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Abstract

Background: This study analyzed the percent of remaining life (PRL) on treatment in patients irradiated for bone metastases. Bone metastases were treated together with other target volumes, if indicated, e.g. a 10-fraction treatment course that included brain and bone metastases. PRL was determined by calculating the time between start and finish of palliative radiotherapy (minimum 1 day in case of a single-fraction regimen) and dividing it by overall survival in days from start of radiotherapy.

Materials and methods: Different baseline parameters were assessed for association with dichotomized PRL (< 5% *vs.* ≥ 5%). The retrospective study included 219 patients (287 courses of palliative radiotherapy). After univariate analyses, multi-nominal logistic regression was employed.

Results: PRL on treatment ranged from 1–23%. Single-fraction radiotherapy resulted in < 5% PRL on treatment in all cases. All courses with 10 fractions resulted in at least 5% PRL on treatment. Significant associations were found between various baseline parameters and PRL category. With fractionation included in the regression model, 3 parameters retained significant p-values: Karnofsky performance status (KPS), none-bone target volume and fractionation (all with $p < 0.001$). If analyzed without fractionation, none-bone target volume

($p < 0.001$), hemoglobin ($p < 0.001$), KPS ($p = 0.01$), lack of additional systemic treatment ($p = 0.01$), and hypercalcemia ($p = 0.04$) were significant.

Conclusions: Fractionation is an easily modifiable factor with high impact on PRL. Patients with KPS < 70 and those treated for additional target types during the same course are at high risk of spending a larger proportion of their remaining life on treatment.

Key words: radiation therapy; bone metastases; palliative treatment; prognostic factors; fractionation

Introduction

An ideal palliative radiotherapy (PRT) scenario consists of efficacious yet nontoxic and convenient treatment, which minimizes interference with patients' other anticancer treatment and daily activity [1]. These goals are not always easy to achieve, but in the context of PRT for painful uncomplicated bone metastases the 8-Gy single fraction regimen is an excellent example for a satisfactory solution [2, 3]. Complicated bone metastases represent a more complex challenge and, often, higher doses of radiation are prescribed to achieve goals beyond pain improvement [4]. Both stereotactic body radiotherapy (SBRT; single dose or hypofractionated) and other, often more fractionated, approaches can be prescribed to achieve these goals [5, 6]. In the literature, variation in practice by patient, tumor, sociodemographic, geographical, and institutional provider factors has been identified [7].

Among other quality of care indicators, percent of remaining life (PRL) has recently received scientific attention [8, 9]. PRL evaluation is accomplished by calculating the time between start and finish of PRT (minimum 1 day in case of a single-fraction regimen) and dividing it by overall survival in days from start of PRT. Patients with short survival receiving prolonged PRT are going to spend a large proportion of their remaining life on treatment, in extreme cases more than 50%, typically between 6 and 25%. A previous study that included single-fraction and other short course regimens reported 8% median PRL [9].

The most efficient way of minimizing PRL is single-fraction radiotherapy, especially when fast track treatment planning results in same day preparations and treatment. Even a patient surviving for 30 days is spending 1 divided by 30 (3%) PRL on treatment. It is not entirely clear whether or not baseline parameters such as age and patterns of metastases have a major impact on PRL, despite an obvious connection between survival/prognostic factors

determining survival (the PRL calculation denominator) and eventual PRL. Therefore, we performed in-depth analyses of potential prognostic factors including but not limited to blood test results and imaging-based disease burden, aiming to identify all contributing variables.

Materials and methods

An arbitrary definition of low PRL on treatment was employed, i.e. < 5%, which was based on previously reported median values of 6 and 8%, respectively [8, 9]. The primary endpoint was identification of factors associated with PRL < 5%. We performed a retrospective analysis of our single institution database of patients with palliatively irradiated bone metastases (bone only or bone plus other target volumes in the same treatment course). We included patients treated from 2014 to 2019. Patients who failed to complete all prescribed fractions were also included. We excluded patients who were treated with ablative radiation doses (SBRT). The study evaluated 219 consecutive patients managed with standard palliative external beam radiotherapy techniques. Examples include a single fraction of 8 Gy, 5 fractions of 4 Gy or 10 fractions of 3 Gy (3-D conformal or intensity-modulated). Fractionation was at the discretion of the treating oncologist. In addition to PRT, all eligible patients received standard-of-care systemic anticancer treatment, if indicated. Patients who returned for a new treatment course in the time period of the study were counted twice, resulting in a total number of 287 evaluable treatment courses. In these cases, actual blood test results, imaging reports, Karnofsky performance status (KPS) and other baseline data, as well as survival were registered for each individual treatment course. Imaging and blood tests were part of our routine oncological assessment and typically no older than 3 weeks before PRT. Blood test results were dichotomized (normal/abnormal) according to the institutional upper and lower limits of normal.

The database was already review-board approved and has been utilized for different quality-of-care projects [10, 11]. Overall survival (time to death) from the first day of PRT was calculated employing the Kaplan–Meier method for all 287 treatment courses (SPSS 28, IBM Corp., Armonk, NY, USA). In 27 cases, survival was censored after median 36 months of follow-up (minimum 28 months). After a minimum follow-up of 28 months, all 27 cases could be assigned to the PRL < 5% group. Date of death was known for all remaining cases/courses. PRL was dichotomized (< 5% *vs.* ≥ 5%) and the chi-square test (2-sided) was

utilized for further analyses. A multi-nominal logistic regression analysis was also employed. P-values < 0.05 were considered statistically significant.

Results

Many treatment courses were administered in patients with prostate or lung cancer, and in the outpatient setting, as shown in Table 1. Commonly, painful bone metastases were irradiated without including non-bone target volumes in the same course. A single fraction was prescribed in 24% of courses. Overall, 9 courses were not completed as planned. The mean age was 68 years. Median actuarial overall survival was 6 months (1-year rate 32%). PRL on treatment ranged from 1-23%, median 8. Less than 5% PRL was recorded in 136 courses (47%).

All baseline parameters included in Table 1 were initially tested for associations with PRL. Those who were significantly associated are displayed in Table 2. Unsurprisingly, single-fraction radiotherapy resulted in < 5% PRL on treatment in all cases. All courses with 10 fractions resulted in at least 5% PRL on treatment. Inclusion of non-bone target volumes in a course resulted in only 15% of patients with < 5% PRL, compared to 55% of patients with bone-only target volumes. In this context, it should be emphasized that single-fraction radiotherapy is not typically utilized for none-bone targets such as lymph node or brain metastases. The remaining statistically significant factors involved very different types of baseline information, e.g. blood test results, KPS, primary tumor type and age.

All parameters displayed in Table 2 were moved forward to multi-nominal logistic regression analysis, to account for interrelated factors such as fractionation and presence of none-bone target volumes. With fractionation included in the model, 3 parameters retained significant p-values: KPS, none-bone target volume and fractionation (all with $p < 0.001$). If analyzed without fractionation, none-bone target volume ($p < 0.001$), hemoglobin ($p < 0.001$), KPS ($p = 0.01$), additional systemic treatment ($p = 0.01$) and hypercalcemia ($p = 0.04$) were significant.

Discussion

This study aimed at identification of variables that impact on PRL < 5%, which may be regarded a minor amount of time spent on palliative radiation treatment. In this context, it

must be emphasized that we chose this arbitrary definition despite the absence of international consensus on adequate or optimal PRL on treatment. Other definitions, such as < 10%, would also be possible. However, previously described median values of 6 and 8% [8, 9], respectively, informed the present cut-off. One may also argue that limited PRL on treatment is not a surrogate of net appropriateness, efficacy or optimal balance. For example, if 3% PRL would result in short-lived and less complete symptom palliation, while 6% would result in a larger gain, patients could be willing to accept prolonged treatment, because the quality of their remaining life improves [12]. Such trade-off would also have to consider toxicity, inconvenience and cost related to transportation, treatment itself and other factors. For the scenario of uncomplicated painful bone metastases, abundant evidence supports single-fraction radiotherapy, which causes minimal PRL on treatment [2, 3]. Other scenarios are less straightforward and require open discussion about the pros and cons of different treatment regimens [13, 14]. Implementation of single-fraction PRT should be accompanied by long-term efforts to support adequate utilization and prevent perishing [15]. A recent study reported the following predictors of single-fraction prescription: poor PS, lung and urologic primaries, and lower half-body as site of irradiation [16]. Spinal metastases were more likely to receive prolonged treatment, i.e. multiple fractions.

The results of our study highlight that fractionation is a major driver of PRL. Also, the inclusion of non-bone target volumes in a course of bone irradiation impacts greatly on PRL. Both reduced survival due to, e.g., brain metastases or a symptomatic primary tumor in the thorax (as compared to bone-only metastases, especially in prostate or breast cancer), and physician preference of more protracted or fractionated radiotherapy if the indication is not limited to uncomplicated painful bone metastases, may explain why PRL on treatment increases in the presence of non-bone target volumes. Patients with KPS < 70 were not very likely to spend < 5% PRL on treatment. This is mainly related to short survival, and numerous prognostic models include KPS as a main driver of poor prognosis [17–19]. We also observed that patients not receiving systemic treatment are in a comparable situation. Typically, poor KPS impacts on eligibility for systemic therapy, but other factors contribute, too, e.g. comorbidity, reduced organ function and lack of available options when numerous lines of treatment have already been administered.

Interestingly, after testing of a large number of potentially relevant variables (Tab. 1), very few were confirmed as major drivers of PRL in multi-nominal logistic regression analysis. Blood test results such as hypercalcemia are not commonly included in radiotherapy-related

prognostic models, but appear to contribute additional information. Their role requires further study in larger databases. Besides number of patients, limitations of the present work include its retrospective single-institution design and the lack of certain baseline data, e.g. lactate dehydrogenase, in a proportion of patients. On the other hand, the study cohort represents a real-world patient population of often elderly patients with highly variable disease burden and survival.

To facilitate decision making in practice, Farris et al. have proposed a pragmatic method to evaluate the suitability of PRT fractionation [8]. They described a novel metric, the palliative appropriateness criteria (PAC) score and provided an online calculator. Our group has recently performed independent validation [9]. Factors significantly associated with long time spent on treatment, i.e. increased PRL, were male gender, Eastern Cooperative Oncology Group (ECOG) PS 3–4, lung or "other" primary diagnosis (vs. breast or prostate), radiotherapy indication (neurological dysfunction *vs.* pain/other), inpatient status, and extraosseous site treatment [8]. However, factors were not uniform across all different fraction regimens. For example, only 4 factors were relevant in the subgroup selected for single-fraction irradiation. ECOG PS 3–4 was universally associated with significantly higher PRL among all regimens. Extraosseous site of treatment was associated with higher PRL for 2–5 and 10 fraction regimens.

Typical, well-established prognostic models for survival, such as TEACHH and others, did not stratify for radiotherapy fractionation and did not calculate PRL [20–22]. Indirectly, they can contribute some, yet limited, information in so far as patients with long survival (≥ 1 year) treated with 10 fractions always will spend < 5% PRL on treatment. TEACHH includes cancer type (lung and "other" versus breast and prostate), older age (> 60 years versus ≤ 60 years), liver metastases, ECOG PS (2–4 *vs.* 0–1), hospitalizations within 3 months before palliative radiotherapy (0 *vs.* ≥1) and prior palliative chemotherapy courses (≥ 2 *vs.* 0–1) [20]. Even simple models, such as the one introduced in 2008 by Chow et al. (3 factors: non-breast cancer, metastases other than bone, and KPS ≤ 60), have demonstrated clinical value [21]. Despite progress in prognostic stratification, survival predictions in oncology tend to be overly optimistic [23, 24]. Not all patients initially thought to represent suitable candidates for PRT are able to complete their treatment. In an analysis of patients who died during PRT, Berger et al. found that once radiotherapy was begun the treatment duration required a median 64% of the remaining lifetime [25]. It is, therefore, clear that prognostic assessment and calculation of PRL have the potential to optimize PRT care pathways.

Conclusions

Radiotherapy fractionation is an easily modifiable factor with high impact on PRL. Patients with KPS < 70 and those treated for additional target types (non-bone) during the same course are at high risk of spending a larger proportion of their remaining life on treatment.

Author contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by C.N. The first draft of the manuscript was written by C.N. and all authors commented on previous versions of the manuscript. All authors have read and agreed to the published version of the manuscript.

Conflicts of interest

The authors declare no conflict of interest.

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Institutional Review Board statement

As a retrospective quality of care analysis, no approval from the Regional Committee for Medical and Health Research Ethics (REK Nord) was necessary. This research project was carried out according to our institutions' guidelines and with permission to access the patients' data.

Informed consent statement

Informed consent was obtained from all subjects involved in the study.

Data availability statement

The dataset supporting the conclusions of this article is available at request from the corresponding author, if intended to be used for meta-analyses.

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Table 1. Baseline characteristics, 219 patients who started 287 treatment courses. Data based on individual treatment courses. Blood test results and disease status (non-irradiated stable versus progression) were not available for all treatment courses

Baseline parameter	Number	Percent
Female sex	118	41
Male sex	169	59
KPS < 70	63	22
KPS ≥ 70	224	78
Outpatient	182	63
Inpatient	105	37
Age 71–80 years	94	33
Age ≥ 81 years	39	14
Prostate cancer	72	25
Non-small cell lung cancer	56	20
Breast cancer	53	19
Small cell lung cancer	11	4
Renal cell cancer	17	6
Colorectal cancer	32	11
Bladder cancer	10	4
Other primary tumors	36	12
Treatment-related variables		
One or two target volumes irradiated	206	72
Three or more target volumes irradiated	81	28
Osseous metastases irradiated (exclusively)	234	82
Extraosseous metastases irradiated	53	18
Pain indication for RT	245	85
Non-pain indication (neurological etc.)	42	15
Prescribed regimen of 10 fractions	100	35

Baseline parameter	Number	Percent
Prescribed regimen of 1 fraction	70	24
Prescribed regimen of 2–5 fractions	117	41
No systemic therapy	63	22
Previous or ongoing systemic therapy	224	78
Corticosteroid concomitant to RT	115	40
No corticosteroid concomitant to RT	172	60
Opioid analgesic concomitant to RT	189	66
No opioid analgesic concomitant to RT	98	34
Palliative care team involved	96	33
Palliative care team not involved	191	67
Early RT, within 2 mo from cancer diagnosis	91	32
Late RT, > 2 months	196	68
Blood test results		
Low hemoglobin	174	61
Normal hemoglobin	112	39
Hypercalcemia	18	6
Normal calcium	262	91
Low albumin	41	14
Normal albumin	229	80
High lactate dehydrogenase	116	40
Normal lactate dehydrogenase	122	43
High alkaline phosphatase	157	55
Normal alkaline phosphatase	111	39
Leukocytosis	54	19

Baseline parameter	Number	Percent
No leukocytosis	232	81
High C-reactive protein	198	69
Normal C-reactive protein	84	29
Abnormal platelet count	56	20
Normal platelet count	229	80
Disease extent and status		
Brain metastases	25	9
Liver metastases	87	30
Lung metastases	93	32
Adrenal gland metastases	23	8
Disease progression in non-irradiated area	132	46
Stable disease outside irradiated area	152	53

KPS — Karnofsky performance status; RT — radiotherapy

Table 2. Association between percent of remaining life (PRL) and baseline parameters in 287 treatment courses

Parameter	**Significance level**	**PRL < 5% (%)**	**PRL < 5% (number)**	PRL ≥5% (number)
Fractionation	< 0.001			
1		100	70	0
2–5		56	66	51
10		0	0	100
Target volume	< 0.001			
Non-bone in addition to bone		15	8	45
Bone alone		55	128	106
Karnofsky performance status	< 0.001			
< 70		24	15	48
≥ 70		54	121	103
Systemic treatment	< 0.001			
None		24	15	48
Any concurrent/ongoing treatment		54	121	103
Timing of radiotherapy	< 0.001			
Early (within 2 months from diagnosis)		33	30	61
Later during the disease trajectory		54	106	90
Hemoglobin level	< 0.001			
Low		56	97	77
Normal		34	38	74
Calcium level	0.007			
High		17	3	15
Normal		50	131	131
Number of irradiated target volumes	0.008			
1–2 in actual course		52	108	98
3 or more in actual course		35	28	53
Primary cancer diagnosis	0.01			
Prostate or breast		56	70	55
Others		41	66	96
Radiotherapy setting	0.01			

Inpatient		37	39	66
Outpatient		53	97	85
Age	0.035			
80 years or older		62	28	17
Younger than 80 years		45	108	134
Type of symptoms	0.038			
Neurological deficit		11	1	8
Others, e.g. pain		49	135	143