Original Article

Palliative radiation for bone metastases from hepatocellular carcinoma: practice patterns and the amount of remaining life spent receiving treatment

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Background: Palliative radiation therapy (RT) for bone metastases (BMs) is a common practice. Wide variation exists in clinically used dose schema despite numerous studies demonstrating palliative equipoise between single and multifraction courses. We hypothesize that fraction scheme for palliating BMs for hepatocellular carcinoma (HCC) significantly affects how patients spend their remaining time.

Methods: Patients with osseous HCC metastases who received RT were identified from the National Cancer Database [2004–2013]. The percentage of remaining life spent receiving radiation therapy (PRLSRT) and the number of incomplete RT courses were calculated. Kaplan-Meier analysis and Cox proportional hazards models were used to evaluate trends and predictors.

Results: A total of 1,331 patients met the inclusion criteria. Median overall survival (OS) was 3.3 months. Just 49 (3.7%) of patients received single fraction RT and 34% received >10 fractions. The mean and median PRLSRT were as follows: 1 fraction (8.9% and 3.0%), 2–5 fractions (32.9% and 24.3%), 6–10 fractions (27.2% and 15.9%), and >10 fractions (24.1% and 14.4%). Of the patients with PRLSRT >50%, 99.6% received multifraction RT. The proportion of incomplete RT courses increased as fraction size decreased from 17.6% with 4 Gy to 34% with 2 Gy.

Conclusions: Single fraction palliative RT is vastly underutilized despite no additional palliative benefit with multifraction RT. PRLSRT significantly increased with multifraction RT. In the palliative treatment of painful BMs from HCC, single fraction treatment reduces time spent receiving radiation treatments and maximizes the number of patients who complete the prescribed treatment.

Keywords: Palliative radiation therapy; bone metastases (BMs); hepatocellular carcinoma (HCC)

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Introduction

As advances in cancer treatment prolong survival, bone metastases (BMs) from underlying malignancy are becoming an increasingly prevalent source of pain leading to significant deterioration in quality of life (1-4). Bone pain is a leading cause of morbidity in patients with cancer, and BMs represent the leading cause for bone pain (3). Complications from BMs include hypercalcemia, decreased function and quality of life, pathological fractures, as well as neurovascular compression (3,5). Indications for the treatment of BMs include pain, skeletal functional impairment, as well as pathological fractures (5).

The diagnosis of hepatocellular carcinoma (HCC) confers a poor prognosis with a 5-year survival of 31% for those with localized disease and 2% for metastatic disease (6). Most patients are diagnosed at advanced stages and receive palliative treatments (7). BMs in HCC are estimated at 6–33%, however a more recent study has estimated as high as 32.9% with annual incidence of 6.4% (8,9). radiation therapy (RT) is an effective means for the palliation of pain caused by BMs with rates of pain relief as high as 79% (10-12). Many studies investigating fractionation schemes of RT for palliation of BMs have demonstrated no difference in pain outcomes, the development of spinal cord compression, or pathologic fracture between those treated with single or hypofractionated treatments versus more protracted radiation courses (13-20). Despite this data there remain a wide number of treatment regimens in use. Current american society for radiation oncology (ASTRO) approved dose-fractionation schema include: 8 Gy/1 Fx, 20 Gy/5 Fx, 24 Gy/6 Fx and 30 Gy/10 Fx (21). A Choosing Wisely recommendation posits that single fraction RT should be used for all uncomplicated BMs (22).

The purpose of this study was to investigate practice patterns in patients treated with palliative RT for BMs from HCC. The hypothesis is that patients undergoing long-course palliative regimens spend a greater portion of their remaining life receiving radiation treatments and higher rates of incomplete courses compared to those receiving single fraction treatments. Due to the poor prognosis of HCC, maximizing quality of life and minimizing travel and time receiving RT should be of the utmost importance. Spending a significant portion of one's remaining time receiving daily palliative radiation treatments may detract from the anticipated benefit of the radiation and patient overall quality of life. We present the following article in accordance with the STROBE reporting checklist (available at https://apm.amegroups.com/article/view/10.21037/apm-21-2657/rc).

Methods

Study design

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The National Cancer Database (NCDB) was queried to identify patients with HCC metastases to the bone who received RT using International Classification of Diseases-Third revision (ICD-3) histology codes 8170-8175 and the codes for radiation treatment volume for bone (24–28, 37, 38, and 40) between 2004 and 2013. Patients with missing or unknown radiation dose data, and lacking follow-up were excluded. The duration of time spent receiving radiation treatment was identified and used to calculate percentage of remaining life spent receiving radiation therapy (PRLSRT):

$$\text{PRLSRT}(\%) = 100\frac{\text{Elapsed days of RT}}{\text{Elapsed days from start of RT to death}} \quad [1]$$

An exploratory analysis was performed to determine the hypothetical percentage of remaining life spent receiving radiation therapy (H_{PRLSRT}) had the patients in the multifraction subset received single fraction RT instead:

$$H_{\text{PRLSRT}}(\%) = 100\frac{\text{Hypothetical single day of RT}}{\text{Elapsed days from start of RT to death}} \quad [2]$$

Finally, we calculated the radiation therapy-free life gained (RTFLG), representing the percentage of a patient's life which could have been spent outside of the hospital setting had they instead received single fraction RT:

$$\begin{aligned}\text{RTFLG}(\%) &= \frac{\text{Elapsed days of RT - Hypothetical single day of RT}}{\text{Elapsed days from start of RT to death}} \\ &= PRLSRT - H_{PRLSRT}\end{aligned} \quad [3]$$

Descriptive analysis of practice patterns including most common dose-fractionation schemes, sites of metastasis and various other demographic and patient related characteristics were performed. To calculate the number of incomplete RT courses, dose per fraction was calculated and compared to standard dose regimens: 4 Gy/fraction (20–24 Gy in 5–6 fractions), 3 Gy/fraction (30 Gy in 10 fractions), 2.5 Gy/fractions (35–37.5 Gy in 14–15 fractions), and 2 Gy/fraction (40 Gy in 20 fractions). Patients with a standard fraction size as defined above, but less than the appropriate number of fractions for a standard regimen we deemed to have an incomplete course. For most analysis, patients were stratified into four treatment groups based on number of fractions received: 1, 2–5, 6–10, and greater than 10.

Statistical analysis

Univariate comparisons were made using Chi-Square, ANOVA, or *t*-tests. Kaplan-Meier Curves and log-rank test were used to examine survival outcomes and Cox proportional hazards models were used to identify predictors of survival. Overall survival (OS) was calculated from the start of RT until death or last follow-up. Hazards ratio (HR), and 95% confidence intervals (CIs) were reported for the Cox regression analysis. Alpha was established at 0.05 for all tests and P<0.05 was considered significant. Statistical analyses were performed using SPSS version 24.0 (IBM Corp., New York, NY, USA).

Results

A total of 1,331 patients received palliative RT for BMs from HCC. For the entire cohort, median patient age was 61 years. The vast majority of patients were male (86.3%) and Caucasian (74.9%). Patient characteristics of the entire cohort as well as subdivided by fractionation group (1 Fx, 2–5 Fx, 6–10 Fx, >10 Fx) are outlined in *Table 1*. Most common sites of treatment were the spine (62.3%), hip/pelvis (18.5%), and shoulder/extremity (10.5%). Most patients received 30 Gy in 10 fractions (36.3%). The ten most common dose-fraction schemes are shown in *Figure 1A* and annual usage trends for RT separated by fraction group are shown in *Figure 1B*. Over time there appeared to be a trend, albeit small, toward decreased utilization of longer (>10 Fx) multifraction regimens and increased utilization of single fraction and hypofractionated (defined as 5 or fewer fractions) regimens. Peak annual usage of single fraction palliative RT was 5.5%. Survival after radiation within this cohort was very poor with median OS, 1- and 2-year OS of 3.3 months, 17.3% and 7.8%, respectively. Survival plots for the entire cohort as well as stratified by fraction group are shown in *Figure 2*. Following the start of RT, 21%, 45.8% and 66.6% of patients died within 1, 3 and 6 months, respectively.

Forty-nine (3.7%) patients received single fraction palliative RT compared to 198 (14.9%), 628 (47.2%), and 456 (34.3%) of patients who received 2–5, 6–10, and >10 Fx, respectively. Of those who received a single treatment, 24 patients (50% of single fractions cohort and 1.8% of the entire cohort) were treated with stereotactic radiosurgery. Overall mean and median PRLSRT were 26.4% and 15.4%, respectively. Mean and median PRLSRT were 8.9% and 3.0% for 1 Fx, 32.9% and 24.3% for 2–5 Fx, 27.2% and 15.9% for 6–10 Fx, and 24.1% and 14.4% for >10 Fx (*Table 2*). Mean and median PRLSRT was significantly different in all fraction groups when compared individually to the single fraction group (all P<0.001). Distributions of PRLSRT as a function of fraction group are shown in *Figures 3,4*. The majority of patients had PRLSRT ≤25% regardless of fraction group. There were no patients in the 1 Fx group who had PRLSRT >75%. Nearly all (248/249 or 99.6%) patients with a PRLSRT ≥50% received multifraction regimens.

The percentage of patients with incomplete courses increased as the dose per fraction decreased and the number of fractions increased. The percent incomplete course was 17.6% for 4 Gy per fraction, 21.7% for 3 Gy/fraction, 24% for 2.5 Gy/fraction, and 34% for 2 Gy/fraction. On multivariate analysis, increasing age, elevated AFP, shorter number of radiation fractions, spine metastasis, not receiving chemotherapy, and palliative RT less than 30 days after diagnosis was associated with shorter survival (*Table 3*).

In our exploratory analysis, mean H_{PRLSRT} compared to mean PRLSRT were 7.2% and 32.9% for 2–5 Fx, 2.2% and 27.2% for 6–10 Fx, and 1.1% and 24.1% for >10 Fx (*Table 2*) and was statistically significant for all groups (P<0.001). Distributions of H_{PRLSRT} as a function of fraction group are shown in *Figure 4*. For the subset of the cohort receiving multiple fraction RT, the mean and median RTFLG were 24.5% and 14.8%, respectively.

Discussion

The diagnosis of HCC with BMs confers a grim prognosis. Median survival in this cohort was 3.3 months with a 17.3% 1-year and a 7.8% 2-year OS. These findings are consistent with the existing literature rates of 1- and 2-year OS of 18.1% and 6.3% reported by Choi *et al.* (23). Given the short survival time and the equivalence of single and multifraction regimens for the treatment of BMs, efforts should be made to reduce palliative RT duration to maximize patient comfort, quality of life and reduce time spent receiving RT. Numerous studies have shown that there is no difference in pain response rates, time to improvement in pain, time to complete pain relief or duration of pain relief when comparing single and multifraction palliative RT for BMs (13-20,24). Despite those findings, this study demonstrates a significant underutilization of single fraction palliative RT in the treatment of BMs from HCC. Only 3.7% of patients received single fraction therapy, of which about half received SRS (1.8% of total population), and a

Table 1 Patient characteristics

Variables	Total cohort (n=1,331) (%)	Division by fraction group				P value
		1 fraction n=49 (3.7%) (%)	2 to 5 fractions n=200 (15.0%) (%)	6 to 10 fractions n=629 (47.3%) (%)	>10 fractions n=453 (34.0%) (%)	
Age (years), median (range)	61 [20–90]	62 [44–86]	61 [45–89]	61 [20–90]	62 [30–89]	0.463
Median OS (months)	3.3	1.1	0.7	3.1	5.1	<0.001
Treatment location						
Rib/chest wall	89 (6.7)	2 (4.1)	16 (8.0)	37 (5.9)	34 (7.5)	0.002
Spine	830 (62.3)	27 (55.1)	135 (67.5)	419 (66.6)	249 (55.0)	
Hip/pelvis	246 (18.5)	8 (16.3)	30 (15.0)	99 (15.7)	109 (24.1)	
Shoulder/extremity	140 (10.5)	10 (20.4)	15 (7.5)	63 (10.0)	52 (11.5)	
Skull	26 (2.0)	2 (4.1)	4 (2.0)	11 (1.7)	9 (2.0)	
Gender (male)	1,149 (86.3)	41 (83.7)	174 (87.0)	534 (84.9)	400 (88.3)	0.378
Ethnicity						
Caucasian	998 (74.9)	36 (73.5)	155 (77.5)	455 (72.3)	352 (77.7)	0.251
African American	230 (17.3)	7 (14.3)	30 (15.0)	127 (20.2)	66 (14.6)	
Other	90 (6.8)	6 (12.2)	13 (6.5)	42 (6.7)	29 (6.4)	
Not specified	13 (1.0)	0 (0.0)	2 (1.0)	5 (0.8)	6 (1.3)	
Insurance						
Private	423 (31.8)	18 (36.7)	65 (32.5)	197 (31.3)	143 (31.6)	0.635
Government	778 (58.5)	25 (51.0)	116 (58.0)	362 (57.6)	275 (60.7)	
Uninsured	110 (8.3)	5 (10.2)	14 (7.0)	60 (9.5)	31 (6.8)	
Unknown	20 (1.5)	1 (2.0)	5 (2.5)	10 (1.6)	4 (0.9)	
Charlson-Deyo score						
0	781 (58.7)	29 (59.2)	111 (55.5)	359 (57.1)	282 (62.3)	0.095
1	304 (22.8)	11 (22.4)	51 (25.5)	161 (25.6)	81 (17.9)	
≥2	246 (18.5)	9 (18.4)	38 (19.0)	109 (17.3)	90 (19.9)	
Chemotherapy (none)	801 (60.2)	33 (67.3)	138 (69.0)	391 (62.2)	239 (52.8)	0.001
Treating facility (academic)	518 (38.9)	19 (38.8)	92 (46.0)	263 (41.8)	144 (31.8)	0.002
Diagnosis to RT start						
≤1 month	780 (58.6)	23 (46.9)	119 (59.5)	379 (60.3)	259 (57.2)	0.524
1< months ≤3	414 (31.1)	20 (40.8)	56 (28.0)	190 (30.2)	148 (32.7)	
>3 months	137 (10.3)	6 (12.2)	25 (12.5)	60 (9.5)	46 (10.2)	
Income quartile						
<$38,000	354 (26.6)	9 (18.4)	57 (28.5)	174 (27.7)	114 (25.2)	0.032
$38,000–$47,999	323 (24.2)	10 (20.4)	53 (26.5)	131 (20.8)	129 (28.5)	
$48,000–$62,999	310 (23.3)	20 (40.8)	39 (19.5)	149 (23.7)	102 (22.5)	
≥$63,000	304 (22.8)	10 (20.4)	46 (23.0)	158 (25.1)	90 (19.9)	
Unknown	41 (3.1)	0 (0.0)	5 (2.5)	17 (2.7)	18 (4.0)	

OS, overall survival; RT, radiation therapy.

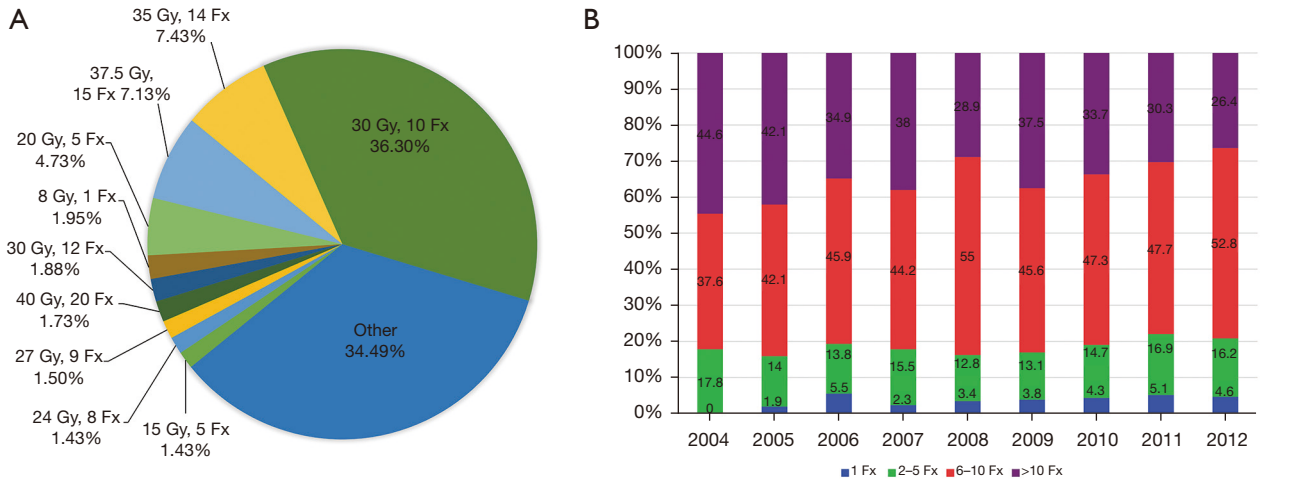

Figure 1 Distribution of fractionation schemes and trends in utilization. (A) Ten most common dose-fractionation schemes; (B) annual utilization trends of palliative RT by fraction group. Gy, gray; Fx, fraction; RT, radiation therapy.

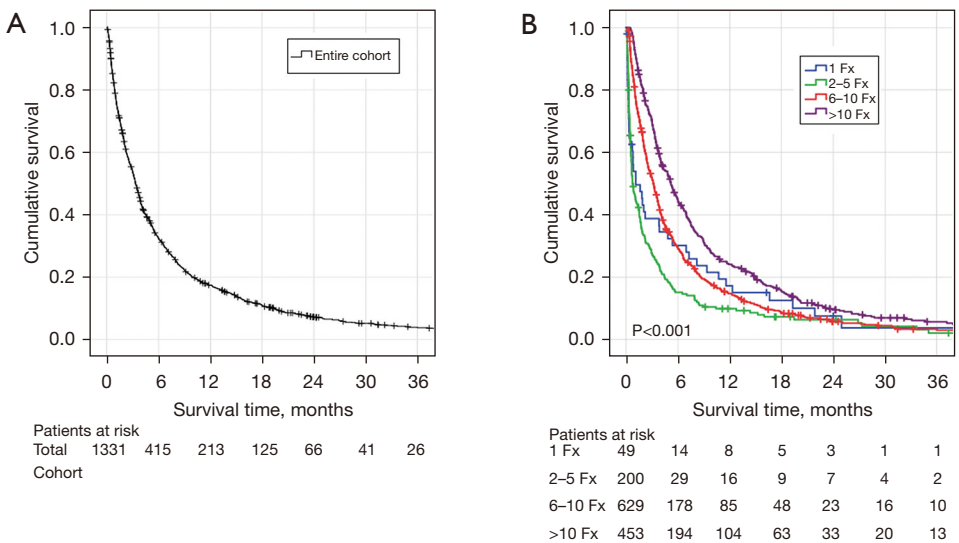

Figure 2 Kaplan-Meier survival curves of overall survival. (A) The entire cohort and (B) stratified by fraction groups. Fx, fraction.

substantial 34% of patients received >10 Fx.

In this study the PRLSRT metric was used to characterize how the choice of dose-fraction scheme affects how patients spend their remaining life. Patients receiving single fraction RT had a mean 8.9% PRLSRT, compared to 32.9%, 27.5%, and 24.1% for patients receiving 2–5, 5–10, and >10 Fx, respectively. Patients receiving multifraction RT spend a significantly higher proportion of their final days receiving RT. Likewise, longer courses increase the proportion of incomplete courses of RT. Approximately one-third of patients prescribed multifraction regimens did not complete their prescribed RT course, which could suggest that the burden of time, energy, and resources required to complete multifraction courses outweighed the potential benefits of completing treatment for many patients. This burden likewise potentially eroded the anticipated benefits of palliative RT.

It was hypothesized that PRLSRT would increase proportionally with number of fractions received, but that trend was not observed in these data. The highest PRLSRT corresponded to the 2–5 Fx group, which also had the lowest median survival at 0.72 months while the

Table 2 PRLSRT, H_{PRLSRT}, and RTFLG metrics stratified by fraction group

Variables	Total cohort (n=1,331)	Division by fraction group			
		1 Fx (n=49) (3.7%)	2–5 Fx (n=200) (15.0%)	6–10 Fx (n=629) (47.3%)	>10 Fx (n=453) (34.0%)
Mean PRLSRT (%)	26.4	8.9	32.9	27.2	24.1
Median PRLSRT (%)	15.4	3.0	24.3	15.9	14.4
Mean H_{PRLSRT} (%)	2.59	N/A	7.2	2.2	1.1
Median H_{PRLSRT} (%)	1.0	N/A	4.6	1.1	0.7
Mean RTFLG (%)	24.5	N/A	25.9	25.1	23.0
Median RTFLG (%)	14.8	N/A	20.1	14.8	13.8

PRLSRT, percentage of remaining life spent receiving radiation therapy; H_{PRLSRT}, hypothetical percentage of remaining life spent receiving radiation therapy; RTFLG, radiation therapy-free life gained; N/A, not applicable.

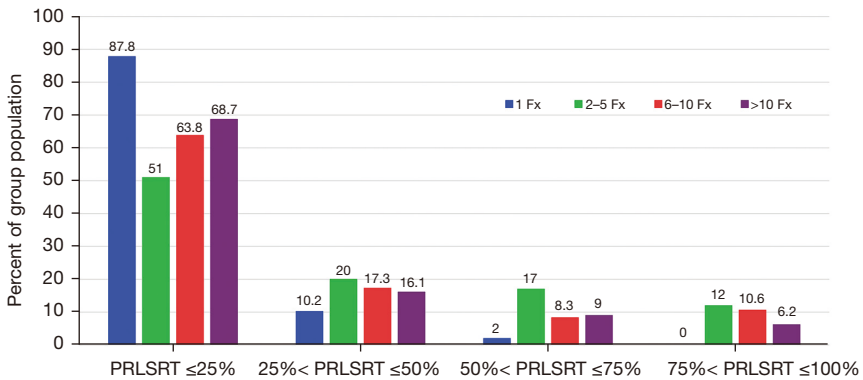

Figure 3 Distribution of PRLSRT by fraction group and PRLSRT quartile. PRLSRT, percentage of remaining life spent receiving radiation therapy; Fx, fraction.

>10 Fx group had the highest median OS at 5.1 months. It is possible that the increased PRLSRT observed in the 2–5 fraction group reflects both a consideration regarding prognosis when selecting fractionation schema and a possible reluctance for single fraction treatments. Instead of receiving a single fraction, patients with the worse prognosis were given a 2–5 fraction regiment because providers may have been more comfortable and experienced with these regimens, which resulted in a higher PRSLRT and shorter survival in this group (25). Clinicians should choose treatment regimens that reflect the patient's prognosis and match the goals of treatment with the goals of care. Given the poor survival in this cohort and in the literature, increased consideration should be given to single fraction palliative RT. If those in the 2–5, 6–10 and >10 Fx groups had received just single fraction RT, without compromising outcome the mean PRLSRT would have improved from 32.9%, 27.2%, and 24.1% to 7.2%, 2.2%, and 1.1%, respectively. Patients also would have gained a mean 25.9%, 25.1%, and 23.0%, respectively, of their remaining life back outside of the hospital setting.

There are a number of reasons why radiation oncologists are reluctant to use single fraction regimens. The most important of which is likely the higher reported retreatment rate after single fraction treatment. Retreatment after single fractions has been previously shown to be in upwards of 20–30% for single fraction RT compared to 7.4% in the multiple fraction group with retreatment likelihood 3.44-fold higher (95% CI: 2.67 to 4.43) (18,24,26). Time to retreatment differs with average of 14 weeks (single fraction) versus 23 weeks (multifraction) (27). Additionally the Bone Pain Trail Working group reported retreatment probability at 3 and 6 months was roughly 10% and 20% for single fraction and 5% and 10% for multi-fraction treatments (24).

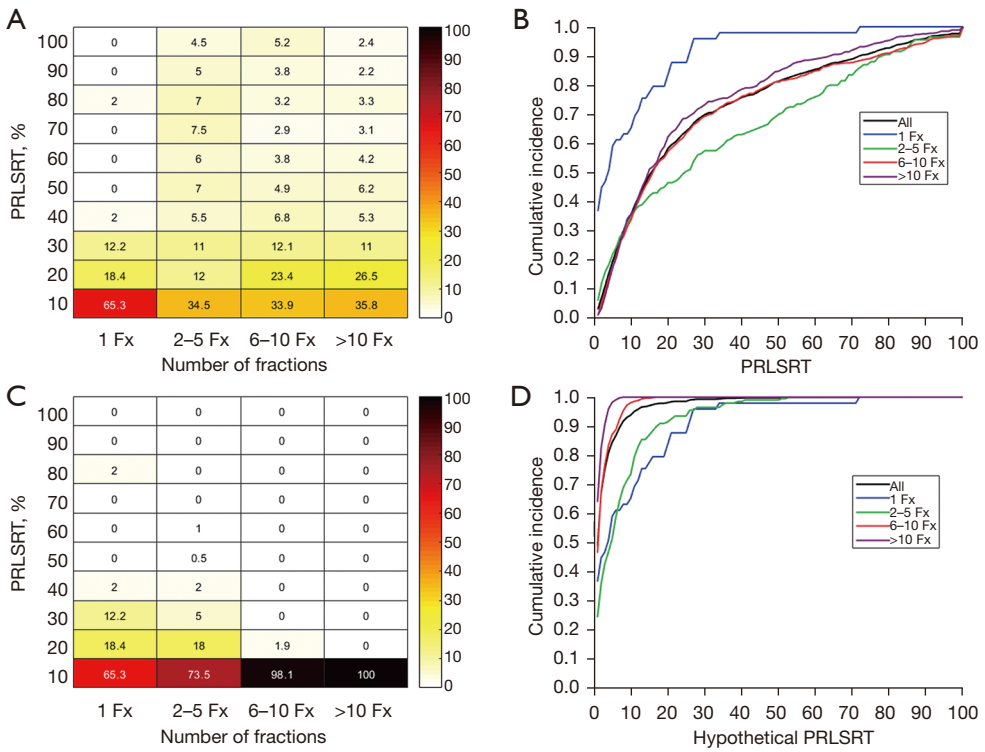

Figure 4 Heat maps and cumulative PRLSRT graphs. (A) and (C) are heat map distributions of PRLSRT tertials by fraction group (A is actual distribution, C is the hypothetical PRLSRT distribution based on all patients receiving single fraction). Y-axis is the PRLSRT tertials, X-axis is the fraction groups. (B) and (D) are cumulative incidence graphs depicting PRLSRT distributions by fraction group (B is actual distribution, D is the hypothetical PRLSRT distribution). Y-axis is the cumulative incidence in percentages, X-axis is the PRLSRT percentage. PRLSRT, percentage of remaining life spent receiving radiation therapy; Fx, fraction.

However, there is no difference in time to first increase in pain (24) and pain scores prior to retreatment were lower or no different in the single fraction group (27). These data suggest that physician bias and increased willingness to give repeat treatment following single dose RT, rather than actual necessity, explains reported differences in retreatment rates (16,24,27). Determination regarding radiation treatment schema should be considered within the context of the underlying malignancy. Most patients with HCC requiring RT for osseous metastases have a poor overall poor prognosis and anticipated survival of only a few months, so the retreatment rates are likely irrelevant since most patients will not live long enough. Considering the prognosis and time to retreatment should help reduce the reluctancy for using single fraction treatment in this cohort, except for those small handful of patients with potential for longer survival.

While most RT is given in the outpatient setting, it is of utmost importance to consider the patient's wishes with their remaining time and the socioeconomic implications of RT when selecting the dose-fraction scheme. Multifraction RT often requires daily trips to the radiation center that may be a significant distance from home (18). This may create a significant hardship, especially in patients with poor performance status. Significant time, energy, strength, and other resources are required from the patients and their caregivers to complete multi-fraction regimens and often, patients fail to complete the planned course of treatment. The number of incomplete courses rose as the fractional dose decreased and the number of treatments increased. When RT courses are stopped early, the anticipated palliative benefits may not be realized.

This study identifies several factors associated with decreased survival for patients with HCC who received palliative radiation for BMs: elevated AFP, spine *vs* non-spine osseous metastasis, age, the use of chemotherapy, and time from diagnosis to receiving palliative RT. Many of these factors have also been reported by others (9,23,28-30).

Table 3 Univariate and multivariate analysis of overall survival after palliative RT

Category	Univariate analysis			Multivariate analysis		
	Hazard ratio	95% confidence interval	P value	Hazard ratio	95% confidence interval	P value
Age continuous variable	1.007	1.002–1.013	0.007	1.007	1.001–1.012	0.017
Sex [male (Ref) *vs.* female]	1.091	0.924–1.288	0.305			
Charlson-Deyo score						
0	(Ref)	(Ref)	(Ref)	(Ref)	(Ref)	(ref)
1	1.161	1.011–1.333	0.034	1.092	0.948–1.259	0.222
2	1.119	0.960–1.303	0.150	1.132	0.969–1.322	0.119
Treating facility						
Academic	(Ref)	(Ref)	(Ref)			
Other	0.956	0.852–1.074	0.452			
Insurance status						
Private	(Ref)	(Ref)	(Ref)	(Ref)	(Ref)	(Ref)
Government	1.132	0.999–1.284	0.052	0.100	0.964–1.255	0.156
Uninsured/unknown	1.237	0.992–1.542	0.058	1.092	0.874–1.368	0.435
Alpha-Feto protein						
Normal	(Ref)	(Ref)	(Ref)	(Ref)	(Ref)	(Ref)
Elevated	1.337	1.098–1.627	0.004	1.282	1.050–1.565	0.015
Unknown	1.235	1.004–1.518	0.045	1.247	1.011–1.537	0.039
Number of fractions						
1 fraction	1.436	1.056–1.954	0.021	1.699	1.244–2.319	0.001
2–5 fractions	2.037	1.707–2.430	<0.001	2.039	1.700–2.446	<0.001
6–10 fractions	1.503	1.165–1.503	<0.001	1.299	1.141–1.478	<0.001
>10 fractions	(Ref)	(Ref)	(Ref)	(Ref)	(Ref)	(Ref)
Months from diagnosis to RT						
≤30 days	1.378	1.131–1.679	0.001	1.286	1.052–1.572	0.014
>30 to ≤90 days	1.189	0.964–1.465	0.106	1.218	1.218–1.505	0.068
>90 days	(Ref)	(Ref)	(Ref)	(Ref)	(Ref)	(Ref)
Osseous site						
Other bone site	(Ref)	(Ref)	(Ref)	(Ref)	(Ref)	(Ref)
Spine	1.404	1.249–1.579	<0.001	1.289	1.142–1.455	<0.001
Chemotherapy						
Yes	(Ref)	(Ref)	(Ref)	(Ref)	(Ref)	(Ref)
No	1.702	1.514–1.912	<0.001	1.701	1.509–1.918	<0.001

RT, radiation therapy; Ref, reference.

Performance status remains one of the most important drivers of prognosis (31-34). In this population of patients with a generally poor overall prognosis who may have been underrepresented in the randomized trials of fractionation for BM, it may be important to differentiate those with the potential for longer survival as several retrospective studies have reported associations between increased radiation dose and improved response duration (28,35), possible improved complete pain response rates (23,30,35), and higher radiographic response rates (35). Since there was little evidence for improved initial pain response, this difference will be most important for those with the longest life expectancy. The only randomized trial of palliative RT for BMs from HCC showed no difference in survival or toxicity based on the number of fractions (20–30 *vs.* 7–10 fractions), but reported a shorter time to response with the more hypofractionated regimen and a longer time to treatment failure in the more fractionated group (36). Any benefits of increased total radiation dose and longer treatment duration need to be weighed against the potential impact on the percent remaining life spent receiving RT and the burden of extended radiation treatment regimens.

There were several limitations in this study. Like most large database retrospective studies, the population of patients who received 1 fraction was relatively low. Additionally, there was no data regarding pain response, quality of life information, retreatment, or the extent of systemic disease at time of RT treatment, which would have provided a more detailed analysis of response and outcomes. The PRLSRT metric is strongly influenced by short survival and radiation duration. Since patients in the present study had poor survival outcomes (median survival after radiation of about 3 months), some may question the generalizability of the study results and the PRLSRT metric, but this must be taken in context. It is acknowledged that several studies of HCC patients reported longer OS outcomes with median survival of 5–11 months (37-40), but these studies typically calculated survival from the diagnosis of BMs instead of the start of RT, included only 50–60% of patients who required palliative RT, and treated patients in a more uniform manner with high proportions receiving systemic treatment with chemotherapy and bisphosphonates. Given these factors, the differences in the reported survival rates are not surprising, since it could be months between the diagnosis of BMs and progression of the lesions to become symptomatic enough to require intervention with radiation. Additionally due to the rarity of the diagnosis, any center reporting significant numbers of patients with HCC BMs are likely centers of excellence with significant experiences managing metastatic HCC, especially compared to the patients in the current study, who were treated at every kind of center. Despite these limitations, the current study gives unique insight into the practice patterns and outcomes after palliative RT for BMs from HCC and is valuable because it is one of the only studies to report the survival from the time of RT, which is crucial for determining prognosis and radiation fractionation.

In conclusion, in this cohort of patients with BMs from HCC, those who receive multifraction palliative regimens have a significantly increased PRLSRT when compared to single fraction RT. Despite equivalence in pain control between single and multi-fraction regimens, there remains a prominent underutilization of single fraction palliative treatments. In the palliative treatment of painful BMs from any malignancy, and particularly those with a poor prognosis such as metastatic HCC, single fraction RT should be utilized to reduce time spent receiving treatment and the number of incomplete courses.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://apm.amegroups.com/article/view/10.21037/apm-21-2657/rc

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