Whole-Brain Radiotherapy Combined with Surgery or Stereotactic Radiotherapy in Patients with Brain Oligometastases

Long-Term Analysis

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Objective: To verify whether the treatment of brain oligometastases with whole-brain radiotherapy (WBRT) plus stereotactic radiotherapy (SRT) or surgical resection results in different outcomes.
Methods: Files of patients affected by brain metastases submitted to surgical resection followed by WBRT (group A) or WBRT + SRT (group B) were retrospectively selected for this study. The two treatment groups were matched for the following potential prognostic factors: WBRT schedule, age, gender, performance status, tumor type, number of brain metastases, extracerebral metastases, and recursive partitioning analysis class (RPA). The outcomes of patients in both groups were evaluated in terms of toxicity, local control, and overall survival.
Results: Total of 97 patients were selected (56 male; 42 female) who were respectively submitted to surgical resection followed by WBRT (group A, n = 50 patients) or WBRT + SRT (Group B, n = 47 patients). Median follow-up was 95 months (range, 8–171 months). The 1-year local control rates were 46.0% and 69.0% respectively. No significant difference in local tumor control was observed between group A and B (p = 0.10). Median overall survival was 15 and 19 months in group A and B, respectively. One-year survival was 56.0% and 62%, respectively. No difference was observed in the two groups (p = 0.40).
Conclusion: Surgery remains the main therapeutic approach in symptomatic patients; nevertheless, our data support the use of WBRT plus SRT in one or two brain metastases smaller than 3 cm.

Key words: **Brain metastases · Oligometastases · Stereotactic radiotherapy · Surgery · Whole-brain radiotherapy**

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Ganzhirnbestrahlung kombiniert mit operativer Entfernung oder stereotaktischer Strahlenbehandlung bei Patienten mit Oligohirnmetastasen: Eine Langzeitstudie

Zielsetzung: Zu untersuchen, ob die Behandlung von Oligohirnmetastasen mit Ganzhirnbestrahlung (whole-brain radiotherapy, WBRT) plus stereotaktischer Radiotherapie (SRT) oder chirurgischer Resektion unterschiedliche Ergebnisse bringt.
Methoden: Krankenakten von Patienten mit operativ entfernten Hirnmetastasen und anschließender WBRT (Gruppe A) oder WBRT + SRT (Gruppe B) wurden retrospektiv für diese Studie ausgewählt. Die zwei Beghandlungsarme wurden für folgende prognostische Parameter gematcht: WBRT-Schema. Alter, Geschlecht, Allgemeinzustand, Art des Primärtumors, Anzahl der Hirnmetastasen, extrazerebrale Metastasen, Recursive-Partioning-Analysis-(RPA-)Klasse. Das Behandlungsergebnis für beide Patientengruppen wurde im Hinblick auf Toxizität, lokale Tumorkontrolle und Gesamtüberleben bewertet.
Ergebnisse: Insgesamt wurden 97 Patienten ausgewählt (56 m; 42 w), die entweder mit operativer Entfernung und anschließender WBRT (Gruppe A, n = 50 Pat.) oder mit WBRT + SRT (Gruppe B, n = 47 Pat.) behandelt wurden. Die mediane Beobachtungszeit betrug 95 Monate (Spanne 8–171). Die lokale Tumorkontrolle nach 1 Jahr betrug 46,0% (Gruppe A) und 69,0% (Gruppe B), ohne dass dieser Unterschied statistisch signifikant wäre (p = 0,10). Das mediane Gesamtüberleben betrug jeweils 15 und 19 Monate in Gruppe A and B. Die 1-Jahres-Überlebensrate betrug jeweils 56,0% and 62%. Es wurde kein Unterschied zwischen den beiden Gruppen gefunden (p = 0,40).

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Schlussfolgerung: Die chirurgische Entfernung bleibt die Behandlungsoption bei symptomatischen Patienten. Unsere Daten sprechen für eine Behandlung mit WBRT plus SRT bei Vorliegen von ein oder zwei Hirnmetastasen, die kleiner als 3 cm sind.

Schlüsselwörter: **Hirnmetastasen · Oligometastasen · Stereotaktische Radiotherapie · Operation · Ganzhirnbestrahlung**

Introduction

Metastatic brain tumors are the most common intracranial neoplasm in adults, and although the exact incidence is unknown, it has been estimated to be as high as 200,000 cases per year [9]. Population-based data suggest that 8–10% of adult cancer patients develop brain metastases during their lives [4, 11, 27], even if the absolute frequency of metastatic carcinoma to the brain is thought to be increasing as cancer patients live longer because of earlier diagnosis and more effective treatments regimens [21].

The prognosis for most patients with brain metastases is poor and their life expectancy is measured in months [24, 29, 32]. Whole-brain radiotherapy (WBRT) represents the most common, palliative treatment. Patients with 1–3 brain metastases and controlled extracranial disease seem to have a slightly better prognosis. Therefore, a more aggressive approach to these cases appears to be justified such as surgical resection of metastases or stereotactic radiosurgery with or without additional WBRT [3, 5, 8, 9, 13, 14, 16, 20, 25, 28].

However, no randomized studies have yet compared stereotactic radiotherapy (SRT) to surgical resection and no definitive conclusions were reached regarding which of these treatments offers the best results in terms of patient safety and outcome.

At our institution, patients with extracranial controlled disease and < 3 metastases are usually referred to a surgeon if they present neurological symptoms or lesions with diameter > 3 cm, while, in the case of any contraindication to surgery or asymptomatic disease and lesion diameter < 3 cm, patients are treated with WBRT followed by a stereotactic boost to the residual tumor. In this analysis, we aimed to verify in a series of cases with the above mentioned disease presentation and treated in the last decade whether treatment of brain oligometastases with WBRT plus SRT would offer different outcome when compared with surgical resection plus WBRT.

Methods

Patients affected by brain metastases of any primary tumor, and treated at our institution with either resection of metastases plus WBRT (group A) or WBRT plus SBRT (group B), were retrospectively analyzed. Further inclusion criteria were the following: no prior radiotherapy or surgery to the brain, less than 3 brain metastases, diameter ≤ 3 cm for group B, confirmed by magnetic resonance imaging (MRI), controlled primary tumor, absent or controlled extracranial metastases, and RPA [10] class 1–2.

Patient immobilization was obtained using a thermoplastic mask during WBRT, while a noninvasive stereotactic relocatable immobilization system (3D-line srl) was used during the stereotactic phase. Image fusion with the MRI scan was performed to contour brain lesions in the stereotactic plan. Treatment planning was carried out with the Eclipse (Varian) for the WBRT phase and with TPS Ergo (3D- Line Medical System) for stereotactic treatment. Two opposite laterolateral fields were used during WBRT, while noncoplanar arc beams were used during the stereotactic phase. The dose was prescribed to the isocenter with the 95% isodose encompassing the whole brain and 80% isodose encompassing the entire GTV for SBRT.

A 6 mV photon beam delivered by a LINAC was used in both phases. In patients of group A, the median total dose was 3,000 cGy (range, 3,000–4,000 cGy), while in patients of group, WBRT was administered with a median total dose of 3,750 cGy (range, 3,000–4,000 cGy) with a median daily dose of 250 cGy (range, 200–300 cGy). Stereotactic boost delivered a total dose of 2,000 cGy in a single or in four fractions. Data regarding baseline characteristics and follow-up were obtained from patient files.

The following potential prognostic factors were evaluated: age, sex, primary tumor type (lung cancer, breast cancer, rectal cancer, other tumors), number and size of lesions, and RPA class. Only recursive partitioning analysis (RPA) class 1 and 2 patients were included in the present study because patients with poor performance status (RPA class 3) are usually not offered SBRT or surgery.

After treatment, patients were evaluated 1 month after treatment by MRI and then quarterly. Toxicity was evaluated according to NCI Common Toxicity Criteria v 2.0. Statistical analysis was performed by MedCalc (www.medcalc.be). The student t-test was used to verify the absence of statistically significant differences in the distributions of prognostic factors between the two groups.

Local control rates and overall survival were calculated using the Kaplan–Meier method [12]. The Cox proportional hazards regression model was used to analyze the effect of covariates on survival.

Results

We retrospectively evaluated 651 files relative to patients submitted to WBRT for brain metastases from January, 1997 to March, 2010, at our institution. Among them, 97 cases were selected (56 males; 42 females) who were respectively submitted to surgical resection before WBRT (group A, n = 50 patients) or SRT after WBRT (group B, n = 47 patients).

Patient characteristics of the entire cohort are summarized in Tables 1 and 2. No statistical difference was found between the two groups in terms of age, histology, number of brain metastasis, and RPA class. The median number of brain metastases was 1 (range, 1–2) and median age of the patients was 58 years

Table 1. Patient characteristics. SRT: stereotactic radiosurgery, FSRT: fractionated stereotactic radiosurgery.

Tabelle 1. Patientencharakteristika. SRT: stereotaktische Strahlentherapie, FSRT: fraktionierte stereotaktische Strahlentherapie.

Characteristics	Total	Group A	Group B	p
Patients, n	97	50	47	
Age, years	58	59	57	NS
RPA class				
1	69	33	36	NS
2	28	17	11	
Fractionation				
SRT	17	0	17	
FSRT	30	0	30	

Table 2. Tumor characteristics.

Tabelle 2. Tumorcharakteristika.

Characteristics	Total	Group A	Group B	p
Primary tumor				
Lung cancer	61	29	32	
Breast cancer	17	7	10	NS
Rectal cancer	7	6	1	
Others	12	8	4	
No brain metastases	1: 83	1: 46	1: 37	NS
	2: 14	2: 4	2: 10	

(range, 37–81 years). All patients submitted to surgery were found without residual tumor at postoperative MRI. Among the patients submitted to SRT (group B), 17 cases, selected on the basis of the site of their single metastasis with respect to brain critical structures, received radiosurgery (SRS, median dose 15 Gy; range, 15–20 Gy).

Toxicity

Grade ≥ 3 acute toxicities, such as headache, hearing problems, nausea, and vomiting did not occur in treated patients. As far as the late toxicity is concerned only 1 patient (group B) revealed radionecrosis, radiologically demonstrated and appeared 6 months after the completion of radiotherapy. Only 1 patient with local relapse presented a neurocognitive deficit (memory loss) 7 years after treatment.

Survival

Median follow-up was 95 months (range, 8–171 months) in all patients. The median local control (LC) for the entire cohort was 16 months. No statistically significant difference was found among patients treated by WBRT + SBRT (18 months) with respect to those treated by surgery + WBRT (11 months; p = 0.10; Figure 1). The 1- and 5-year LC rates were 46.0% and 41.4%, respectively, in group A, and 69.0% and 32.0%, respectively, in group B.

Median survival time was 17 months for the entire cohort, 15 months for patients treated with surgery + WBRT, and 19 months for those patients treated with WBRT + SRT. The 1-year, 3-year, and 5-year survival were 56.0%, 29.0%, and 13.0%, respectively, in group A, and 62.0%, 25.1%, and 9.4%, respectively, in group B. Neither treatment proved to significantly impact OS (p = 0.40; Figure 2). Cox proportional hazard regression showed that survival was not significantly associated with the primary tumor (p = 0.49) and RPA class (p = 0.31).

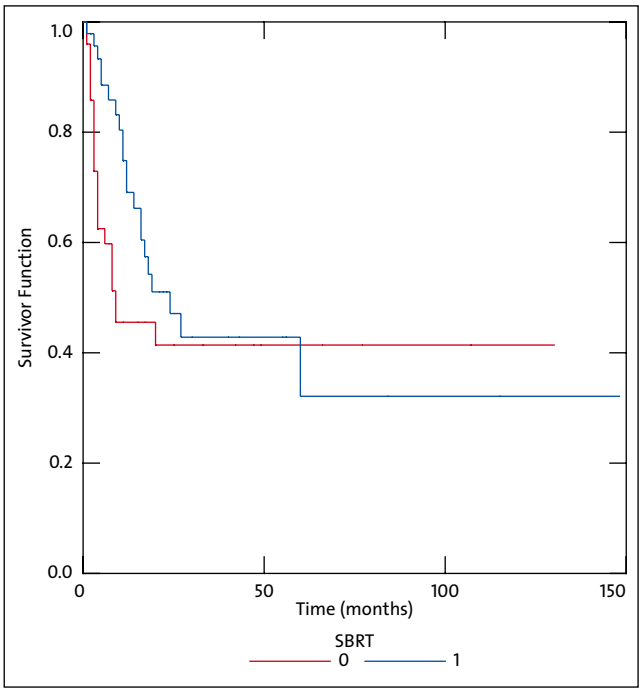

Figure 1. Local control in group A (red line) compared to local control of patients in group B (blue line) over time (months). See text for details.

Abbildung 1. Lokale Tumorkontrolle in Gruppe A (rote Linie) verglichen mit der lokalen Tumorkontrolle der Patienten in Gruppe B (blaue Linie) im zeitlichen Verlauf (Monate). Einzelheiten s. Text.

Discussion

Patients with brain metastases generally have a poor prognosis and WBRT is the most common treatment modality. Recent studies [3, 28] have demonstrated that life expectancy of these patients is influenced not only by the number of brain lesions, but also by several factors, such as the number of extracranial metastases, the patient's age, Karnofsky Performance Scale (KPS), and the status of primary disease. Therefore, patients who have a limited number of lesions and a controlled extracranial disease could benefit from more aggressive treatments, including surgery or SBRT. In fact, these therapeutic approaches represent, together with WBRT, the standard treatment of 1–3 brain metastases [18].

A meta-analysis of randomized trials on adult cancer patients with single or multiple brain metastases from cancer of any histology was published in 2005 to investigate the role of radiotherapy in the management of brain metastases [30]. Among the 27 trials included in this review of the evidence, pooled results from three randomized trials of surgical exci-

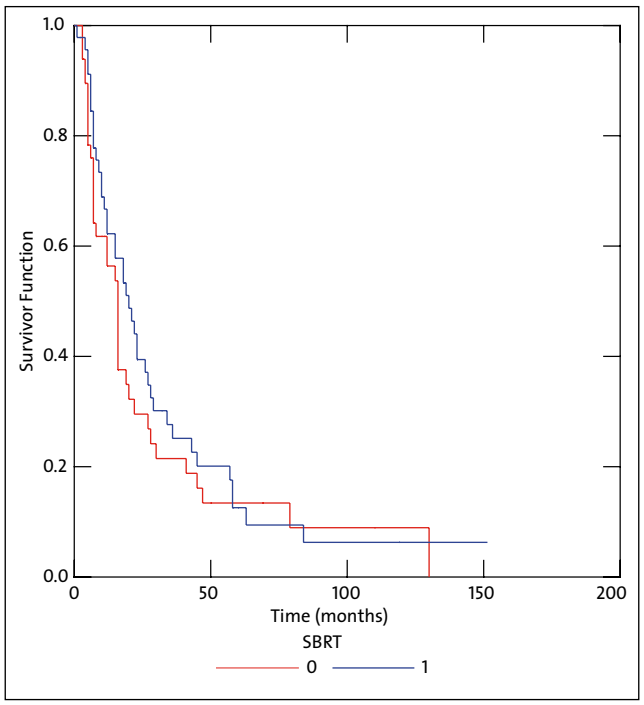

Figure 2. Mean survival in group A (red line) compared to the survival in group B (blue line) over time (months). See text for details.

Abbildung 2. Mittleres Überleben in Gruppe A (rote Linie) verglichen mit dem Überleben der Patienten in Gruppe B (blaue Linie) im zeitlichen Verlauf (Monate). Einzelheiten s. Text.

sion combined with WBRT showed no improvement in overall survival as compared to WBRT alone in patients with single brain metastasis [17, 23, 31]. A prospective trial including patients who underwent gross resection of a single brain metastasis indicated that there was an improvement in local control for patients who received postoperative WBRT without any significant difference in overall survival [22]. Three randomized studies have directly examined whether the addition of SRS to WBRT provides therapeutic benefit over WBRT alone [1, 6, 15]. These studies suggested that better brain control was achieved with the combined approach than with WBRT alone, although no significant difference was observed in terms of median overall survival.

The meta-analysis by Tsao et al. [30] did not include two retrospective studies comparing treatments more similar to the therapeutic approaches given to patients in our series. In particular Schoggl et al. [26] compared 67 patients who were treated with SRS and 66 who were treated with microsurgery. The median survival was 12 months after SRS and 9 months after microsurgery. This difference was not statistically significant ($p = 0.19$); in SRT cases, local tumor control was better than in the microsurgery group ($p < 0.005$). O'Neill et al. [20] reported no significant difference ($p = 0.15$) in overall survival between 74 patients treated by neurosurgery and 23 patients treated with SRS and none of the SRS group had local recurrence compared to 19 patients of the neurosurgical group.

Unlike the majority of published studies, our data compare patients undergone surgery plus WBRT to patients submitted to WBRT followed by SRT always performed by linear accelerators: this technology does not need a dedicated tool such as the gamma-knife nor does it require the positioning of a fixed stereotactic frame. It can be delivered in an outpatient setting and usually it is not burdened by acute side effects with respect to conventional radiotherapy. The toxicity rates were, in fact, relatively low in both groups, which is in agreement with the evidence from the literature [7].

In particular, we reported only 1 case of neurocognitive deficit after 7 years, but it must be taken into account that control of the brain tumor remains the most important factor for stabilizing neurocognitive function [2]; therefore, WBRT is still part of standard treatment for brain metastases.

Our study, with the limits of any retrospective analysis, proves that after a considerable follow-up the efficacy of SRT is favorable comparable to surgery in producing adequate local control with the same overall survival. Our survival analysis also failed to find any statistically significant association with the traditional prognostic factors (e.g., RPA class, primary tumor, number of brain lesions): this finding can be explained by selection bias, the small sample size, the effectiveness of brain metastases treatment, but also obviously by the impact of all treatments offered to patients during their clinical history. The continuity of care even after brain progression and the confidence that the mere presence of brain metastases does not preclude an aggressive approach to patient care may explain the long survival and the lack of differences in the various subgroups analyzed.

In conclusion, our data suggest that WBRT + SRT may be an effective, noninvasive approach which can be offered to patients affected by small brain metastases (< 3 cm), especially when their extracranial disease is controlled and for personal or clinical reasons they are not candidates for metastasectomy; surgery still remains the preferable treatment in symptomatic patients.

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