Prediction of Prognosis Regarding Fractionation Schedule and Survival in Patients with Whole-brain Radiotherapy for Metastatic Disease

ANDREAS MEYER*, DIANA STEINMANN*, LILIANA MALAIMARE, JOHANN H. KARSTENS and MICHAEL BREMER

Department of Radiation Oncology, Medical School Hannover, 30625 Hannover, Germany

Abstract. *Aim: To look at differences between fractionation schedules regarding established prognostic factors in patients treated with whole-brain radiotherapy (WBRT) for metastasis and actual survival. Patients and Methods: One hundred and forty-six patients with brain metastases treated with WBRT with three different fractionation schedules with respect to the single dose (SD) 20×2.0 Gy (SD2), 15×2.5 Gy (SD2.5) and 10×3 Gy (SD3) were included. Results: The median overall survival in the SD2, SD2.5 and SD3 groups was 10.3, 10.3 and 5.5 months (p=0.005) while in recursive partitioning analysis (RPA) classes I, II and III it was 16.7, 8.1 and 3.7 months, respectively (p<0.0001). Statistically significant variables for overall survival were age (<60 years, p<0.0001) and primary site (breast, p=0.049) in the univariate analysis, and age (p=0.003) and RPA class (p<0.0001) in the multivariate analysis. Conclusion: The dose fractionation schedule for WBRT of metastases adequately reflected the clinical estimate of more favourable prognosis. Reduced single doses due to neurocognitive decline may be considered in patients with RPA class I.*

In palliative radiotherapy, life expectancy is an important factor in decision making. For those patients predicted to have short survival, protracted radiation schedules may be a burden (1). Priority is given to controlling symptoms and improving quality of life (QoL) instead of concerns about radiation-induced late effects.

On the other hand, assessing life expectancy for patients with advanced cancer is rather inaccurate. There are very limited data addressing the accuracy of survival prediction by radiation oncologists in the palliative setting (2). The predicted survival time in patients with brain metastases influences the decision on dose fractionation in whole-brain radiotherapy (WBRT), with lower single doses given to patients with longer estimated life expectancy, and the choice of radiotherapy dose fractionation is often based on the radiation oncologist's estimate of a patient's survival (3).

The aim of the study was to analyse the WBRT fractionation schedule for patients with brain metastases and to retrospectively compare the radiation oncologists' survival estimate and the actual survival in addition to well established prognostic factors.

Patients and Methods

Between 01/2000 and 12/2002, 146 consecutive patients with newly diagnosed brain metastases received WBRT at a single institution and were retrospectively analysed. The patients characteristics are shown in Table I. Ninety-two patients were female (63%) and fifty-four male (37%). Breast and lung cancer represented 74% of all the primary tumour sites (Table I). A single brain metastasis was present in 39 patients (27%). Neurosurgical excision prior to WBRT was performed in 25 patients (17%). Chemotherapy was given to 45 patients (31%) within a 3 month period before WBRT; but not concomitantly with radiation. A stereotactic radiosurgical boost with a median dose of 15 Gy was applied to 6 patients following WBRT, in these patients the WBRT single dose was always kept below 3 Gy. In 15 patients (10%), WBRT was discontinued prematurely after a median of 15 Gy due to progressive decline in general condition, early death or the patient's decision to terminate the treatment.

The patients were grouped according to three different dose fractionation schedules with respect to the single dose (SD), 20×2.0 Gy (SD2) in 38 patients (26%), 15×2.5 Gy (SD2.5) in 71 patients (49%) and 10×3 Gy (SD3) in 37 patients (25%). Recursive partitioning analyses (RPA) generated three prognostic classes as shown in Table I (4). The leading criterion for assigning patients to the prognostically unfavourable RPA class III is a Karnofsky performance score (KPS) <70%, whereas patients in the more favourable RPA class I must fulfil all criteria with a KPS of at least

*Both authors contributed equally to this work.

Correspondence to: Andreas Meyer, MD, Department of Radiation Oncology, Medical School Hannover, Carl-Neuberg-Str. 1, 30625 Hannover, Germany. Tel: +49 5115323590, Fax: +49 5115329797, e-mail: Meyer.A@mh-hannover.de

Key Words: Palliative radiotherapy, whole-brain radiotherapy, brain metastases, survival prediction.

Table I. *Patient characteristics.*

	Number of patients
Median age (range)	60 years (34-87)
Median overall survival (range)	8.8 months (0.1-50.6)
Primary site	
Breast	52 (36%)
Lung	56 (38%)
Colorectal	7 (5%)
Malignant melanoma	7 (5%)
CUP	7 (5%)
others	17 (12%)
Fractionation schedule	
20×2 Gy (SD 2)	38 (26%)
15×2.5 Gy (SD2.5)	71 (49%)
10×3 Gy (SD3)	37 (25%)
RPA prognostic group	
Class I	32 (22%)
Class II	80 (55%)
Class III	34 (23%)

CUP, Carcinoma of unknown primary; RPA, recursive partitioning analysis.

Table II. *Comparison between patients with single doses <3 Gy (group SD2 and SD 2.5) vs. 3 Gy (group SD3).*

Fractionation group	SD2 / SD2.5 (n=109)	SD3 (n=37)	*p*-value
Mean age ± SD (years)	57.8±11.1	62.6 ±11.9	0.028
RPA prognostic group			0.184
Class I	27 (25 %)	5 (14 %)	
Class II	60 (55 %)	20 (54 %)	
Class III	22 (20 %)	12 (32 %)	
Primary site			
Breast	45 (41 %)	7 (19 %)	0.014
Lung	40 (37 %)	16 (43 %)	0.479
Single brain metastasis	34 (31 %)	5 (14 %)	0.036
Neurosurgical excision	22 (20 %)	3 (8 %)	0.092
Chemotherapy within 3 months	36 (33 %)	9 (24 %)	0.322
Premature discontinuation of RT	10 (9 %)	5 (14 %)	0.453
Median survival (months)	10.3	5.5	0.005
95% CI (months)	8.4-12.2	4.9-6.0	

SD, Standard deviation; 95% CI, 95% confidence interval; RT, radiotherapy.

70%, age <65 years and absence of extracerebral tumour activity including a controlled primary tumour. All the other patients are classified within the intermediate RPA class II.

Statistical analysis was performed using the commercially available software package Statistical Package for Social Sciences (SPSS V14.0). Tests for differences between the fractionation groups were performed using Chi-square tests for categorical variables (two to three categories) and the *t*-test for continuous variables (age). Survival time was measured from the time of first radiotherapy. The end-point analysed was overall survival with death from any cause defined as the event. The actuarial survival time was calculated by the product-limit method of Kaplan and Meier and the differences were compared using the log-rank test. A multivariate step-wise Cox proportional regression analysis was used to identify significant prognostic factors for survival. The following parameters were included in the analysis as categorical variables, fractionation group (SD2, SD2.5 and SD3), RPA prognostic group (RPA class I , II and III), age (<60 years *vs.* ≥60 years), primary site (breast cancer *vs.* other primaries), single brain metastasis (yes *vs.* no), neurosurgical excision (yes *vs.* no) and chemotherapy within 3 months prior to WBRT (yes *vs.* no). A two-sided p-value <0.05 was considered to be significant.

Results

At the time of data analysis, all the patients had died. The median survival of all the patients was 8.8 months after first WBRT (range 0.1 to 50.6 months) with an actuarial 1- and 2-year survival of 37% and 5%, respectively. The median survival of the patients in the SD2, SD2.5 and SD3 fractionation groups was 10.3, 10.3 and 5.5 months (Figure 1, p=0.005), while that of the patients with RPA class I, II and III was 16.7, 8.1 and 3.7 months, respectively (Figure 2, p<0.001). Additional variables with significant influence on overall survival in univariate analysis were age (<60 years *vs.* ≥60 years, p<0.001) and breast cancer *vs.* other primaries (p=0.049). In multivariate analysis, only RPA prognostic group (p<0.001) and age (p=0.003) remained statistically significant prognosticators of survival.

Due to the very similar survival figures, the patients in the SD2 and SD2.5 fractionation groups (n=109) were grouped together for further analysis and compared to the remaining patients with 3 Gy single dose (SD3, n=37). The patients with single doses <3 Gy were statistically significantly younger (mean difference 4.8 years, p=0.028), more frequently breast cancer patients (p=0.014) and presented more often with a single brain metastasis (p=0.036) than the patients with 3 Gy single doses (Table II). Despite the prognostic value of RPA class on survival, the distribution of patients with RPA class I-III within the two fractionation groups was not significantly different (p=0.184, Table II).

Discussion

The patients of the SD2 and SD2-5 groups lived significantly longer, with the median survival time being almost double compared to patients with 3 Gy single doses (10.3 *vs.* 5.5 months, p=0.005). This obviously reflected an adequate assessment of life expectancy by the radiation oncologist at the time of treatment decision. It should be stressed that the fractionation schedule itself had no influence on survival as consistently described by others. Shorter fractionation schemes such as 5×4 Gy were associated with similar survival to local control as the "standard" scheme of 10×3 Gy (5-7). In most of these studies, statistically significant factors influencing overall

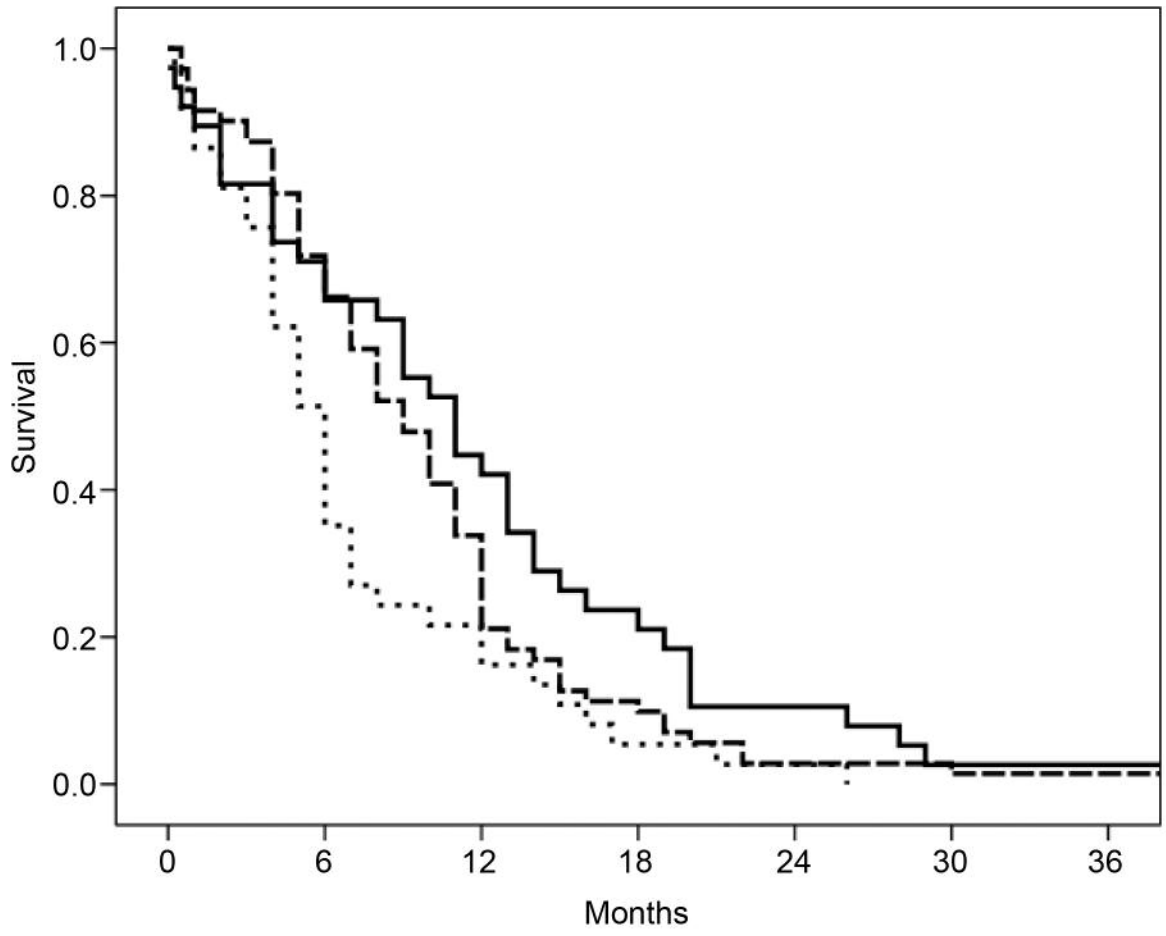

Figure 1. *Actuarial survival of 146 patients with treated WBRT for newly diagnosed brain metastases according to the dose fractionation schedule. SD2=20×2 Gy (n=38; solid line), SD2.5=15×2.5 Gy (n=71; broken line), SD3=10×3 Gy (n=37; dotted line). The difference in survival between SD2/SD2.5 vs. SD3 was significant (log-rank test, p=0.005).*

survival were lower RPA class, younger age and higher KPS. The present study demonstrated that not the fractionation scheme, but only the RPA class and age remained statistically significant prognostic factors of survival in multivariate analysis.

In the literature there are only a few studies specifically addressing the accuracy of survival prediction by radiation oncologists in the palliative setting (2, 8). In their prospective study, Chow *et al*. found that the prediction of survival tended to be overly optimistic, especially in patients with an actual short lifespan (<12 weeks). In contrast, in patients actually surviving >1 year, the radiation oncologists underestimated the survival (2). Gripp *et al*. demonstrated that physicians' survival estimates were unreliable, especially in the case of patients near death (8). The authors also found an overly optimistic estimate of the survival. Notably, 2% of patients survive 5 years or more from their diagnosis of brain metastases (9) and those patients living beyond 5 years have extended survival with a median of 9.3 years (10).

Although the clinician's judgement largely depends on their level of experience, survival estimates should not be based on intuition only, but should take into account the performance status and proven scores or indices as well (11-13). The prognostic significance of the RPA classification, which is a simple and reliable tool to estimate the survival time of patients with brain metastases, was confirmed in the present study (3). There was a clear tendency for single doses <3 Gy to be given to younger patients, to those with breast cancer and to those with a single brain metastasis that more often were in a favourable RPA class. However, the discriminative ability of the fractionation groups (single dose <3 Gy *vs*. 3 Gy) was limited because the distribution of patients with RPA classes I-III as a proven prognostic index was not significantly different between the fractionation groups (Table II). In almost half of our patients, the fractionation schedule was 15×2.5 Gy. This was mainly due to an adaptation to the corresponding fraction size used in the RTOG 9508 trial (WBRT with or

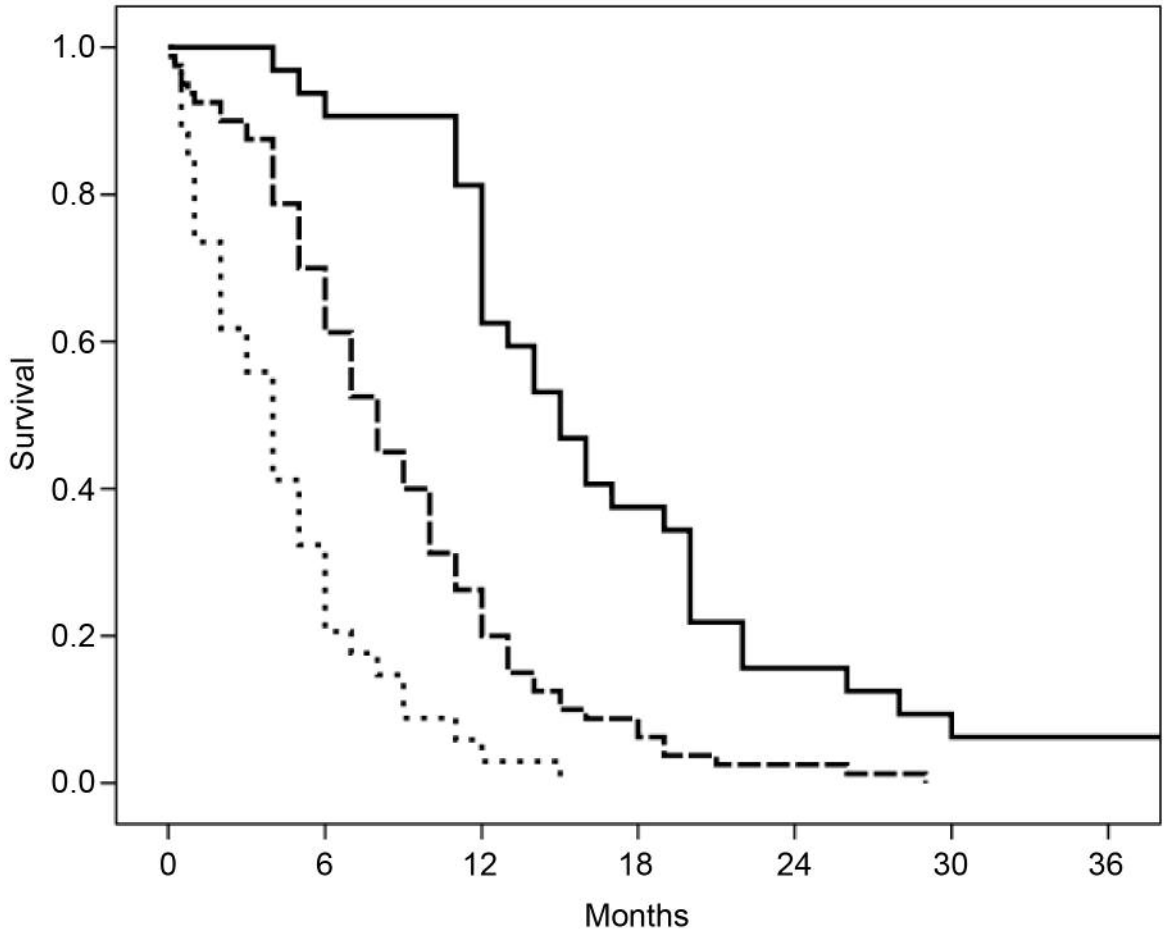

Figure 2. *Actuarial survival according to the patient distribution in prognostic classes RPA I-III. RPA I, n=32 (solid line); RPA II, n=80 (broken line); RPA III, n=34 (dotted line). The differences in survival between the respective RPA classes were highly significant (log-rank test, p<0.001).*

without radiosurgery boost (14)) in the patients potentially being candidates for stereotactic radiosurgery as a boost or salvage treatment following WBRT.

This analysis included only patients with brain metastases receiving WBRT. In patients with newly diagnosed brain metastases of suitable size and number (up to three), especially those from malignant melanoma or renal cell carcinoma (excluding small cell lung cancer, germ cell tumours or haematological malignancies), it is our continuing policy to offer stereotactic radiosurgery or hypofractionated stereotactic radiotherapy (15) alone after informed consent. Although stereotactic radiotherapy without up-front WBRT results in higher intracranial relapse rates, preservation of neurological function and survival is not inferior compared to the combined treatment (16), making it an acceptable option in patients complying with repeated MRI-based intracerebral monitoring (17).

The most commonly used WBRT fractionation schedule for brain metastases is 10×3 Gy and represents a compromise between tumour control and limiting the neurotoxicity of WBRT within a multimodality approach including surgery, radiosurgery or chemotherapy where applicable. Although clinical data are limited WBRT may contribute to cognitive impairment in long-term survivors after fractionation schedules with single doses as low as 3 Gy (18). However, dementia becomes clinically apparent in only 2-5% of cases (19). This has led to recommendations to employ more protracted radiation schedules for good-prognosis patients in accordance with the high fractionation sensitivity (low α/β value) of normal brain tissue. Late radiation effects are generally irreversible and progressive and may appear more than 6 months after WBRT in a manner similar to small vessel disease, as is often seen with vascular dementia (20). Within this context WBRT single doses <3 Gy might first be considered in patients with RPA class I.

Palliative radiation therapy continues to play a crucial role in maintaining QoL for many advanced cancer patients. Up to now, prospective data on QoL after WBRT are too scarce

(14, 16, 21) to adequately guide clinical decision making. An ongoing German prospective multicentre evaluation of QoL in patients receiving WBRT hopefully will shed more light on this important issue.

To conclude, the fractionation schedule applied for metastatic WBRT adequately reflected the clinical perception of a more favourable prognosis. There was a clear tendency towards single doses <3 Gy in younger patients, those with breast cancer and those with a single brain metastasis. Reduced single doses due to concerns about neurocognitve late effects may be considered first in patients with RPA class I.

Conflict of Interest Statement

The authors certify that there is no actual or potential conflict of interest in relation to this article. None of the authors had any financial or personal relationships with other people or organisations that could inappropriately influence their work.

References

1 Chow E, Fung K, Panzarella T, Bezjak A, Danjoux C and Tannock I: A predictive model for survival in metastatic cancer patients attending an outpatient palliative radiotherapy clinic. Int J Radiat Oncol Biol Phys *53*: 1291-1302, 2002.

2 Chow E, Davis L, Panzarella T, Hayter C, Szumacher E, Loblaw A, Wong R and Danjoux C: Accuracy of survival prediction by palliative radiation oncologists. Int J Radiat Oncol Biol Phys *61*: 870-873, 2005.

3 Rades D, Raabe A, Bajrovic A and Alberti W: Treatment of solitary brain metastasis. Resection followed by whole brain radiation therapy (WBRT) and a radiation boost to the metastatic site. Strahlenther Onkol *180*: 144-147, 2004.

4 Gaspar LE, Scott C, Rotman M, Asbell S, Phillips T and Wasserman T: Recursive partitioning analysis (RPA) of prognostic factors in three Radiation Therapy Oncology Group (RTOG) brain metastases trials. Int J Radiat Oncol Biol Phys *37*: 745-751, 1997.

5 Fleckenstein K, Hof H, Lohr F, Wenz F and Wannenmacher M: Prognostic factors for brain metastases after whole-brain radiotherapy. Data from a single institution. Strahlenther Onkol *180*: 268-273, 2004.

6 Tsao MN, Lloyd N, Wong R, Chow E, Rakovitch E and Laperriere N: Whole-brain radiotherapy for the treatment of multiple brain metastases. Cochrane Database Syst Rev *3*: 1-57, 2006.

7 Rades D, Kieckebusch S, Lohynska R, Veninga T, Stalpers LJ, Dunst J and Schild SE: Reduction of overall treatment time in patients irradiated for more than three brain metastases. Int J Radiat Oncol Biol Phys *69*: 1509-1513, 2007.

8 Gripp S, Moeller S, Bölke E, Schmitt G, Matuschek C, Asgari S, Asgharzadeh F, Roth S, Budach W, Franz M and Willers R: Survival prediction in terminally ill cancer patients by clinical estimates, laboratory tests, and self-rated anxiety and depression. J Clin Oncol *25*: 3313-3320, 2007.

9 Lutterbach J, Bartelt S and Ostertag C: Long-term survival in patients with brain metastases. J Cancer Res Clin Oncol *128*: 417-425, 2002.

10 Chao ST, Barnett GH, Liu SW, Reuther AM, Toms SA, Vogelbaum MA, Videtic GM and Suh JH: Five-year survivors of brain metastases: a single-institution report of 32 patients. Int J Radiat Oncol Biol Phys *66*: 801-809, 2006.

11 Christakis NA and Lamont EB: Extent and determinants of error in doctors' prognoses in terminally ill patients: prospective cohort study. BMJ *320*: 469-474, 2000.

12 Chow E, Harth T, Hruby G, Finkelstein J, Wu J and Danjoux C: How accurate are physicians' clinical predictions of survival and the available prognostic tools in estimating survival times in terminally ill cancer patients? A systematic review. Clin Oncol (R Coll Radiol) *13*: 209-218, 2001.

13 Johansen R, Westin AA, Bofin AM and Lundgren S: Outcome of whole-brain irradiation for breast cancer patients. Acta Oncol *47*: 261-266, 2008.

14 Andrews DW, Scott CB, Sperduto PW, Flanders AE, Gaspar LE, Schell MC, Werner-Wasik M, Demas W, Ryu J, Bahary JP, Souhami L, Rotman M, Mehta MP and Curran WJ Jr: Whole-brain radiation therapy with or without stereotactic radiosurgery boost for patients with one to three brain metastases: phase III results of the RTOG 9508 randomised trial. Lancet *363*: 1665-1672, 2004.

15 Ernst-Stecken A, Ganslandt O, Lambrecht U, Sauer R and Grabenbauer G: Phase II trial of hypofractionated stereotactic radiotherapy for brain metastases: results and toxicity. Radiother Oncol *81*: 18-24, 2006.

16 Aoyama H, Shirato H, Tago M, Nakagawa K, Toyoda T, Hatano K, Kenjyo M, Oya N, Hirota S, Shioura H, Kunieda E, Inomata T, Hayakawa K, Katoh N and Kobashi G: Stereotactic radiosurgery plus whole-brain radiation therapy *vs*. stereotactic radiosurgery alone for treatment of brain metastases: a randomized controlled trial. JAMA *295*: 2483-2491, 2006.

17 Nieder C and Grosu AL: Stereotaktische Radiochirurgie von Hirnmetastasen – routinemäßig mit Ganzhirnbestrahlung? Strahlenther Onkol *183*: 52-53, 2007.

18 Nieder C, Astner ST, Grosu AL and Molls M: Evaluation of late neurological adverse events in patients with brain metastases from non-small cell lung cancer. Anticancer Res *27*: 1701-1704, 2007.

19 DeAngelis LM, Delattre JY and Posner JB: Radiation-induced dementia in patients cured of brain metastases. Neurology *39*: 789-796, 1989.

20 Khuntia D, Brown P, Li J and Mehta MP: Whole-brain radiotherapy in the management of brain metastasis. J Clin Oncol *24*: 1295-1304, 2006.

21 Kocher M, Eich HT, Semrau R, Güner SA and Müller RP: Phase I/II trial of simultaneous whole-brain irradiation and dose-escalating topotecan for brain metastases. Strahlenther Onkol *181*: 20-25, 2005.

Received July 7, 2008
Revised September 3, 2008
Accepted September 20, 2008