FACULTY OF MEDICINE AND HEALTH SCIENCES

THE USE OF SINGLE-FRACTION AND MULTIPLE-FRACTION RADIOTHERAPY FOR THE PALLIATION OF PAINFUL BONE METASTASES: PATTERNS OF PRACTICE IN THE UNIVERSITY HOSPITAL OF GHENT

Julie Vandewiele
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Supervisor: Prof. Dr. Piet Ost, MD, PhD

A dissertation submitted to Ghent University in partial fulfilment of the requirements for the degree of Master of Medicine in Medicine

Academic year: 2016 – 2018

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Contents

1 Samenvatting

In deze thesis was er een evaluatie van de voorgeschreven fractionatie schema's voor de palliatie van pijnlijke botmetastasen voorgeschreven tussen 1 januari 2013 en 31 december 2015 op de dienst radiotherapie van het Universitair Ziekenhuis Gent. Er werd gekeken naar het percentage voorgeschreven enkele fracties ten opzichte van gefractioneerde schema's en een evolutie over de drie studiejaren werd geanalyseerd. Een vergelijking van de voorgeschreven schema's met de aanbevolen richtlijnen in het UZ Gent en internationaal werd uitgevoerd. We voerden een retrospectieve analyse van een dataset met patiënt- en tumorgegevens uit. Volgende factoren werden geëxtraheerd uit de patiëntendossiers: fractionatie schema (1 x 8 Gray of 10 x 3 Gray), bestraalde anatomische locatie, herbestraling, gelijktijdige meta elders in het lichaam, Karnofsky score, RPA, NRF, het al dan niet gecompliceerd zijn van een meta, ruggenmerg of cauda equina compressie, neurologische uitvalssymptomen, indeukingsfracturen, spinal instability neoplastic score, primaire tumor, geslacht en leeftijd op moment van bestraling. De analyse van het voorschrijfgedrag was gebaseerd op de afzonderlijke metastasen, in plaats van patiënten. Een Mann-Whitney U en chi-square test werden gebruikt om verschillen in proporties van variabelen tussen de fractionatie schema's te analyseren, alsook om trends in voorschrijfgedrag over de tijd weer te geven. De overeenkomst van de voorgeschreven schema's met het internationaal en het lokale UZ protocol werd vergeleken. In totaal werden 364 patiënten, bestraald voor 599 botmetastasen geanalyseerd. Zesenzeventig procent van alle metastasen kreeg een enkele fractie van radiotherapie, in vergelijking met 24% voor meerdere fracties. Het voorschrijven van enkele fracties steeg over de jaren (68,8% in 2013, 78,4% in 2014 en 82,7% in 2015). Meer patiënten die initieel met een enkele fractie bestraald werden moesten herbestraald worden (13,6% vs 2,8%). Het voorschrijven van enkele fracties stemde in 80% en 90% overeen met het UZ en internationaal protocol respectievelijk. Voor mutipele fracties was dit 80% voor het UZ protocol en 42% voor het internationale protocol. Het voorschrijfgedrag van enkele fracties voor gecompliceerde botmetastasen kwam het minst overeen met de richtlijnen in het UZ. Ondanks dat het gebruik van enkele fracties in het UZ Gent het hoogst gerapporteerd is in vergelijking met artikels met een gelijkaardige studieopzet (76%), is er nog steeds ruimte voor verbetering. Twintig procent van de metastasen krijgt nog lange schema's wanneer het protocol eigenlijk enkele fracties aanbeveelt. Een stijging in het gebruik van enkele fracties werd gezien over de drie studiejaren, door het UZ protocol beter in de praktijk te implementeren.

2 Abstract

Introduction and purpose: This paper evaluates the prescribed radiotherapeutic fractionation schedules for the palliation of painful bone metastases from 1 january 2013 until 31 december 2015 at the radiotherapy department in Ghent. Temporal trends in SFRT use are analyzed. A comparison of the received treatment with the recommended schedules according to the protocol in the University Hospital Ghent and international guidelines is carried out.

Materials and methods: A retrospective review of a dataset containing hospital records was conducted. The following treatment, tumour and patient factors were included: fractionation schedule (1 x 8 Gy or 10 x 3 Gy), irraditated anatomical site, retreatment rate, simultaneous non-osseous meta, Karnofsky score, RPA and NRF model, if a metastasis was complicated or not, spinal cord compression, neurologic symptoms, vertebral compression, spinal instability neoplastic score, primary tumour, gender and age at radiation. Patterns of care analysis was lesion based. Mann-Whitney U and chi-square test were used to assess differences in proportions between fractionation schedules, and to determine temporal trends in prescription. The prescribed fractionation schedules were compared to both international and UZ Ghent recommendations.

Results: In total 364 patients, with 599 bone metastases were analyzed. Median overall survival was 7,4 months (95% CI 5,5-9,4) for the whole group. Seventy-six percent of all metastases received a single fraction of radiotherapy in comparison to 24% for multiple fractions. An increasing tendency of SFRT prescription was seen over the three study years (68,8% in 2013, 78,4% in 2014 and 82,7% in 2015). The retreatment rate was higher in patients primarily treated with SFRT (13,6% vs 2,8% for MFRT). The adherence rate to UZ and international protocols was 80% and 90% for SF use respectively, and 80% and 42% for MF use respectively. The lowest adherence rate was seen for SFRT for complicated bone metastases.

Discussion and conclusions: The utilization rate of single fraction regimens found in this paper (76%) is the highest reported in comparison to studies with similar setup, but there is still room for improvement. Twenty percent of bone metastases still received MFRT when SFRT was actually prescribed in the protocol. An increasing trend for SF use was seen over the three study years, due to better adherence to the UZ protocol (increasing in adherence to the protocol can be seen from 2013 till 2015 for SF use, but not for MF use). The adherence rate to the UZ protocol is the lowest for SF use for complicated bone metastases.

3 Introduction

Bone metastases are a common manifestation of advanced cancer, especially of cancers of the lung, breast, and prostate [1,2]. They are a significant cause of morbidities, which are potentially devastating. They are not only the most common cause of cancer-related pain [3], but also induce immobility, spinal cord compression (SCC), hypercalcemia, pathologic fractures and overall reduction in performance status and quality of life [4–7].

Radiotherapy (RT) has been examined extensively in clinical trials over 30 years and has proven to be the most efficaceous treatment. Being the standard therapeutic option for the palliation of painful bone metastases for years now, it makes up for a substantial workload in any RT department [3]. Next to its durable analgesic effect (significant pain relief in up to 60% of patients and complete pain relief in about 25% [8]), radiation therapy also helps maintaining the skeletal integrity, thus preserving the function of the patient and preventing complications such as fracture or injury to the spinal cord. Because of these effects, it succeeds to fulfill the main aim of palliative therapy, which is improving the quality of life [1, 2, 5, 6]. Because radiation therapy in painful bone metastases doesn't have a curative, but a palliative goal, the time span during which it is administered should be kept as short as possible and it must provide comfort to the patient, with as little treatment related side-effects as possible [9].

Next to radiotherapy, there are still other therapeutic options that can be considered for the management of pain resulting from bone metastases: analgesics, radiopharmaceuticals (Strontium-89 and Samarium-153), bisphosphonates, and surgery (kyphoplasty, vertebroplasty, decompression) [4, 10]. Few therapeutic guidelines exist for the treatment of metastatic disease because of the complexity of the problem (different types of cancer and different sites of involvement). The roles of the several existing modalities, alone or in combination, still have not been fully defined [9]. The use of bisphosphonates, surgery and radionuclides as therapeutic options with their own indications are still being used in the management of painful bone metastases but mostly don't obviate the need for external beam radiotherapy (EBRT) for appropriate patients [4, 11]. Surgical decompression and stabilization plus post-operative radiotherapy should be considered for selected patients with single level spinal cord compression or spinal instability, taken performance status, primary tumor site, extent and dis-

tribution of metastases and expected survival into account. In the post-operative period, external beam radiotherapy is administered most commonly as 30 Gy in 10 fractions. Radiopharmaceuticals (Strontium-89 and Samarium-153) are an important care option for multifocal osteoblastic bone metastases, in which EBRT isn't possible (not convenient or safe) due to the extensiveness of the lesions. Kyphoplasty and vertebroplasty could be a palliative option for patients where surgery is not feasible or indicated, but there are no data to suggest that the addition of vertebroplasty or kyphoplasty further improve symptoms or have a greater impact on clinically significant endpoints than EBRT alone. So with radiotherapy being the standard therapy, additional randomised prospective trials should be done to further define for which patients these other therapeutic modalities could play a role [4].

In the past, several retrospective and prospective studies, including randomised controlled trials, have conducted a comparison between single-fraction radiotherapy (SFRT) and multiple-fraction radiotherapy (MFRT). Not only equivalence of pain relief rates were reported (complete pain responses of 23% and 24% and overall pain responses (complete and partial) of 60% vs 61% were seen for respectively SF arms and MF arms [8]), authors also stated little discernible difference in toxicity [2, 3, 6, 9, 12–18]. There were no significant differences in duration of the pain relief response reported [10, 12, 17] and two studies described equivalence in overall survival [9, 17]. Although these studies have proven similar efficacy between single fraction (SFRT) and multiple fraction radiotherapy (MFRT) in the past, longer fractionation schedules are still being overused [8, 12, 14, 19].

This paper evaluates the prescribed radiotherapeutic fractionation schedules from 1 january 2013 until 31 december 2015 at the radiotherapy department in Ghent. Temporal trends in SFRT use are analyzed. A comparison of the received treatment with the recommended schedules according to the protocol in the University Hospital Ghent (UZ Ghent) and international guidelines [14] is carried out. According to Lutz et al. (United States, ASTRO Evidence-Based Guideline), a single fraction schedule is the treatment of choice for uncomplicated bone metastases. Uncomplicated bone metastases are defined as painful bone metastases not associated with impending or existing pathologic fracture or existing spinal cord or cauda equina compression [20]. Femoral lesions with more than 3 centimeter axial and/or 50% circumferential cortical involvement and spinal lesions with a spinal instability neoplastic score between 7 and 12 are considered as impending pathologic fractures. Longer schedules can be considered for complicated metastases or patients who have undergone surgical

stabilization [14]. These guidelines are considered as an international standard. At the radiotherapy department in Ghent, only patients with symptomatic spinal cord/cauda equina compression and a life expectancy of more than 28 weeks (NRF > 2) should receive MFRT.

Furthermore, a survival analysis is conducted. The main purpose is to gain insights in the prescription behaviour for the palliation of painful bone metastases at the radiotherapy department Ghent, and see if the care reflects the published literature.

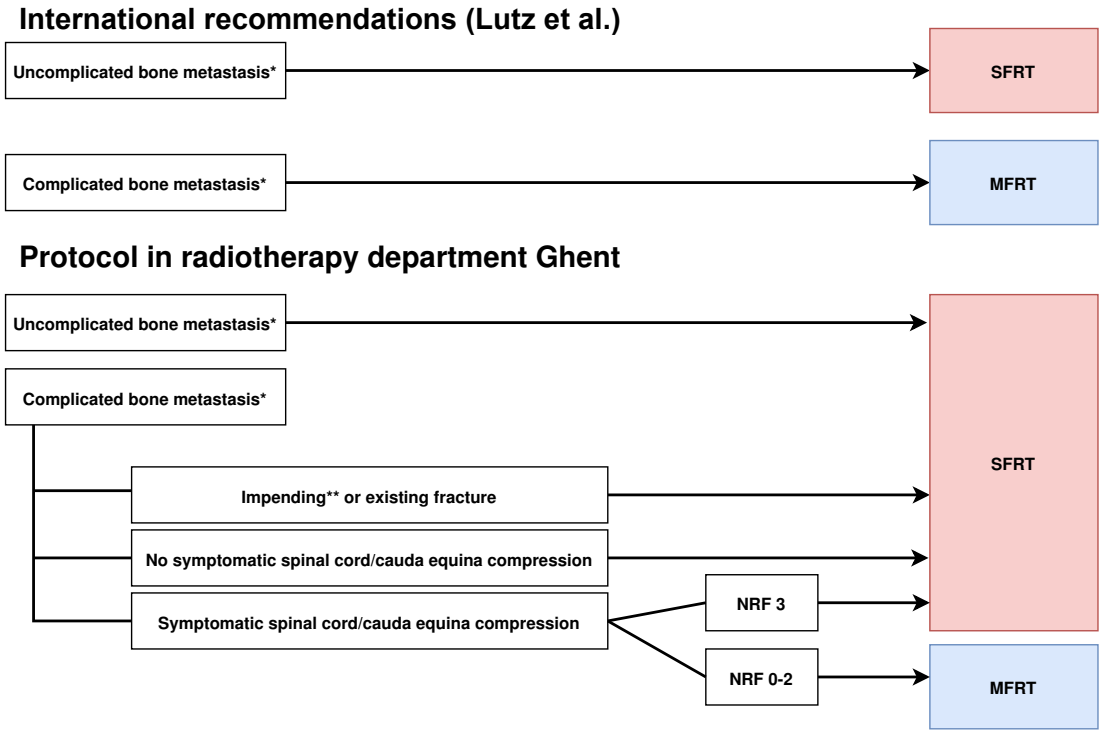

Figure 3.1: **Schematic overview of the UZ Ghent and international radiotherapy protocols for the palliation of painful bone metastases.**
SFRT: single fraction radiotherapy; MFRT: multiple fraction radiotherapy; NRF: number of risk factors, a model generated by Chow et al. to predict survival for all patients with metastatic cancer attending a palliative radiotherapy clinic.
*Complicated bone metastases are defined as painful bone metastases associated with impending or existing pathologic fracture or existing spinal cord or cauda equina compression [20].
**Impending fractures are femoral lesions with more than 3 centimeter axial and/or 50% circumferential cortical involvement and spinal lesions with a SINS between 7 and 12.

4 Method

The following research questions were raised: 'Is there an increase in SFRT use from january 2013 until december 2015?', 'Do the actual prescribed treatments reflect the guidelines in the University Hospital Ghent and proposed by Lutz et al. and Wu et al.?' and 'What are the prognostic factors in radiotherapy for bone metastases?'. Trying to answer the research questions, a retrospective review of a dataset containing hospital records was conducted. Ethical approval was obtained from the hospital Research Ethics Board (EC2017/0740).

4.1 Sample and data collection

Data from a patient cohort referred for analgesic palliative radiotherapy for bone metastases between 1 january 2013 and 31 december 2015 was used to build the dataset. The following treatment, tumour and patient factors were included: fractionation schedule (1 x 8 Gy or 10 x 3 Gy), irraditated anatomical site (axial and spinal, axial and non-spinal, non-axial or irradiation of axial and non-axial metastases in one field), retreatment rate, simultaneous non-osseous meta, Karnofsky score, RPA and NRF model, complicated bone metastases, spinal cord compression, neurologic symptoms, vertebral compression, spinal instability neoplastic score, primary tumour (cancer of the prostate, lung, breast, gastro-intestinal and others), gender and age at radiation. Following metastases were exluded: primary cancer of the bone and patients who received 30 Gy in 10 fractions in a postoperative setting. In total 364 patients irradiated for 599 bone metastases met the inclusion criteria, as shown in figure 4.1.

In table 5.1 and 5.2, an overview of the extracted variables is given. To evaluate spinal cord or nerve compression, the (reports of the) radiology examinations taken before the administration of RT were evaluated. For neurologic symptoms, a differentiation was made between dermatomal pain pattern, paresthesia, hyperreflexia, sensory loss, motor loss, both sensory and motor loss or both dermatomal pain pattern and motor loss, a combination that occurred in some patients. The spinal instability neoplastic score (SINS) was assigned to every patient with a spinal metastasis to make a distinction between stable, potentially instable or stable metastases. The different elements of the SINS are formulated in table 8.1.The classification system includes global spinal location of the tumor, type and presence of pain, bone lesion type, spinal alignment, extent of vertebral body collapse,

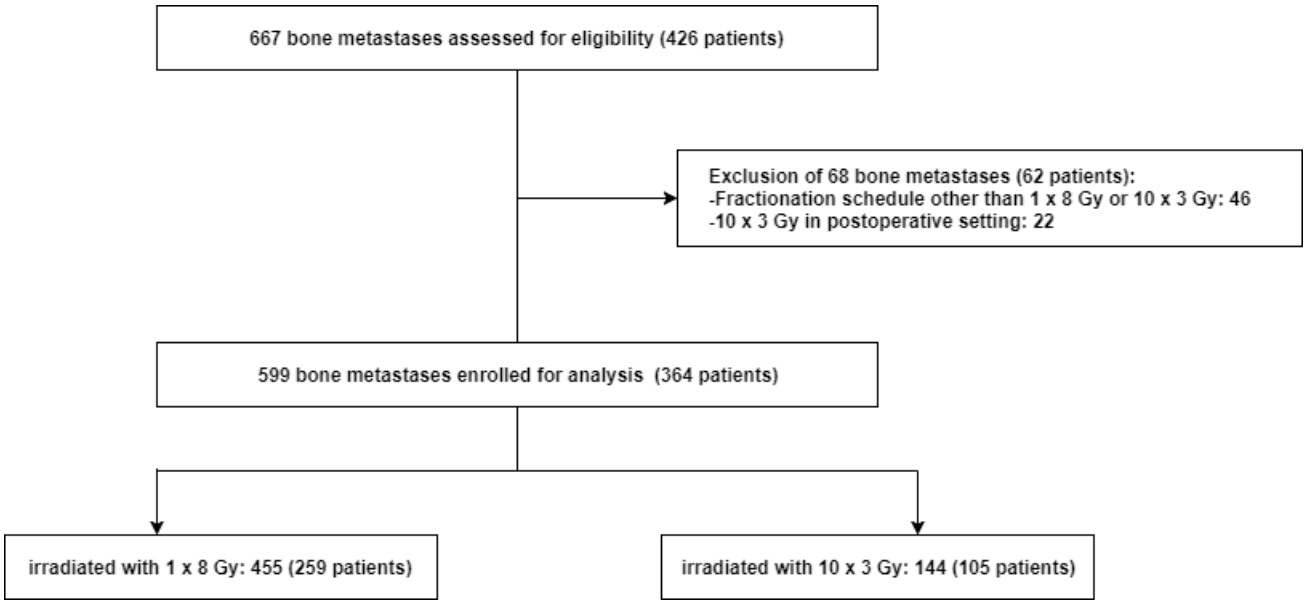

Figure 4.1: **Flow chart of bone metastasis inclusion**

and posterolateral spinal element involvement. The Karnofsky Performance Status Scale (KPS) was determined for each patient, as well as the NRF and RPA model, two models of survival prediction to objectify patient prognosis. [21]. The first one, the NRF model, was generated by Chow et al. [22]. This is a survival prediction score applicable on all patients with metastatic cancer attending a palliative radiotherapy clinic. It is based on three risk factors: non-breast primary cancer, metastases other than bone and KPS $\leq$60. In 2012, Chao et al. [23] also generated a classification system that is predictive for overall survival, the RPA model. This system includes three variables, which are the interval between primary diagnosis and radiotherapy for bone metastases, age and KPS.

4.2 Statistical analysis

4.2.1 Patterns of care analysis

The analyses were lesion based, patients who received more than 1 course of RT were considered independently for each course.

Descriptive statistics to estimate frequencies and proportions of the SFRT and MFRT groups were applied for categorical variables. 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. This was done once for all metastases and once for spinal metastases only. Fisher's exact test was employed

when more than 20% of the cells in a crosstab had an expected count more than 5. The chi-square test was carried out to determine temporal trends in SFRT and MFRT treatments. The prescribed fractionation schedules were compared to both international and UZ Ghent recommendations. An overview of the recommendations is pictured in figure 3.1.

4.2.2 Survival analysis

The analysis of survival following palliative RT was patient based. Of patients who were irradiated at two or more anatomical sites, only the metastasis that was irradiated last was selected.

A Kaplan-Meier curve and log-rank test was performed. This was conducted several times with different factors each time. Differences in survival were analyzed for the following factors: fractionation schedule, NRF, RPA (this was done once for all metastases, once for only spinal metastases and once for all the non-spinal metastases), SINS and complicated vs non-complicated metastases.

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.

5 Results

5.1 Patterns of care analysis

5.1.1 Analysis of the whole cohort

The total dataset consisted of 426 patients irradiated at 667 bone metastases. Forty-six bone metastases were irradiated with a fractionation schedule other than one fraction of 8 Gy or 10 fractions of 3 Gy and 22 bone metastases received a postoperative multiple fraction schedule, thus exceeding the inclusion criteria. The eventual cohort contained 364 patients, irradiated at 599 bone metastases. Table 5.1 gives an overview of patient and metastasis characteristics.

Seventy-six percent of all metastases received a single fraction of radiotherapy in comparison to 24% for multiple fractions. Lung cancer was the most common primary tumor (25,2%), followed by primary tumours which occurred in anatomical sites differing from prostate, breast, lung or the gastro-intestinal tract (24,7%). These two groups were followed by prostate cancer (20,5%). Of all the anatomical sites which received radiotherapy, 315 were spinal sites, which accounted for the vast majority (52,6%). Seventy-five percent of patients had metastasis other than bone at time of radiotherapy. The retreatment rate was higher in patients primarily treated with SFRT (13,6% vs 2,8% for MFRT; P= 0,001). If a bone metastasis had to be retreated, it was mainly (in 74 of 82 cases) prescribed a single fraction.

Within the SFRT cohort, the majority belonged to class 2 of the RPA model (67%) and had 2 risk factors of the NRF model (58,2%). The same result was reported for the MFRT cohort (58,1% and 53,3% respectively). Approximately one fourth of patients who received MFRT are in the lowest class of RPA and NRF (thus with the lowest predicted prognosis).

There is no significant difference in distribution of NRF between the SFRT and the MFRT cohort, as seen in table 5.1 (P=0,849).

5.1.2 Temporal trends in single fraction use

Proportions of osseous metastases treated with SFRT increased over the three study years. The rates of SFRT use increased significanly over the three study years, from 68,8% in 2013 (148/215 cases) to 82,7% in 2015 (115/139 cases), which is presented in table 5.1 (P=0,006). Figure 5.1 gives an overview of the frequencies of single fraction and multiple fraction schedules.

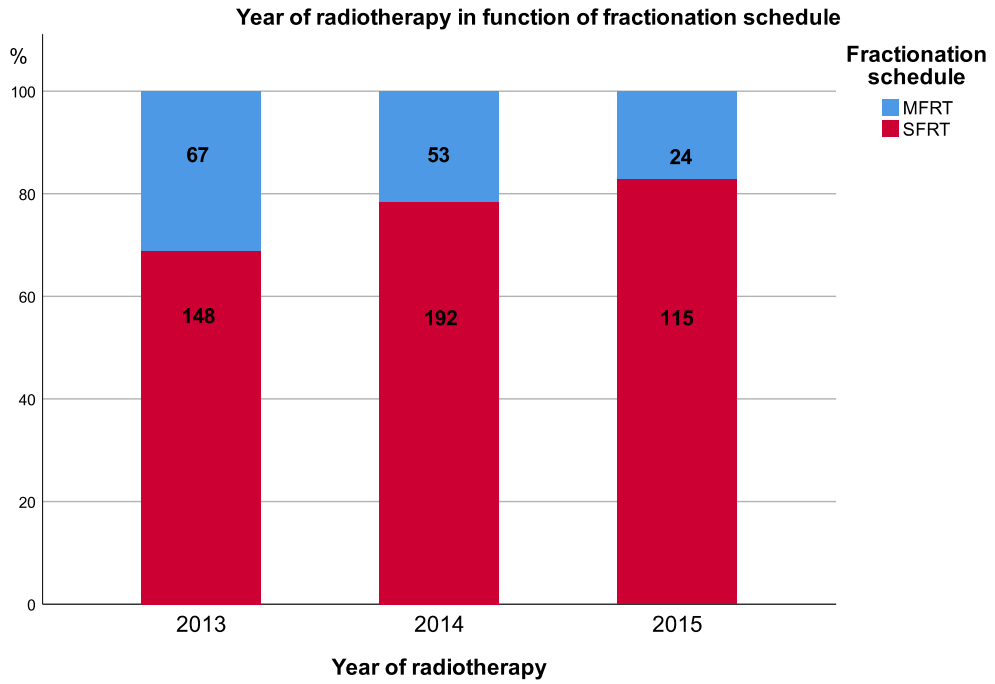

Figure 5.1: **Frequencies of SFRT and MFRT by year of radiotherapy.** An increasing tendency of SFRT prescription was seen (2013: 68,8%, 2014: 78,4%, 2015: 82,7%). In 2015, patients were more likely to receive a single fraction treatment (P= 0,006). The numbers correspond with the absolute frequencies in the patient cohort.

5.1.3 Analysis of the spinal metastases

Whether a metastasis caused spinal cord compression, neurologic deficit or vertebral compression and was complicated or remained stable according to the spinal instability neoplastic score could only be determined for metastases in the vertebrae. The majority of the spinal metastases was complicated. Eighty-six percent of metastases which caused spinal cord compression also caused neurologic symptoms (95/139 cases). Table 5.2 summarizes these characteristics by fractionation schedule. Patients who received a multiple fraction regimen had a higher incidence of spinal cord or nerve root compression (P<0,001), neurologic symptoms (P<0,001), vertebral collapse (P= 0,003) and complicated metastases (P<0,001).

5.1.4 Actual received radiation schedules compared to University Ghent and international protocols

Figure 3.1 shows the guidelines on which prescription of fractionation schemes is based according to the radiotherapy department in the University Hospital of Ghent and according to international recommendations. In the SFRT cohort, 447 (80% of 559) and 303 (90% of 338) bone metastases received the correct fractionation schedule according to the UZ protocol and international protocol respectively, as seen in table 5.3. Of the MFRT group, 80% (32/40) received a long schedule as in accordance with the UZ protocol in comparison to 42% (109/261) according to the international recommendations.

To evaluate a temporal trend in adherence rate to the UZ protocol, a bar graph was plotted. A distinction between the adherence rate for SFRT for complicated and uncomplicated bone metastases over the three study years (overall) was seen with the lowest adherence for complicated bone meta's. An increasing trend in adherence to the protocol can be seen from 2013 till 2015 for SF use, but not for MF use (5.2).

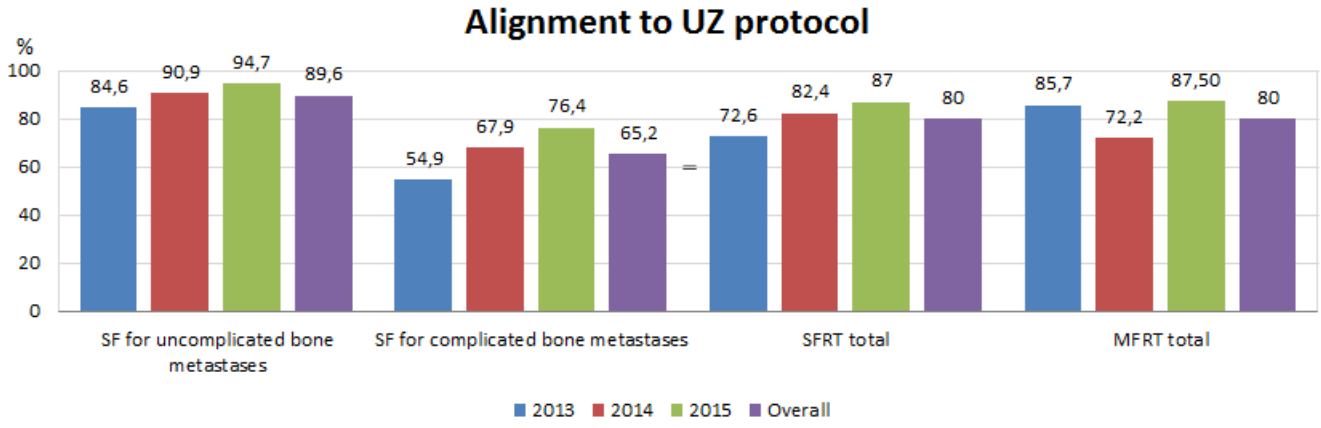

Figure 5.2: **Alignment of prescribed fractionation schedules to recommended schedules by the UZ protocol.** The percentages correspond with the ratio of bone metastases that actually received a certain schedule indicated on the x-axis, to the total number of metastases that should have received that particular schedule prescribed by the UZ protocol.

5.2 Survival analysis

Table 5.4 is a patient-based summary of clinical variables by fractionation schedule. The median age at radiation was 67 years (range 5-92). Two hundred fifty-nine patients (72,3%) had died at time of the analyses. An equal proportion of both fractionation schedules died within 4 weeks after treatment (15,9% and 14,9%; P= 0,934). Median overall survival was 7,4 months (95% CI 5,5-9,4)

for the whole group (6,7 months for SFRT, as compared to 8,4 months for MFRT (P= 0,493)), as seen in table 5.5. A significant difference in distribution of time between radiotherapy and death was achieved for following variables: RPA (for all bone metastases and for non-spinal metastases only) and NRF model. Time distributions are pictured in figures 5.3, 5.4, and 8.1, 8.2 8.3, , 8.4, 8.5 and 8.6 in appendix. Further analysing these variables by conducting a two by two comparison, following comparisons didn't achieve a significant P-value: RPA class 2 with 3 for all three situations (all patients, spinal metastases and non-spinal metastases) and NRF 2 with NRF 3 (P=0,482; P= 0,938; P= 0,190; P= 0,471 respectively). Even though survival analysis of all patients with spinal metastases concerning the RPA classes wasn't significant, the comparison of only patients in class 1 and 2 did reach the significance level.

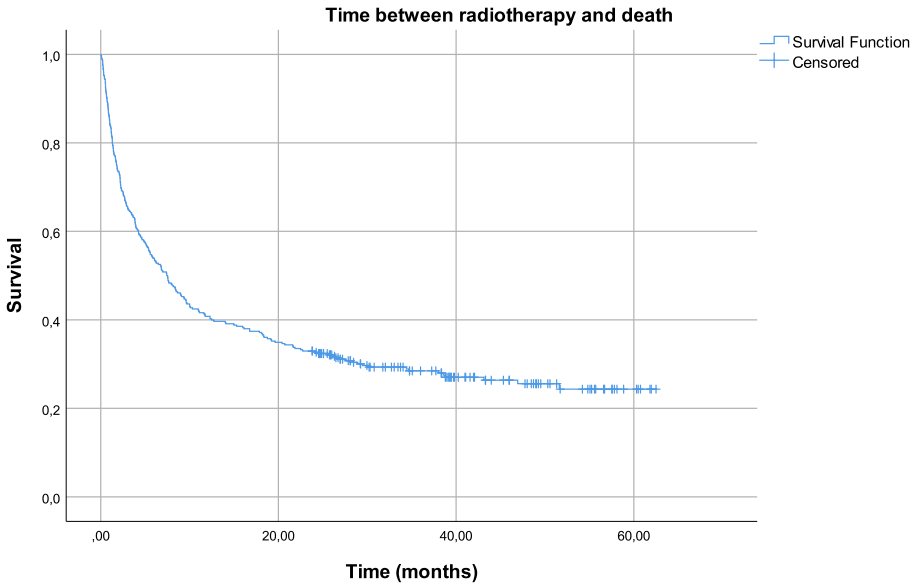

Figure 5.3: **Kaplan-Meier reporting time between radiotherapy and death for all patients.** Median overall survival was 7,4 months (95% CI: 5,5-9,4).

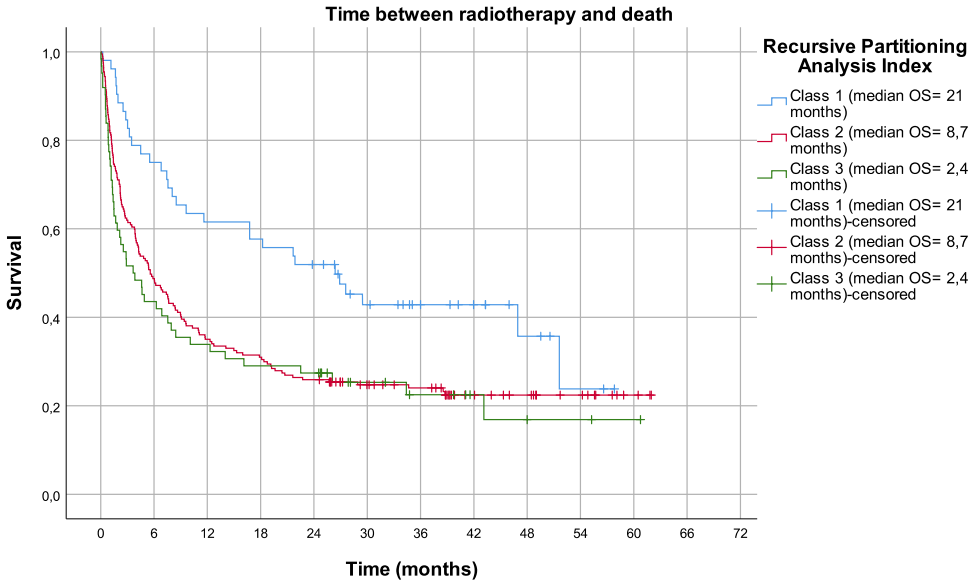

Figure 5.4: **Kaplan-Meier reporting time between radiotherapy and death, comparing RPA classes.** A significant difference in survival distribution was reported (P= 0,004).

Table 5.1: **Overview of patient and metastasis characteristics extracted from the electronic patient files by fractionation schedule**

Characteristics	All bone metastases (n=599)	SFRT (n=455; 76%)	MFRT (n=144; 24%)	P-value*
Year of RT				
2013	215 (35,9%)	148 (32,5%)	67 (46,5%)	**0,006**
2014	245 (40,9%)	192 (42,2%)	53 (36,8%)	
2015	139 (23,2%)	115 (25,3%)	24 (16,7%)	
Gender				
Man	302 (50,4%)	226 (49,7%)	76 (52,8%)	0,579
Woman	297 (49,6%)	229 (50,3%)	68 (47,2%)	
Age at radiation (years)				
Mean ± standard deviation	64,8 ± 13,7	64,8 ± 13,8	64,7 ± 13,9	0,572
Median (range)	66 (5-92)	66 (18-90)	67 (5-92)	
Patient dead				
Number of evaluable bone metastases**	591 (98,7%)	449 (98,7%)	142 (98,6%)	0,773
No	149 (25,2%)	115 (25,6%)	34 (23,9%)	
Yes	442 (74,8%)	334 (74,4%)	108 (76,1%)	
Primary tumour				
Prostate	123 (20,5%)	92 (20,2%)	31 (21,5%)	**0,001**
Breast	107 (17,9%)	86 (18,9%)	21 (14,6%)	
Lung	151 (25,2%)	117 (25,7%)	34 (23,6%)	
Gastro-intestinal	71 (11,9%)	54 (11,9%)	17 (11,8%)	
Other	147 (24,7%)	106 (23,3%)	41 (28,5%)	
Anatomical site				
Axial and spinal	315 (52,6%)	210 (46,2%)	105 (72,9%)	**<0,001**
Axial and non-spinal	99 (16,5%)	90 (19,8%)	9 (6,3%)	
Non-axial	165 (27,5%)	141 (31%)	24 (16,7%)	
Axial and non-axial irradiated in one field	20 (3,3%)	14 (3,1%)	6 (4,2%)	
Meta other than bone				
No	151 (25,2%)	117 (25,7%)	34 (23,6%)	0,692
Yes	448 (74,8%)	338 (74,3%)	110 (76,4%)	
Bone metastasis that received retreatment				
No	517 (86,3%)	381 (83,7%)	136 (94,4%)	**0,002**
Yes	82 (13,7%)	74 (16,3%)	8 (5,6%)	
Bone metastasis that had to be retreated afterwards				
No	533 (89%)	393 (86,4%)	140 (97,2%)	**0,001**
Yes	66 (11%)	62 (13,6%)	4 (2,8%)	
KPS				
Number of evaluable metastases**	445 (74,3%)	340 (74,7%)	105 (72,9%)	**0,005**
Median (range)	70 (30-100)	70 (30-100)	70 (50-90)	
KPS <70	159 (35,7%)	128 (37,7%)	31 (29,5%)	
KPS ≥ 70	286 (64,3%)	212 (62,4%)	74 (70,5%)	
RPA				
Number of evaluable metastases**	520 (86,8%)	391 (85,9%)	129 (89,6%)	**<0,001**
Class 1: Median OS = 21 months	100 (19,2%)	82 (21%)	18 (14%)	
Class 2: Median OS = 8.7 months	337 (64,8%)	262 (67%)	75 (58,1%)	
Class 3: Median OS = 2.4 months	83 (16%)	47 (12%)	36 (27,9%)	
NRF				
Number of evaluable metastases**	445 (74,3%)	340 (74,7%)	105 (72,9%)	0,849
0 risk factors: median OS 64 weeks	19 (4,3%)	14 (4,1%)	5 (4,8%)	
1 risk factor: median OS 64 weeks	81 (18,2%)	60 (17,7%)	21 (20%)	
2 risk factors: median OS 28 weeks	254 (57,1%)	198 (58,2%)	56 (53,3%)	
3 risk factors: median OS 10 weeks	91 (20,5%)	68 (20%)	23 (21,9%)	
Complicated				
Number of evaluable metastases***	332 (99,1%)	221 (98,7%)	111 (100%)	**<0,001**
No	80 (24,1%)	73 (33%)	7 (6,3%)	
Yes	252 (75,9%)	148 (67%)	104 (93,7%)	

RT: radiotherapy; KPS: karnofsky performance score; RPA: recursive partitioning analysis index; NRF: number of risk factors.
*The P-value reflects the comparison of characteristics of bone metastases which received SFRT with bone metastases which received MFRT.
Non-parametric tests (Mann-Whitney U, Chi-square and Fisher's exact) were used.
**Non-missing values

Table 5.2: **Characteristics of spinal metastases by fractionation schedule**

Characteristics	All spinal metastases (n=335)	SFRT (n=224; 66,9%)	MFRT (n=111; 33,1%)	P-value*
Spinal cord compression				
Number of evaluable metastases**	320 (95,5%)	213 (95,1%)	107 (96,4%)	**<0,001**
No	181 (56,6%)	166 (77,9%)	15 (14%)	
Yes	139 (43,4%)	47 (22,1%)	92 (86%)	
• Invasion of spinal canal without compression of the spinal cord	24 (7,5%)	10 (4,7%)	14 (13,1%)	
• Spinal cord compression	63 (19,7%)	20 (9,4%)	43 (40,2%)	
• Invasion of neuroforamen without compression of the nerve root	9 (2,8%)	5 (2,3%)	4 (3,7%)	
• Nerve root compression	29 (9,1%)	8 (3,8%)	21 (19,6%)	
• Both spinal cord and nerve root compression	14 (4,4%)	4 (1,9%)	10 (9,3%)	
Neurologic deficit				
Number of evaluable metastases**	320 (95,5%)	213 (95,1%)	107 (96,4%)	**<0,001**
No	225 (70,3%)	184 (86,4%)	41 (38,3%)	
Yes	95 (29,7%)	29 (13,6%)	66 (61,7%)	
• Dermatomal pain pattern	28 (8,8%)	13 (6,1%)	15 (14%)	
• Paresthesia	4 (1,3%)	1 (0,5%)	3 (2,8%)	
• Sensory loss	12 (3,8%)	3 (1,4%)	9 (8,4%)	
• Motor loss	24 (7,5%)	4 (1,9%)	20 (18,7%)	
• Sensory and motor loss	19 (5,9%)	5 (2,3%)	14 (13,1%)	
• Hyperreflexia	5 (1,6%)	2 (0,9%)	3 (2,8%)	
• Dermatomal pain pattern and motor loss	3 (0,9%)	1 (0,5%)	2 (1,9%)	
Vertebral compression				
Number of evaluable metastases**	319 (95,2%)	211 (94,2%)	108 (97,3%)	**0,003**
No	243 (76,1%)	164 (77,7%)	79 (73,2%)	
Yes	76 (23,8%)	47 (22,3%)	29 (26,9%)	
• < 50% collapse	57 (17,9%)	34 (16,1%)	23 (21,3%)	
• $\geq$ 50% collapse	19 (6%)	13 (6,2%)	6 (5,6%)	
SINS				
Number of evaluable metastases**	318 (94,9%)	210 (93,8%)	108 (97,3%)	0,228
Median (range)	8 (2-18)	7 (2-14)	8 (2-18)	
Stable (score 1-6)	105 (33%)	74 (35,2%)	31 (28,7%)	
Potentially unstable (score 7-12)	204 (64,2%)	132 (62,9%)	72 (66,7%)	
Unstable (score >12)	9 (2,8%)	4 (1,9%)	5 (4,6%)	
Complicated				
Number of evaluable metastases**	332 (99,1%)	221 (98,7%)	111 (100%)	**<0,001**
No	80 (24,1%)	73 (33%)	7 (6,3%)	
Yes	252 (75,9%)	148 (67%)	104 (93,7%)	

SFRT: single fraction radiotherapy; MFRT: multiple fraction radiotherapy: SINS: spinal instability neoplastic score.
*The P-value reflects the comparison of characteristics of bone metastases which received SFRT with bone metastases which received MFRT.
Non-parametric tests (Mann-Whitney U, Chi-square and Fisher's exact) were used. **Spinal metastases and non-missing values

Table 5.3: **Comparison of actual received fractionation schedule with protocols**

	Actual radiation schedule			
	SFRT	MFRT	Total	P-value*
UZ protocol				
SFRT	447	112	559	**<0,001**
MFRT	8	32	40	
Total	455	144	599	
International protocol				
SFRT	303	35	338	**<0,001**
MFRT	152	109	261	
Total	455	144	599	

*The P-value reflects the comparison of actual received fractionation schedules with schedules the bone metastases should have been prescribed according to the protocols.
Non-parametric Chi-square test was used.

Table 5.4: **Overview of patients variables relevant for survival analysis by fractionation schedule**

Characteristics	All patients (n=364)	SFRT (n=261; 71,7%)	MFRT (n=103; 28,3%)
Age at radiation (years)			
Mean ± standard deviation	65,1 ± 13,2	65,2 ± 12,8	65 ± 14,4
Median (range)	67 (5-92)	66 (19-90)	68 (5-92)
Died within 4 weeks of RT			
Number of evaluable patients*	359 (98,6%)	258 (98,9%)	101 (98,1%)
No	303 (84,4%)	217 (84,1%)	86 (85,1%)
Yes	56 (15,6%)	41 (15,9%)	15 (14,9%)
Time between RT and death (weeks)			
Mean ± standard deviation	64,9 ± 70,9	61,9 ± 68,7	72,5 ± 76,1
Median (range)	30,1 (0,14-250)	27,1 (0,33-250)	33,4 (0,14-243)
RPA			
• All patients			
Number of evaluable patients*	316 (86,8%)	222 (85,1%)	94 (91,3%)
Class 1 (median OS = 21 months)	52 (16,5%)	42 (18,9%)	10 (10,6%)
Class 2 (median OS = 8.7 months)	201 (63,6%)	147 (66,2%)	54 (57,5%)
Class 3 (median OS = 2.4 months)	63 (19,9%)	33 (14,9%)	30 (31,9%)
• Patients with spinal metastases			
Number of evaluable patients*	185 (55,2%)	113 (50,4%)	72 (64,9%)
Class 1 (median OS = 21 months)	31 (16,8%)	25 (22,1%)	6 (8,3%)
Class 2 (median OS = 8.7 months)	115 (62,2%)	70 (61,9%)	45 (62,5%)
Class 3 (median OS = 2.4 months)	39 (21,1%)	18 (15,9%)	21 (29,2%)
• Patients with non-spinal metastases			
Number of evaluable patients*	131 (49,6%)	109 (47,2%)	22 (66,7%)
Class 1 (median OS = 21 months)	21 (16%)	17 (15,6%)	4 (18,2%)
Class 2 (median OS = 8.7 months)	86 (65,6%)	77 (70,6%)	9 (40,9%)
Class 3 (median OS = 2.4 months)	24 (18,3%)	15 (13,8%)	9 (40,9%)
NRF			
Number of evaluable patients*	264 (72,5%)	189 (72,4%)	75 (72,8%)
0 risk factors (median OS 64 weeks)	12 (4,6%)	8 (4,2%)	4 (5,3%)
1 risk factor (median OS 64 weeks)	46 (17,4%)	30 (15,9%)	16 (21,3%)
2 risk factors (median OS 28 weeks)	140 (53%)	103 (54,5%)	37 (49,3%)
3 risk factors (median OS 10 weeks)	66 (25%)	48 (25,4%)	18 (24%)

RPA: recursive partitioning analysis index; NRF: number of risk factors.
*non-missing values

Table 5.5: **Univariate analysis of survival**

Characteristics	Number of patients	Median overall survival (95% CI)	P-value*
Overall survival			
Number of evaluable patients**	358 (98,4%)	7,4 months (5,5-9,4)	
Fractionation schedule			0,493
Number of evaluable patients**	358 (98,4%)		
SFRT	257 (71,8%)	6,7 months (4,7-8,8)	
MFRT	101 (28,2%)	8,4 months (5,7-11)	
spinal instability neoplastic score			0,966
Number of evaluable patients**	197 (54,1%)		
Stable	60 (30,5%)	8,4 months (3,7-13,1)	
Potentially instable	129 (65,5%)	7,7 months (3,9-11,5)	
Instable	8 (4,1%)	1,3 months (0-46,4)	
Complicated metastasis			0,683
Number of evaluable patients**	357 (98,1%)		
Yes	164 (45,9%)	7,6 months (4,5-10,6)	
No	193 (54,1%)	7,4 months (5,2-9,7)	
RPA			
• All patients			**0,004**
Number of evaluable patients**	311 (85,4%)		
Class 1 (median OS = 21 months)	52 (16,7%)	26,4 months (14,5-38,2)	
Class 2 (median OS = 8.7 months)	197 (63,3%)	5,6 months (3,4-7,7)	
Class 3 (median OS = 2.4 months)	62 (19,9%)	3,7 months (1,1-6,2)	
• Patients with spinal metastases			0,144
Number of evaluable patients**	181 (85,4%)		
Class 1 (median OS = 21 months)	31 (17,1%)	21,7 months (5,2-38,1)	
Class 2 (median OS = 8.7 months)	112 (61,9%)	5,4 months (2,7-8,2)	
Class 3 (median OS = 2.4 months)	38 (21%)	4,6 months (0-10,7)	
• Patients with non-spinal metastases			**0,01**
Number of evaluable patients**	130 (85,5%)		
Class 1 (median OS = 21 months)	21 (16,2%)	51,6 months	
Class 2 (median OS = 8.7 months)	85 (65,4%)	5,7 months (2,6-8,8)	
Class 3 (median OS = 2.4 months)	24 (18,5%)	2,1 months (0-4,5)	
NRF			**0,001**
Number of evaluable patients**	261		
0 risk factors ()median OS= 64 weeks)	12 (4,6%)	172,5 weeks (26,5-318,5)	
1 risk factor (median OS= 64 weeks)	46 (17,7%)	102,9 weeks (49-156,7)	
2 risk factors (median OS= 28 weeks)	138 (53,1%)	22,3 weeks (11,4-33,2)	
3 risk factors (median OS= 10 weeks)	65 (24,6%)	18,4 weeks (6,6-30,3)	

RPA: recursive partitioning analysis index; NRF: number of risk factors.
*The P-value reflects the comparison of survival distribution.
Log-rank test was used.
**Non-missing values

6 Discussion

This paper gives an overview of the prescription behaviour of fractionation schedules for the palliation of painful bone metastases in a radiotherapy department in Ghent. The primary outcomes were utilization and retreatment rate of both fractionation schedules, temporal trends in prescription behaviour, assessment of the (in)congruence with the local and international recommendations and survival after radiotherapy. In the ana

6.1 Utilization rate of SFRT

An overall SFRT utilization rate of 76% was found. Of the articles with similar study setup read for this research, not one with a utilization rate this high was found. Table 6.1 displays the SFRT utilization rates, as well as temporal trends. The high utilization rate of single fraction regimens found in this paper is beneficial both for the radiotherapy centre and patients. It is the most cost-effective treatment option, it reduces the radiotherapy department workload and consequently the waiting times, and minimizes the treatment burden for the patients. As opposed to this study, the majority of articles report a marked underutilization of SFRT. To understand the global reluctance in SFRT use, it's important to be aware of the aspects that influence radiotherapy oncologists in prescription behaviour. They can be classified in four main categories, enlisted in table 6.2: oncologist-related, patient-related, tumour-related and setting-related. Next to published trials which prove equal efficacy of SFRT and MFRT, there is an abundance of factors to be taken into account by radiation oncologists when they want to prescribe a certain fractionation schedule for a certain patient. Not only do they have to consider patient and tumour factors, each physician is also influenced by his/her practice experience and has financial incentives inherent to the practice they are working in and country they are living in. Consequently, despite the fact that there is published evidence about the equal pain relief rates between SFRT and MFRT, SFRT is still underutilized in some countries, due to different beliefs about relative efficacy and toxicity, lack of experience with single fractions, financial incentives and a higher retreatment rate for SFRT.

6.1.1 Financial incentives

Lievens et al. found that reimbursement modality influences the prescribed fractionation regimen independently 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 pre-

scribed in countries where the remuneration depends on the number of treatments [24]. This is the case in the US; private insurance companies will pay the oncologists more for prescribing protracted courses [6]. This could be an important reason for the lower utilization of SFRT (Fairchild et al. reported a rate of 2-20% for example, depending on different cases [10]). In Belgium, the single and multiple fraction treatment modality of 10 fractions are in the same category for reimbursement (cut-off for a higher reimbursement is 11 fractions). Financial incentive is not an influencing factor for Belgian physicians.

6.1.2 Retreatment rate

The retreatment rate in this study was significantly higher following SFRT compared to MFRT (13,6% vs 2,8%, P= 0,001), which is in agreement with Bhalla et al. who reported retreatment rates of 11% for SFRT and 3% for MFRT [3]. Chow et al. also reported that bone metastases treated with SFRT are 2,6 times more likely to be retreated (20% retreatment rate for SFRT vs 8% for longer schedules) [8]. Both articles stated that this may be influenced by the fact that radiation oncologists are still reluctant to prescribe repeated radiotherapy to a site following delivery of MFRT, rather than this being a measure of lower efficacy of SFRT compared to MFRT.

6.2 Temporal trends

An increasing tendency of SFRT prescription was seen over the three study years (68,8% in 2013, 78,4% in 2014 and 82,7% in 2015 with P= 0,006). Except for Olson, Haddad and Bhalla, the other authors enlisted in table 6.1 also show an increase in their studies. It should be said that the utilization rate in all three study years remains the highest at the radiotherapy department in Ghent.

One reason for increased SFRT prescription from 2014 to 2015 could be the more stricter adjustments to the protocol for the palliation of painful bone metastases at the radiotherapy center in Ghent (that was developed in 2010). This protocol was based on international recommendations, but was then adjusted with practice experience of all the radiation oncologists. According to this guideline, MFRT should only be prescribed for patients with symptomatic spinal cord or nerve root compression with a NRF of less than 3, as opposed to international recommendations that state that each patient with a complicated bone metastasis should receive a multiple fraction treatment. The local protocol was internally approved. Because of this consensus, physicians could be more willing to adhere to it and consequently prescribe more SFRT. For the increase in SF use from 2013 to 2014, a direct reason wasn't investigated.

In analogy with this finding, Ashworth et al. found that the rate of the use of SFs increased from 42.3%

(in 1999-2003) to 52,6% (in 2004-2007) after implementation of a clinical practice guideline endorsing the use of SFs developed by Wu et al. in 2004. This increasing tendency however decreased significantly once again to 44% in the 2008 to 2012 period.

Table 6.1: **Overview of SFRT utilisation rate and temporal trends in different studies**

	Overall utilization rate of SFRT	Study period	Temporal trends in SFRT use	Where
Ellsworth et al. [25]	8%	2007-2012	after march 15, 2011*: 8% before march 15, 2011*: 8%	United States
Petrushevski et al. [16]	29%	1997-2009	1997: 8% 2004: 38%	Australia
Laugsand et al. [13]	31%	1997-2007	1997: 16% 2007: 41%	Norway
Haddad et al. [26]	32%	1998-2002	1998: 37% 2000: 43% 2002: 28%	Canada
Ashworth et al. [18]	41,3 %	1984-2012	1999-2003: 42,3% 2004-2007: 52,6% 2009-2012: 44%	Canada
Olson et al [2].	49%	2007-2011	2007: 50,5% 2011: 48%	Canada
Bhalla et al. [3]	53,6%	2000 and 2006	2000: 42% 2006: 40%	United Kingdom
Bradley et al. [27]	65%	1999-2005	1999: 51% 2005: 66%	Canada
Thavarajah et al. [7]	65%	2005-2012	2005: 66,4% 2012: 57,3%	Canada
This study	76%	2013-2015	2013: 68,8% 2014: 78,4% 2015: 82,7%	Belgium

*Publication of the ASTRO guideline

6.3 Adherence to protocols

6.3.1 UZ Protcol

Of all the patients who actually received a single fraction schedule, 98,2% is in accordance with the local protocol (5.3). This proportion is higher than the accordance with the international recommendations (66,6%). Reason for this is that there are more criteria for receiving a MFRT in the local than in the international protocol.. Not only should the metastasis be complicated, the patient also needs to have neurologic symptoms and a NRF less than 3.

Even though the 80% SFRT conformity percentage is very high, and there is a high SFRT rate at the radiotherapy department Ghent (76%, 6.1), still too much bone metastases receive a multiple fractionated schedule. Of the 559 bone metastases that should have received a SF schedule if the local protocol would have been applied perfectly, still 112 metastases received a long schedule (20%). One explanation for this is that patients in the lowest class of NRF still receive multiple fractions where they should receive a SF schedule (see table 5.1: 21,9% of patients who received MF belonged to the NRF 3 group).

The adherence rate to the UZ protocol is the lowest for SF use for complicated bone metastases for all three study years. An increasing trend in adherence to the protocol can be seen from 2013 till 2015 for SF use, but not for MF use.

6.3.2 International

Lutz et al. and Wu et al. stated that all uncomplicated bone metastases should receive a single fraction schedule [14, 28]. Of the researched patient cohort in this paper, this should have been 56,4%, but in reality 76% underwent a single fraction of radiotherapy.

Next to the financial reason (see supra 6.1.1), two other explanations for a low utilization rate of SF in the US can be suggested: the fact that the ASTRO guideline by Lutz et al. suggests SF use only for uncomplicated bone metastases (and not for non-symptomatic complicated bone metastases) and a low willingness to adhere to guidelines bij American radiation oncologists [6]. Ellsworth et al. confirmed this last statement by saying that prescription in the US is influenced by deeply rooted and historical practice patterns favoring MF courses [25].

6.4 Survival

Almost all patients with painful osseous metastases have an infaust prognosis. This could also be seen in this research. When investigating the differences between the different fractionation schedules, survival of patients receiving SFRT was very similar to those receiving MFRT and almost equal proportions of patients died within 4 weeks of treatment. 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. When including all patients (with spinal and non-spinal metastases) in survival analysis, a significant difference in distribution of survival following radiotherapy was noted for RPA classes and NRF. Patients in the highest class of RPA (1) and NRF (0 or 1) lived significantly longer than those in RPA class 3 or patients with a NRF of 3 respectively. This finding confirms both survival models as prognostic factors for patients with bone metastases. Fur-

ther analyses couldn't confirm significance when comparing RPA class 2 to 3 and NRF 2 to 3. It is remarkable that the comparison of survival distribution of patients in all RPA classes did reach significance for non-spinal metastases, but not for spinal metastases, because this index was developed and validated specifically for metastases in the spine [23]. When further looking in to this, two by two comparisons (2 classes at a time) did confirm a longer survival of patients with spinal metastasis in class 1 than in class 3.

6.5 Limitations

For the survival analysis, only one metastasis was selected for patients, more precisely the last irradiated metastasis. Because of this selection, some cases may have been overlooked.

Every irradiated bone metastasis of a patient was considered as a separate case for the analysis of the whole cohort. Because of this, the fact that previous courses might have confounded the use of SFRT or MFRT for subsequent treatments wasn't taken into account.

When looking at the number of bone metastases irradiated in each study year, 2015 only consists of 139 cases, which is remarkably less than 2013 and 2014. A specific reason for this finding wasn't withheld.

The role of beliefs and judgement of the physicians prescribing the palliative RT wasn't investigated. Consequently, specific reasons for prescribing prolonged courses wasn't considered in the analyses.

Table 6.2: **Factors influencing prescription behaviour as mentioned by different authors**

Factors influencing prescription behaviour	Mentioned by
Oncologist-related:	
• Beliefs (about the relative efficacy and toxicity of SF and MF)	[18, 29]
• Level of experience	[6, 18, 29]
• Past training	[13, 17, 29]
• Influence by local opinion leaders	[13]
Patient-related:	
• Distance to radiotherapy centre	[27, 29]
• Age	[6, 10, 26, 27, 29, 30]
• Prognosis	[6, 10, 15, 17, 29, 30]
• Performance status	[10, 15, 17, 26, 27, 30]
• Previous radiotherapy	[10, 30]
• Gender	[27]
Tumour-related:	
• Tumour site	[3, 6, 15, 17, 26, 27, 29, 30]
• Primary cancer site	[27, 29]
• Risk of SCC	[10]
• Time until first increase in pain	[30]
• Responsiveness to analgesics	[30]
• Number of metastases	[30]
• Radiological appearance of the lesion	[15]
Setting-related:	
• Local traditions	[13]
• Financial factors (type of reimbursement)	[1, 8, 15, 18]
• Waiting list	[10, 29]
• Departmental policies	[8, 10, 29]
• Size of radiation centre	[29]
• Type of practice	[17]
• Country (location of practice)	[8, 17]
Other:	
• Published evidence	[10, 29]
• Year of RT	[26]

SF: single fraction; MF: multiple fraction; SCC: spinal cord compression; RT: radiotherapy

7 Conclusion and future perspective

The limited prognosis of the majority of patients with BMs obligates the use of the shortest and most cost-effective treatment schedule that provides equal pain relief. In this way, a decrease in time visiting the radiotherapy center near a patient's end of life and a reduction of the radiotherapy workload and consequently waiting lists can be achieved.

The radiotherapy department in Ghent has a high SF use in comparison to studies with an equal research setup, but there is still room for improvement.

In the future, including 2016 and 2017 as study years could be useful to look at the SF use of the last two years, and see if the increasing trend is still ongoing, because at time of this study, the MF use still was higher than the protocol prescribes. Univariate and multivariate logistic regression analyses could also be done to identify specific predictors for SF or MF use.

This study included only conventional radiation therapy techniques. Further studies looking into practice patterns of the use of new technology, such as stereotactic body radiation therapy (SBRT), which allows for the delivery of high doses of radiation to oligometastatic bone with great precision, would be very useful.

8 Appendix

8.1 Elements of the spinal instability neoplastic score

Elements of the spinal instability neoplastic score	Granted score
Patient specific	
• Pain	
Mechanical pain	3
Occasional pain but not mechanical	1
Pain free	0
Spine specific	
• Location	
Junctional spine: occiput-C2, C7-T2, T11-L1, L5-S1	3
Mobile spine: C3-C6, L2-L4	2
Semi-rigid spine: T3-T10	1
Rigid spine: S2-S5	0
• Spinal alignment	
Subluxation/translation	4
Kyphosis/scoliosis	2
Normal	0
• Presence of vertebral compression fracture	
$\geq$ 50% collapse	3
<50% collapse	2
No collapse with $\geq$ 50% body involved	1
none of the above	0
Tumour specific	
• Type of lesion	
Osteolytic	2
Mixed	1
Osteosclerotic	0
• Posterolateral involvement of spinal elements	
Bilateral	3
Unilateral	1
None	0
	Maximum score of 18 • Score 0-6: stable lesion • Score 7-12: potentially instable lesion • Score >12: instable lesion

Table 8.1: Calculation of the Spinal Neoplastic Instability Score (SINS)

8.2 Kaplan-meier plots

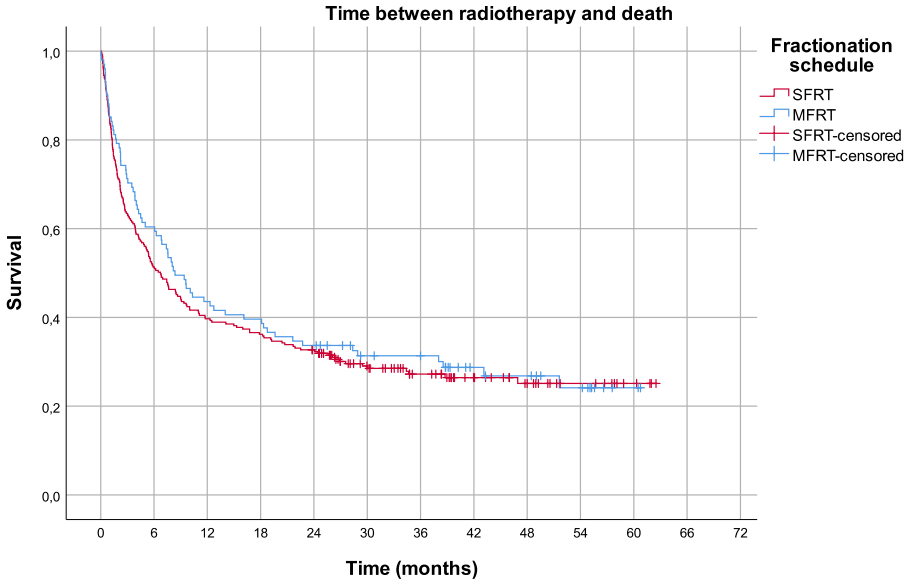

Figure 8.1: **Kaplan-Meier reporting time between radiotherapy and death, comparing fractionation schedules.** No significant difference in survival distribution was reported (P=0,493).

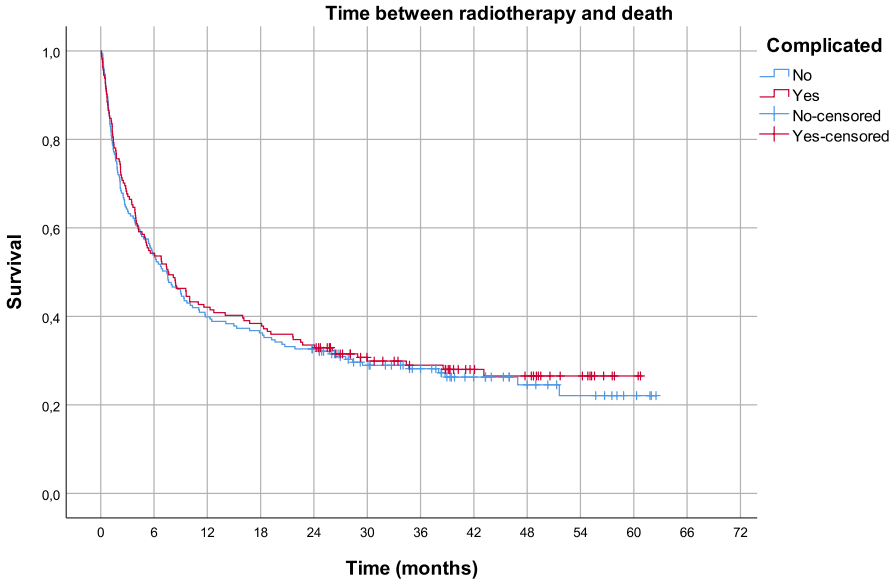

Figure 8.2: **Kaplan-Meier reporting time between radiotherapy and death, comparing complicated with uncomplicated metastases.** No significant difference in survival distribution was reported (P= 0,683).

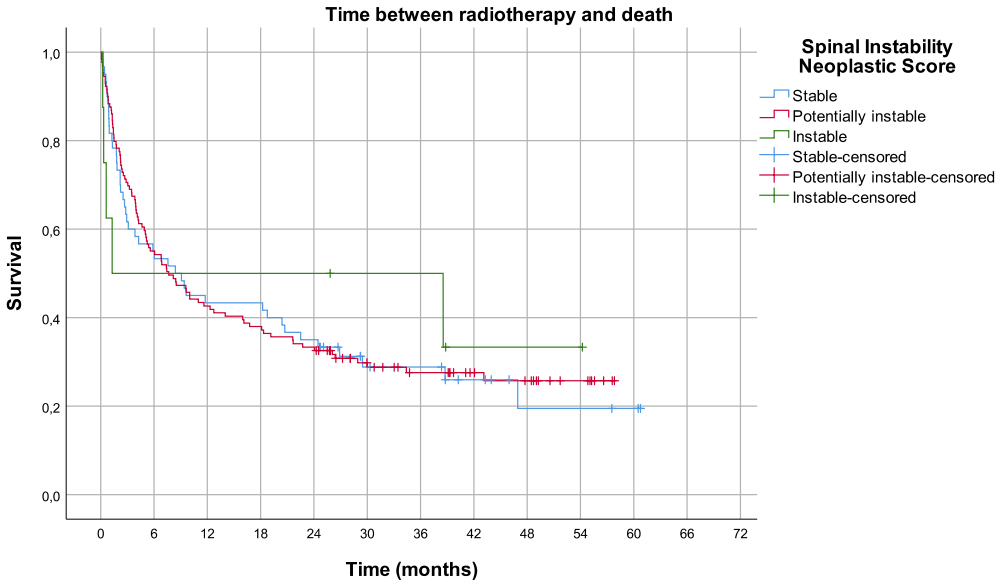

Figure 8.3: **Kaplan-Meier reporting time between radiotherapy and death, comparing SINS classes.** No significant difference in survival distribution was reported (P= 0,966).

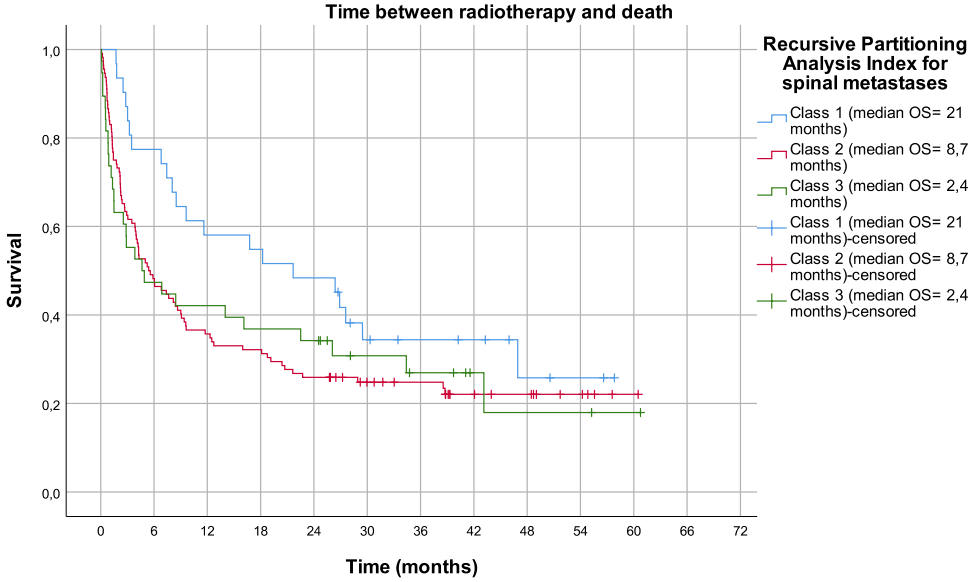

Figure 8.4: **Kaplan-Meier reporting time between radiotherapy and death, comparing RPA classes for spinal metastases only.** No significant difference in survival distribution was reported (P= 0,144).

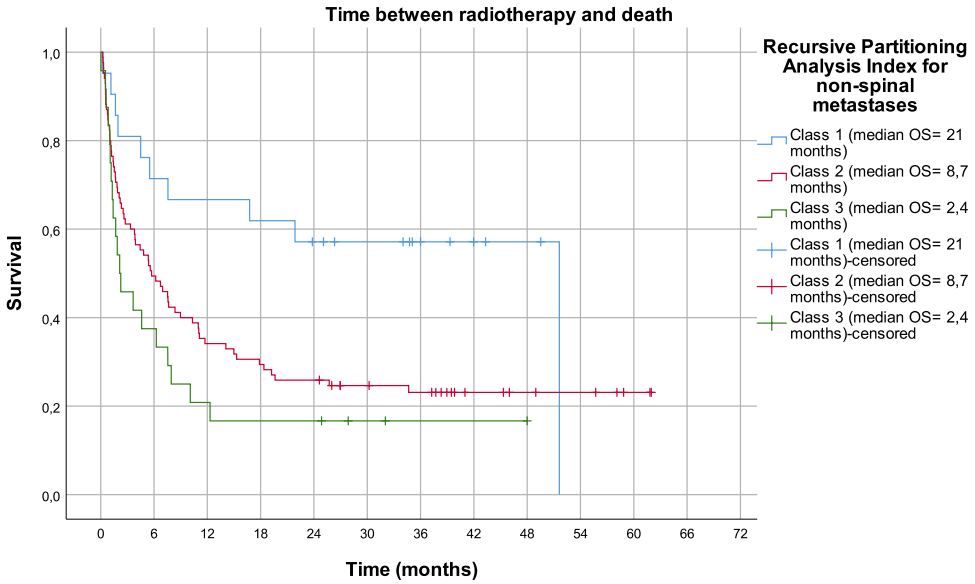

Figure 8.5: **Kaplan-Meier reporting time between radiotherapy and death, comparing RPA classes for non-spinal metastases only.** A significant difference in survival distribution was reported (P= 0,01).

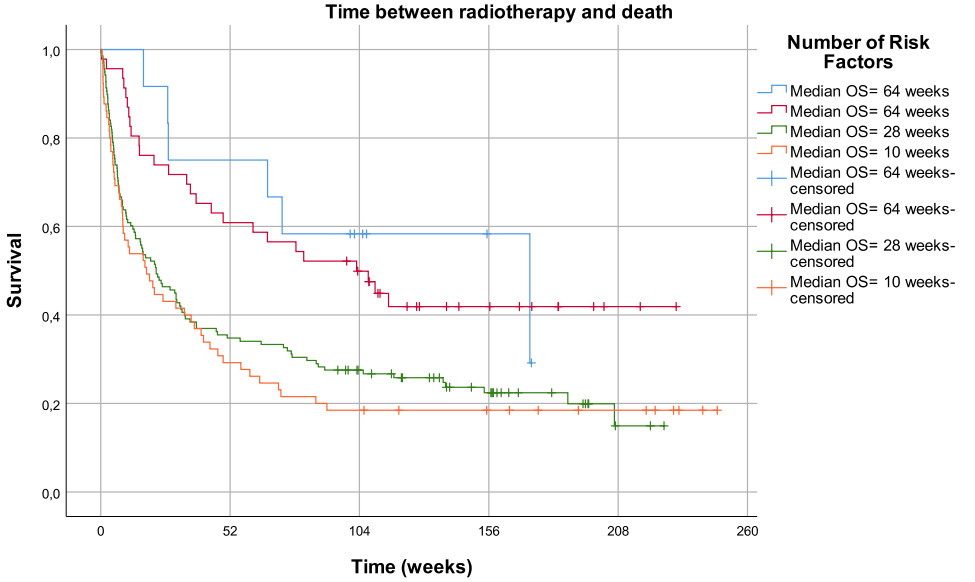

Figure 8.6: **Kaplan-Meier reporting time between radiotherapy and death, comparing NRF groups.** A significant difference in survival distribution was reported (P= 0,001).

References

[1] Kachnic L, Berk L. Palliative Single-Fraction Radiation Therapy: How Much More Evidence Is Needed? Journal of the National Cancer Institute. 2005;97(11):11–13.

[2] Olson RA, Tiwana MS, Barnes M, Kiraly A, Beecham K, Miller S, et al. Use of single-versus multiple-fraction palliative radiation therapy for bone metastases: Population-based analysis of 16,898 courses in a Canadian Province. International Journal of Radiation Oncology Biology Physics. 2014;89(5):1092–1099. Available from: http://dx.doi.org/10.1016/j.ijrobp.2014.04.048.

[3] Bhalla N, Wong H, Ibrahim a, Green A J. Palliative radiotherapy for bone metastases: assessment of factors influencing dose-fractionation schedules at a UK cancer centre. Journal of Radiotherapy in Practice. 2013;12(3):208–217. Available from: http://search.ebscohost.com/login.aspx?direct=true{\&}AuthType=ip,shib{\&}db=jlh{\&}AN=2012921647{\&}site=ehost-live.

[4] Lutz ST, Berk LB, Chang EL, Chow E, Hahn CA, Hoskin PJ, et al. Palliative Radiotherapy for Bone Metastases: An ASTRO Evidence-Based Guideline;p. 1–49.

[5] Rutter CE, Yu JB, Wilson LD, Park HS. Assessment of national practice for palliative radiation therapy for bone metastases suggests marked underutilization of single-fraction regimens in the united states. International Journal of Radiation Oncology Biology Physics. 2015;91(3):548–555. Available from: http://dx.doi.org/10.1016/j.ijrobp.2014.10.045.

[6] McDonald R, Chow E, Lam H, Rowbottom L, Soliman H. International patterns of practice in radiotherapy for bone metastases: A review of the literature. Journal of Bone Oncology. 2014;3(3-4):96–102. Available from: http://dx.doi.org/10.1016/j.jbo.2014.10.003.

[7] Thavarajah N, Zhang L, Wong K, Bedard G, Wong E, Tsao M, et al. Patterns of practice in the prescription of palliative radiotherapy for the treatment of bone metastases at the Rapid Response Radiotherapy Program between 2005 and 2012. Current Oncology. 2013;20(5).

[8] Chow E, Zeng L, Salvo N, Dennis K, Tsao M, Lutz S. Update on the Systematic Review of Palliative Radiotherapy Trials for Bone Metastases. Clinical Oncology. 2012;24(2):112–124. Available from: http://dx.doi.org/10.1016/j.clon.2011.11.004.

[9] Janjan N, Lutz ST, Bedwinek JM, Hartsell WF, Ng A, Pieters RS, et al. Therapeutic guidelines for the treatment of bone metastasis: a report from the American College of Radiology Appropriateness Criteria Expert Panel on Radiation Oncology. Journal of palliative medicine. 2009;12(5):417–26. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19416037.

[10] Fairchild A, Barnes E, Ghosh S, Ben-Josef E, Roos D, Hartsell W, et al. International Patterns of Practice in Palliative Radiotherapy for Painful Bone Metastases: Evidence-Based Practice? International Journal of Radiation Oncology Biology Physics. 2009;75(5):1501–1510.

[11] Hoskin P, Sundar S, Reczko K, Forsyth S, Mithal N, Sizer B, et al. A Multicenter Randomized Trial of Ibandronate Compared With Single-Dose Radiotherapy for Localized Metastatic Bone Pain in Prostate Cancer. Journal of the National Cancer Institute. 2015;107:1–9.

[12] Foro Arnalot P, Fontanals AV, Galcerán JC, Lynd F, Latiesas XS, de Dios NR, et al. Randomized clinical trial with two palliative radiotherapy regimens in painful bone metastases: 30 Gy in 10 fractions compared with 8 Gy in single fraction. Radiotherapy and Oncology. 2008;89(2):150–155.

[13] Laugsand TS, Kaasa S, Romundstad P, Johannesen TB, Lund JÅ. Radiotherapy for bone metastases: practice in Norway 1997-2007. A national registry-based study. Acta oncologica (Stockholm, Sweden). 2013;52(6):1129–1136. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23244670.

[14] Lutz S, Balboni T, Jones J, Lo S, Petit J, Rich S, et al. Palliative Radiotherapy for Bone Metastases: Update of an ASTRO Evidence-Based Guideline. Practical Radiation Oncology. 2016;Available from: http://dx.doi.org/10.1016/j.prro.2016.08.001.

[15] Nieder C, Pawinski A, Dalhaug A. Continuous controversy about radiation oncologists' choice of treatment regimens for bone metastases: should we blame doctors, cancer-related features, or design of previous clinical studies? Radiation oncology (London, England). 2013;8(1):85. Available from: http://www.ro-journal.com/content/8/1/85.

[16] Petrushevski AN, Gabriel GS, Hanna TP, Allen S, Allison RW, Barton MB. Factors affecting the use of single-fraction radiotherapy for the palliation of bone metastases in Australia. Clinical Oncology. 2015;27(4):205–212. Available from: http://dx.doi.org/10.1016/j.clon.2014.11.027.

[17] van der Linden Y, Roos D, Lutz S, Fairchild A. International Variations in Radiotherapy Fractionation for Bone Metastases: Geographic Borders Define Practice Patterns? Clinical Oncology. 2009;21(9):655–658. Available from: http://dx.doi.org/10.1016/j.clon.2009.08.004.

[18] Ashworth A, Kong W, Chow E, MacKillop WJ. Fractionation of palliative radiation therapy for bone metastases in Ontario: Do practice guidelines guide practice? International Journal of Radiation Oncology Biology Physics. 2016;94(1):31–39. Available from: http://dx.doi.org/10.1016/j.ijrobp.2015.07.2291.

[19] Dennis K, Makhani L, Zeng L, Lam H, Chow E. Single fraction conventional external beam radiation therapy for bone metastases: A systematic review of randomised controlled trials. Radiotherapy and Oncology. 2013;106(1):5–14. Available from: http://dx.doi.org/10.1016/j.radonc.2012.12.009.

[20] Cheon PM, Wong E, Thavarajah N, Dennis K, Lutz S, Zeng L, et al. A definition of " uncomplicated bone metastases " based on previous bone metastases radiation trials comparing single-fraction and multi-fraction radiation therapy. Journal of Bone Oncology. 2015;4(1):13–17. Available from: http://dx.doi.org/10.1016/j.jbo.2014.12.001.

[21] Mor V, Laliberte L, JN M, Wiemann M. The Karnofsky Performance Status Scale. Cancer. 1984;53:2002–2007.

[22] Chow E, Abdolell M, Panzarella T, Harris K, Bezjak A, Warde P, et al. Predictive model for survival in patients with advanced cancer. Journal of Clinical Oncology. 2008;26(36):5863–5869.

[23] Chao ST, Koyfman SA, Woody N, Angelov L, Soeder SL, Reddy CA, et al. Recursive partitioning analysis index is predictive for overall survival in patients undergoing spine stereotactic body radiation therapy for spinal metastases. International Journal of Radiation Oncology Biology Physics. 2012;82(5):1738–1743.

[24] Lievens Y, Van den Bogaert W, Rijnders A, Kutcher G, Kesteloot K . Palliative radiotherapy practice within Western European countries: impact. Radiotherapy & Oncology. 2000;56(3):289–295.

[25] Ellsworth SG, Alcorn SR, Hales RK, McNutt TR, Deweese TL, Smith TJ. Patterns of care among patients receiving radiation therapy for bone metastases at a large academic institution. International Journal of Radiation Oncology Biology Physics. 2014;89(5):1100–1105. Available from: http://dx.doi.org/10.1016/j.ijrobp.2014.04.028.

[26] P H, R K S W, G R P, F S, D W, M M, et al. Factors influencing the use of single vs multiple fractions of palliative radiotherapy for bone metastases: A 5-year review. Clinical Oncology. 2005;17(6):430–434. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS{\&}PAGE=reference{\&}D=emed7{\&}NEWS=N{\&}AN=2005368812.

[27] Bradley NME, Husted J, Sey MSL, Sinclair E, Li KK, Husain AF, et al. Did the Pattern of Practice in the Prescription of Palliative Radiotherapy for the Treatment of Uncomplicated Bone Metastases Change between 1999 and 2005 at the Rapid Response Radiotherapy Program? Clinical Oncology. 2008;20(5):327–336.

[28] Wu JSy, Wong RKS, Lloyd NS, Johnston M, Bezjak A, Whelan T, et al. painful bone metastases – an evidence-based practice guideline. BMC Cancer. 2004;7:1–7.

[29] Bradley NME, Husted J, Sey MSL, Husain AF, Sinclair E, Harris K, et al. Review of patterns of practice and patients' preferences in the treatment of bone metastases with palliative radiotherapy. Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer. 2007;15(4):373–85. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17093915.

[30] Popovic M, Den Hartogh M, Zhang L, Poon M, Lam H, Bedard G, et al. Review of international patterns of practice for the treatment of painful bone metastases with palliative radiotherapy from 1993 to 2013. Radiotherapy and Oncology. 2014;111(1):11–17. Available from: http://dx.doi.org/10.1016/j.radonc.2014.01.015.