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Research Paper

Incidence and radiotherapy treatment patterns of complicated bone metastases

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HIGHLIGHTS

- Approximately 37% of bone metastases are classified as complicated.
- The vast majority are of spinal origin.
- The majority of complications were related to impending fracture.
- Patients with complicated bone metastases have a median survival of 4 months.

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ABSTRACT

Background: Despite the encouraging results of the SCORAD trial, single fraction radiotherapy (SFRT) remains underused for patients with complicated bone metastases with rates as low as 18–39%. We aimed to evaluate the incidence and treatment patterns of these metastases in patients being referred to a tertiary centre for palliative radiotherapy.

Materials and methods: We performed a retrospective review of all bone metastases treated at our centre from January 2013 until December 2017. Lesions were classified as uncomplicated or complicated. Complicated was defined as associated with (impending) fracture, existing spinal cord or cauda equina compression. Our protocol suggests using SFRT for all patients with complicated bone metastases, except for those with symptomatic neuraxial compression and a life expectancy of $\geq$28 weeks.

Results: Overall, 37 % of all bone metastases were classified as complicated. Most often as a result of an (impending) fracture (56 %) or spinal cord compression (44 %). In 93 % of cases, complicated lesions were located in the spine, most commonly originating from prostate, breast and lung cancer (60 %). Median survival of patients with complicated bone metastases was 4 months. The use of SFRT for complicated bone metastases increased from 51 % to 85 % over the study period, reaching 100 % for patients with the poorest prognosis.

Conclusions: Approximately 37 % of bone metastases are classified as complicated with the majority related to (impending) fracture. Patients with complicated bone metastases have a median survival of 4 months and were mostly treated with SFRT.

1. Introduction

Single fraction radiotherapy (SFRT) is the standard of care in the treatment of painful uncomplicated bone metastases[1–4]. In 2015, Cheon et al. defined uncomplicated bone metastases as bone metastases without (impending) fracture, spinal cord or cauda equina compression (SCC)[5]. Spinal cord and/or cauda equina compression will further be taken together as neuraxial compression. All other bone metastases are complicated. For these complicated bone metastases, the ideal treatment schedule is less clear, resulting in an adoption rate of SFRT below 18 % in a 2010 international survey and around 39 % in a population-based RT program[6,7]. The recent non-inferiority, randomized SCORAD-

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trial did suggest that the a single dose of 8 Gy in patients with SCC was as effective as multiple fractions for ambulatory status at 4 weeks[8].

In order to improve the adoption rate of SFRT for complicated bone metastases, we implemented an in-house protocol with SFRT being the treatment of choice for all painful bone metastases except for patients with symptomatic neuraxial compression and a life expectancy of ≥28 weeks. We estimated life expectancy using the number of risk factor (NRF) model developed by Chow et al. Risk factors for a worse survival are non-breast cancer, metastases other than bone, and KPS less than or equal to 60.

The goal of this paper is to estimate the proportion of patients with complicated bone metastases over time, survival distribution of SFRT versus multiple fraction radiotherapy (MFRT) and different types of complications. Furthermore, we tried to evaluate the temporal trends in SFRT and MFRT over a 5-year period in a tertiary academic centre.

2. Methods and material

2.1. Data collection

A retrospective review of hospital records was performed for all patients who received RT for complicated bone metastases from January 1, 2013 till December 31, 2017. Approval was obtained from the Hospital Research Ethics Board. We included patients who were treated for painful bone metastases with either 1x8Gy or 10x3Gy, which was our department's multifractional schedule of choice at that moment. We excluded post-operative radiotherapy, primary bone tumors and other fractionation schedules. Complicated bone metastases were defined as being associated with (impending) fracture, existing spinal cord and/or cauda equina compression[5]. For spinal metastases we used the spinal instability neoplastic score (SINS)[9]. 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, as were femoral lesions with more than 3 cm axial and/or 50 % circumferential cortical involvement [10]. Patients were stratified in prognostic groups using the number of risk factors (NRF) model. NRF 0–1, 2 and 3 corresponded to a predicted median survival of 64, 28 and 10 weeks respectively. SINS and NRF scores were determined by lead authors (CP, JV).

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 metastases. Means, medians, standard deviations and ranges were reported for continuous variables. The non-parametric Mann-Whitney U and χ^2 test were used to assess differences in proportions of continuous and categorical variables for both groups, respectively.

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. Survival time was calculated as time from the diagnosis of complicated metastases till death. To analyse differences in survival distributions, log-rank tests were performed for the following variables: age, gender, death within four weeks after RT and NRFs. Two-sided P values for statistical significance were set at 0.05. All analyses were carried out using the ®IBM ®SPSS Statistics software version 27.0.

3. Results

3.1. Patterns of care analysis

The total data set consisted of 947 bone metastases of which 353 (37.3 %) were complicated.

Table 1
Overview of metastasis and patient characteristics.

Metastasis characteristics				
Characteristics	**All complicated bone metastases (n = 353)**	**SFRT (n = 226; 64 %)**	**MFRT (n = 127; 36 %)**	**p-value**
Primary tumor				0.37
Prostate	72 (20 %)	46 (20 %)	26 (21 %)	
Breast	66 (19 %)	48 (21 %)	18 (14 %)	
Lung	73 (21 %)	42 (19 %)	31 (24)	
Gastro-intestinal	50 (14 %)	34 (15 %)	16 (13 %)	
Other	92 (26 %)	56 (25 %)	36 (28 %)	
Anatomical site				0.89
Axial and spinal	327 (93 %)	209 (92 %)	118 (93 %)	
Axial and non-spinal	4 (1 %)	3 (1 %)	1 (1 %)	
Non-axial	10 (3 %)	6 (3 %)	4 (3 %)	
Unspecified	12 (3 %)	8 (4 %)	4 (3 %)	
Simultaneous non-osseous metastases				0.33
No	108 (30.6 %)	72 (32 %)	36 (28 %)	
Yes	244 (69.1 %)	154 (68 %)	90 (71 %)	
Unknown	1 (0.3 %)	0	1 (1 %)	
Features of complication				<0.01
Neuraxial compression	154 (44 %)	60 (27 %)	94 (74 %)	
SINS ≥ 7 without neuraxial compression	191 (54 %)	163 (72 %)	28 (22 %)	
Non-spinal (impending) fracture	8 (2 %)	3 (1 %)	5 (4 %)	

Patient characteristics				
Characteristics	**All patients (n = 209)**	**SFRT (n = 131; 63 %)**	**MFRT (n = 78; 37 %)**	**p-value**
Sex				0.2
Male	111 (53 %)	68 (48 %)	43 (55 %)	
Female	98 (47 %)	63 (52 %)	35 (45 %)	
Age at radiation				0.25
Mean ± standard deviation	65.86 ± 13	66.82 ± 13	64.24 ± 14	
Median (range)	67 (24–94)	67 (25–94)	68 (24–92)	
Death within four weeks of RT				0.30
Yes	31 (15 %)	22 (17 %)	9 (12 %)	
No	175 (85 %)	107 (83 %)	68 (88 %)	
Number of risk factors				0.46
Number of evaluable patients	150	100	50	
NRF 0–1	39 (26 %)	23 (23 %)	16 (32 %)	
NRF 2	78 (5 %)	53 (53 %)	25 (50 %)	
NRF 3	33 (22 %)	24 (24 %)	9 (18 %)	

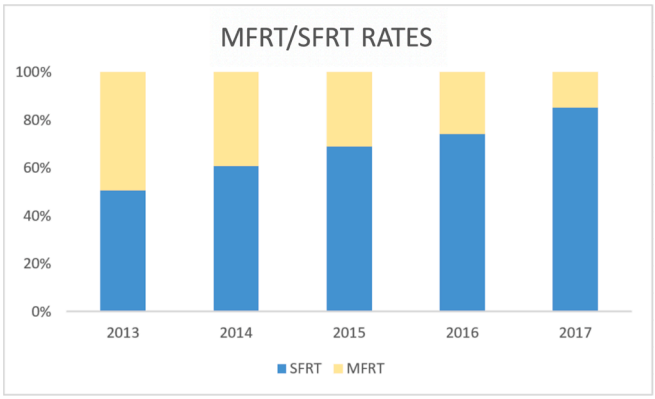

Fig. 1. Evolution in adoption of SFRT for complicated metastases over the five study years.

It included a total of 561 patients of whom 209 had complicated bone metastases. Table 1 gives an overview of metastasis and patient characteristics. In 93 % of cases, the lesions were located in the spine, most originated from primary prostate, breast or lung cancer (60 %). Groups were well balanced except for type of complication. The percentage of SFRT rose from 51 % in 2013 to 85 % in 2017 as shown in Fig. 1. In the NRF 0–1 group the use of MFRT rose from 42 % to 47 % from 2013 to 2015. After 2015 it started dropping reaching 15 % by 2017. In the NRF 2 group use of MFRT steadily declined from 48 % in 2013 to 17 % in 2017. In the NRF 3 group the use of MRFT declined from 60 % to 0 % by 2015. There was a slight rise in 2016 to 20 % but it fell to 0 % again by the end of 2017. There was no difference in distribution of NRF groups between SFRT and MFRT. These numbers are shown in Fig. 3. The most common cause of complication was SINS $\geq$ 7 without cord compression (54 %) followed by spinal cord compression (44 %) as shown in Fig. 2. There was a difference in reirradiation between SFRT (20 %) and MFRT (4 %). Total number of metastases dropped over the study period (213 in

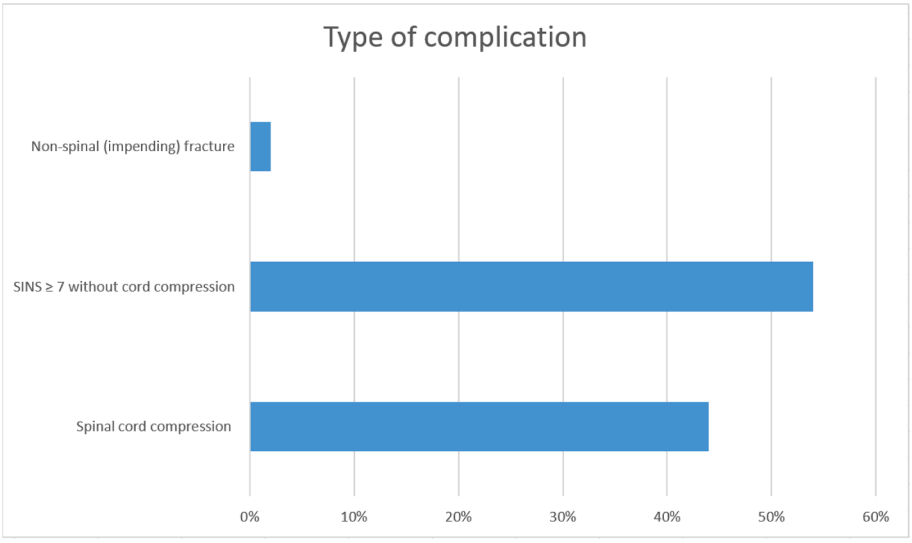

Fig. 2. Distribution of the features of complication.

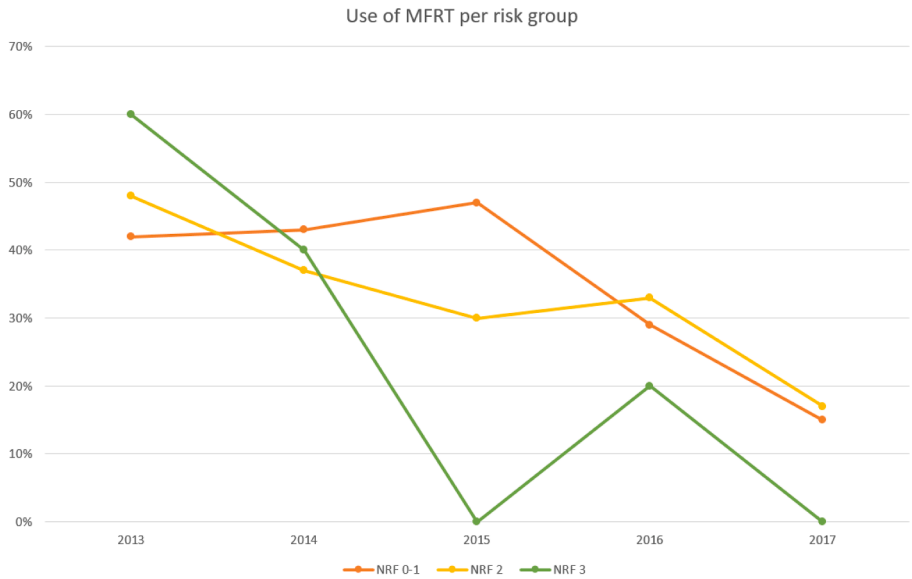

Fig. 3. Evolution of the use of MFRT per NRF group over the study period.

Table 2
Univariate survival analysis according to treatment type, features of complication, year of treatment and NRF categories.

Characteristics	Number of patients	Median overall survival (95 % CI)	P-value
General			0.35
All metastases	207	4.3 months (3.02–5.27)	
SFRT	130	4 months (2.6–5.4)	
MFRT	77	4.5 months (2.57–6.43)	
Features of complication			0.12
Number of evaluable patients	207		
Neuraxial compression	96 (46.4 %)	3.5 months (2.41–4.59)	
SINS ≥ 7	106 (51.2 %)	5 months (2.87–7.13)	
Non-spinal (impending) fracture	5 (2.4 %)	7.8 months (0–16.88)	
Per Year			0.73
SFRT			
2013	26	5 months (2.84–7.16)	
2014	24	3.8 months (0–10.95)	
2015	34	4 months (0.90–7.10)	
2016	24	2.5 months (0.82–4.18)	
2017	22	4.3 months (0.11–8.39)	
MFRT			
2013	22	4.5 months (0–14.27)	
2014	27	4.3 months (1.07–7.43)	
2015	13	5.8 months (1.93–9.57)	
2016	10	3 months (0.29–5.71)	
2017	5	2.8 months (1.14–4.36)	
NRF categories			<0.01
NRF 0–1	23 (23 %)	9.8 months (2.72–16.79)	
NRF 1	53 (53 %)	4 months (3.04–4.96)	
NRF 2	24 (24 %)	2.8 months (0.87–3.63)	

2013 to 167 in 2017) as shown in Table 4.

3.2. Survival analysis

Our final dataset included 209 patients. At the time of analyses 195 patients (94.2 %) had died resulting in a median OS of 4 months for SFRT and 4.5 months for MFRT (p = 0.35). Median survival per year fluctuated between 2.5 and 5 months in SFRT and 2.8 and 5.8 months in MFRT throughout the study period. Similar proportions died within 4 weeks (SFRT 17 % vs. MFRT 12 %). Metastases with neuraxial compression had comparable median overall survival compared to SINS ≥ 7 and non-spinal (impending) fracture (3.5 months vs. 5 months vs. 7.8 months, p = 0.12). Survival between NRF groups differed. NRF 0–1 group had a median survival of 9.8 months, compared to 4 months and 2.8 months for NRF 2 and NRF 3 groups respectively (p < 0.01). The details are shown in Table 2.

Table 4
Evolution of number of complicated vs uncomplicated metastases per year.

Years	Complicated	Uncomplicated	Total
2013	97	116	213
2014	102	143	245
2015	64	75	139
2016	50	133	183
2017	40	127	167

3.3. Discussion

To the best of our knowledge this is one of the first studies looking at incidence and patterns of treatment for complicated bone metastases. Our data shows that of the 947 bone metastases treated at Ghent University Hospital over a period of 5 years 353 (37.3 %) were complicated. These numbers are comparable to a Canadian population-based clinical series[7]. The reirradiation rate was higher in the SFRT group (20 %) as compared to the MFRT group (4 %) but this was comparable to the randomized trials reported (SFRT: 20 % vs MFRT 8 %) [3]. Evaluation of functional outcome after reirradiation goes beyond the scope of this review. Maranzano et al did show that this approach is safe for spinal cord compression and is successful in maintaining ambulatory status [11]. The most common cause of complication was impending fracture without cord compression corresponding to a SINS ≥ 7. A recent systematic review showed that approximately 9.6 % of spinal metastases show signs of spinal cord compression[12]. In our total cohort (including uncomplicated bone metastases) this was about 32 %. A reason for this higher number might be that Van Den Brande et al. included autopsy studies and our cohort was heavily biased due to only including referrals for radiotherapy. This meant asymptomatic cases were excluded. Despite features of complication being seen in more than 1/3 of bone metastases the optimal fractionation choice and a proper definition remain unclear[7,13]. The definition of complicated used in our study contained bone metastases with (impending) fracture, existing spinal cord and/or cauda equina compression. We found that 93 % of all complicated bone metastases were spinal compared to just 25.6 % in uncomplicated cases [14]. No significant difference in survival was found for the different types of complication. The randomized evidence guiding our fractionation choice is limited to neuraxial compression. Table 3 gives an overview of these trials. An Italian trial, using a less commonly prescribed fractionation schedule, showed similar symptom control at 4 weeks between 2 × 8 Gy and 1 × 8 Gy [15]. Thirion et al. showed comparable mobility status at 5 weeks between 5 × 4 Gy and 1 × 10 Gy [16]. The largest trial to date was the SCORAD III-trial which randomized 686 patients between 1 × 8 Gy and 5 × 4 Gy. Their multifraction schedule (5 × 4 Gy) had a lower BED compared to ours (10 × 3 Gy). Several trials have shown no detriment to oncological outcome in

Table 3
Summary of randomized trials on radiotherapy in the setting of spinal cord compression.

Study	ITT	Treatment	Primary endpoint	Assessable for primary analysis	Results	Primary endpoint met
Italian trial Maranzano et al. (2009)	327	2 × 8 Gy vs. 1 × 8 Gy	Response rate (symptom control)	303 (93 %)	MFRT (53 %) vs. SFRT (52 %)	✓
Cancer Trials Ireland ICORG 05–03 Thirion et al. (2020)	112	5 × 4 Gy vs. 1 × 10 Gy	Mean change in mobility scores between baseline and the 5-week follow-up	73 (65 %)	MFRT (−0.3) vs. SFRT (−0.06)	✓
SCORAD III Hoskin et al. (2019)	686	5 × 4 Gy vs. 1 × 8 Gy	Ambulatory status at 8 weeks	342 (50 %)	MFRT (72.7 %) vs. SFRT (69.3 %)	×

de-escalating the multifraction dose [17,18]. Despite them narrowly missing their primary endpoint at 8 weeks, they did show non-inferiority of 1 × 8 Gy for maintaining ambulatory status at 4 weeks[8]. One of the reasons why this trial could not prove non-inferiority at 8 weeks is the high mortality rate in both arms. In the time leading up to the 8 weeks assessment more than 1/3 of all patients had already died. In our study 15.1 % of all patients died within 4 weeks of radiotherapy. The median survival for patients with neuraxial cord compression in our data was 3.5 months which is comparable to literature[8,15,19]. The limited prognosis of these patients warrants a treatment that best maintains their quality of life. The median survival for both MFRT (4.5 months) and SFRT (4 months) were well below 28 weeks which was a criterion for our fractionation choice. The worst prognosis group (NRF 3) had a predicted median survival of just 10 weeks. Despite this dismal survival about 27 % of these patients received MFRT. In the best prognosis group (NRF 0–1), with a predicted median survival of 64 weeks, approximately 59 % of patients received SFRT despite our protocol mandating a longer course. This leads us to believe that besides life expectancy there are other factors influencing fractionation choice such as physician preference, tumor size and/or patient preference. Throughout the study period the number of patients receiving SFRT in NRF 3 group did increase reaching 100 % by 2017. No clear reason for the high percentage of SFRT in the best prognosis group was found. A possible explanation could be the increasing use of more hypofractionated schedules such as stereotactic body radiotherapy (SBRT) in this setting which were not included in our data. The fact that the number of metastases dropped sharply over the study period adds further credence to this hypothesis.

In general, the rationale most often used to choose MFRT over SFRT is improved local control, despite this not being a clinically relevant endpoint in most palliative patients[20–22]. Over the past few years, there has been a noticeable increase in the utilization of SBRT for patients with improved prognoses and/or limited disease. [23]. These patients are often explicitly referred with the intent of durable local control. The evidence for the use of SBRT in spinal cord compression is limited to retrospective series which do show encouraging results [24,25]. It could lead to better outcome but has its inherent difficulties. Due to spinal cord compression presenting urgently the use of a complex technique is challenging in a short timeframe. Until the arrival of prospective evidence such an approach should not be used outside of clinical trials[26]. For complicated metastases, the goal of treatment is symptom control and/or maintaining an ambulatory status. There is ample evidence that SFRT is equivalent to MFRT in terms of pain control [20,27]. Despite the evidence for equivalence in terms of ambulatory status not being as strong as for pain control Hoskin et al. do make a strong case for the implementation of SFRT in this setting[8]. Its percentage rose to 85 % in our centre in 2017 which is well above published rates (<40 %)[7,28].

The limitations of this study are its retrospective design with an inherent selection and referral bias. Prospective trials are still needed to properly define patient's response to treatment and further define the role and dose of SFRT in complicated bone metastases. The lack of a common operational definition and the limited prognosis in the majority of these patients complicates the development of these trials. A second limitation is the small sample size limiting the statistical power of our study. Due to the lack of academic consensus defining the characteristics of complicated bone metastases, the definition we employed may have inadvertently excluded bone metastases exhibiting other risk features.

4. Conclusion

In our patient cohort, about one third of all bone metastases were complicated with the vast majority having features relating to (impending) fracture. Patients with complicated bone metastases have a dismal median survival of 4.3 months and were mostly treated with SFRT at our centre.

Author statement

The study was approved by the ethical committee of Ghent University Hospital. The retrospective nature of the study does not require individual informed patient consent.

CRediT authorship contribution statement

Cedric Peters: Data curation, Formal analysis, Validation, Writing – original draft, Writing – review & editing. **Julie Vandewiele:** Data curation, Validation. **Yolande Lievens:** Validation. **Marc van Eijkeren:** Validation, Writing – review & editing. **Valérie Fonteyne:** Validation. **Tom Boterberg:** Validation, Writing – review & editing. **Pieter Deseyne:** Visualization, Writing – review & editing. **Liv Veldeman:** Validation, Writing – review & editing. **Wilfried De Neve:** Visualization, Writing – review & editing. **Chris Monten:** Validation, Writing – review & editing. **Sabine Braems:** Visualization. **Fréderic Duprez:** Validation, Writing – review & editing. **Katrien Vandecasteele:** Validation, Writing – review & editing. **Piet Ost:** Supervision, Validation, Writing – review & editing, Conceptualization.

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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