



EFFECT OF WHOLE BRAIN RADIATION THERAPY ON SYMPTOM CONTROL AND QUALITY OF LIFE IN PATIENTS WITH MULTIPLE BRAIN METASTASES.

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ABSTRACT **Background:** Brain metastases are the most frequent intracranial neoplasms in adults. Given their poor life expectancy in general, quality of life and symptom improvement is becoming an increasingly useful endpoint.

Aim: To study the benefits of whole brain radiation therapy (WBRT) in decreasing the headache and other symptoms due to multiple brain metastasis and also analyse the improvement in quality of life thereafter.

Materials and methods: During March 2013 to December 2015, a total of 64 patients, previously untreated, inoperable brain metastases were included in the study. This study was a retrospective analysis of prospectively maintained data. All patients underwent WBRT with Co-60 or 6MV Photons. EORTC quality of life questionnaires QLQ-C30 and QLQ-BN20 were used at baseline and at end of treatment. The patient details and questionnaires were accessed from the patient records. The mean initial and final scores were compared using Student test.

Results: Quality of life improved significantly in several functional domains: physical (53 vs 65), role functioning (33 vs 49), emotional (52 vs 85), global health status (45 vs 67). Symptom scores decreased significantly in most items, corresponding to an improvement in the symptom burden: headache (66 vs 5), nausea and vomiting (50 vs 12), visual disorder (31 vs 14), seizures (35 vs 5), motor dysfunction (51 vs 22). Symptom scores for fatigue and drowsiness increased significantly (56 vs 79, respectively 42 vs 75), indicating worsening of symptoms.

Conclusions: WBRT 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, headache, quality of life

INTRODUCTION:

Brain metastases are a common problem in cancer care, occurring in 10 to 30 percent of adult patients[1]. The apparent incidence of brain metastases is increasing as diagnostic tools are refined and advances in systemic therapy that improve survival may also be leading to an actual increase[2,3]. The development of brain metastases may have substantial prognostic implications by causing neurologic symptoms or death.

Brain metastases occur with a variety of cancers, which may have different subtypes or molecular profiles that respond differently to treatment[3]. Primary tumors that most commonly metastasize to the brain are lung cancer (30–60% of all brain metastases), breast cancer (5–30% of brain metastases in women), and melanoma (5–21%); this systematic review will focus on these primary cancer types.

Treatment options for brain metastases include whole brain radiation therapy (WBRT), stereotactic radiosurgery (SRS), conventional surgery, and systemic therapies. WBRT is administered to the entire brain, typically over multiple treatments (although hippocampal-avoidance WBRT is more selective regarding the dose for different areas of the brain). SRS is a treatment option that delivers precisely-targeted radiation to the brain metastases. Finally, for some patients with a very poor prognosis, supportive care alone may be appropriate.[4]

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). 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 [5]. 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 [6]

Material and methods:

During March 2013 to December 2015, a total of 64 patients, previously untreated, inoperable brain metastases treated at our institute were included in the study. This study was a retrospective analysis of prospectively maintained data. All patients underwent WBRT with Co-60 or 6MV Photons. EORTC quality of life questionnaires QLQ-C30 and QLQ-BN20 were used at baseline and at end of treatment. The patient details and questionnaires were accessed from the patient records. The mean initial and final scores were

compared using Student test.

At diagnosis of brain metastasis, the follow variables were analyzed : age, sex, number of brain metastasis, primary tumor type, and extent of disease, initial ECOG score, dose and fractionation radiotherapy schedule. The supportive care (oral or parenteral steroids) and neurological status and head ache (pain score on Numeric Rating scale) was also evaluated. Brain metastases were detected by contrast-enhanced cerebral computed tomography (CECT) or magnetic resonance imaging (MRI). WBRT was performed in all patients with cobalt 60 gamma rays or with 6 MV photons of a linear accelerator. The whole brain was irradiated by usual bilateral fields that encompassed the cranium with a 1 cm margin. The total dose was 30Gy in 10 fractions with daily fractions of 3.0 Gy, five fractions per week. The supportive care (oral or parenteral steroids) was introduced in beginning of treatment or during radiotherapy. Symptom assessment was done on weekly basis.

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. 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. For comparing averages between the groups the student's Independent 't' test was used. If the number of mean categories is more than two ANOVA (analysis of variance) was carried out to compare the averages.

Results:

Patient characteristics

A total of 64 patients were included in the study, with clinical characteristics summarized in Table I.

Table 1: Patient Characteristics

Median age at diagnosis	65 years
Gender	
Male	22(34%)
Female	42(65%)
KPS	
80-100	25(39%)
60-70	11(17%)
20-50	28(43%)
Primary	
Breast	42.86%
Lung	25.71%
Number of brain lesions	
Solitary	40.71%
Multiple	59.29%

Quality of life**(i)QLQ-C30 questionnaire (Table 2)**

In several functional domains of the QLQ-C30 questionnaire there was a significant improvement between baseline and end-of-treatment score. A proportion of 42% of patients reported an improvement of their physical condition, with mean scores increasing significantly from 53 to 65 ($p<0.01$). There was a significant improvement of the emotional status from a mean score of 52 to 85 ($p<0.01$), reported by 80% of patients. Scores in the social domain also increased significantly between baseline and end of treatment from a mean of 32 to 49 ($p<0.01$). Overall, the global health status was improved in 82% of patients from a mean score of 45 at baseline, to 67 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 56 to 15 ($p<0.01$) and nausea-vomiting where mean scores decreased from 50 to 12 ($p<0.01$). On the other hand, in the fatigue domain there was a significant increase of the mean score, from 56 to 79 ($p<0.01$), which translates into a worsening of this symptom.

Table 2: Symptoms score on QLQ – questionnaire

	Beginning	End
Physical condition	53	65
Emotional status	52	85
Social domain	32	49
Global health status	45	67
Pain	56	15
Nausea – vomiting	50	12
Fatigue	56	79

(ii)QLQ-BN20 questionnaire (Table 3)

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). At the end of treatment, there were lower mean scores in the domains for future uncertainty (63 vs 25), motor dysfunction (51 vs 22) and visual disorders (31 vs 14), compared to baseline ($p<0.01$). The symptom items where a significant decrease at the end of treatment was registered were: headache (66 vs 5), seizures (35 vs 5) and weakness of legs (60 vs 32) ($p<0.01$). The mean score for drowsiness significantly increased from baseline until the end of treatment, from 42 to 75 ($p<0.01$).

Table 3: Symptoms score on QLQ-BN20 questionnaire

	Beginning	End
Headache	66	5
Motor dysfunction	51	22
Seizures	35	5
Weakness of legs	60	32
Drowsiness	42	75
Visual disorders	31	14
Future uncertainty	63	25

DISCUSSION:

Metastatic brain lesions cause symptoms like headache ,vomiting, seizures and rapid deterioration of performance status. The prognosis

of patients with brain metastases is reserved, with approximately one to two months median survival in the absence of treatment . Non-randomized trials have suggested that WBRT increases survival to 3–6 months in these patients. [7].

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 . 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 [8].

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 , 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 [9] 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 , or radiation related neurotoxicity, such as neurocognitive dysfunction .

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. 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.

CONCLUSION

WBRT is a feasible technique which improves the QOL of patients with a reduced number of brain metastases Since OS of this patient population is limited, QOL assessment represents a good indicator of treatment efficacy. The improvement in major symptoms like headache and vomiting QOL .

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