Linac Radiosurgery Versus Whole Brain Radiotherapy for Brain Metastases

A Survival Comparison Based on the RTOG Recursive Partitioning Analysis

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Background and Purpose: For patients with inoperable brain metastases, whole brain radiotherapy (WBRT) has been the standard treatment for decades. Radiosurgery is an effective alternative strategy, but has failed to show a substantial survival benefit so far. The prognostic factors derived from the RTOG recursive partitioning analysis (RPA) provide a framework that allows a nonrandomized comparison of the two modalities.

Patients and Methods: From 1991 to 1998, 117 patients with one to three previously untreated cerebral metastases underwent single-dose linac radiosurgery (median dose 20 Gy) without adjuvant WBRT. After radiosurgery, 26/117 patients (22%) had salvage WBRT, radiosurgery or neurosurgical resection of recurrent (4/117) and/or new (24/117) metastases. Survival of these patients was compared to a historical group of 138 patients with one to three lesions treated by WBRT (30–36 Gy/3-Gy fractions) from 1978 to 1991; only nine of these patients (7%) had salvage WBRT. All patients were classified into the three RPA prognostic classes based on age, performance score, and presence of extracranial tumor manifestations.

Results: In RPA class I (Karnofsky performance score ≥ 70, primary tumor controlled, no other metastases, age < 65 years), radiosurgery resulted in a median survival of 25.4 months (n = 23, confidence interval [CI] 5.8–45.0) which was significantly longer than for WBRT (n = 9, 4.7 months, CI 3.8–5.5; $p < 0.0001$). In RPA class III (Karnofsky performance score < 70), no significant difference in survival between radiosurgery (n = 20, 4.2 months, CI 3.2–5.3) and WBRT (n = 68, 2.5 months, CI 2.2–2.8) was found. In RPA class II (all other patients), radiosurgery produced a small, but significant survival advantage (radiosurgery: n = 74, 5.9 months, CI 3.2–8.5, WBRT: n = 61, 4.1 months, CI 3.4–4.9; $p < 0.04$).

Conclusion: Radiosurgery in patients with one to three cerebral metastases results in a substantial survival benefit only in younger patients with a low systemic tumor burden when compared to WBRT alone. It cannot be excluded that this effect is partially caused by the available salvage options after radiosurgery.

Key Words: Stereotactic radiosurgery · Whole brain radiotherapy · Cerebral metastases

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Radiochirurgie versus Ganzhirnbestrahlung bei Hirnmetastasen. Ein Vergleich der Überlebenszeiten innerhalb der RPA-Prognosegruppen

Hintergrund und Ziel: Für Patienten mit inoperablen Hirnmetastasen ist die Ganzhirnbestrahlung (WBRT) seit Jahrzehnten die Standardtherapie. Die Radiochirurgie stellt eine effektive Therapiealternative dar, jedoch wurde bisher kein eindeutiger Überlebensvorteil nachgewiesen. Die Risikogruppen der rekursiven Partitionsanalyse (RPA) der RTOG ermöglichen einen sinnvollen, nicht randomisierten Vergleich von WBRT und Radiochirurgie.

Patienten und Methodik: Von 1991 bis 1998 erhielten 117 nicht vorbehandelte Patienten mit ein bis drei Hirnmetastasen eine Linac-Radiochirurgie (mediane Dosis 20 Gy) ohne adjuvante WBRT. Zusätzlich wurden 26/117 Patienten (22%) wegen eines lokalen Metastasenrezidivs (4/117) oder neu aufgetretener Hirnmetastasen (24/117) erneut mittels Radiochirurgie, WBRT oder neurochirurgischer Resektion behandelt. Das Überleben dieser Patienten wurde mit einer historischen Gruppe verglichen (n = 138), die von 1978 bis 1991 bei ein bis drei Hirnmetastasen eine alleinige Ganzhirnbestrahlung (30–36 Gy/3-Gy-Fraktionen) erhielt. Hiervon wurden nur neun Patienten (7%) wegen eines Rezidivs erneut mit einer WBRT behandelt. Alle Patienten wurden entsprechend ihrem Alter, dem Allgemeinzustand (Karnofsky-Index) und der Präsenz extrakranieller Tumormanifestationen in die drei RPA-Klassen eingeteilt.

Ergebnisse: In der RPA-Klasse I (Karnofsky-Index ≥ 70, Primärtumor kontrolliert, keine weiteren Metastasen, Alter < 65 Jahre) führte die Radiochirurgie zu einem medianen Überleben von 25,4 Monaten (n = 23, Konfidenzintervall [CI] 5,8–45,0) und war so-

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mit der WBRT signifikant überlegen (n = 9, 4,7 Monate, CI 3,8–5,5; p < 0,0001). In der RPA-Klasse III (Karnofsky-Index < 70) ließ sich kein signifikanter Vorteil der Radiochirurgie (n = 20, 4,2 Monate, CI 3,2–5,3) gegenüber der WBRT (n = 68, 2,5 Monate, CI 2,2–2,8) nachweisen. In der RPA-Risikoklasse II (alle anderen Patienten) führte die Radiochirurgie nur zu einem geringen, aber signifikanten Überlebensvorteil (Radiochirurgie: n = 74, 5,9 Monate, CI 3,2–8,5, WBRT: n = 61, 4,1 Monate, CI 3,4–4,9; p < 0,04). **Schlussfolgerung:** Im Vergleich zur alleinigen WBRT führt die Radiochirurgie bei Patienten mit ein bis drei Hirnmetastasen nur in jüngerem Alter und bei geringer systemischer Tumorausbreitung zu einer Prognoseverbesserung. Möglicherweise spielt hierfür die höhere Verfügbarkeit von Salvage-Therapien eine Rolle.

Schlüsselwörter: Stereotaktische Radiochirurgie · Ganzhirnbestrahlung · Hirnmetastasen

Introduction

Radiosurgery is, nowadays, a widely accepted treatment modality for inoperable brain metastases. Several retrospective studies [7, 8, 10, 18, 23] and one randomized study [4] have shown increased local control rates of the irradiated lesions when compared to whole brain radiotherapy (WBRT) alone [15], and most of these studies also suggested an increase in median survival from 3–4 months (WBRT) to 7–12 months (radiosurgery) [1, 5, 7, 8, 10, 12, 18, 20, 23]. Randomized trials, however, have failed to demonstrate a general survival benefit of radiosurgery so far [4, 11], probably because these metastatic patients have a high risk to die from extracranial tumor spread and intercurrent death, such that only about 30–40% will eventually experience neurologic death.

The RTOG performed a recursive partitioning analysis (RPA) of > 1,000 patients treated by WBRT and identified three major risk groups [6]. The classification is mainly based on the patient's general ability to resist the malignant disease (age, performance score) and on the presence of extracranial tumor (primary tumor, other extracranial metastases). This analysis provides a framework that allows to group patients and analyze treatment effects in a nonrandomized manner. For the present investigation, it was used to compare the survival times in patients with inoperable brain metastases treated by radiosurgery to those of a historical collective treated by WBRT alone. Only patients with one to three metastases were studied, because, according to institutional policy, only up to three metastases were treated by radiosurgery and, in addition, evidence exists that in case of four or more metastases, the RPA loses its predictive power [14].

Patients and Methods

Treatment Groups

From 1991 to 1998, 117 previously untreated patients (41 females, 76 males, median age 60 years) with one to three cerebral metastases were treated by single-dose linac radiosurgery (median marginal dose 20 Gy, range 15–25 Gy) without adjuvant WBRT. Details of the radiosurgical procedure have been described before [10]. The most frequent primary tumor type was non-small-cell lung cancer (30%), followed by malignant melanoma (27%), hypernephroma (13%), breast carcinoma (12%), and other types (18%). Patients with singular metastases in this group had either deep-situated tumors not suitable for resection or were referred for radiosurgery rather than surgery because of the physician's or patient's preference.

Survival of these patients was compared to a historical group (1978–1991) of 138 patients (58 females, 80 males, median age 58 years) with one to three otherwise untreated brain metastases who received WBRT (30–36 Gy/3-Gy fractions in 80%, ≥ 40 Gy/2-Gy fractions or boost up to 50 Gy in 20%) in the same institution. In this group, non-small-cell lung cancer (28%) was also dominant, but breast cancer (19%) which is thought to have a slightly better prognosis [9] was more frequent (melanoma 6%, hypernephroma 5%, others 42%). Patients with singular metastases in this group were either unresectable because of localization or size of the lesion. During the same time period, 35 patients with singular metastases had neurosurgical resection and were irradiated postoperatively (results not shown).

All patients in both groups were classified into the three RPA prognostic classes, based on age, performance score, and presence of extracranial tumor manifestations. The RPA demonstrated that all other known prognostic factors such as histology, primary site, time interval, number of lesions, and neurologic function are of minor importance. Nevertheless, in Table 1, details of the RPA prognostic factors in all groups are shown together with some of the other minor factors.

Salvage Therapy

Type and frequency of salvage therapies differed substantially between the two treatment groups. In the radiosurgery group, seven patients developed local recurrences within the radiosurgery planning target volumes, and 38 patients experienced new outfield metastases. Altogether, 26/117 patients (22%) had salvage procedures. In twelve patients, WBRT (30–36 Gy/3-Gy fractions) was used, seven patients had salvage radiosurgery, five received both WBRT and radiosurgery, and four had their recurrences resected. The median time interval between primary radiosurgery and salvage therapy amounted to 4.8 months (range 1.3–31 months).

In the WBRT group, radiosurgery was not available neither for primary nor salvage therapy. Of all patients who had recurrent brain metastases (number not known), only 9/138 (7%) received a second course of WBRT (26–33 Gy/2-Gy

Table 1. Patient and treatment characteristics. KI: Karnofsky index; OP: operation; RPA: recursive partitioning analysis; RS: radiosurgery; WBRT: whole brain radiotherapy.

Tabelle 1. Patienten und Therapie. KI: Karnofsky-Index; OP: Operation; RPA: rekursive Partitionsanalyse; RS: Radiochirurgie; WBRT: Ganzhirnbestrahlung.

	n	Age (years)	Performance score (KI)	Histology (%) (breast/ lung/other)	Extracranial disease n (%)	Singular brain metastases n (%)	Diameter of brain metastases > 3 cm n (%)	Salvage therapy (RS/WBRT/ RS + WBRT/OP) n (%)
RPA class I								
RS	23	53 (30–65)	90 (70–100)	30/22/48	–	14 (61)	3 (13)	1/3/2/1 (30)
WBRT	9	52 (45–61)	80 (70–90)	33/33/34	–	3 (33)	1/6 (17)[a]	0/1/0/0 (11)
RPA class II								
RS	74	62 (32–79)	80 (70–100)	8/38/54	60 (81)	53 (72)	10 (14)	6/9/3/1 (26)
WBRT	61	58 (23–78)	80 (70–90)	20/30/50	56 (92)	37 (61)	12/38 (32)[a]	0/5/0/0 (8)
RPA class III								
RS	20	63 (37–78)	60 (50–60)	5/10/85	15 (75)	13 (65)	5 (25)	0/0/0/0 (0)
WBRT	68	58 (21–78)	50 (10–65)	16/25/59	53 (78)	41 (60)	13/35 (37)[a]	0/3/0/0 (4)

[a]not known for all patients

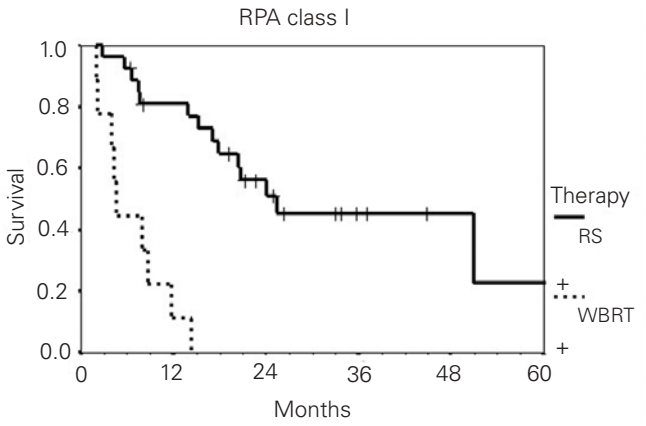

Figure 1a – Abbildung 1a

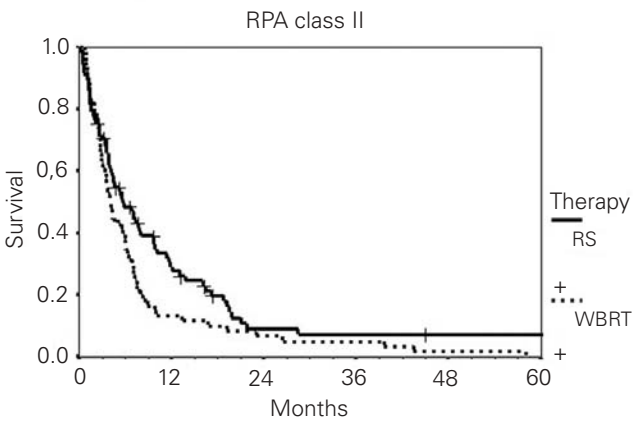

Figure 1b – Abbildung 1b

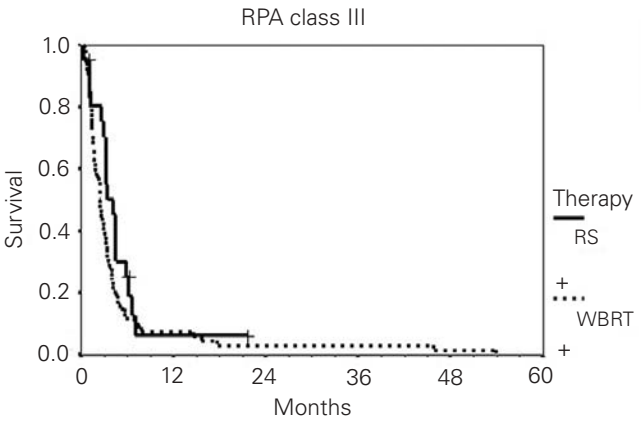

Figure 1c – Abbildung 1c

Figures 1a to 1c. Survival times of patients treated by radiosurgery (RS) or whole brain radiotherapy (WBRT) according to the RTOG recursive partitioning analysis (RPA) classes. a) Class I includes patients < 65 years, with a Karnofsky performance score ≥ 70, primary tumor control, and absence of extracranial metastases. b) Class III consists of patients with a Karnofsky performance score < 70. c) Class II comprises all other patients.

Abbildungen 1a bis 1c. Überlebenszeiten von Patienten mit Hirnmetastasen nach Radiochirurgie (RS) oder Ganzhirnbestrahlung (WBRT) in Abhängigkeit von den RPA-Klassen (rekursive Partitionsanalyse). a) Klasse I enthält Patienten < 65 Jahre mit einem Allgemeinzustand nach Karnofsky ≥ 70%, bei denen der Primärtumor kontrolliert ist und keine anderen Fernmetastasen vorliegen. b) In Klasse III finden sich Patienten mit einem Karnofsky-Index < 70%. c) Klasse II enthält alle anderen Patienten.

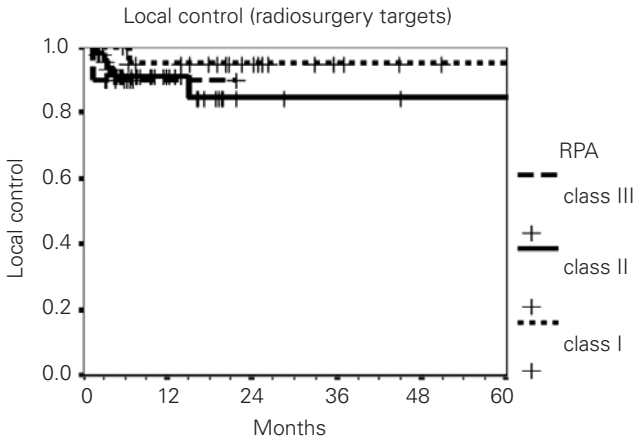

Figure 2. Local control of the metastases treated by radiosurgery for the three RPA classes.

Abbildung 2. Lokale Kontrolle der mittels Radiochirurgie behandelten Metastasen in den drei RPA-Klassen.

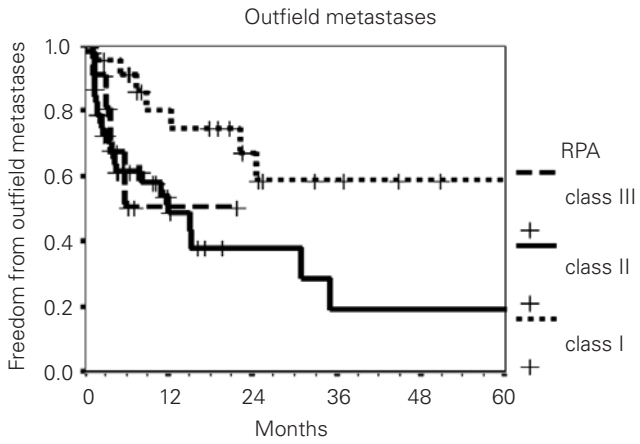

Figure 3. Freedom from distant intracerebral failure (outfield metastases) for the radiosurgery patients in the three RPA classes. Most of the class II and III patients had extracranial disease.

Abbildung 3. Anteil der radiochirurgisch behandelten Patienten, die keine neuen Hirnmetastasen entwickelten, in den drei RPA-Klassen. Die meisten Patienten in Klassen II und III hatten extrazerebrale Tumormanifestationen.

fraction) after a median time interval of 9.5 months (range 2.1–42 months), none of the patients had salvage neurosurgery.

Results

Survival

In RPA class I patients (Karnofsky performance score ≥ 70, primary tumor controlled, no other metastases, age < 65 years), radiosurgery resulted in a median survival of 25.4 months (n = 23, confidence interval [CI] 5.8–45.0) which was significantly longer than for WBRT (n = 9, 4.7 months, CI 3.8–5.5; $p < 0.0001$). In RPA class III (Karnofsky performance score < 70), no significant difference in survival between radiosurgery (n = 20, 4.2 months, CI 3.2–5.3) and WBRT (n = 68, 2.5 months, CI 2.2–2.8) was found. In RPA class II (all other patients), radiosurgery produced a small, but significant survival advantage (radiosurgery: n = 74, 5.9 months, CI 3.2–8.5, WBRT: n = 61, 4.1 months, CI 3.4–4.9; $p < 0.04$; Figure 1).

Local and Intracranial Control

In the radiosurgery group, local control of the irradiated metastases was equally high in all RPA groups (Figure 2). The development of new outfield metastases was, however, significantly higher in RPA groups II and III than in group I, probably because of reseeding from active extracranial tumor (Figure 3; $p < 0.03$). Local control and freedom from new intracerebral metastases could not be evaluated in the WBRT group.

Side Effects

In the radiosurgery group, 6/117 patients (5%) had evidence of radiation necrosis [13] indicated by CT and/or MRI scans 15 (5–18) months after irradiation. In four patients, radiation necrosis caused focal neurologic symptoms, which were treated by corticosteroids. In the WBRT group, radiation necrosis was never diagnosed. In both groups, signs or symptoms of dementia or neuropsychological dysfunction [17] were not observed after WBRT.

Discussion

While it seems unequivocal that radiosurgery improves local control of the irradiated metastases when compared to WBRT [4], a substantial survival benefit has not been demonstrated yet. Probably, the reason for this observation stems from the fact that patients with brain metastases have, in addition to local brain recurrence, competing risks, namely systemic progression, distant intracranial failure, and intercurrent death. Obviously, radiosurgery of the visible brain metastases solves only part of the problem these metastatic patients have.

Therefore, one can expect a survival advantage as a result of an increased local control rate of the irradiated brain metastases only in patients in good condition with a low systemic tumor burden and for whom effective means to control intracranial distant relapses are available. The latter goal can probably either be achieved by adjuvant WBRT [16] or by salvage therapies. Taking these considerations into account, the results of this analysis can be interpreted consistently. Only patients in the RPA class I group fulfill the aforementioned criteria and may, therefore, substantially benefit from radiosurgery. RPA class III patients have a poor prognosis per se which cannot be altered by localized irradiation of the brain. Some of the class II patients may benefit as well.

Comparable retrospective and randomized analyses have been conducted for the combined treatment with radiosurgery

plus WBRT compared to either of the modalities alone [2, 11]. The addition of adjuvant WBRT to radiosurgery seems to increase local control and to decrease the frequency of new intracranial failures, but survival by RPA class remains unchanged [3, 4, 21]. The addition of radiosurgery to WBRT resulted in a survival benefit for patients of all RPA classes in one retrospective study [19], but a phase III trial that has recently been published in abstract form showed a survival advantage (2 months) only for RPA class I patients [22].

In a retrospective analysis such as the one presented here, selection effects can never by completely avoided. One of the main differences between the class I patients was the availability of salvage therapies. In the radiosurgery group, 7/22 (30%) of all patients had subsequent salvage radiosurgery (n = 1), WBRT (n = 3), radiosurgery and WBRT (n = 2), or neurosurgery (n = 1), while only 1/9 patients in the WBRT group had another WBRT. This difference suggests that radiosurgery does not only increase survival when used as the primary treatment, but also when used as part of a salvage management. The lack of survival benefit for the elderly patients in bad condition (RPA class III), however, is unequivocally demonstrated by this work.

References

1. Auchter RM, Lamon JP, Alexander E III, et al. A multiinstitutional outcome and prognostic factor analysis of radiosurgery for resectable brain metastases. Int J Radiat Oncol Biol Phys 1996;35:27–35.
2. Buchsbaum JC, Suh JH, Lee SY, et al. Survival by Radiation Therapy Oncology Group recursive partitioning analysis class and treatment modality in patients with brain metastases from malignant melanoma: a retrospective study. Cancer 2002;94:2265–72.
3. Chidel MA, Suh JH, Reddy CA, et al. Application of recursive partitioning analysis and evaluation of the use of whole brain radiation among patients treated with stereotactic radiosurgery for newly diagnosed brain metastases. Int J Radiat Oncol Biol Phys 2000;47:993–9.
4. Chougule PB, Burton-Williams M, Saris S, et al. Randomized treatment of brain metastasis with gamma knife radiosurgery, whole brain radiotherapy or both. Int J Radiat Oncol Biol Phys 2000;48:Astro-Abstracts 2000:114.
5. Flickinger JC, Kondziolka D, Lunsford D, et al. A multi-institutional experience with stereotactic radiosurgery for solitary brain metastases. Int J Radiat Oncol Biol Phys 1994;28:797–802.
6. Gaspar L, Scott C, Rotman M, et al. Recursive partitioning analysis (RPA) of prognostic factors in three radiation therapy oncology group (RTOG) brain metastases trials. Int J Radiat Oncol Biol Phys 1997;37:745–51.
7. Herfarth KK, Izwekowa O, Thilmann C, et al. Linac-based radiosurgery of cerebral melanoma metastases. Strahlenther Onkol 2003;179:366–71.
8. Joseph J, Adler JR, Cox RS, et al. Linear accelerator-based stereotactic radiosurgery for brain metastases: the influence of number of lesions on survival. J Clin Oncol 1996;14:1085–92.
9. Kocher M, Müller R-P, Staar S, et al. Long-term survival after brain metastases in breast cancer. Strahlenther Onkol 1995;171:290–5.
10. Kocher M, Voges J, Müller RP, et al. Linac radiosurgery for patients with a limited number of brain metastases. J Radiosurg 1998;1:9–15.
11. Kondziolka D, Patel A, Lunsford LD, et al. Stereotactic radiosurgery plus whole brain radiotherapy versus radiotherapy alone for patients with multiple brain metastases. Int J Radiat Oncol Biol Phys 1999;45:427–34.
12. Moriarty TM, Loeffler JS, Black PM, et al. Long-term follow-up of patients treated with stereotactic radiosurgery for single or multiple brain metastases. Radiosurgery 1996;1:83–91.
13. Münter MM, Karger CP, Schröck H, et al. Strahlenspätveränderungen nach kleinvolumiger radiochirurgischer Bestrahlung des Rattenhirns. Strahlenther Onkol 2001;177:354–61.
14. Nieder C, Andratschke N, Grosu A, et al. Recursive partitioning analysis (RPA) class does not predict survival in patients with four or more brain metastases. Strahlenther Onkol 2003;179:16–20.
15. Nieder C, Nestle U, Walter K, et al. Dose/effect relationship for brain metastases. J Cancer Res Clin Oncol 1998;124:346–50.
16. Patchell RA, Tibbs PA, Regine WF, et al. Postoperative radiotherapy in the treatment of single metastases to the brain. JAMA 1998;280:1485–9.
17. Penitzka S, Steinvorth S, Sehlleier S, et al. Erfassung kognitiver Funktionen nach prophylaktischer und therapeutischer Ganzhirnbestrahlung mittels neuropsychologischer Testverfahren. Strahlenther Onkol 2002;178:252–8.
18. Pirzkall A, Debus J, Lohr F, et al. Radiosurgery alone or in combination with whole-brain radiotherapy for brain metastases. J Clin Oncol 1998;16: 3563–9.
19. Sanghavi SN, Miranpuri SS, Chapell R, et al. Radiosurgery for patients with brain metastases: a multi-institutional analysis, stratified by the RTOG recursive partitioning analysis method. Int J Radiat Oncol Biol Phys 2001; 51:426–34.
20. Sneed PK, Lamborn KR, Forstner JM, et al. Radiosurgery for brain metastases: is whole brain irradiation necessary? Int J Radiat Oncol Biol Phys 1999;43:549–58.
21. Sneed PK, Suh JH, Goetsch SJ, et al. A multi-institutional review of radiosurgery alone vs. radiosurgery with whole brain radiotherapy as the initial management of brain metastases. Int J Radiat Oncol Biol Phys 2002; 53:519–26.
22. Sperduto PW, Scott C, Andrews D, et al. Stereotactic radiosurgery with whole brain radiation therapy improves survival in patients with brain metastases: report of RTOG phase III study 9508. Int J Radiat Oncol Biol Phys 2002;54:Suppl:3.
23. Young RF, Jacques DB, Duma C, et al. Gamma knife radiosurgery for treatment of multiple brain metastases. Radiosurgery 1996;1:92–101.

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