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Bone Metastasis Reirradiation Predictors of Quality of Life

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Abstract: ***Background**: Many patients, once irradiated for bone metastasis, may need to be reirradiated, as palliative radiotherapy of painful bone metastasis is important for pain relief. Our aim was to assess the predictive value of reirradiation features on quality of life of these patients. **Methods and materials**: Between 2012 and 2016 we reirradiated 44 patients with in-field bone recurrence. The first irradiation dose varied from 27-60 Gy and all patients showed complete or partial pain relief. Patients were retreated either in the vertebral spine (cervical, thoracic and lumbar vertebras), humeral head or pelvic bones. Both single dose (8Gy; 22 patients) and multifractionated (5x4Gy or 10x3Gy, 22 patients) radiotherapy were employed. Quality of life was assessed both at baseline and after reirradiation. **Results**: The median interval between irradiations was 30 months (7-80months), and the median follow-up after retreatment was 13 months (2-39 months). While age, cancer type and treatment region did not have any significant role in improvement of quality of life, longer distance between two irradiations and higher Karnofsky score had a significant positive impact. **Conclusion**: Longer periods between irradiations predict better quality of life achievement after reirradiation.*

Keywords: Reirradiation, quality of life, predictors, bone, metastasis, palliative

1. Introduction

Palliative radiotherapy is a standard treatment for cancer patients with painful bone metastasis (1). Improvements of treatment in cancer patients have led to a longer overall survival and to a higher probability of developing in-field recurrence after the first treatment with radical purpose (2). Many patients may need to be reirradiated, but retreatment still remains a challenge for the radiation oncologist as a result of the existed limited evidence. Some studies have tried to identify predictive factors for pain response after palliative radiation therapy, like primary tumor type, age, performance status, irradiation dose, absence of visceral metastasis, and radiotherapy treatment region that will help us to find the category of patients with painful bone metastasis who really would benefit from treatment (3,4). However till now does not exist a validated predictive model so it is very important to balance between symptoms relief associated with improvements in quality of life and probably caused side effects (5). The aim of our study was to identify reirradiation predictors that may inform on the quality of life (QoL) achieved by reirradiating bone metastasis patients with in-field recurrence.

2. Methods and materials

We reirradiated 44 patients with in-field bone recurrence. They received single or multifractionatedreirradiation for painful bone metastases. All of them had received multimodality treatment before and also were on steroid therapy. Ten patients presented visceral metastasis at the moment of retreatment. The reason of the second irradiation was refractory pain to analgesics. Anatomical locations of the retreatment were the vertebral spine (cervical, thoracic and lumbar vertebras) in 38 patients and humeral head or pelvic bones in 6 others. The total dose of the first irradiation ranged from 30 to 60Gy, and all patients had multifractionated treatment. The median interval between two irradiations was 30 months (range 7-80 months) and the total dose of reirradiation varied from 8 to 30 Gy, with daily fraction of 3–8Gy. 22 patients received single dose radiotherapy and 22 others multifractionated treatment. A Cobalt 60 machine using a three-dimensional conformal irradiation technique was used for retreatment of 29 patients and a Linear accelerator for the other 15 patients. Single dose reirradiation was used more in patients with lower Karnofsky Performance Status and shorter period between irradiations. Pain relief was assessed according to the Brief Pain Inventory score. All patients filled out the questionnaires at the baseline, after 2 months of retreatment and thereafter every 3 months until 2 years of follow up or death. QoL was assessed through a self-assessment questionnaire on seven domains, including general activity, mood, walking ability, normal work, relation with others, sleep and enjoyment of life. Each domain was measured with a scale from 0 to 10, where 0 pointed the highest level of satisfaction and 10 the lowest level of satisfaction. To assess associations and predictive value between reirradiation features and quality of life, we employed: dependent samples t-test for assessing the difference between baseline and after reirradiation, partial correlations adjusted for age, gender and primary cancer type, and linear regression between reirradiation features significantly correlated to quality of life and its elements.

3. Results

The most common primary tumors were breast, prostate, lung and rectal cancer with a total of 37 patients. The other seven patients had primaries like cervical or renal cancer; sarcoma and lymphoma (see tab. 1). Nineteen of the reirradiated patients were women and twenty-five were men with a median age of 56years (range 28-75 years). Reirradiation was well-tolerated by all patients. After the second month of retreatment 46% of patients had complete pain relief, 43% partial pain relief and 11% had no

response.No patient had acute side effects of more than grade 2. Five patients developed dysphagia G1 and two others oral mucositis G1. Diarrhea G1 and G2 was seen in two other patients retreated at the lumbar vertebras. Afterwards all patients were followed-up every three months. In the next 6 months, no patient with complete response complained pain as a major symptom. The median follow up was 13 months (range 8-28 months). As shown in Table 2, in dependent samples t-test analysis, patients presented statistically significant improvement in Karnofsky score, QoLand each composing element of it. In fact, a 56.6% improvement in quality of life and a 20.7% improvement in Karnofsky score was observed. In partial correlation analysis (Table 3), adjusted for age, gender and primary cancer type, period between first irradiation and reirradiation was significantly and positively correlated with improvement in QoL and Karnofsky score. In fact such a period, expressed in months, presented a correlation of -0.460 (p = 0.002) with quality of life and 0.409 (p = 0.008) with the Karnofsky score. In the same analysis, no other reirradiation feature, including dose of the first irradiation, dose of reirradiation and reirradiated region, showed any statistically significant correlation with either quality of life or Karnofsky score. Therefore only period between irradiations was further assessed in linear regression analysis as an independent predictor of quality of life (Table 4). After employing two different models in multivariate linear regression analysis, the period between irradiations was significantly associated with better quality of life in both basic and full models. In details, in the basic model, adjusted for age, gender, baseline quality of life and dose of the first irradiation, for every one month increase before reirradiation, quality of life increased by 0.191 (p = 0.017) in the absolute scale and by 0.62% in the relative scale. In the full model, further adjusting for age, gender, baseline quality of life and dose of the first irradiation, dose of the reirradiation, type of radiating machine, irradiation region and type of primary cancer, did not change the association depicting that for every one month increase before reirradiation, quality of life increased by 0.190 (p = 0.015) in the absolute scale and by 0.62% in the relative scale.

Table 1: Patients characteristics

Characteristic	Number of patients
Age	
<50years	9
≥50years	35
Gender	
Female	19
Male	25
Karnofsky performance status	
< 80	26
≥ 80	18
Type of tumor	
Breast cancer	14
Prostate cancer	11
Lung cancer	6
Rectal cancer	6
Renal cancer	3
Lymphoma	1
Sarcoma	1
Cervical cancer	2
Visceral metastasis at the time of retreatment	
Yes	10
No	34
Retreatment region	
Cervical vertebras	6
Thoracic vertebras	22
Lumbar vertebras	10
Pelvis bones	5
Humeral head	1
Time between two RT treatments	
≤ 12months	11
> 12months	33
Reirradiation schedule Single dose	
8Gy	22
Multiple fractions	
5x4Gy	14
10x2,5Gy	1
10x3Gy	7

Table 2: Difference of Quality of Life after Reirradiation*

Variables	Before Reirradiation (SD)	After Reirradiation (SD)	Mean Difference	95% Confidence Interval	*p*-value
Karnofsky Score	0.734	0.886	0.152	0.125, 0.180	<0.001
Quality of Life	30.93	13.43	-17.500	-20.186, -14.814	<0.001
General Activity	4.64	1.91	-2.727	-3.112, -2.343	<0.001
Mood	4.11	1.91	-2.205	-2.647, -1.762	<0.001
Walking Ability	4.02	1.86	-2.159	-2.584, -1.734	<0.001
Normal Working	4.14	1.93	-2.205	-2.642, -1.767	<0.001
Relation with Others	4.57	1.86	-2.705	-3.106, -2.303	<0.001
Sleep Quality	4.68	1.93	-2.750	-3.155, -2.345	<0.001
Life Enjoyment	4.77	2.02	-2.750	-3.155, -2.345	<0.001
* Dependent Samples *t*-test					

Table 3: Partial Correlations* between Reirradiation Features and Quality of Life

Variable	**Karnofsky**	**Quality of Life**	**General Activity**	**Mood**	**Walking Ability**	**Normal Work**	**Relation with Others**	**Sleep**	**Life Enjoyment**
Period between Irradiations (months)	0.409 $p = 0.008$	-0.460 $p = 0.002$	-0.540 $p < 0.001$	-352 $p = 0.024$	-0.303 $p = 0.054$	-0.349 $p = 0.025$	-0.477 $p = 0.002$	-0.501 $p = 0.001$	-0.501 $p = 0.001$
1st Irradiation Dose (gray)	Ns	Ns	Ns	Ns	Ns	Ns	Ns	Ns	Ns
2nd Irradiation Dose (gray)	Ns	Ns	Ns	Ns	Ns	Ns	Ns	Ns	Ns
Irradiation Region	Ns	Ns	Ns	Ns	Ns	Ns	Ns	Ns	Ns

* Adjusted for Age, Gender and Cancer type

Table 4: Association of Period between Irradiations (continuous variable) with the Improvement in Quality of Life

Period (months)	Beta	95 % CI	P value
Basic model	-0.191	-0.343, -0.038	0.015
Full model	-0.19	-0.343, -0.036	0.017

Values are standardized regression coefficients (95% confidence interval) and reflect the change in quality of life per unit increase (months) in the period between irradiations. Basic model is adjusted for age, gender, baseline quality of life, and dose of the first irradiation. Full model is additionally adjusted for age, gender, baseline quality of life, first irradiation dose, reirradiation dose, type of radiating machine, irradiation region and type of primary cancer.

4. Discussion

Our data demonstrated a significant improvement in quality of life and each of its domains can be predicted by longer periods before the reirradiation is needed, a figure that can help clinicians to predict quality of life outcomes in individual patients. Such an improvement of quality of life and pain goes in line with previous studies showing that reirradiation of bone metastasis patients not only resulted in reduction in pain and analgesic consumption but also led to superior quality of life scores and less functional interference (6,7). Also they support the results of the study by Choi et al. (8) whichreported that in patients with spinal metastasesrecurring in close proximity to previous irradiated area, an interval time less than 12 months, beteen two irradiations, was a significant predictor of local failure.Although the majority of our retreated patients (89%) had pain relief and improvement of all domains of QoL measuredby the Brief Pain Inventory Score, we should take into account that all of them took analgesics for the relief of pain and we did not calculate this which may have confounded the results andoverestimate the response to reirradiation. Anyway what we can say is that patients who had improvement of pain had also improvement of quality of life which correspond with the data in the literature (9,10).A study conducted by Zeng et al in 386 patients demonstrated that treatment region had no effect on response rate(4)which complies with the results of our study.While the study by Hird et al showed that primary tumor did not have any impact on response to treatment in patients with painful bone metastasis (11),another study by Westhoff et al demonstrated that patients with breast or prostate cancer had a better quality of life than patients with lung cancer. Also they showed that younger age, good performance status, absence of visceral metastases and using opioids were predictors for a pain response (5). However this study did not have enough discriminative power to predict which patients are likely to respond to radiation therapy. In our study primary tumor did not show to have any impact on QoL but we can say that it has also its limitations, as it included a limited number of patients and retreatment regimens reflected radiation oncologist decisions based on estimated Karnofsky performance score, life expectancy and treatment machine. In the future we hope to conduct studies with larger number of patients which can consolidate the results and provide clear conclusion. As reirradiation has the likelihood to overcome normal tissue tolerance, we paid special attention not to exceed constrains. It was more appropriate to sum the biologically effectivedoses (BEDs) from the initial and repeat treatment regimens in order to estimate the toxicity risk (12). No one of our retreated patients had side effect of more than G2 and did not developed myelopathy or neuropathy.

5. Conclusion

Longer period between reirradiations could be predictive of better quality of life after reirradiation. Meanwhile no other reirradiation feature showed an association with quality of life or its domains.

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