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Original Research Article

Adoption of single fraction radiotherapy for uncomplicated bone metastases in a tertiary centre

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ABSTRACT

Background: Single-fraction radiotherapy (SFRT) offers equal pain relief for uncomplicated painful bone metastases as compared to multiple-fraction radiotherapy (MFRT). Despite this evidence, the adoption of SFRT has been poor with published rates of SFRT for uncomplicated bone metastases ranging from <10% to 70%. We aimed to evaluate the adoption of SFRT and its evolution over time following the more formal endorsement of the international guidelines in our centre starting from 2013.

Materials and methods: We performed a retrospective review of fractionation schedules at our centre for painful uncomplicated bone metastases from January 2013 until December 2017. Only patients treated with 1 × 8 Gy (SFRT-group) or 10 × 3 Gy (MFRT-group) were included. We excluded other fractionation schedules, primary cancer of the bone and post-operative radiotherapy. Uncomplicated was defined as painful but not associated with impending fracture, existing fracture or existing neurological compression. Temporal trends in SFRT/MFRT usage and overall survival were investigated. We performed a lesion-based patterns of care analysis and a patient-based survival analysis. Mann-Whitney U and Chi-square test were used to assess differences between fractionation schedules and temporal trends in prescription, with Kaplan-Meier estimates used for survival analysis (p-value <0.05 considered significant).

Results: Overall, 352 patients and 594 uncomplicated bone metastases met inclusion criteria. Patient characteristics were comparable between SFRT and MFRT, except for age. Overall, SFRT was used in 92% of all metastases compared to 8% for MFRT. SFRT rates increased throughout the study period from 85% in 2013 to 95% in 2017 (p = 0.06). Re-irradiation rates were higher in patients treated with SFRT (14%) as compared to MFRT (4%) (p = 0.046). Four-week mortality and median overall survival did not differ significantly between SFRT and MFRT (17% vs 18%, p = 0.8 and 25 weeks vs 38 weeks, p = 0.97, respectively).

Conclusions: Adherence to the international guidelines for SFRT for uncomplicated bone metastasis was high and increased over time to 95%, which is the highest reported rate in literature.

1. Introduction

Bone metastases are a common manifestation of advanced cancer and are a significant cause of morbidity. Radiotherapy (RT) is a proven effective treatment in the management of painful bone metastases. Next to its analgesic effect , RT also improves quality of life [1–5].

In the past, several randomised controlled trials compared single-fraction radiotherapy (SFRT) with multiple-fraction radiotherapy (MFRT). They have shown equivalence in pain relief. Chow et al. showed overall pain response (complete or partial) of 60% and 61% for SFRT and MFRT respectively [1,2]. The authors also noted little discernible difference in toxicity. There were no significant differences in duration of the pain relief response or overall survival reported [6–8]. Consequently, the ASTRO Evidence-Based Guideline endorses SFRT as the treatment of choice for uncomplicated bone metastases [9]. Longer schedules can be considered for complicated metastases or patients who have undergone surgical stabilization. These guidelines are considered the international

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standard of care. Nevertheless, international patterns of care studies indicate that longer fractionation schedules are still being overused with reported rates of SFRT in literature ranging from 4.1% to 70.4% [10–13]. In 2013, our department decided to more formally implement the international guidelines. The goal of this paper is to evaluate the temporal trends in SFRT and MFRT for uncomplicated bone metastases over a 5-year period in a tertiary academic centre and the survival distributions of these patients.

2. Methods

2.1. Sample and data collection

We conducted a retrospective chart review of patients referred for palliative radiotherapy for uncomplicated bone metastases between January 1, 2013 and December 31, 2017. The following treatment, tumour and patient factors were included: gender, age at radiation, fractionation schedule (1×8 Gy or 10×3 Gy), patient survival status, primary tumour, irradiated anatomical site, retreatment rate, simultaneous extra-osseous meta, Karnofsky score, the Number of Risk Factors (NRF) and the Recursive Partitioning Analysis (RPA) [14,15]. Both NRF and RPA estimate prognosis. The NRF is based on three risk factors: non-breast primary cancer, metastases other than bone and KPS $\leq$ 60. The RPA model includes three variables, which are the interval between primary diagnosis and radiotherapy for bone metastases, age and KPS. Furthermore we performed an in depth review of individual files and cases looking for reasons for guideline violations.

Following patients were excluded: primary cancer of the bone, patients who received postoperative radiotherapy for bone metastases and complicated metastases. Uncomplicated was defined as painful but not associated with impending fracture, existing fracture or existing spinal cord or cauda equina compression. For spinal metastases we used the spinal instability neoplastic score (SINS) [16]. A SINS between 7 and 12 was defined as an impending fracture and higher than 12 was seen as unstable. Both were viewed as complicated. Furthermore, spinal lesions with a SINS lower than 7 but with existing pathologic fracture or existing spinal cord or cauda equina compression were excluded. As were femoral lesions with more than 3 cm axial and/or 50% circumferential cortical involvement [17].

2.2. Statistical analysis

2.2.1. Patterns of care analysis

The analyses were lesion based, patients who received more than 1 course of RT were evaluated for each course separately. Descriptive statistics were applied to estimate frequencies and proportions of the SFRT and MFRT groups. Means, medians, standard deviations and ranges were reported for continuous variables. The non-parametric Mann-Whitney U and chi-square test were used to assess differences in proportions of respectively continuous and categorical variables between fractionation schedules. The chi-square test was carried out to determine temporal trends in SFRT and MFRT treatments.

2.2.2. Survival analysis

The survival analysis was patient-based. If patients were irradiated at two or more anatomical sites, only the lesion that was irradiated last was selected (594 metastases corresponding for 352 patients). To analyse differences in survival distributions, log-rank tests were performed for the following variables: fractionation schedule, NRF, RPA and a Kaplan-Meier curve was plotted for differences in survival between fractionation schedules. Two-sided P values for statistical significance were set at 0.05. All analyses were carried out using the ®IBM ®SPSS Statistics software version 25.0.

3. Results

3.1. Patterns of care analysis

The total data set consisted of 1041 bone metastases of which 594 were uncomplicated and met inclusion criteria. The eventual cohort contained 352 patients irradiated for 594 bone metastases. Table 1 gives an overview of patient and metastasis characteristics.

Overall, 91.6 percent of all metastases received a single fraction of radiotherapy in comparison to 8.4% for multiple fractions. Patient and metastasis characteristics between single and multiple fractions were comparable, except for age with patients treated with MFRT being older (table 1). The retreatment rate was higher in patients treated with SFRT (14% vs 4%; P = 0.046). SFRT adoption increased over the five study years from 85.5% in 2013 (99/116 cases) to 95.3% in 2017 (121/127) (Fig. 1, P = 0.055). In depth review of individual files and cases could not identify objective reasons for choosing MFRT over SFRT.

3.2. Survival analysis

Two hundred thirty-eight patients (68%) had died at the time of the analyses. The 4-week mortality was comparable between SFRT (17%) and MFRT (18.4%) (P = 0.8). Median overall survival was 6.5 months (95% CI 5–8) for the whole group (6.2 months for SFRT, as compared to 9.4 months for MFRT (P = 0.978)), as seen in table 2. Both the RPA and NRF model stratified patients in prognostic groups following radiotherapy. Kaplan-Meier curves showing survival for NRF and RPA models are included in Fig. 2A and B.

3.3. Discussion

From 2013 to 2017, the use of SFRT increased in our department from 85% to 95%, with a retreatment rate comparable to reported literature [5]. Our use of SFRT exceed the ones reported in literature, which range from 4.1% to 70.4% [11,13]. SFRT has several advantages over MFRT including shorter treatment time and better cost-effectiveness. Despite the published evidence showing equal pain relief rates radiation-oncologists still seem reluctant to implement SFRT. The factors influencing prescription behavior can be classified into four categories relating to patient, tumour, setting and/or oncologist [18–21]. Our retrospective review could not reveal any tumour related factors that significantly predicted choice of MFRT over SFRT for uncomplicated bone metastases. In terms of patient related factors oddly enough the MFRT-group included older patients. A reason for this could be that, despite longer overall treatment time, the need for retreatment was seen as too bothersome for older patients. A third category are the setting related factors. Our hospital is located in the Ghent metropolitan area in Belgium. Belgium is one of the most densely populated countries in the world. Ghent has a high linac density of about 1.25/100.000 population. This is on par with other high income countries [22]. In countries without a reimbursement per fractions there is a disincentive for the use of MFRT in uncomplicated bone metastases. Lievens et al. found that reimbursement modality influences the prescribed fractionation regimen in West-European radiotherapy centers. In budget and case payment financing a lower total number of fractions and lower total dose is prescribed. Longer courses tend to be more prescribed in countries where the remuneration depends on the number of treatments [12,23]. In Belgium, both SFRT and MFRT for palliation are reimbursed equally. This leads us to believe that setting related

Table 1
Overview of patient and metastasis characteristics.

Characteristics	All uncomplicated bone metastases (n = 594)	SFRT (n = 544; 91.6%)	MFRT (n = 50; 8.4%)	p-value
Gender				0.593
Man	342 (57.6%)	315 (57.9%)	27 (54%)	
Woman	252 (42.4%)	229 (42.1%)	23 (46%)	
Age at radiation				0.008
Mean ± standard deviation	64.19 ± 13.28	62.95 ± 13.54	67.78 ± 11.16	
Median (range)	66 (18–94)	64 (18–94)	69 (35–85)	
Primary tumour				0.552
Prostate	120 (20.2%)	110 (20.2%)	10 (20%)	
Breast	77 (13%)	69 (12.7%)	8 (16%)	
Lung	153 (25.8%)	137 (25.2%)	16 (32%)	
Gastro-intestinal	88 (14.8%)	84 (15.4%)	4 (8%)	
Other	156 (26.3%)	144 (26.5%)	12 (24%)	
Anatomical site				0.582
Axial and spinal	151 (25.6%)	136 (25.2%)	15 (30%)	
Axial and non-spinal	154 (26.1%)	144 (26.7%)	10 (20%)	
Non-axial	263 (44.6%)	241 (44.6%)	22 (44%)	
Unspecified	22 (3.7%)	19 (3.5%)	3 (6%)	
Simultaneous extra-osseous metastases				0.831
No	210 (35.3%)	194 (35.6%)	16 (32%)	
Yes	383 (64.5%)	349 (64.2%)	34 (68%)	
Unknown	1 (0.2%)	1 (0.2%)	0	
Needed re-irradiation				0.046
No	516 (86.9%)	468 (86%)	48 (96%)	
Yes	78 (13.1%)	76 (14%)	2 (4%)	
Karnofsky Performance Score				0.591
Median (range)	70 (30–100)	70 (30–100)	70 (50–90)	
KPS < 70	141 (33.73%)	129 (33.86%)	12 (32.43%)	
KPS $\geq$ 70	277 (66.27%)	252 (66.14%)	25 (67.57%)	

*for 176 patients no KPS.

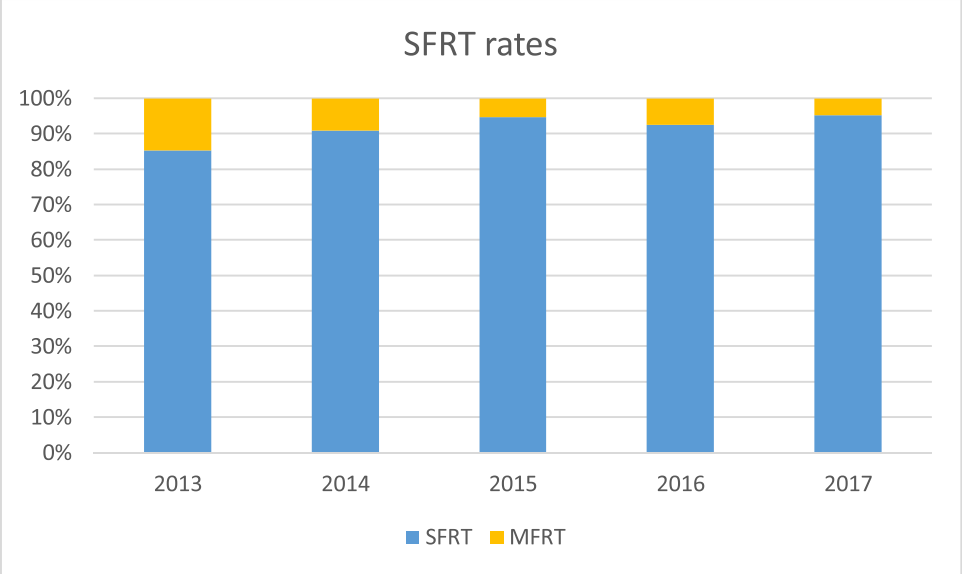

Fig. 1. Graph showing the adoption of SFRT over the five study years.

factors are not a major issue in our case. A final category are the oncologist related factors including level of training and personal beliefs [24]. The number of patients being treated with MFRT is too low to perform meaningful statistical analyses. In depth review of individual files and cases revealed a subjective reason for choosing MFRT in a number of cases, leading us to believe that oncologist related factors are the most important driver of prescription choice in our study.

Both RPA and NRF models are suggested as survival prediction tools to objectify patient prognosis in patients with spinal bone metastases and with general metastatic cancer, respectively. In the current analysis, we were able to confirm the discriminative power of these models. Four-week mortality did not differ between treatment groups which leads us to believe that a significant portion of patients with the worst prognosis did not receive SFRT. Seven patients in the MFRT-group died within 4 weeks of the

Table 2
Univariate survival analysis.

Characteristics	Number of patients (n = 352)	Median overall survival (95% CI)	P-value
Fractionation schedule			
Number of evaluable patients	348		0.978
SFRT	310 (89.1%)	6.2 months (5–7.4)	
MFRT	38 (10.9%)	9.4 months (6–12.9)	
RPA*			
All patients			
Number of evaluable patients	298		<0.001
Class 1	43 (14.4%)	29.5 months (7.2–51.75)	
Class 2	200 (67.1%)	4.8 months (3.18–6.4)	
Class 3	55 (18.5%)	3.65 months (0.1–7.21)	
NRF*			
Number of evaluable patients	241		<0.001
0 risk factors	14 (5.8%)	Not reached	
1 risk factor	54 (22.4%)	11.1 months (0–24.58)	
2 risk factors	118 (49%)	4.04 months (1.32–6.75)	
3 risk factors	55 (22.8%)	2.23 months (1.13–3.33)	
Died within 4 weeks of RT			0.825
All patients		/	
Number of evaluable patients	350		
Yes	60 (17.1%)		
No	290 (82.9%)		
SFRT			
Number of evaluable patients	312		
Yes	53 (17%)		
No	259 (83%)		
MFRT			
Number of evaluable patients	38		
Yes	7 (18.4%)		
No	31 (81.6%)		

*RPA: recursive partitioning analysis index; NRF: number of risk factors.
Log-rank test was used.

end of their treatment. This might mean that they did not live long enough to enjoy any treatment effect.

There are several limitations of our study. The first being its retrospective nature. This meant there was no standardised way of assessing patients' pain response. As such pain response wasn't reported. The retrospective nature also limited our ability to thoroughly examine prescription behavior. Prospectively collected data could have included questionnaires that would help us understand the rationale of choosing MFRT in uncomplicated bone metastases. Because of the high uptake of SFRT in our centre the MFRT groups consisted of only 50 metastases. This limited our ability to find factors that drove further prescription of longer courses. The past few years have seen the rise of local treatment for oligometastatic disease namely SBRT [25–27]. Our review only looked at 1 × 8Gy and 10 × 3Gy schedules. As such any other schedule, including for oligometastatic disease, were excluded.

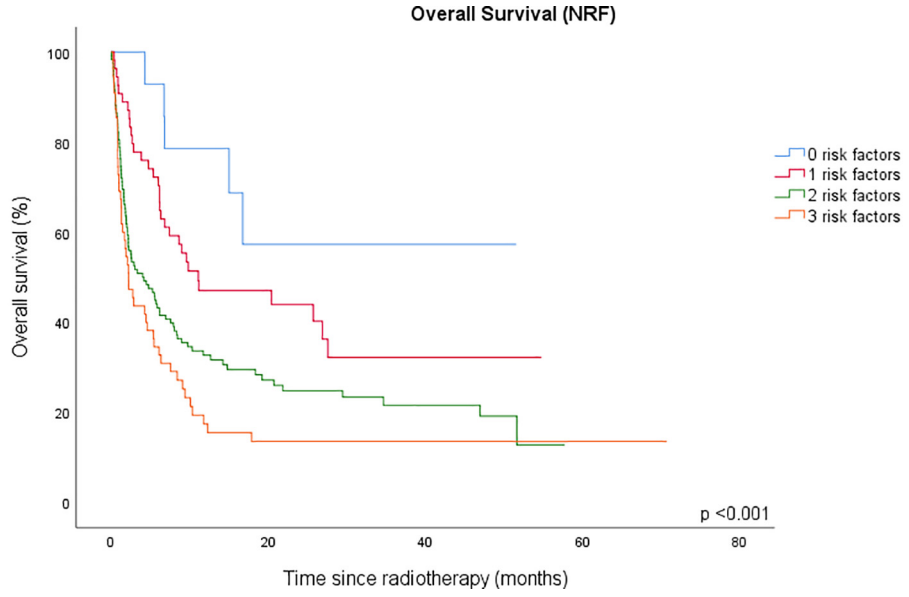

Fig. 2. (A) Kaplan-Meier reporting time between radiotherapy and death stratified per NRF. (B) Kaplan-Meier reporting time between radiotherapy and death stratified per RPA.

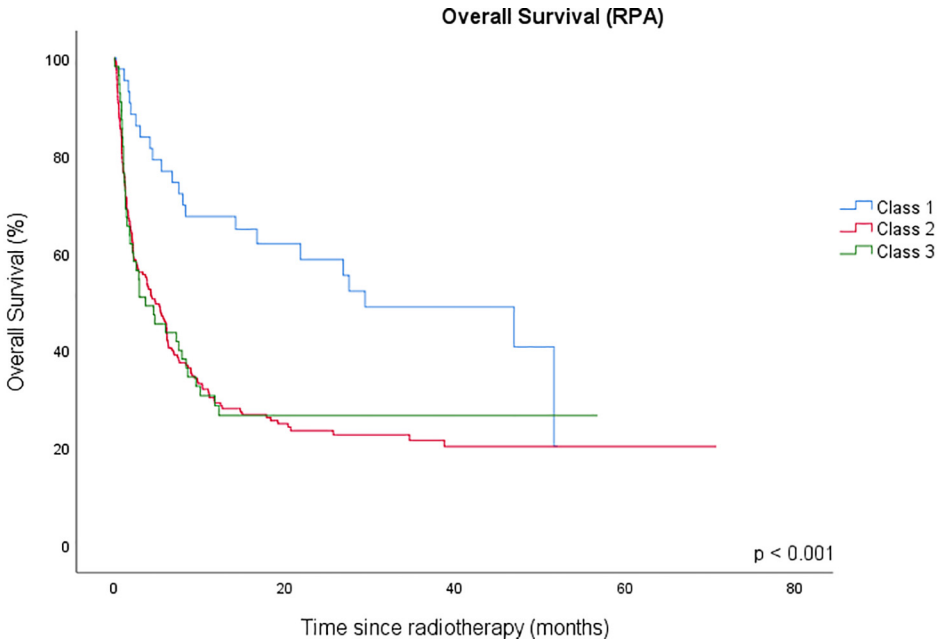

Fig. 2 (*continued*)

4. Conclusion

Adherence to the international guidelines for SFRT for uncomplicated bone metastasis was high and increased over time to 95%, which is the highest reported rate in literature.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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