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Clinical Investigation

Course of Quality of Life After Radiation Therapy for Painful Bone Metastases: A Detailed Analysis From the Dutch Bone Metastasis Study

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Summary

Although radiation therapy for painful bone metastases often leads to a meaningful pain response, most domains of quality of life (QoL) do not improve after treatment. In general, QoL stabilizes after 1 month and deteriorates toward the end of life. Psychosocial QoL improves slightly after treatment. For most QoL domains, a high pain score

Purpose: To study the course of quality of life (QoL) after radiation therapy for painful bone metastases.

Patients and Methods: The Dutch Bone Metastasis Study randomized 1157 patients with painful bone metastases between a single fraction of 8 Gy and 6 fractions of 4 Gy between 1996 and 1998. The study showed a comparable pain response of 74%. Patients filled out weekly questionnaires for 13 weeks, then monthly for 2 years. In these analyses, physical, psychosocial, and functional QoL domain scores and a score of general health were studied. Mixed modeling was used to model the course of QoL and to study the influence of several characteristics.

Results: In general, QoL stabilized after 1 month. Psychosocial QoL improved after treatment. The level of QoL remained stable, steeply deteriorating at the end of life. For most QoL domains, a high pain score and intake of opioids were associated with worse QoL, with small effect sizes (−0.11 to −0.27). A poor performance score was associated with worse functional QoL, with a medium effect size (0.41). There is no

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and intake of opioids are associated with worse QoL. A poor performance score is associated with worse functional QoL.

difference in QoL between patients receiving a single fraction of 8 Gy and 6 fractions of 4 Gy, except for a temporary worsening of physical QoL after 6 fractions.
Conclusion: Although radiation therapy for painful bone metastases leads to a meaningful pain response, most domains of QoL do not improve after treatment. Only psychosocial QoL improves slightly after treatment. The level of QoL is related to the actual survival, with a rather stable course of QoL for most of the remaining survival time and afterward a sharp decrease, starting only a few weeks before the end of life. Six fractions of 4 Gy lead to a temporary worse physical QoL compared with a single fraction of 8 Gy.

Introduction

Radiation therapy is an effective treatment for patients with painful bone metastases, with a pain response rate of more than 60%. Several randomized trials have shown an equal effectiveness in pain response of a single fraction of 8 Gy compared with multiple fractions. Therefore, the golden standard is to treat these patients with a single fraction of 8 Gy (1-3). Although reduction of pain is the main aim of treatment in patients with painful bone metastases, it is also important to focus on other goals of treatment. In the palliative setting, the traditional oncologic treatment endpoints, like disease control or survival, are often less or even not appropriate. The treating physician has to weigh the impact of treatment against the benefit it provides for the individual patient. Therefore, palliative treatments focus on maintaining or improving quality of life (QoL) (4).

Health-related QoL is defined as a multidimensional construct encompassing perceptions of both positive and negative aspects of physical, emotional, cognitive, and social functions, due to the sequelae of a disease and its treatment (5). Painful bone metastases have a negative impact on the QoL of patients (6, 7). Despite this, few of the numerous randomized trials that were published since the late 1990s documented the impact of bone metastases and its treatments on QoL. If patients and their treating doctors have a better understanding of the expected course of QoL, this may help them to make decisions about treatment of painful bone metastases in the context of a possibly short life expectancy.

Some studies reported that radiation therapy improved QoL, mainly in patients experiencing a pain response (8-14). Two of these publications had a very short follow-up of only 1 month (10, 11), and only 2 studies were randomized (12, 13). One of the latter studies compared different treatment schedules and found that improvements of QoL were of similar magnitude irrespective of fractionation schedule (single or multiple fractions) (12), The second, more recent, randomized study compared 2 treatment schedules for re-irradiation of painful bone metastases and found a better QoL 2 months after retreatment in responders compared with nonresponders (13). None of these studies reported the course of specific domains of QoL after treatment.

Initial analyses of the Dutch Bone Metastasis Study (DBMS), the largest randomized trial comparing the effect of single versus multiple fractions on pain response, found no differences in global QoL between patients treated with a single fraction and those treated with multiple fractions (1, 15). More recent analyses report that patients responding to radiation therapy have a better QoL during the first 3 months after treatment than nonresponding patients (16). The aim of the present analysis was to study the detailed course of the physical, psychosocial, and functional domains of QoL and general health after radiation therapy for painful bone metastases with a maximum of 2 years' follow-up after treatment and to create a model of its course. We also analyzed the influence of baseline and follow-up variables on the course of QoL.

Patients and Methods

The DBMS was a nationwide, randomized, controlled trial in 17 of the 21 radiation therapy institutions for patients with painful bone metastases in the Netherlands. Between 1996 and 1998, a total of 1157 patients with painful bone metastases were randomized between a single fraction of 8 Gy or 24 Gy in 6 fractions. The main endpoint of the study was pain response. Detailed descriptions of the study protocol have been published previously. (1) The medical ethics committees of participating institutions approved the study, and all patients provided informed consent. The database was updated for survival and closed in December 1998.

Questionnaires

At randomization and during follow-up, patients filled out weekly questionnaires for 13 weeks and monthly thereafter until 2 years of follow-up, death, or closure of the study. These questionnaires contained in total 43 items, including items from the Rotterdam Symptom Checklist (17), 3 questions about possible side effects of radiation therapy, and 2 questions from the European Organization for Research and Treatment of Cancer (EORTC) Core Quality of Life Questionnaire (QLQ)-C30 (18) regarding whether physical condition or medical treatment influenced family life or social activities. Furthermore, questionnaires consisted of a visual analogue general health scale (VAS-gh) and a question on the intake of pain medication. At randomization, the treating physician rated performance

using the Karnofsky performance status (KPS) (19). Pain was measured using an 11-point numeric rating scale, ranging from 0 (no pain) to 10 (worst pain imaginable). A pain score of at least 2 was required to enter the study (1). The VAS-gh is a self-reported global assessment of general health, which was noted on a line from 0 (no complaints) to 100 (worst general health possible). Missing data were imputed using the expectation maximization algorithm, when patients filled out at least half of the questionnaires. Of all questionnaires, 67.5% were filled out completely, without missing values. Twenty-two percent of all questionnaires were missing only 1 value.

QoL analyses

In total, data of 1115 patients (96.4%) were used. The remaining 42 patients were not analyzed, because they never filled out a (complete) questionnaire. Principal component analysis with oblique rotation was used to reduce the number of QoL items from the questionnaires into components (or domains). Principal component analysis is considered a valid method to summarize data into factor scores. The advantage of this method is that we were able to convert individual items from the different questionnaires that were used in the DBMS into clinically meaningful and relevant sum scores. Three domains were found and labeled as physical health, psychosocial health, and functional status. Table 1 presents the rotated and standardized component loadings, with a score for the contributive ability of the item on the domain. As shown in Table 1, some of the items contribute to 2 or 3 domains, whereas others contribute to a single domain. The domain scores were standardized to scores (z scores), with a mean of 0 and a standard deviation of 1, to facilitate interpretation of the subsequent regression analyses. The domain z scores were used for further analyses. A multilevel regression analysis was used to study the course of QoL (the 3 domain scores and the VAS-gh) during follow-up and to create a model based on these patient data. The higher the total score, the better the QoL. The multilevel model enables the analysis of all available data, as opposed to only complete data. The repeated measures have a first-order autoregressive covariance structure. We studied the influence of the following baseline variables on the course of QoL: age, gender, KPS, primary tumor (breast, prostate, lung cancer, and other), and treatment arm (1 × 8 Gy, 6 × 4 Gy). In addition, we studied the influence of 2 variables varying over time: pain score and intake of opioids. An α level of 0.05 was used to judge statistical significance of effects. Because both predictors and outcome variables have been standardized, the regression coefficients can be interpreted as effect size r and d for continuous and dichotomous predictors, respectively. Regression coefficients for binary predictors can be interpreted as effect size Cohen's d, with values of 0.2-<0.5, 0.5-<0.8, and ≥0.8, indicating small, medium, and large effect sizes, and regression coefficients for continuous predictors can be interpreted as effect size r, with values of 0.1-<0.3, 0.3-<0.5, and ≥0.5, indicating small, medium, and large effect sizes, respectively (20, 21). Negative values indicate a negative effect on QoL, positive values a positive effect.

Survival groups for the course of QoL

To identify the course of QoL in relation to remaining survival, we divided patients into 5 separate survival groups, with an observed survival of <3, 3-<6, 6-<12, 12-<18, and 18-<24 months. Quality of life was modeled as a composite of 2 latent curves, modeling both time since the first measurement and time to death. This model thus takes into account the impact of impending death, because this can have a marked impact on QoL.

The database was analyzed using IBM SPSS statistics for Windows version 20.0 (IBM, Armonk, NY).

Results

General outcome

The primary results of the DBMS have been previously published (1, 15). In short, of the 1115 evaluable patients, the mean age was 65 years (range, 32-89 years), and 46% of patients were female. The mean KPS was 70 (range, 20-100), and in 28% of patients visceral metastases were documented. The most common primary tumors were breast (39%), prostate (23%), and lung cancer (25%). The overall pain response rate was 74%, with no difference between the 2 treatment schedules. The median and mean survivals were 30 and 49 weeks, respectively, with a range of 0.3 to 142 weeks. After 1 year, 320 patients (28%) were still alive and returning questionnaires. At closure of the study, with a maximum follow-up of 142 weeks (approximately 2.7 years), 860 patients (74%) had died.

Quality of life

Figure 1 shows the modeled course of the QoL domains physical health, psychosocial health, and functional status and of the VAS-gh in patients surviving <3, 3-<6, 6-<12, 12-<18, and 18-<24 months after randomization. The level of QoL is related to the actual survival, with a rather stable course of QoL for most of the remaining survival time and afterward a sharp decrease, starting several weeks before the end of life. In general, treatment with radiation therapy does not lead to an improvement of QoL. After start of treatment, immediate deteriorations in the first week of the physical domain, the functional domain, and VAS-gh are noticed. For the physical domain only, an improvement is seen after this initial decline. In both other domains the deterioration flattens until it further decreases near death. Only in the psychosocial domain an improvement after treatment occurs, which persists until the steep decline toward death.

Table 1 Allocation of the variables to the 3 QoL domains, with accompanying standardized component loadings

Source	Item	Physical	Psychosocial	Functional
RSCL	Lack of appetite	0.49		0.26
	Irritability		0.59	
	Tiredness	0.44	0.30	
	Worrying		0.91	
	Sore muscles	0.38		
	Depressed mood		0.87	
	Lack of energy	0.34	0.46	
	Low back pain	0.41		
	Nervousness		0.83	
	Nausea	0.62		
	Despairing about future		0.90	
	Difficulty sleeping	0.29	0.31	
	Headaches	0.45		
	Vomiting	0.54		
	Dizziness	0.52		
	Decreased sexual interest		0.25	
	Tension		0.85	
	Abdominal (stomach) aches	0.55		
	Anxiety		0.91	
	Constipation	0.40		
	Diarrhea	0.30		
	Acid indigestion	0.59		
	Shivering	0.49		
	Tingling hands or feet	0.43		
	Difficulty concentrating	0.26	0.45	
	Sore mouth/pain when swallowing	0.49		
	Loss of hair	0.20		
	Burning/sore eyes	0.44		
	Shortness of breath	0.31		
	Dry mouth	0.53		0.21
	Care for myself (wash, etc)			0.82
	Walk about the house			0.83
	Light housework/household jobs			0.84
	Climb stairs			0.85
	Heavy housework/household jobs			0.85
	Walk out of doors			0.88
	Go shopping			0.86
	Overall valuation of life	0.40	0.28	0.29
QLQ-C30	Interference with family life		0.31	0.34
	Interference with social activities		0.30	0.47
Added questions	Itching	0.45		
	Painful skin	0.42		
	Bone pain	0.37	0.20	

Abbreviations: QLQ-C30 = European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire; RSCL = Rotterdam Symptom Checklist.

To facilitate interpretation of the domains, we only display items with a factor loading $\geq$0.20.

Impact of baseline and follow-up variables on QoL

Table 2 describes which baseline and follow-up variables influenced the course of the different QoL domain scores and the VAS-gh, including the effects sizes. Higher pain score and intake of opioids are associated with lower levels of QoL for almost all domains, with varying effect sizes. There are small, but clinically relevant, effects of intake of opioids on the physical and functional domain and on VAS-gh (−0.27, −0.21, and −0.21, respectively) and of pain score on the physical and psychosocial domain and on VAS-gh (−0.14, −0.11, and −0.24, respectively). The largest effect size is for the influence of KPS on the functional domain, with a medium effect size of 0.41. Age has a small effect on the functional domain, of −0.12. Thus, a lower baseline performance score or higher age is associated with significantly worse functional status. Furthermore, primary tumor has a small effect on the physical and

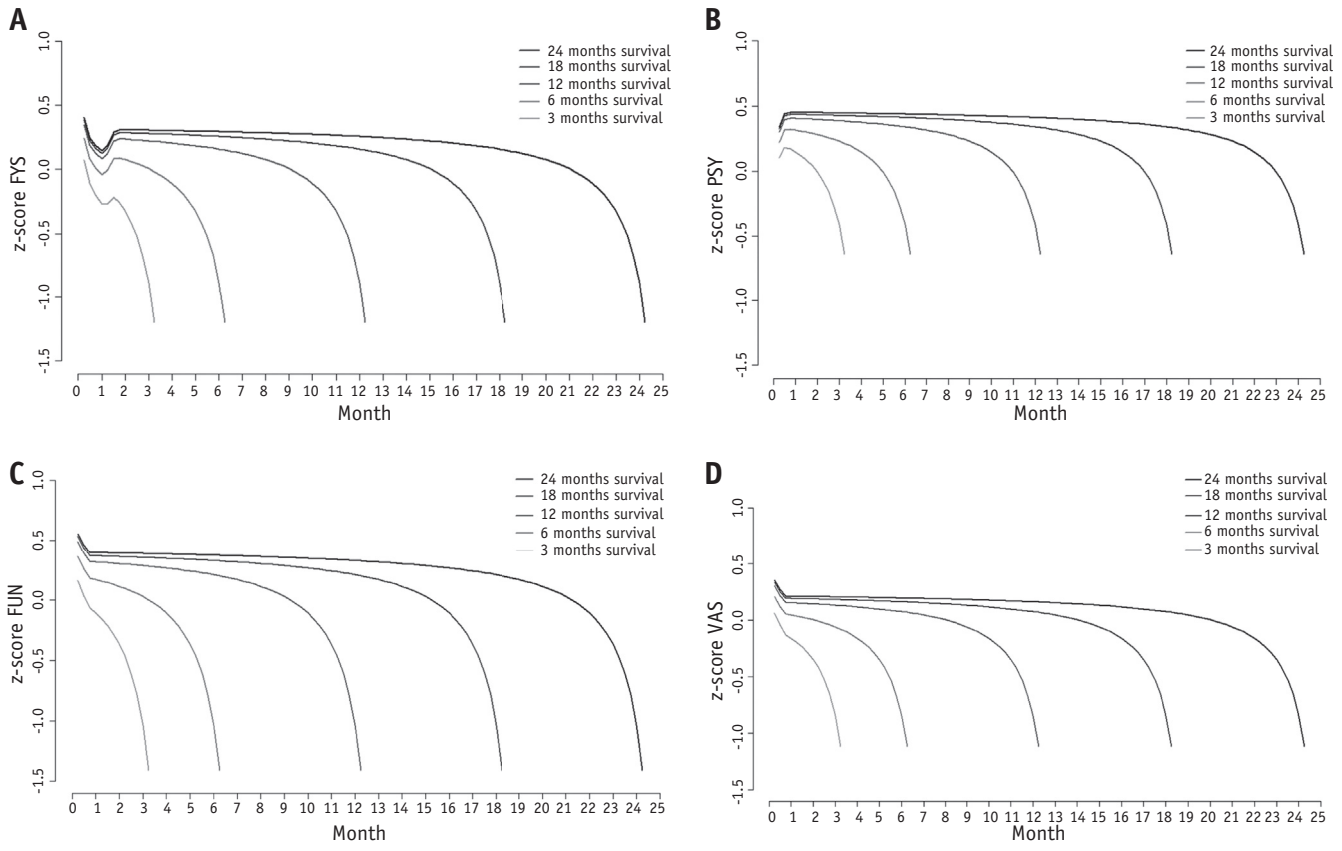

Fig. 1. The modeled course of quality of life (QoL) after radiation therapy for painful bone metastases, represented in survival groups (patients surviving <3, 3-<6, 6-<12, 12-<18, and 18-<24 months after randomization). The *x* axis represents the months after treatment, where month 0 is the baseline measurement before treatment and month 1 the first months after treatment. The *y* axis reflects the domain score of QoL, where the average is 0, with a standard deviation of 1. The higher the score, the better the QoL. (A) Physical domain. (B) Psychosocial domain. (C) Functional domain. (D) Visual analogue general health scale (VAS-gh).

Table 2 Influence of baseline and follow-up variables on QoL domains, with effect sizes

	QoL domain							
	Physical		Psychosocial		Functional		VAS-gh	
Variable	Effect size	*P*	Effect size	*P*	Effect size	*P*	Effect size	*P*
Baseline								
Age	0.01	.72	0.03	.24	−0.12*	<.001	0.01	.65
Gender (reference: male)	−0.11	.26	−0.17	.11	−0.19	.02	−0.06	.45
KPS	0.00	.93	0.06	.04	0.41*	<.001	0.09	<.001
Primary tumor (reference: other)								
Breast	−0.08	.43	−0.12	.28	−0.27*	.002	−0.14	.11
Prostate	−0.20*	.03	−0.18	.06	−0.22*	.003	−0.11	.11
Lung	0.06	.44	−0.04	.63	−0.10	.16	0.00	.95
Follow-up								
Treatment arm (reference: 1 × 8 Gy)	−0.12 to −0.17†	<.001	0.06	.24	0.02	.57	0.03	.42
Pain score	−0.14*	<.001	−0.11*	<.001	−0.07	<.001	−0.24*	<.001
Intake of opioids (reference: no opioids)	−0.27*	<.001	−0.05	.001	−0.21*	<.001	−0.21*	<.001

Abbreviations: KPS = Karnofsky performance status; QoL = quality of life; VAS-gh = visual analogue scoring of general health.

Binary variables (gender, primary tumor, treatment arm, and intake of opioids): effect sizes between −0.19 and 0.19 are considered minor effects and are not clinically relevant. Continuous variables: effect sizes between −0.09 and 0.09 are considered minor effects and are not clinically relevant. A positive direction of the effect size means improvement of QoL by increase of the variable/compared with the reference.

* Clinically relevant effect.

† The effect size varies each week, ranging from −0.12 (week 4), to −0.13 (week 2), to −0.17 (week 3).

functional domain, with patients with prostate cancer having worse functional and physical QoL after radiation therapy, whereas patients with breast cancer have a worse functional QoL compared with patients with other types of cancer. Other effect sizes are smaller and therefore not considered clinically relevant.

Impact of treatment schedule on QoL

Patients receiving either 8 Gy in a single fraction or 6 fractions of 4 Gy have comparable QoL outcomes, except for the physical domain (Fig. 2). Treatment with 6 fractions of 4 Gy leads to a temporary worsening of QoL on the physical domain during the first 4 weeks after treatment, compared with a single fraction of 8 Gy. This is represented in the difference between the dotted and the solid lines in Figure 2, with superimposing lines afterward (effect size each week below 0.2, indicating a minor effect, $P<.001$; Table 2).

Discussion

Our analyses describe the detailed course toward death of different QoL domains after radiation therapy in patients with painful bone metastases. Quality of life initially remains stable after treatment, until a steep deterioration occurs near the end of life. It is an important finding for both patients and physicians to be aware of the rather stable QoL, until several weeks before death. This stabilization may reflect the benefit of treatment, because a decline can be expected without treatment in most patients. However, because untreated patients were not studied, it may also reflect the natural course of the disease in these patients. The course of QoL toward death is in accordance with the pattern described by Murray et al (22). Their paper, which is frequently cited in palliative care, shows a distinctive pattern for cancer patients versus patients with other life-threatening diseases, such as COPD and cardiac failure. Cancer patients show a predictable pattern, characterized by an initial rather stable course of QoL, followed by a short and swiftly declining phase toward death. Our model, based on actual patient data, therefore confirms the hypothesis by Murray et al also for patients with painful bone metastases.

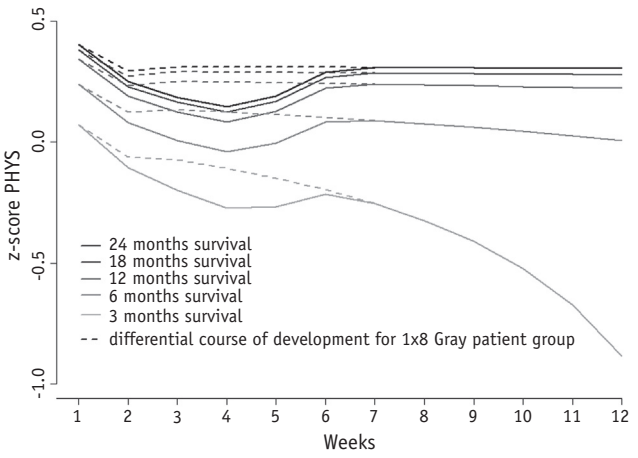

Fig. 2. The modeled course of the physical domain 12 weeks after randomization, represented in survival groups (patients surviving <3, 3-<6, 6-<12, 12-<18, and 18-<24 months after randomization). The temporary difference between both fractionation schemes is shown in the dotted lines (1 × 8 Gy) and the solid lines (6 × 4 Gy). The *x* axis represents the weeks after start of treatment. The *y* axis reflects the physical domain score, where the average is 0, with a standard deviation of 1. The higher the score, the better the physical quality of life.

There seems to be a discrepancy in our results that, although 74% of patients experienced a pain response, most domains of QoL of these patients did not improve after radiation therapy. This is in line with the fact that we found little effect in the multilevel regression analyses of pain score on the QoL domains. The main reason for this is probably the influence of many other variables on QoL, like the presence of other symptoms these patients suffer, related to their advanced disease and possibly also side effects from medication and/or systemic therapies. Concerns about end of life and worrying about the future might also influence QoL (23). These concerns are not likely to resolve after radiation therapy for painful bone metastases. Nevertheless, in a population like this, even stabilization of QoL may be considered very meaningful to patients. Without treatment, QoL might have deteriorated sooner. The improvement in psychosocial status after treatment might be due to the care given by doctors and nurses at the radiation therapy department, in combination with the hope and expectation of a beneficial treatment outcome. Notable is the temporary decline of physical health after 6 fractions of 4 Gy, which does not occur after a single fraction of 8 Gy, although with a minor effect size. The difference may be due to more treatment side effects and the burden of 5 additional visits to the radiation therapy facility.

On the one hand, our results, indicating no apparent improvement of QoL after radiation therapy for painful bone metastases, are in line with the results from Caissie et al (8). They prospectively studied the QoL of a cohort of 178 patients with uncomplicated painful bone metastases, using the EORTC-QLQ-C15-PAL questionnaire at 1, 2, 4, and 8 weeks after treatment. Unfortunately, at 3 of the 4 time points a maximum of 40% of patients returned the questionnaires. The pain response rate was 65% after 2 months. They reported no improvement of total QoL up to 2 months after radiation therapy, whereas pain, insomnia, and constipation improved. In a recent randomized study on retreatment for painful bone metastases, in 528 evaluable patients, no clinically relevant improvement of global QoL was noticed after a pain response (13).

The results of the present study seem to be in contradiction with our earlier analyses showing that responders have a better QoL compared with nonresponders. However, this difference is mainly caused by a deterioration of QoL in nonresponders. Apparently, it is a matter of selection: the

patients without a pain response are patients with a poorer QoL, both before and after treatment, and an observed shorter survival (16, 24). The temporary decrease in physical health in the multiple fraction regimen we found in our present analyses might be in line with some increase in fatigue the first 2 weeks after treatment, which was described in another article, prospectively studying 518 patients (9).

On the other hand, our results contradict several other studies stating that radiation therapy leads to improvement of QoL (9-13). However, these other studies have some limitations. For example, they only studied QoL at a limited amount of time points (10, 11, 13), focused on limited items (9, 12), or included small patient numbers (11). Moreover, statistically significant improvement of QoL does not necessary reflect clinically relevant improvement.

Although our study is based on a unique and large cohort of patients with bone metastases from the Netherlands, the data originate from the late 1990s, which may be considered a limitation due to changes in systemic and symptomatic treatments in the past years, which have altered the course of the disease. On the other hand, in the present report we showed that, irrespective of survival, the pattern of QoL is similar in all patient groups. Quality of life remains stable for a long period and only deteriorates briefly before the end of life. Although the systemic treatment of patients with painful bone metastases and their survival has changed over time, the standard local treatment has remained palliative radiation therapy, with a single fraction of 8 Gy (3). Therefore, we believe these QoL results are still applicable to current patients with painful bone metastases. The Rotterdam Symptom Checklist and EORTC QLQ-C30 questionnaires that were used are not specifically designed for patients with painful bone metastases. Therefore, small but meaningful differences might have been missed by these global QoL questionnaires. For future studies we would recommend using a bone metastases−specific questionnaire, like the EORTC QLQ-BM22, which contains 22 questions relevant to patients with bone metastases. Moreover, we would advise the EORTC PAL15 questionnaire instead of the C30 (25). Another possible limitation is that follow-up data may be biased, because patients with a good QoL and good performance status will be more likely to complete a questionnaire than patients in poor physical condition. However, because 74% of the patients died during follow-up, we believe that the results toward death provide a meaningful outcome. A final shortcoming might be that we did not study patients with painful bone metastases who did not receive radiation therapy. Therefore, we cannot determine whether the stabilization of QoL is a benefit of treatment, although it seems reasonable to conclude that without treatment QoL would have deteriorated sooner.

Conclusion

Although radiation therapy for painful bone metastases often leads to a meaningful pain response, most domains of QoL do not improve after treatment. Only psychosocial QoL improves slightly after treatment. The level of QoL is related to the actual survival, with a rather stable course of QoL for most of the remaining survival time and afterward a sharp decrease, starting several weeks before the end of life. For most QoL domains, a high pain score and intake of opioids are associated with worse QoL. A poor performance score is associated with worse functional QoL. There is no difference in QoL between patients receiving a single fraction of 8 Gy and 6 fractions of 4 Gy, except for a temporary worsening of physical QoL after 6 fractions, up to 4 weeks after start of treatment.

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