The Role of Postoperative Radiotherapy after Resection of a Single Brain Metastasis

Combined Analysis of 643 Patients

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Background and Purpose: The extent of treatment in patients with single brain metastasis is a controversial topic. Especially the issue of whole-brain radiotherapy (WBRT) after local treatment of the lesion is largely unresolved. Therefore, the authors performed a pooled analysis of all available clinical data, based on a comprehensive literature search and on prospectively defined inclusion criteria and endpoints (in particular local brain control at the original site and development of new brain metastases).
Material and Methods: Overall, 643 patients from ten publications met the inclusion criteria. 106 patients were treated with surgery alone, 66 with surgery plus local radiotherapy, and the others with surgery plus WBRT (Table 1).
Results: Both types of additional radiotherapy significantly improved local control at the original site (relative risk of local failure < 0.5). WBRT also reduced new lesions significantly (relative risk 0.6). Within the available range of doses, no significant dose-response relationship was observed (Figure 1). Even after WBRT, new lesions remained the predominant type of brain failure. One of the underlying causes might be continuous reseeding of cells from active extracranial sites. Toxicity and quality of life were not well described in the publications.
Conclusion: The present data favor moderate-dose WBRT, but the pros and cons of each option should be discussed with each patient. Higher radiation doses or local boost treatment are not supported by these data, but might be considered under certain circumstances, e.g., after incomplete resection.

Key Words: Brain metastases · Cerebral metastases · Neurosurgery · Resection · Radiotherapy

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Die Rolle der postoperativen Strahlentherapie nach Resektion einer singulären Hirnmetastase. Kombinierte Analyse von 643 Patienten

Hintergrund und Ziel: Das Behandlungskonzept für Patienten mit singulären Hirnmetastasen ist ein kontrovers diskutiertes Thema. Die Rolle einer Ganzhirnbestrahlung (GHB) nach lokaler Behandlung der Läsion ist weitgehend unklar. Daher führten die Autoren eine Analyse aller verfügbaren klinischen Daten durch, basierend auf einer umfassenden Literatursuche sowie prospektiv definierten Einschlusskriterien und Endpunkten (insbesondere lokale Kontrolle im Bereich der Läsion und Auftreten neuer Hirnmetastasen).
Material und Methodik: Insgesamt 643 Patienten aus zehn Publikationen erfüllten die Einschlusskriterien. 106 Patienten wurden mit einer alleinigen Operation behandelt, 66 mit Operation plus lokaler Strahlentherapie und die anderen mit Operation plus GHB (Tabelle 1).
Ergebnisse: Beide Strahlentherapiekonzepte führten zu einer signifikant verbesserten lokalen Kontrolle im Bereich der ursprünglichen Läsion (relatives Lokalrezidivrisiko < 0,5). Die GHB reduzierte auch die Rate neuer Metastasen signifikant (relatives Risiko 0,6). Innerhalb des verfügbaren Dosisspektrums wurde keine signifikante Dosis-Wirkungs-Beziehung gefunden (Abbildung 1). Selbst nach GHB blieben neue Hirnmetastasen die vorherrschende Progressionsform. Einer der Gründe hierfür könnte das kontinuierliche Aussenden von Zellen aus vitalen extrakraniellen Manifestationen sein. Toxizität und Lebensqualität wurden in den Publikationen nicht sehr detailliert beschrieben.
Schlussfolgerung: Die aktuellen Daten favorisieren eine moderat dosierte GHB, allerdings sollten die Vor- und Nachteile jeder Option mit den einzelnen Patienten diskutiert werden. Der Stellenwert höherer Bestrahlungsdosen oder lokaler Dosisaufsättigungen wird durch diese Analyse nicht bestätigt. Dennoch sind im Einzelfall, z.B. nach unvollständiger Resektion, Ausnahmen zu erwägen.

Schlüsselwörter: Hirnmetastasen · Zerebrale Metastasen · Neurochirurgie · Resektion · Strahlentherapie

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Introduction

Brain metastases often occur in advanced-stage lung and breast cancer [6, 12, 32]. Patients with a single brain metastasis represent an inhomogeneous group with large variations in survival [21]. However, as effective long-term control of brain metastases can be achieved with either surgical resection or radiosurgery (RS), many oncologists feel that these patients should undergo thorough evaluation of both their prognostic factors and treatment options for extracranial tumor manifestations. If the survival expectation exceeds those 3–6 months that often were observed after palliative whole-brain radiotherapy (WBRT), aggressive local treatment of the lesion is usually recommended. Yet, a large body of controversy exists with regard to routine administration of WBRT after resection or RS of the metastatic lesion [1, 21]. While WBRT might reduce the risk of in-brain recurrence, it might also cause certain adverse events. In this context, neurocognitive decline is of particular concern. Both local tumor cell kill (and thus ultimate local control) and normal-tissue effects are dose-dependent. An optimal balance between high local control and minimal toxicity requires detailed analysis of the dose-response relationships. However, no such analysis has yet been published for postoperative radiotherapy after resection of a single brain metastasis. To evaluate both the results of postoperative radiotherapy and the dose-response relationships, we collected a large number of patients from all peer-reviewed publications on that topic. The analysis includes patients treated with WBRT and different types of local "partial-brain" radiotherapy.

Table 1. Analyzed studies on postoperative radiotherapy after resection of a single brain metastasis. BT: brachytherapy; EBRT: external-beam radiotherapy; RT: radiotherapy; WBRT: whole-brain radiotherapy.

Tabelle 1. Ausgewertete Studien zur postoperativen Strahlentherapie nach Resektion einer singulären Hirnmetastase. BT: Brachytherapie; EBRT: perkutane Strahlentherapie; RT: Strahlentherapie; WBRT: Ganzhirnbestrahlung.

Study	Patients (n)	RT	Incomplete resection	Extracranial metastases	Brain-only disease	Median follow-up	Crude local control[a]	Actuarial local control at 1 year	Both local and distant brain relapse	Crude rate of distant brain relapse[a]
Maiuri et al. 1998 [14]	20	None	None	None	34%	Not known	65%	Not known	Not known	Not known
Schackert et al. 2001 [28]	28	None	None	Not known	Not known	Not known	64%	Not known	14%	25%
Patchell et al. 1998 [21]	46	None (randomized)	None	26%	35%	43 weeks	54%	33%	13%	37%
Patchell et al. 1998 [21]	49	50.4 at 1.8 Gy WBRT (randomized)	None	24%	37%	48 weeks	90%	80%	6%	14%
Maiuri et al. 1998 [14]	150	36 at 2 Gy WBRT	None	None	34%	Not known	88%	Not known	6%	Not known
Patchell et al. 1990 [22]	25	36 at 3 Gy WBRT	None	39%	17%	40 weeks	80%	77%	12%	20%
Schöggl et al. 2000 [29]	66	30 at 3 Gy WBRT	Not known	26%	Not known	Not known	83%	At least 75%[c]	5%	15%
Nieder et al. 1998 [19]	66	30 at 3 Gy WBRT[b]	18%	45%	Not known	28 weeks	88%	At least 75%[c]	3%	14%
Rades et al. 2004 [24]	17	40 at 2 Gy WBRT	27%[d]	12%	Not known	Not known	53%	Not known	Not known	53%
Rades et al. 2004 [24]	16	Same WBRT plus 10 Gy boost	27%[d]	6%	Not known	Not known	81%	Not known	Not known	63%
Muacevic et al. 1999 [17]	52	40 at 2 Gy WBRT plus 10 Gy boost	Not known	52%	Not known	69 weeks	Not known	75%	Not known	12%
Coucke et al. 1998 [4]	12	50.4 at 1.8 Gy, local EBRT only	Probably none	None	Not known	Not known	75%	Not known	25%	50%
Rogers et al. 2006 [25]	54	60 Gy, local BT only	Not known	43%	Not known	Not known	83%	82%	7%	44%

[a] Percentages include the patients with both local and distant relapse
[b] 10 patients received 40 at 2 Gy, but this small subgroup did not alter the results of the study (for all dose-effect analyses this study was included at the 30-at-3-Gy level)
[c] estimated from the Kaplan-Meier curves, not reported in detail
[d] 27% refers to all 33 patients evaluated in the article; numbers not available for the two subgroups with or without boost

Material and Methods

This pooled analysis is based on a systematic literature search by use of MEDLINE (PubMed by the National Library of Medicine, National Institutes of Health, Bethesda, MD, USA, last access June 01, 2007). Studies were identified by entering all possible combinations of the key words "resection or neurosurgery" and "brain metastases, cerebral metastases or secondary brain tumo(u)r". In addition, the reference lists of all articles were searched. All publications reporting on patient groups with single brain metastasis were selected for initial review. Those with clearly defined radiation doses and evaluation of the brain relapse pattern were included in the present analysis. We excluded reports that did not separate between local brain relapse at the originally resected site and new distant metastases [5, 16, 20, 27, 30] and reports where the patients received a broad range of radiation doses but no stratification for dose levels was provided [3, 5, 30, 31, 33–35]. From all finally eligible studies, prespecified variables were extracted and compared. It should be noted that most studies had excluded patients with small cell lung cancer and lymphoma and that non-small cell lung cancer and breast cancer were the most common primary tumors. The studies varied with regard to follow-up intervals and methods. Differences in brain control rates were evaluated by use of the Mann-Whitney test. A p-value < 0.05 was considered statistically significant.

Results

Patients from ten studies were included in this pooled analysis. Table 1 shows the extracted variables. After surgery alone (n = 94 from three studies, all had complete resection), 38 patients developed a local relapse at the original site (40%). After additional radiotherapy (n = 224 from three studies, all had complete resection), 28 patients developed this type of failure (12.5%; $p < 0.01$). Few patients had incomplete resection without radiotherapy (n = 12, reported by Maiuri et al. [14], not shown in Table 1). Their local relapse rate was 66%. The same authors reported on 30 patients with incomplete resection who received additional radiotherapy (not shown in Table 1). Their local relapse rate was 20%, which is very close to the rate of 18% in the 231 patients from all the studies in Table 1 that included patients with incomplete resection or did not report in detail on this parameter [4, 19, 24, 25, 29]. Rades et al. [24] noted a doubling of the median time to local relapse after complete versus incomplete resection (16 vs. 8 months, all patients had received radiotherapy). No significant difference was found between local relapse rates after WBRT and local "partial-brain" radiotherapy, respectively. The local relapse rate was 16% for all 485 radiotherapy patients combined. The actuarial data at 1 year (Table 1) also suggest that postoperative radiotherapy at least doubles the local control rate compared to surgery alone.

After having demonstrated that radiotherapy improves local control, the question arises whether higher doses are better than lower doses. As different fractionation schedules were used in all the original studies, the doses were converted to biologically equivalent doses (BED) according to the linear-quadratic model. The α/β value used for this calculation was 10 Gy. The BED ranged from 39 Gy_{10} (30 Gy in ten fractions) to 60 Gy_{10} (50 Gy in 25 fractions) for external-beam radiotherapy and was even higher for the 60-Gy brachytherapy regimen used by Rogers et al. [25]. Within this dose range, no significant dose-response relationship was observed. This finding remained unaltered when the analysis was limited to the cases with complete resection (Figure 1). As the absence of a significant dose-response relationship over such a relatively large dose range is counterintuitive, we did attempt to account for the confounding effects of tumor cell reseeding from active extracranial sites. Such reseeding of course cannot be durably prevented by a course of radiotherapy. Therefore, two different types of local failures exist, i.e., surviving local tumor cells after treatment (this type of failure ideally should be preventable by postoperative radiotherapy) and reseeding (not preventable unless systemic treatment can fully control extracranial disease). Exact information on extracranial disease status at the time of relapse is not available in any of the studies. Information from the time when brain metastases were diagnosed is available from few studies only (Table 1) and might be misleading, e.g., because of differences in staging procedures. The fact that the two studies with higher percentages of brain-only disease (34% and 37%, respectively) also reported a better local control (90% and 88%, respectively) than the study with only 17% brain-only disease (local control 80%) should not be overestimated, because the latter study had only 25 patients. In the end, the available data did not allow us to reliably estimate reseeding effects.

Development of new brain metastases away from the originally resected lesion ("new distant lesions") occurred in 32% after surgery alone (74 cases) and 45% after surgery plus local radiotherapy (66 cases). It was significantly reduced to 19% by WBRT (291 cases; $p < 0.01$). With the given WBRT dose range (30–50.4 Gy converted to the respective BED), no significant dose-response relationship was observed. As already suggested, the rate of new distant lesions was significantly higher in patients with active extracranial disease [19].

Very few data related to late side effects are available. Neurotoxicity > grade 1 was observed in 1/66 patients after WBRT [19]. Patchell et al. [21] noted that the length of functional independence was similar between patients treated by surgery alone and those that received surgery plus WBRT. Aoyama et al. [1] found leukoencephalopathy in 3/65 patients after WBRT in their study of RS alone versus RS plus WBRT. There were no significant differences between the two groups regarding longitudinal development of Mini-Mental Status Examination results and Karnofsky Performance Status. The patient group treated with postoperative brachytherapy had a high rate of histologically verified radionecrosis (n = 9, actuarial rate 23% at 1 year) [25]. Six of these patients developed other grade 3 side effects, e.g., hydrocephalus, hemorrhage, and hemiplegia.

Discussion

The present study with 643 pooled patients, which includes 95 patients from a prospective randomized trial [21], is the largest one on the subject of postoperative treatment of single brain metastases. Compared to a large prospective randomized trial, all studies of this type might have the disadvantage of variations in inclusion criteria, staging examinations, treatment, and follow-up protocols in the individual trials. We tried to reduce sources of bias by defining strict inclusion criteria for this analysis. In the absence of large randomized trials, the present data might add relevant information to the literature. We have shown that both local and whole-brain radiotherapy significantly reduce local recurrence at the original site and that WBRT also reduces the development of new lesions. The latter finding has also been confirmed in a randomized trial of RS with or without WBRT [1]. A dose-response relationship was not observed. This finding is supported by data from Iwadate et al. [10]. Their study was excluded from the pooled analysis because many patients had multiple rather than single brain metastases. Local relapse was 8/15 (53%) after surgery alone, 5/44 (11%) after additional radiotherapy with 40–50 Gy, and 8/65 (12%) after additional ≥ 50 Gy. Possible conclusions are that a dose-response relationship does indeed not exist or that confounding factors prevent its detection. It is, for example, known that many patients die from extracranial disease progression before a cerebral relapse can be detected. Another issue is the large variation in number of residual tumor cells after resection (truly complete resection vs. undetectable microscopic residues vs. macroscopic incomplete resection). Although recent data confirm that brain metastases are very well circumscribed with minimal invasion [2], current imaging methods do not allow reliable estimation of the tumor cell number after resection. There is also no reliable method to account for the effect of continuous reseeding from extracranial sites, which will create a nonpreventable type of brain failure. In other words, we are not able to provide a 100% local control rate in the typical patient population, whatever the radiation dose might be.

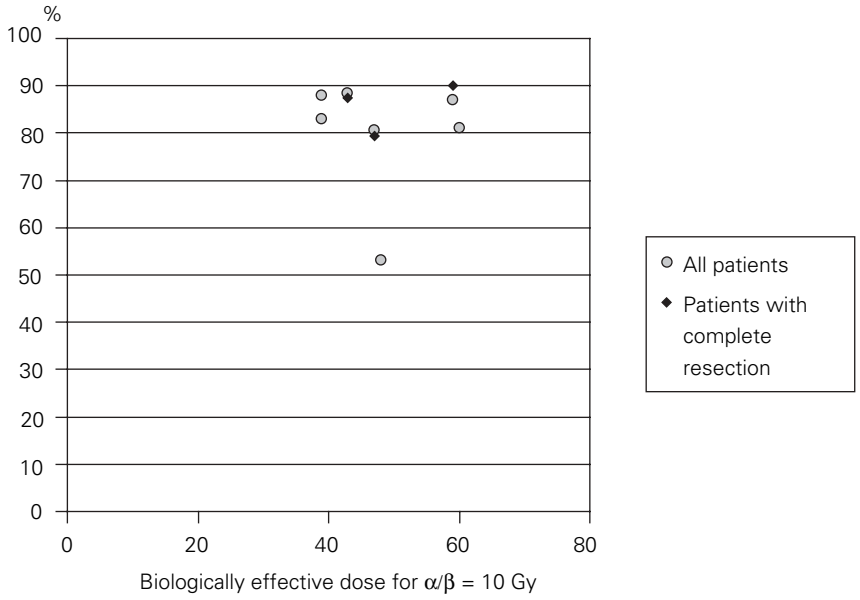

Figure 1. Dose-response relationship for local control at the originally resected site (external-beam radiotherapy): all patients irrespective of resection status (n = 431) and patients with complete resection only (n = 224).

Abbildung 1. Dosis-Wirkungs-Beziehung für die lokale Kontrolle der operierten Läsion (perkutane Strahlentherapie): alle Patienten unabhängig vom Resektionsstatus (n = 431) bzw. ausschließlich Patienten mit kompletter Resektion (n = 224).

The risk of serious toxicity after WBRT appears low (present data, [15]). Furthermore, we do have to acknowledge that any type of cancer treatment might cause measurable neurocognitive decline [9, 13, 26] and that some postradiation symptoms might be caused by certain drugs rather than radiation itself [11, 18]. Given these facts, what does prevent us from recommending routine moderate-dose WBRT after surgery? Most WBRT studies reviewed here and one that did not fulfill the inclusion criteria [33] indicate that, despite WBRT, distant brain failures are more common than true local relapses. Furthermore, the randomized trials were not able to demonstrate a prolongation of survival by WBRT after either surgery or RS [1, 21]. Survival is largely dependent on other factors, such as Karnofsky Performance Status and extracranial disease status [7]. Survival was not the endpoint of the present analysis, given the tremendous inhomogeneity of prognostic factors in the studies available, precluding a formal meta-analysis. However, we performed a combined analysis of 1-year survival rates of the individual nonrandomized studies from the published Kaplan-Meier graphs in order to explore survival trends and their consistency with the findings from the randomized trials (note that not all publications provided actuarial 1-year survival rates). Most of the studies that did not provide local control data could be included in the survival analysis, such as [5, 16, 20, 27, 30]. Based on 100 available patients from the surgical series, a 1-year survival rate of 46% was found, compared to 47% after resection plus WBRT (417 patients).

We currently recommend an individual discussion on the magnitude of benefit from the different types of postoperative radiotherapy and think that the present data are probably the best available estimates we can provide to our patients. The ongoing, but slowly recruiting randomized trials by the European Organisation for Research and Treatment of Cancer (EORTC 22952) and the Neurooncological Working Group

of the German Cancer Society (NOA-06) will hopefully provide further high-quality data on the subject of postoperative WBRT. Importantly, the present analysis does not support high-dose WBRT or local boost treatment, unless incomplete resection was performed. Whether postoperative assessment with new imaging modalities [8, 23] can improve our ability to detect residual tumor remains to be shown.

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