

# Is Whole-Brain Radiotherapy Effective and Safe in Elderly Patients with Brain Metastases?

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## Key Words

Brain metastases · Whole-brain radiotherapy

## Abstract

**Objective:** The outcome of whole-brain radiotherapy in elderly patients with brain metastases is not well documented. As the number of such patients is expected to increase, we evaluated our results. **Methods:** Seventeen patients aged 75–82 years were identified for this retrospective analysis. The majority received 30 Gy in 10 fractions plus steroids (without other local or systemic measures). The median Karnofsky performance score (KPS) was 70. **Results:** Symptomatic improvement was observed in 53%. Median survival of the responding patients was 4.5 months. However, median survival of the non-responding patients was 1.4 months only. All patients that survived for more than 4 months had a KPS  $\geq 70$  and metachronous brain metastases. None of the patients with KPS  $< 70$  survived for more than 2.2 months. None of the patients developed severe acute toxicity. One patient developed severe late neurotoxicity. **Conclusions:** Most elderly patients with brain metastases have an unfavourable prognosis. However, as in other populations, assessment of KPS and few other factors might guide the choice of treatment. Radiation therapy might lead to symptomatic responses in approximately half of the patients, but

long-term survivors appear at risk of neurotoxicity. As promising results were published from a retrospective radiosurgery series, prospective trials appear warranted.

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Despite many recent advances in cancer treatment, development of brain metastases continues to represent a significant clinical problem [1]. Related to the general demographic trends in the Western countries, an increasing number of elderly patients with brain metastases might require treatment, although the incidence is higher in those under 65 years of age [2]. Advanced age ( $\geq 65$  years) was shown to represent an adverse prognostic factor in the large analysis that led to development of the recursive partitioning analysis (RPA) classes in irradiated patients [3]. Overall, 200 patients in this age group were included and 156 of them were older than 70 years. Even within the group of patients with a Karnofsky performance score (KPS)  $\geq 70$ , median overall survival in those aged 65 years or higher was limited to 4 months (compared with 6 months in younger patients). Several groups have shown that patients aged 70 years or higher even had a median survival time of less than 3 months [4, 5]. In addition, various types of comorbidity and a reduced tissue regeneration capacity might influence the

**Table 1.** Overview of patient characteristics and results

Pa-tient	Sex	Age years	Primary tumour	Interval <sup>1</sup> months	Number of brain metastases	Diameter of brain metastases, cm	KPS	Extra-cranial metastases	Dexamethasone dose before WBRT, mg	WBRT regimen Gy	Clinical response	Survival months
1	male	76	NSCLC	14	3	up to 3.0	90	no	20–30	30/3	CR	21.1
2	male	77	NSCLC	8	1	2.0	70	no	20–30	30/3	PR	9.2
3	male	78	NSCLC	8	3	up to 4.0	80	no	20–30	40/2	PR	6.0
4	male	75	NSCLC	3	3	up to 1.2	70	no	10–20	30/3	PR	4.5
5	male	82	melanoma	104	2	2.4–1.1	70	yes	20–30	30/3	PR	6.4
6	male	77	bladder	67	1	3.0	80	yes	10–20	40/2	CR	4.4
7	male	80	NSCLC	0	12	up to 1.7	70	no	20–30	40/2	PR	1.8
8	male	77	NSCLC	0	6	up to 1.5	50	no	10–20	30/3	PR	2.2
9	male	75	NSCLC	0	4	up to 2.5	60	no	10–20	30/3	PR	1.2
10	male	78	NSCLC	0	5	up to 1.0	70	no	20–30	30/3	none	2.2
11	male	76	bladder	37	4	up to 2.8	50	yes	20–30	30/3	none	1.6
12	male	76	NSCLC	19	3	up to 2.5	50	yes	10–20	30/3	none	1.3
13	male	76	NSCLC	3	8	up to 1.5	70	yes	10–20	30/3	none	0.6
14	female	77	NSCLC	0	7	up to 2.2	70	yes	10–20	30/3	none	1.4
15	female	75	SCLC	0	2	2.0–1.0	50	no	up to 10	30/3	none	1.2
16	female	77	SCLC	0	2	1.0–1.0	60	no	10–20	30/3	none	1.0
17	male	77	SCLC	0	2	2.7–1.5	50	yes	10–20	24/2	none	0.5

<sup>1</sup> From primary tumour diagnosis to brain metastases. NSCLC = Non-small cell lung cancer; CR = complete response; PR = partial response; SCLC = small cell lung cancer.

tolerance to treatment [6]. Based on these considerations, the question arises whether whole-brain radiotherapy (WBRT) represents a useful routine treatment option in all age groups. As detailed data from patients aged 75 years or higher are very scarce, we decided to evaluate our experience with WBRT in this particular subset.

### Patients and Methods

We retrospectively analysed all patients  $\geq 75$  years of age treated with WBRT as the sole treatment modality for brain metastases from solid tumours. They were identified from the hospital databases. WBRT was administered via standard lateral opposed 6-MV beams from a linear accelerator with 5 fractions per week and use of a thermoplastic mask fixation of the head. The dose was prescribed to the midline. A baseline clinical examination was performed within 1 week before the start of WBRT. Follow-up took place every 3 months and included contrast-enhanced computed tomography.

### Results

Seventeen patients  $\geq 75$  years of age received WBRT for brain metastases (maximum age 82 years). Their data are shown in table 1. All were clinically symptomatic and

treated with dexamethasone in addition to WBRT. None of the patients received systemic therapy after diagnosis of brain metastases. None of the lesions were treated by surgical resection or radiosurgery. Most patients had primary lung cancer and many of them had brain metastases already at first diagnosis. The median number of lesions was 3. The median KPS was 70 (range 50–90). We used 10 fractions of 3 Gy in most patients, but some treated before the year 2000 received 20 fractions of 2 Gy because it was believed that the risk of neurotoxicity would be lower with this more protracted regimen. In the light of the limited survival time, 2-Gy fractions were no longer used in recent years. One patient (from the 40-Gy group, patient No. 17) was not able to complete WBRT due to rapid systemic progression.

Based on physician assessments, 9 of 17 patients (53%) had improved symptoms after WBRT plus dexamethasone and were able to reduce their dexamethasone dose. Six of these had computed tomography follow-up, which confirmed regression of the lesions, while the other 3 died early from their untreated, progressive primary lung cancer. Median survival of the responding patients was 4.5 months. However, median survival of the non-responding patients was 1.4 months only. All patients that survived for more than 4 months had a KPS  $\geq 70$  and

metachronous brain metastases. All patients with small cell lung cancer died very rapidly. None of the patients developed severe acute toxicity requiring a treatment break. One patient (No. 1, with the longest survival time) developed severe late neurotoxicity resulting in permanent loss of functional independence. Other reasons for this deterioration, e.g. leptomeningeal spread, could be excluded.

## Discussion

The present retrospective analysis confirms earlier reports that suggested an unfavourable prognosis in elderly patients with brain metastases [3–5]. Lutterbach et al. [7] reported that the worse prognosis for older patients with brain metastases was not determined by age-related differences in access to health care or state-of-the-art therapy. Our data show that the 4 patients that would belong to RPA class I, if the age criterion is disregarded (patients No. 1–4), survived for 4.5–21.1 months. Therefore, a combination of KPS  $\geq$ 70, controlled primary tumour and absence of extracranial metastases might identify patients with better prognosis. In addition, patients in RPA class II had a better outcome if they had metachronous brain metastases. A clinical benefit from WBRT was seen in approximately half of the patients, but some of these had very short survival times and might have been adequately treated with steroids alone. None of the patients with KPS <70 (RPA class III) survived for more than 2.2 months. The patient with the longest survival time developed permanent neurotoxicity, which could not be linked to any other type of cancer treatment or comorbidity. Acute toxicity was unremarkable and the only patient that failed to complete WBRT had rapidly progressing small cell lung cancer. The latter type of disease was associated with a remarkably poor outcome in this study, although the number of patients is very small. A recent prospective trial confirmed that acute toxicity of WBRT

(37.5 Gy in 2.5-Gy fractions) in the subgroup of patients over 70 years is limited (grade I in 32% and grade II in 30%) [8]. Unfortunately, no other results were reported for this subgroup. The same holds true for 2 other randomised trials, which included patients with up to 78 years of age treated with WBRT plus radiosurgery or surgical resection [9, 10].

What alternatives to WBRT might exist for the group of elderly patients in whom best supportive care appears not to be appropriate? Noel et al. [11] reported on 117 patients aged 65–86 years treated with radiosurgery (22 were  $\geq$ 75 years old). Some of them (32%) received additional WBRT, usually as first-line treatment followed by salvage radiosurgery. The majority of patients had lung cancer. Median KPS was 80, and 40% had controlled systemic disease. Median survival was 8 months. Local control was over 90%. Symptomatic response was achieved in 61% (complete in 20%). Within this age group, age was not correlated with survival. A low KPS was associated with unfavourable prognosis. No detailed data on quality of life are available. When searching the literature, no prospective trials of radiotherapy in elderly patients with brain metastases were identified.

## Conclusions

Elderly patients with brain metastases should not be denied treatment on the basis of age. As in other populations, KPS and extracranial disease extent might guide the choice of treatment. Radiation therapy might lead to symptomatic responses in 50–60% of patients, but long-term survivors appear at risk of WBRT-associated neurotoxicity. The high local control rate makes radiosurgery an attractive option in patients with a limited number of metastases. Prospective studies on treatment effects and quality of life in this patient subgroup appear warranted.

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