal	n (%)	211 (7.1%)	493 (8.3%)
CRC	n (%)	177 (6.0%)	357 (6.0%)
Sarcoma	n (%)	154 (5.2%)	369 (6.2%)
Thyroid	n (%)	93 (3.1%)	200 (3.4%)
Melanoma	n (%)	75 (2.5%)	156 (2.6%)
Bladder	n (%)	65 (2.2%)	120 (2.0%)
Pancreas	n (%)	52 (1.8%)	88 (1.5%)
Other	n (%)	558 (18.8%)	1,030 (17.3%)
Unknown	n (%)	100 (3.4%)	196 (3.3%)
Site of metastasis			
Spine	n (%)	1,708 (57.5%)	3,345 (56.2%)
Non-spine	n (%)	1,261 (42.5%)	2,607 (43.8%)
KPS	median (IQR)	80 (70–90)	–
Treatment setting			
Main hospital	n (%)	1,811 (61.0%)	3,888 (65.3%)
Regional clinic	n (%)	1,158 (39.0%)	2,074 (34.7%)

Abbreviations: IQR = interquartile range; SBRT = stereotactic body radiation therapy; SCLC = small-cell lung cancer; NSCLC = non-small-cell lung cancer; CRC = colorectal cancer; KPS = Karnofsky Performance Scale.

fractions, $n = 234$). The majority (76%) of all treatments were ≤ 5 fractions, and > 10 fractions was infrequent (2.7% in 2016, 1.1% in 2018). The median number of fractions planned for SBRT and non-SBRT episodes was 3 (IQR 3–3) and 5 (IQR 5–10), respectively. The most common dose and fractionation regimen for SBRT was 27 Gy in 3 fractions ($n = 1,460, 52\%$). A small proportion ($n = 272, 4.6\%$) of episodes were not completed.

A multinomial logistic regression model showed a significant change in the RT regimens prescribed over time ($p < 0.01$). Use of SBRT increased from 2016 to 2018 (39% to 53%, $p < 0.01$) while 30 Gy in 10 fractions decreased (26% to 12%, $p < 0.01$) (Fig. 1). There was no change in the proportion of episodes using 8 Gy \times 1 ($p = 0.28$) or “other” regimens ($p = 0.45$). From 2016 to 2018, the increase in the proportion of patients treated with SBRT was most prominent in patients treated at the community-based regional outpatient clinics (19% to 48%, $p < 0.01$) though the main hospital setting also showed a significant increase (52% to 59%, $p = 0.02$) (Fig. 2). Meanwhile, the proportion of patients who received 30 Gy \times 10 decreased from 47% to 21% ($p < 0.01$) and 20% to 12% ($p < 0.01$) in the regional clinics and main hospital, respectively.

Patients who received 8 Gy \times 1 fraction were more likely to be older (median = 70 [60–78] years vs. 64 [55–72] years, $p < 0.01$) and have a lower KPS (median = 70 [60–80] vs. 80 [70–90], $p < 0.01$) compared to all other regimens. On multivariable logistic regression, factors associated with receipt of SBRT were high KPS, a non-radiosensitive primary tumor histology, location in spine, and treatment at the main hospital. The odds of receiving SBRT increased over time in greater magnitude in the regional setting compared to the main campus; at the main campus the odds increased in 2017 compared to 2016 (OR: 1.64, 95% confidence interval (CI) 1.14–2.36) and increased in 2018 compared to 2016 (OR: 2.42, 95% CI 1.63–3.57) (Table 2).

Overall, the rate of any radiation for bone metastases within 30 days of death was 8.4%; 10% in 2016 and 8.1% in 2018 ($p = 0.09$) (Fig. 3). Death within 30 days occurred among 24% of all 8 Gy \times 1 treatments and 3.8% of all SBRT treatments ($p < 0.01$). There was no significant change in the rate of RT use within 30 days of death by RT regimen.

4. Discussion

This investigation presents recent trends in radiation dose and fractionation for bone metastases at a large multi-site tertiary cancer center in the United States. We found that 30 Gy in 10 fractions of conventional radiation has largely been replaced by SBRT, which is most often delivered in 3 fractions. A prior analysis of Medicare claims from 2010 to 2014 observed an increase in the use of SBRT for bone metastases, though overall use was still low [17]. In our study, nearly half of patients are receiving SBRT for bone metastases.

With randomized evidence addressing the use of SBRT for bone metastases still emerging, ASTRO guidelines (last updated 2017) recommend using SBRT in the setting of a clinical trial [4]. Nonetheless, during the study period (2016–2018) for patients with high performance status and radioresistant histology, SBRT appears to be the preferred option among metastatic specialists at our institution. Use of SBRT for bone metastases in the spine is based on institutional experience suggesting improved long-term tumor control with high-dose RT [13,18], which prompted early development of institutional guidelines in 2009 [19,20], and was later supported by prospective, albeit single-arm, data from other institutions [20]. More recently, randomized evidence suggests SBRT may provide more rapid as well as more durable pain control in patients with non-spine bone metastases surviving at least

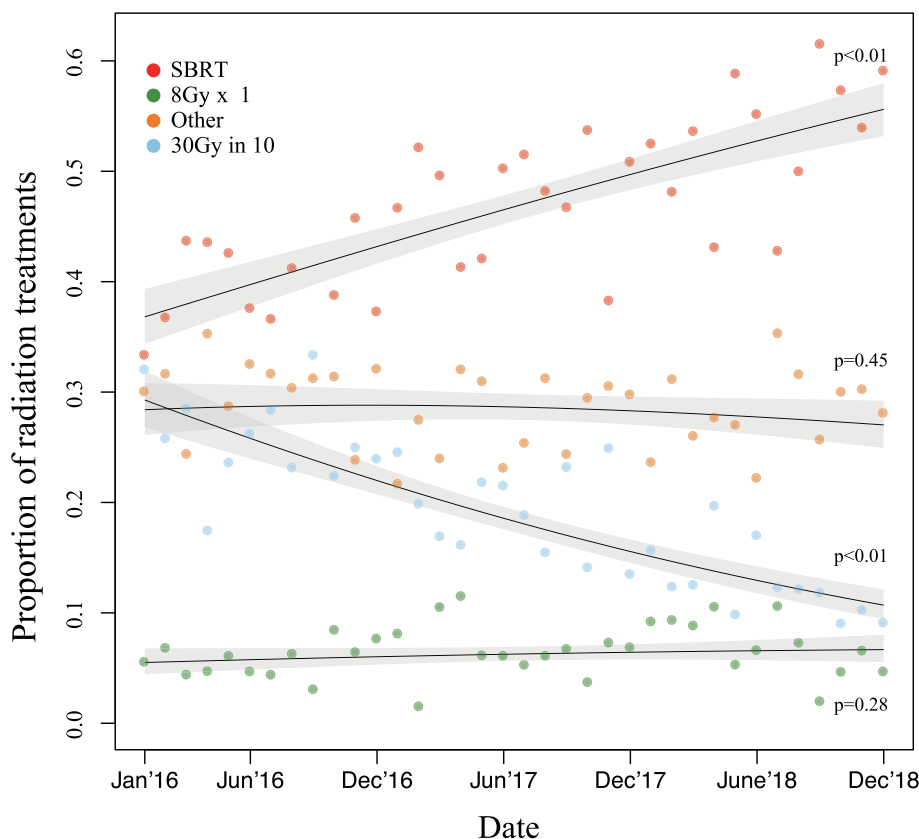


Fig. 1. Radiation treatment regimens for bone metastases from 2016 to 2018.

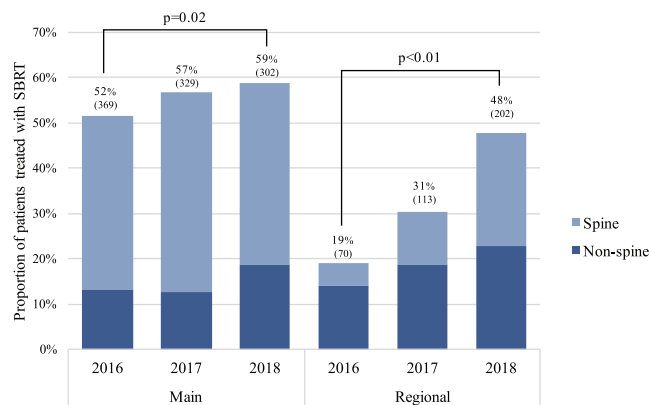


Fig. 2. Proportion of patients treated with stereotactic body radiation therapy for bone metastases by clinic setting, 2016–2018.

3 months [8,21] and improve progression-free and overall survival in the setting of oligometastatic disease [22]. Importantly, SBRT reduces the number of patient visits for patients otherwise receiving 30 Gy in 10 fractions, which could reduce financial toxicity to the patient [23] and limit time off systemic therapy [24].

The overall rate of use of single fraction conventional radiation (8 Gy × 1) in this study is low but similar to the 4–9% rate previously reported among Medicare beneficiaries [7,17]. This technique has been associated with a higher incidence of re-irradiation compared to multiple-fraction RT [25], which is the rationale for limiting use among experts at our institution, recognizing this data may be confounded by a lower threshold to retreat in setting of lower prior radiation dose. Nonetheless, ASTRO guidelines recommend use of 8 Gy × 1 specifically in patients with limited life expectancy [4]; in our cohort, receipt of 8 Gy × 1 was associated with older age, lower functional status, and death within 30 days, consistent with these recommendations.

With increasing use of SBRT, it is important to ensure avoidance of overuse at the end of life, given probable limited benefit in this population. Among all SBRT treatments, 3.8% of patients died within 30 days. Importantly, despite an increasing proportion of

SBRT treatments over time, there was no concomitant increase in the proportion of patients dying within 30 days of SBRT. Prognostic models could further improve appropriate selection of RT regimen at the end of life, reducing cost as well as time spent in simulation and treatment in a patient’s final days. Current models designed for patients with metastatic disease include TEACHH [26] and the NEAT [27], though accuracy of prognostic predictions may be limited by rapidly evolving systemic treatments. Additionally, evaluation of biomarkers that predict tumor and symptom response to SBRT is warranted and currently underway to optimize treatment selection.

It is noteworthy that the increase in utilization of SBRT from 2016 to 2018 was most evident in our community-based regional outpatient clinics, which now have similar rates of SBRT as our main campus. Reduction in variation is generally desirable [28] and was achieved in part through an institutional initiative (started in 2014) to improve consistency in practice across our Regional Care Network. Specific strategies included 1) establishment of dedicated specialized radiation oncologists for treatment of metastatic disease at each clinical site, 2) development, dissemination, and semi-annual retreats to review practice guidelines in both Spine and Metastatic disease teams within radiation oncology, 3) access to multidisciplinary tumor boards with contour review for difficult cases, 4) standardized cross-campus workflows for simulation and treatment setup, 5) centralized peer review for all metastatic radiation plans, and 6) ongoing monitoring of practice patterns with feedback.

There are several limitations to this investigation, including the lack of detailed clinical characteristics available, such as extent of metastatic disease (i.e. presence of oligometastasis), visceral organ involvement, and presence of soft tissue extension, which may further determine RT regimen selection. Additionally, for patients that had more than one recorded RT episode within our study period, certain clinical variables were only available for the first episode due to limitations of the database query. Nonetheless, this report provides a snapshot of the recent preference for avoiding radiation that extends longer than 5 fractions, and reinforcing considerations of factors such as KPS and histology in the consideration for SBRT use in both spine and non-spine bone metastases.

Table 2
Factors associated with use of SBRT (vs. other modalities).

Factor	Univariable analysis OR (95% CI)	P value	Multivariable analysis OR (95% CI)	P value
Age				
≤ 64 years	—		—	
> 64 years	1.14 (0.88–1.47)	0.31	1.58 (1.18–2.12)	<0.01
KPS				
≤ 80	—		—	
> 80	8.99 (6.17–13.09)	<0.01	7.88 (5.37–11.56)	<0.01
Primary tumor histology				
Radiosensitive	—		—	
Non-radiosensitive	6.85 (4.91–9.55)	<0.01	9.36 (6.43–13.62)	<0.01
Site of metastasis				
Non-spine	—		—	
Spine	3.01 (2.44–3.71)	<0.01	2.84 (2.27–3.55)	<0.01
Location*				
Main	—		—	
Regional	0.31 (0.20–0.49)	<0.01	0.37 (0.24–0.59)	0.01
Year*				
2016	—		—	
2017	8.10 (4.77–13.75)	<0.01	8.68 (4.95–15.21)	<0.01
2018	14.92 (8.65–25.75)	<0.01	12.98 (7.29–23.13)	<0.01

Abbreviations: SBRT = stereotactic body radiation therapy; OR = odds ratio; CI = confidence interval.

*Estimates shown are for 2018 only. A similar relationship was seen in 2016 and 2017.

*Estimates shown are for regional site only.

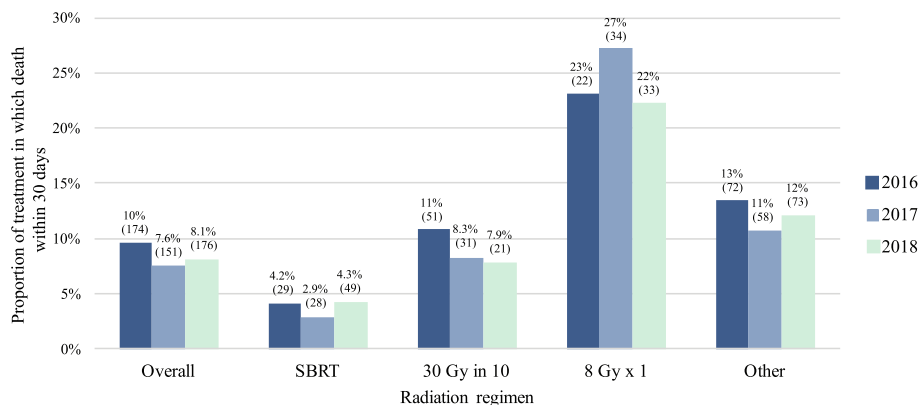


Fig. 3. Proportion of patients undergoing radiation therapy for bone metastases within 30 days of death, 2016–2018.

5. Conclusions

For patients with high performance status, longer life expectancy, and non-radiosensitive tumors that might have historically received 10 fractions, SBRT is increasingly favored over conventional radiation. Rapid uptake is feasible in the community-based outpatient clinic setting when leadership prioritizes network integration, and clinical practice guidelines are supported by difficult case conferences and peer review. Use of algorithms that accurately predict life expectancy is warranted to increase use of 8 Gy x1 for bone metastases within a patient's last 30 days, further optimizing patient-centered care and treatment-related costs.

6. Conflicts of Interest/Disclosures

EFG is a cofounder of the educational website eContour.org. KL is in a research fellowship funded by grants for research and education related to eContour.org. CJT is a consultant with Varian Medical Systems, Inc. All other authors have no disclosures.

Credit authorship contribution statement

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Methodology, Writing - original draft, Writing - review & editing. **Divya Yerramilli:** Conceptualization, Supervision, Writing - original draft, Writing - review & editing. **Oren Cahlon:** Conceptualization, Supervision, Writing - original draft, Writing - review & editing. **T. Yang:** Conceptualization, Methodology, Resources, Supervision, Writing - original draft, Writing - review & editing.

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