Original Research

ONCOLOGY

Survival and quality of life after whole brain radiotherapy with 3D conformal boost in the treatment of brain metastases

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Abstract

Background. Brain metastases are the most frequent intracranial neoplasms in adults. Although overall survival (OS) is an important endpoint in patients receiving radiotherapy, given their poor life expectancy in general, quality of life is becoming an increasingly useful endpoint. Objectives: to evaluate whole brain radiotherapy (WBRT) with 3D conformal boost in brain metastases patients with regard to OS and quality of life.

Methods. During April 2015-May 2017, a total of 35 patients with ≤5, previously untreated, inoperable brain metastases were included prospectively. All patients underwent WBRT followed by 3D conformal boost to the metastatic lesions. EORTC quality of life questionnaires QLQ-C30 and QLQ-BN20 were used at baseline and at end of treatment. The mean initial and final scores were compared using Student test. One-year OS with brain metastases was computed with Kaplan Maier method.

Results. Median survival with brain metastases was 4.43 months (0.73-78.53). The one-year OS for patients with one metastasis was 42% versus 15% for more than one ($p<0.04$). The presence of extracerebral metastases significantly decreased OS from 39% without extracerebral metastases to 19%. ($p<0.05$). Quality of life improved significantly in several functional domains: physical (48 vs 60.29), role functioning (28.1 vs 44.7), emotional (47.1 vs 80.2), global health status (40.9 vs 62.3). Symptom scores decreased significantly in most items, corresponding to an improvement in the symptom burden: headache (61.9 vs 0.9), nausea and vomiting (45.7 vs 7.1), visual disorder (26.3 vs 9.2), seizures (30.4 vs 0.9), motor dysfunction (46.6 vs 17.1). Symptom scores for fatigue and drowsiness increased significantly (51.1 vs 74.9, respectively 37.1 vs 70.4), indicating worsening of symptoms.

Conclusions. WBRT with 3D conformal boost is a feasible technique which improves quality of life in brain metastases patients. Since survival is limited, the assessment of quality of life is a good indicator of the treatment outcome.

Keywords: brain metastases, whole brain radiotherapy, 3D boost, survival, quality of life

Background

Brain metastases are the most frequent intracranial neoplasms in adults, with a frequency of occurrence varying between 10-15% of patients diagnosed with cancer. Most brain metastases are diagnosed in patients with lung, breast cancer and melanoma [1].

The management of brain metastases is complex and requires taking into account factors related to the patient (performance status, comorbidities), the primary tumor (local and distant control), but also to the intracerebral status of the disease. Hence, one choice of treatment is not the solution for all patients. Although there are multiple treatment options, in most cases the outcome is symptom palliation and an overall survival (OS) benefit [2]. A useful instrument for estimation of patient survival, with the purpose of better selecting candidates for available treatment modalities, is the recursive partitioning analysis (RPA) [3]. Class I patients, aged under 65, with a Karnofski performance status (KPS) over 70 and controlled primary tumor, with no extracerebral metastases (ECM), have the best prognosis. Class III includes patients with a KPS <70, who have the most reserved prognosis and class II includes the rest of the patients, with an intermediate prognosis.

For patients with multiple brain

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metastases or presenting with uncontrolled primary tumor or multiple extracerebral metastases, whole-brain radiotherapy (WBRT) is the treatment of choice, associated with corticosteroids as symptomatic treatment. Fractionation schedules are varied (30 Gy in 10 fractions, 20 Gy in 4 or 5 fractions), but none has proven superiority in terms of prolonging OS [4]. Still, it has been postulated that patients with a more favorable survival prognosis could benefit from a protracted radiotherapy (RT) regimen, whereas patients with a poorer prognosis should receive shorter course RT [5].

More aggressive treatments such as surgery or stereotactic radiosurgery (SRS) are reserved for patients with a good performance status, with limited number (<5) of brain metastases (oligometastatic disease) and an intracerebral tumor volume under 3 cm3. The addition of WBRT to localized treatment has been reported to improve OS and is the recommended approach in this patient category [6]. Other options for delivering a high radiation dose to the intracerebral tumor volume besides SRS are linac-based stereotactic techniques such as image-guided intensity modulated radiotherapy (IMRT) [7] or helical tomotherapy simultaneously integrated boost [8,9]. Although the above mentioned radiation techniques have proven to be effective, their general availability must be taken into account. Recent studies have outlined that for low to middle income countries, the standard radiation technique is 3D conformal radiotherapy (3DCRT), compared to high income countries where IMRT represents 50% of treatment techniques [10].

When analyzing different radiation regimens, common endpoints such as local control, progression free survival and OS are useful, but considering the overall poor prognosis of brain metastasis patients and their limited survival, an endpoint that becomes more frequently employed is the quality of life (QOL). QOL is an important endpoint in oncologic patients, especially useful when cure is no longer achievable. QOL analysis can aid physicians as well as patients together with family members to take informed decisions regarding treatment options [11]. One of the most commonly employed QOL evaluation instruments in oncologic patients is the EORTC (European Organization for Research and Treatment of Cancer) questionnaire QLQ-C30, version 3.0 [12]. Alongside it, the QLQ-BN20 module, initially designed for patients with primary intracranial tumors is currently being used for patients with brain metastases as well [13].

The purpose of this study is to evaluate the efficacy of WBRT with 3DCRT boost in oligometastatic patients with brain metastases, in terms of OS and QOL.

Material and methods

Patient characteristics

During April 2015- May 2017 we prospectively included consecutive patients over 18 years old, presenting with one to 5 previously untreated, inoperable brain metastases, regardless of the primary tumor.

For all patients included, brain metastases were identified on either contrast enhanced computed tomography (CT), or contrast enhanced magnetic resonance of the brain. All patients underwent CT simulation at which point they were immobilized with personalized thermoplastic masks.

WBRT was administered by two lateral opposed fields from a 6 MV linac. The prescribed doses were 30 Gy in 10 fractions, respectively 20 Gy in 5 fractions. RT boost to the metastatic lesions was administered by 3DCRT, sequentially, after the completion of WBRT, with total doses ranging from 8 Gy to 20 Gy and doses per fraction between 2 Gy and 4 Gy. The fractionation regimens for WBRT and boost were prescribed according to the patients' KPS, with higher total doses and lower doses per fraction for patients with better KPS and according to dose-volume histograms of organs at risk. Where multiple metastases were situated in proximity of each other, they were included in a single target volume. In cases where lesions were situated in different regions of the brain, separate target volumes were delineated and a boost plan was elaborated for each of them. For the statistical analysis of these heterogeneous regimens, total doses were normalized to 2 Gy and the biologically equivalent dose (BED) was calculated, with a α/β ratio of 3, for long term toxicities in brain tumors.

Demographic and basic tumor data recorded were age, sex, KPS, primary tumor, initial stage at diagnosis, presence of extracerebral metastases, date of diagnosis of brain metastases, number and volume of brain metastases.

Patients were included in the study after completion of the informed consent. The study was approved by the Ethics Committees of both Iuliu Haţieganu University of Medicine and Pharmacy, and "Prof. Dr. I. Chiricuţă" Oncology Institute, Cluj-Napoca.

Quality of life evaluation

The Romanian version of EORTC QLQ-C30 and QLQ-BN20 questionnaires was applied to patients at baseline and at the end of treatment.

The QLQ-C30 questionnaire has 30 items and it is used to evaluate a wide range of symptoms and endpoints in oncologic patients. It comprises 5 functional domains which investigate the social, cognitive, physical, emotional aspects, role functioning and the global health status. In addition, there are 3 symptom domains, 5 singular symptom items and an item investigating the financial difficulties. Each item receives a score from 1 to 4, 1 being "not at all", 2- "a little", 3- "quite a bit" and 4- "very much". The 2 questions from the global health status domain have scores from 1 ("very poor") to 7 ("excellent"). The QLQ-BN20 questionnaire contains 20 items, comprising 4 symptom domains and 7 singular symptom items.

For both questionnaires the raw scores were computed, after which the linear transformation was applied, according to the EORTC scoring manual [12]. On a scale from 0 to 100, a higher score on a symptom item

corresponds to worse symptoms, whereas in functional domains higher scores are favorable.

Statistical analysis

For comparisons regarding the QLQ-C30 and QLQ-BN20 questionnaires, the baseline and end-of-treatment median transformed scores were compared using Student's test. Overall survival was calculated with the Kaplan Maier method, considering the interval from the date of diagnosis of brain metastases until death or end of the study (July 30th 2017). Survival differences according to several variables were evaluated using the log-rank test. The statistical analysis was performed with the STATA package (2013, STATA Statistical Software 13 ed; Stata Corporation, College Station, Texas, USA). All tests were considered statistically significant for $p<0.05$.

Results

Patient and treatment characteristics

A total of 35 patients were included in the study, with clinical characteristics summarized in Table I. Median age at diagnosis of brain metastases was 60 years (range 41-80 years). Most patients (40%) had a KPS between 60 and 70 and only a third (34.28%) had a KPS over 80. The most frequent primary site was lung (42.86%), followed by breast (25.71%) and melanoma (11.43%). A single brain metastasis was present in most patients (45.71%), while the rest presented with 2 to 5 metastatic lesions. More than half of the patients (57.14%) had extracerebral metastases (ECM). Overall, 65.71% of the patients were in RPA class III, followed by 28.57% patients in class II and 5.71% in class I.

The majority of patients (88.57%) were prescribed 30 Gy in 10 fractions for the WBRT sequence and more than half (68.57%) received a boost of 12-18 Gy with 3 Gy fractions on the brain metastases. For 25.71% of patients the boost was administered with 4 Gy fractions and only 2 (5.71%) patients received the boost with 2 Gy fractions. The BED to the metastases ranged between 39.2 and 54 Gy in 48.57% of patients, and in 51.43% of patients it was between 54-60 Gy (Table II).

Survival analysis

The median follow-up of patients was 7 months, with a minimum of 2 months and a maximum of 34 months. At the end of the study period, 25 deaths were registered (71%).

The median survival with brain metastases was 4.43 months, ranging from 0.73 months to 78.53 months.

The one-year OS rates did not differ significantly between sexes: 44% for men versus 20% for women ($p=0.91$). The presence of two or more brain metastasis significantly decreased the one-year OS rate to 15%, versus a 42% rate in patients with only one brain metastasis. ($p<0.04$) (Figure 1). OS of patients with an intracerebral tumor volume under 5 cm3 was significantly higher compared to that of patients with over 5 cm3 tumoral

Table I. Baseline characteristics of patients.

Gender	n (%)
Female	19 (54.29)
Male	16 (45.71)
KPS	
80-100	12 (34.28)
60-70	14 (40)
20-50	9 (25.71)
RPA classification	
I	2 (5.71)
II	10 (28.57)
III	23 (65.71)
Primary tumor	
Lung	15 (42.86)
Breast	9 (25.71)
Melanoma	4 (11.43)
Gynecologic	3 (8.57)
Genitourinary	2 (5.71)
Colorectal	1 (2.86)
Initial stage of primary tumor	
I	2 (5.71)
II	7 (20)
III	10 (28.57)
IV	16 (45.71)
Local control of primary tumor	
Yes	15 (42.86)
No	20 (57.14)
ECM	
Yes	20 (57.14)
No	15 (42.86)
No of ECM sites	
1	10 (50)
2	7 (35)
3-4	3 (8.57)
Number of brain metastases	
1	16 (45.71)
2	12 (34.29)
3-5	5 (20)
Total patients	**35 (100%)**

KPS- Karnofski performance status, RPA- Recursive Partitioning Analysis, ECM- extracerebral metastases,

Table II. Treatment characteristics of patients

Fractionation of WBRT (Gy)	n (%)
10 X 3	31 (88.57)
5 X 4	6 (17.14)
Fractionation of 3DCRT (Gy)	**n %**
4-6 X 3	24 (68.57)
4-5 X 4	9 (25.71)
12-14 X 2	2 (5.71)
BED to the metastases (Gy)	**n %**
39.2-54	3 (48.57)
54-60	2 (51.43)
Total patients	**35 (100)**

WBRT- whole brain radiotherapy, 3DCRT- 3D conformal radiotherapy, BED- biologically equivalent dose

burden (32% vs. 22%, p=0.04) (Figure 2). Extracerebral metastases (ECM) also significantly decreased the one-year OS rates: compared to patients with only brain metastases, where the OS rate was 39%, patients with ECM had an OS rate of 19% (p<0.05) (Figure 3). The total dose delivered to the metastases did not significantly impact the one-year OS. There was no difference between OS rates in patients receiving a BED on the target volume between 39.2-54 Gy versus a BED between 54.2-60 Gy (p=0.98) (Figure 4).In our series, neither the KPS, nor the local control of the primary tumor had a significant influence on survival rates. Patients with KPS of 80-100 had an OS rate of 35% versus patients with KPS<70 where OS was 23% (p=0.83). Similarly, in patients where local control of the primary was achieved, the one-year OS was 22%, versus 31% in patients without local control (p=0.57).

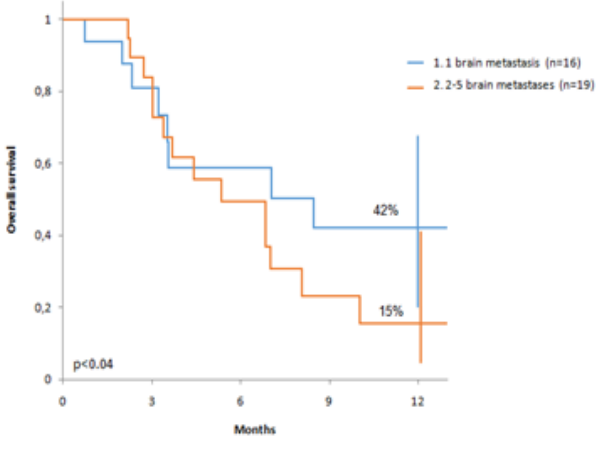

Figure 1. One-year overall survival rates according to the number of brain metastases.

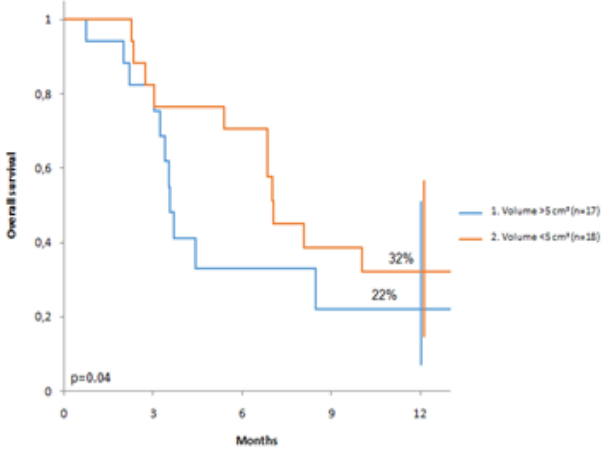

Figure 2. One-year overall survival rates according to the volume of brain metastases.

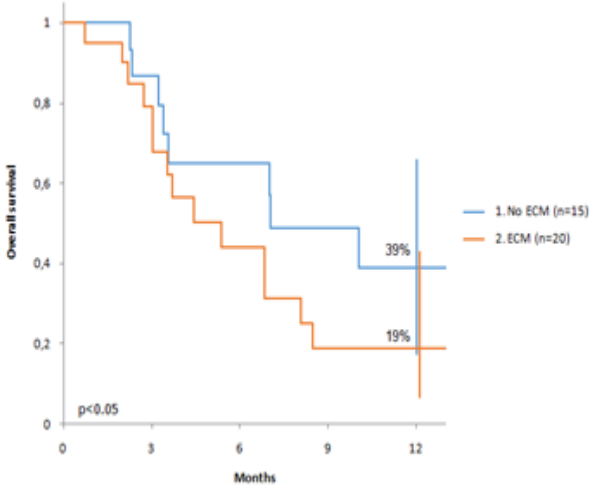

Figure 3. One-year overall survival rates according to the presence or absence of extracerebral metastases (ECM).

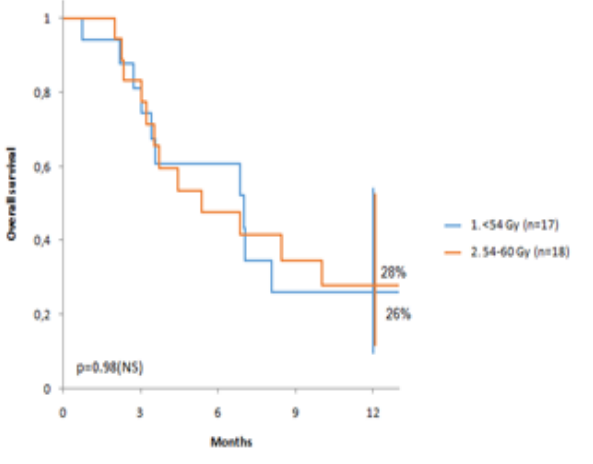

Figure 4. One-year overall survival rates according to the biologically equivalent dose delivered to the brain metastases.

Quality of life

QLQ-C30 questionnaire

In several functional domains of the QLQ-C30 questionnaire there was a significant improvement between baseline and end-of-treatment scores (Figure 5). A proportion of 37% of patients reported an improvement of their physical condition, with mean scores increasing significantly from 48 to 60.29 ($p<0.01$). There was a significant improvement of the emotional status from a mean score of 47.14 to 80.24 ($p<0.01$), reported by 80% of patients. Scores in the social domain also increased significantly between baseline and end of treatment from a mean of 28.1 to 44.76 ($p<0.01$). Overall, the global health status was improved in 82% of patients from a mean score of 40.95 at baseline, to 62.3 at the end of treatment ($p<0.01$).

Symptom scores had variable trends. Several scores decreased significantly, which corresponds to a symptomatic improvement. This was observed in the domains for pain, where mean scores dropped from 51.43 to 10.95 ($p<0.01$) and nausea-vomiting where mean scores decreased from 45.71 to 7.14 ($p<0.01$). On the other hand, in the fatigue domain there was a significant increase of the mean score, from 51.11 to 74.92 ($p<0.01$), which translates into a worsening of this symptom.

QLQ-BN20 questionnaire

Regarding the QLQ-BN20 questionnaire, we analyzed data from 3 symptom domains (future uncertainty, visual disorders and motor dysfunction) and 4 symptom items (headache, seizures, drowsiness, weakness of legs) (Figure 6). At the end of treatment, there were lower mean scores in the domains for future uncertainty (58.33 vs 20.71), motor dysfunction (46.67 vs 17.14) and visual disorders (26.35 vs 9.21), compared to baseline ($p<0.01$).

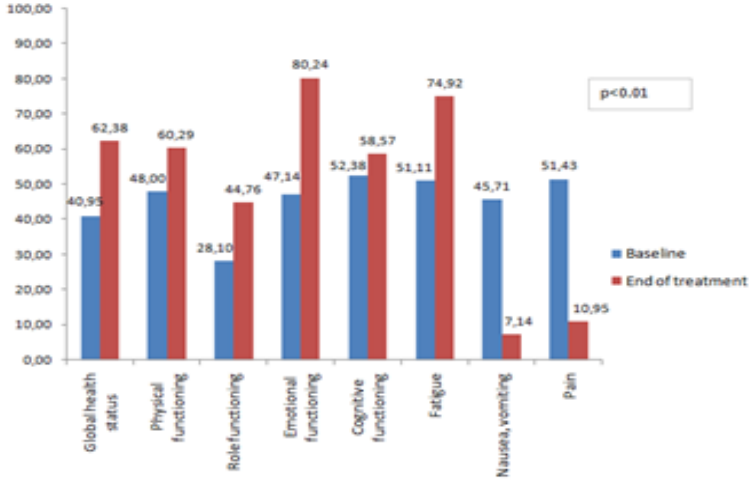

Figure 5. EORTC QLQ-C30 mean scores before and after radiotherapy. Higher scores in functioning/quality of life scales indicate better functioning and quality of life. Higher scores in symptom scales indicate worse symptomatology; all items were statistically significant.

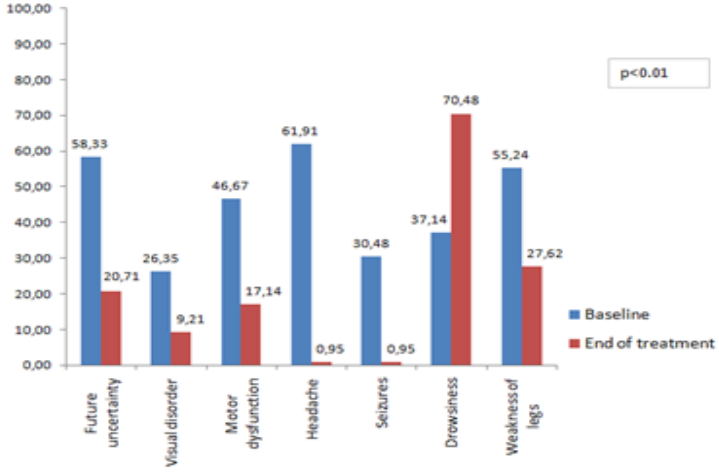

Figure 6. EORTC QLQ-BN20 mean scores before and after radiotherapy. Higher scores in all symptom scales indicate worse symptomatology; all items were statistically significant.

The symptom items where a significant decrease at the end of treatment was registered were: headache (61.91 vs 0.95), seizures (30.48 vs 0.95) and weakness of legs (55.24 vs 27.62) ($p<0.01$).

The mean score for drowsiness significantly increased from baseline until the end of treatment, from 37.14 to 70.48 ($p<0.01$).

Discussion

The prognosis of patients with brain metastases is reserved, with approximately one to 2 months median survival in the absence of treatment [14]. Non-randomized trials have suggested that WBRT increases survival to 3-6 months in these patients [4]. Although different fractionation schedules of WBRT do not influence survival [4,15], it appears that escalating the dose to the metastatic lesions increases intracerebral control as well as OS, compared to WBRT alone [16-18]. On the other hand, in oligometastatic patients, the use of WBRT has lately been put under question especially in patients with good prognosis, calling upon its late toxicities which might lead to neurocognitive impairment whilst not conferring a survival advantage [19-21]. In contrast, Aoyama et al published in 2015 the results of a secondary analysis of the Japanese Radiation Oncology Study Group trial comparing RSR+WBRT versus SRS alone in oligometastatic patients and concluded that the addition of WBRT significantly improved OS in patients with good prognosis, highlighting its role in this patient subset [22].

In our study, the median survival after WBRT with sequential 3D boost of the metastatic lesions was 4.43 months. Antoni et al reported in their series treated with the same technique a median survival of 5.9 months [23]. Rodrigues et al obtained the same median survival of 5.9 months after WBRT with arc-based simultaneously integrated boost [24]. However, an important aspect in our patient series is the distribution of cases in RPA classes. More than half of the patients were in RPA class III, which presents the poorest prognosis. In contrast, the above mentioned studies, as well the majority of studies recruit patients who are more frequently classified as RPA II or I [25], where median survival can be as high as 7-10 months [3]. Aside from selecting patients with better prognosis, trials of SRS or IMRT boost report high rates of intracerebral control, due to the technical advantages offered by these methods, which might translate into a survival benefit in selected patients. Another aspect known to influence survival in patients with brain metastasis is the number of lesions. Reportedly there are significant differences in survival between patients with a single brain metastasis, 2 to 3 lesions and more than 3 [26]. Our results are in accordance, indicating a statistically significant survival difference between patients with one metastasis versus patients with 2 or more. On the other hand, not only the number of metastases is important, but also the total volume of intracerebral lesions influences survival. The first studies that reported this aspect assessed the role of SRS after WBRT in oligometastatic patients [27]. In our study, a total tumor volume over 5 cm3 was shown to significantly decrease survival. The presence of ECM is one of the most agreed upon unfavorable prognostic factors for survival [23,28], with a proportion as high as 47% of patient deaths occurring from extracranial disease progression [24]. In our series, 57% of patients had ECM and the one year OS in this group was significantly lower than in patients without ECM.

Health is defined by the World Health Organization as "a state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity" [29]. In this respect, aspects pertaining to health-related quality of life of patients are increasingly important, especially when it comes to oncologic patients in advanced or metastatic stages, when cure is seldom achievable [30]. According to an American Society of Clinical Oncology working group, the most important endpoints to consider in the therapeutic management of oncologic patients should be survival and quality of life, over other endpoints such as response to treatment [31]. Most trials focusing on brain metastasis patients evaluated the efficacy of various treatment options through common endpoints such as survival, imagistic response rate, neurologic status or time to intracerebral recurrence [16,25,32]. A smaller number of trials focused on evaluating health-related quality of life in these patients [33] and their results are variable, partly because of the highly heterogeneous nature of this patient population [34]. In our study we employed the EORTC QLQ-C30 and QLQ-BN20 questionnaires at baseline and at the end of treatment. Although it is often difficult to establish the relevance of a single value of a certain score in determining a patient's quality of life [35], our results indicated a significant improvement of several symptom scores and functional domains after radiotherapy, described by a large proportion of the patients. For example, 80% of patients described an improved emotional status and 82% reported an improved global health status. This could be explained by the significant decrease from baseline of several symptom scores, such as headache, nausea and vomiting or seizures, which could have a strong impact on the overall health status and also the emotional status. Interestingly, this favorable trend of improvement was maintained despite the significant increase of the symptom scores for fatigue and drowsiness. Results reported in literature are variable. Several authors reported the same increase of scores for fatigue and drowsiness, which are more likely to be adverse reactions to radiotherapy [11,36-38]. On the other hand, in the domain of global health status, most authors observed a stationary aspect of the scores [36,39,40], whereas some reported significant decreases [38,41]. Studies where significant improvements in QOL were observed were more likely to include patients

with better prognostic factors for survival [42-44]. There are several reasons explaining the inconsistencies in QOL results between studies. First of all, only a few studies have QOL as primary endpoint [45]. Second, the multitude of questionnaires available for QOL assessment makes comparisons between results very difficult to interpret [46]. And last, data collection in patients with short life expectancy is difficult, leading to dropout bias, which can affect the final results [33].

The difference between our study and others investigating QOL is the timing of the second questionnaire. We applied the questionnaire at the end of treatment, as opposed to other authors who timed it at 2-3 months after radiotherapy, in which case, the impaired QOL could be attributed to either intracerebral disease progression, which can cause symptom worsening [47], or radiation related neurotoxicity, such as neurocognitive dysfunction [34]. Since neurocognition and QOL are correlated in patients with brain metastases receiving WBRT [48], one strategy to mitigate the neurotoxicity of WBRT is hippocampal avoidance [49]. The sparing of the hippocampal neural stem cell population from injury during WBRT contributes to memory preservation and in consequence helps maintain QOL [50,51].

To our knowledge, this is the first study performed in our country, which assesses quality of life by a standardized questionnaire in the brain metastases patient population. The strength of this study resides in the fact that the patient sample is representative of the brain metastases patient population from the point of view of QOL, since it includes patients with various primary tumors and all RPA prognostic categories. Moreover, we report a 100% compliance rate to the completion of questionnaires- during the study period there were no patients who refused to fill the questionnaires.

The main limitation of this study is the small sample size, which together with its heterogeneity has led to a lack of statistical significance for several results regarding survival. In addition, because of the timing of the second QOL questioning at the end of radiotherapy, QOL results should be cautiously interpreted. The difficulties encountered, which prevented us from applying the questionnaires at a longer interval of time from radiotherapy were of practical nature- most patients' places of residence were in other regions of the country, making it difficult to maintain contact in order to fill the lengthy QOL questionnaires.

In **conclusion**, WBRT with 3D conformal boost is a feasible technique which improves the QOL of patients with a reduced number of brain metastases, regardless of the fractionation regimen or the total dose administered to the metastatic lesions. Since OS of this patient population is limited, QOL assessment represents a good indicator of treatment efficacy. The superior OS rates of patients with a single metastatic lesion and smaller intracerebral tumor volumes suggests that this patient category might benefit the most from a boost dose in addition to WBRT.

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