Clin Transl Oncol (2007) 9:590-595
DOI 10.1007/s12094-007-0108-2

Incidence of radiation-induced leukoencephalopathy after whole brain radiotherapy in patients with brain metastases

C. Conill[a], J. Berenguer[b], M. Vargas[a], A. López-Soriano[b], I. Valduvieco[a], J. Marruecos[a] and R. Vilella[c]

[a]Department of Radiation Oncology. Hospital Clínic. Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS). University of Barcelona. Barcelona, Spain
[b]Department of Radiology. Hospital Clínic. Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS). University of Barcelona. Barcelona, Spain
[c]Department of Immunology. Hospital Clínic. Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS). University of Barcelona. Barcelona, Spain

Abstract *Introduction:* Whole brain radiation therapy (WBRT) remains a recommended treatment for patients with brain metastases in terms of symptom palliation, especially when extracranial systemic disease is present. The aim of the study was to determine the clinical correlation between pre-existing leukoaraiosis and posterior leukoencephalopathy secondary to WBRT. *Methods and materials:* We retrospectively reviewed the results of WBRT treatment in 44 patients with melanoma brain metastases. The neuroimaging abnormalities of the white matter (T2-weighted MRI) were graded over time. Results: From the 37 evaluable patients the mean age was 53 years old, 23 male and 14 female. Vascular risk factors were present in 22 patients (59.5%). The WBRT total dose was 20 Gy/5fr (n=21) and 30 Gy/10fr (n=16). Leukoaraiosis pre-WBRT was observed in 9/37 patients (24.3%) and leukoencephalopathy post-WBRT in 2/37 (5.4%). Univariate analysis of prognostic factors (sex, age and vascular risk factors) for leukoaraiosis was conducted observing statistically significant differences for patients with age ≥65 years old (p=0.003). Nineteen patients survived more than 3 months. Twelve patients (63.2%) suffered from vascular risk factors. Univariate analysis demonstrated previous leukoaraiosis as a prognostic factor for developing further leukoencephalopathy after WBRT (p=0.015). *Conclusions:* Radiation-induced leukoencephalopathy is greater in patients with pre-existing leukoaraiosis. Because of the potential of long-term survival in a small subset of patients with brain metastases and the risk of radiation-induced dementia, neurotoxicity reduction in patients with leukoaraiosis is an important goal of treatment.

Key words Central nervous system • Radiation therapy • Radiation toxicity • Magnetic resonance imaging • Late radiation effects • Leukoencephalopathy • Leukoaraiosis

Conill C, Berenguer J, Vargas M et al (2007) Incidence of radiation-induced leukoencephalopathy after whole brain radiotherapy in patients with brain metastases. Clin Transl Oncol 9:590-595

Introduction

Brain metastases represent an important cause of morbidity and mortality in cancer patients. In metastatic melanoma brain metastases are clinically diagnosed in 40–60% of patients and its incidence increases to 70–90% at autopsy [1]. Whole brain radiation therapy (WBRT) as a treatment of brain metastases was first described 50 years ago by Chao et al. [2], and it is accepted as the main treatment modality in terms of symptom palliation, especially when extracranial systemic disease is present. Total dose and fractionation regimens more commonly used have been 20 Gy in 5 fractions or 30 Gy in 10 fractions. Nevertheless, patients' outcomes remain poor, with a median survival time (MST) ranging from 3 to 6 months [3, 4]. The use of chemotherapy has been limited to agents that have antitumour activity and penetrate central nervous system by crossing the blood–brain barrier, such as nitrosureas (BCNU) and fote-

C. Conill (✉)
Department of Radiation Oncology
Hospital Clinic
C/ Villarroel, 170
ES-08036 Barcelona, Spain
E-mail: cconill@clinic.ub.es

Received 19 April 2007 / Accepted 2 July 2007

mustine. Recent studies have reported complete remission of melanoma's brain metastases after treatment with temozolomide (TMZ) (200 mg/m^2) as a single agent chemotherapy [5, 6] or in combination with WBRT [7]. Efforts are underway to assess the additive benefit of TMZ to WBRT in brain metastases. In a previous study, WBRT (20 Gy/5 fractions) and adjuvant TMZ-based chemotherapy, demonstrated a benefit on survival when compared with WBRT alone [8].

Frequently these patients have severe neurological symptoms resulting in a decreased quality of life. In patients with long-term survival, necrosis and cognitive dysfunction due to leukoencephalopathy are the main delayed complications of brain irradiation [9]. Pathophysiology includes both small vessel and glial cell damage. Diffuse radiation leukoencephalopathy may yield to a global cognitive or personality dysfunction dementia. The aim of this retrospective study was to determine the clinical correlation between pre-existing leukoaraiosis and posterior leukoencephalopathy secondary to WBRT in patients with melanoma brain metastases.

Methods and materials

Between July 1997 and May 2004, 44 patients with melanoma brain metastases were treated with WBRT. The diagnosis of brain metastases and leukoencephalopathy was established by magnetic resonance imaging (MRI). The patients' performance status was assessed using the Karnofsky performance status (KPS) index [10, 11]. The Radiation Therapy Oncology Group (RTOG) Recursive Partitioning Analysis (RPA) [12] model was used for patient classification: Class I, patients with KPS≥70, younger than 65 years old with controlled primary tumour and no extracranial metastases; Class III, KPS< 70; Class II, all others. Presence of vascular risk factors such us smoking, hypertension, diabetes, hypercholesterolaemia and heart disease was noted. In all patients WBRT was delivered with 6 Mv photons covering all cranial content through two isocentre parallel and opposed fields, up to a total dose of 20 Gy/5 fractions or 30 Gy/10 fractions. TMZ was administered as a single agent [(200 mg/m^2) during 5 days, 28-day cycle] or in combination with other cytotoxic or immunotherapeutic agents (150 mg/m^2) after WBRT up to clinical or MRI progression. MRI was performed in stage III melanoma patients during their follow-up at 4-month intervals or when required depending on neurological status.

White matter neuroimaging abnormalities (leukoaraiosis) was referred as bilateral patchy or diffuse hyperintensity areas on T2-weighted MRI. Progressive multifocal leukoencephalopathy (PML) was defined as a demyelinating cerebral disease with multifocal hyperintense T2-high signals with restricted diffusion at the MRI.

In order to evaluate white matter changes over time, the Zimmerman system was adopted [13]. Five periventricular hyperintensity (PVH) patterns of increasing extent and intensity were scored: grade 0, no PVH; grade 1, discontinuous PVH – rounded hyperintense foci seen at the angles of frontal horns bilaterally, caps of hyperintensity surrounding occipital horns medially and laterally, and streaks of hyperintensity extending along the atria of lateral ventricles; grade 2, continuous PVH – a pencil-thin continuous line of hyperintensity surrounding the ventricles; grade 3, periventricular halo – a band of hyperintensity of variable thickness with smooth lateral margins surrounding the ventricles; and grade 4, diffuse white matter abnormality – hyperintensity extending from the ventricular lining to the corticomedullary junction involving all or most of the white matter, lateral margins with irregular hyperintensity.

Statistical analysis

Survival was calculated for all patients from the date of radiotherapy to the date of death or last follow-up. Actuarial survival curves were plotted according to the Kaplan-Meier method. Statistical significance was defined as $p<0.05$ (two-tailed). To assess the effect of prognostic variables, factors were compared univariately by Chi-square analysis.

Results

From the total of 44 patients treated, 37 fulfilled our inclusion criteria. Seven patients were excluded because MRI scans previous to brain metastases diagnosis were not available. The mean age was 53 years (min. 17; max. 84). Twenty-three patients were male and fourteen female (Table 1). KPS was equal to or higher than 70 for the whole group. Thirty-four patients were classified as RPA Class II and three patients were RPA Class I. Vascular risk factors were present in 22 patients (59.5%). The total dose of WBRT was 20 Gy in 21 patients (57%) and 30 Gy in 16 patients (43%). In 27 patients (73%) TMZ was administered after WBRT. Previous to diagnosis of brain metastases, MRI white matter changes or leukoaraiosis were observed in 9 patients. MRI changes were defined as grade I in seven patients, and grade II in two. In two patients leukoencephalopathy was developed after WBRT.

Table 1 Description of patients

Total of patients	44
Number of evaluable patients	37
Gender (men/women)	23/14
Age (mean)	53 years old (min. 17; max. 84)
≤65 years old	25 (67.6%)
≥65 years old	12 (32.4%)
Vascular risk factors	22 (59.5%)
WBRT 20 Gy/5fr	21 (57%)
WBRT 30 Gy/10fr	16 (43%)
WBRT+TMZ	27 (73%)
Leukoaraiosis pre-WBRT	9/37 (24.3%)
Grade I	7
Grade II	2
Leukoencephalopathy post-WBRT	2/37 (5.4%)

Table 2 Univariate analysis. MRI changes of leukoaraiosis previous to diagnosis of brain metastases. Evaluable patients (n=37)

	Leukoaraiosis Presence/absence	p*
Sex		
Male	6/17	NS
Female	3/11	
Age		
<65 years old	2/23	0.003
≥65 years old	7/5	
Vascular risk factors		
Present	7/15	NS
Absent	2/13	

*Chi-square test

Prognostic factors for MRI changes

Sex, age and vascular risk factors were analysed. We found statistically significant differences in patients older than 65 years (p=0.003) (Table 2).

MST was 4 months (confidence interval [CI] 95%: range 2–6 months) (Fig. 1). Nineteen patients survived more than 3 months and twelve patients (63.2%) suffered from vascular risk factors. Correlation of leukoencephalopathy with sex, age, total radiation dose, TMZ-based chemotherapy or previous leukoaraiosis was also analysed. We found statistically significant differences in patients with leukoencephalopathy and previous leukoaraiosis (p=0.0015). No other statistical differences were found (Table 3).

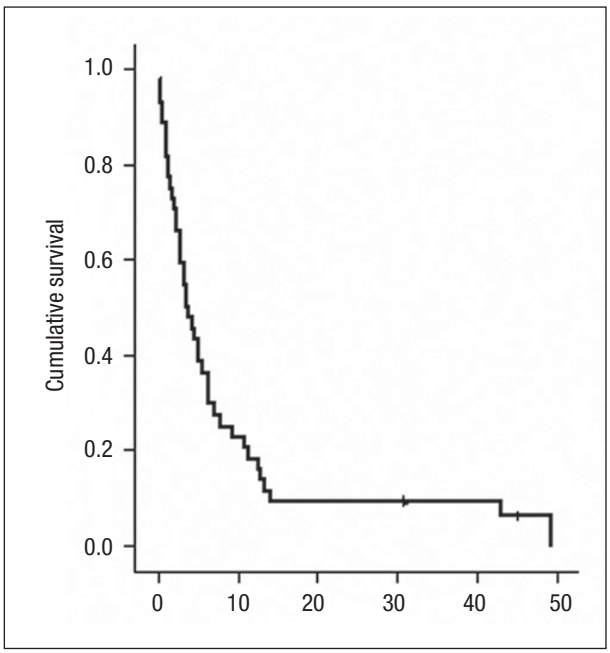

Fig. 1 Kaplan–Meier plot of survival time for the total group of patients with melanoma brain metastases treated with whole brain irradiation

Table 3 Incidence of leukoencephalopathy in patients with survival superior to 3 months (n=19). Univariate analysis

	Leukoencephalopathy		p*
	Presence	Absence	
Sex			
Male	5	6	NS
Female	0	8	
Age			
<65 years old	3	11	NS
>65 years old	2	3	
Total radiation dose			
20 Gy	2	7	NS
30 Gy	3	7	
WBRT			
No TMZ	0	1	NS
With TMZ	5	13	
Vascular risk factors			
Presence	5	7	NS
Absence	0	7	
Previous leukoaraiosis			
Presence	3	0	0.015
Absence	2	14	

*Chi-square test

In the subset of patients with leukoaraiosis survival was less than 3 months in six out of nine patients, and three patients lived more than 3 months, with an increase in white matter abnormalities at 2, 5 and 9 months after WBRT (Fig. 2A–C). Two patients without previous signs of MRI abnormalities developed further leukoencephalopathy after 8 and 10 months respectively (Table 4) (Fig. 2D–F).

Discussion

Neurotoxicity in terms of leukoencephalopathy is known to be a serious late adverse effect related to WBRT and it is a great concern in patients with brain metastases, especially in long-term survivors without evidence of disease. Radiation-induced white matter lesions are similar in aspect and pathology to those of vascular or hypertensive origin [14] and it is unknown whether vascular risk factors play a role in the development of radiation-induced encephalopathy. The pathological examination in autopsies revealed a basic pattern consisting on a diffuse pallor with axonal and myelin loss in white matter associated with astrocytic gliosis and small foci of necrosis [15]. It has been shown that the risk of delayed encephalopathy is greater in older patients and after high fraction doses [9, 16]. Metastases themselves may adversely affect neurobehavioral function. Delayed neurotoxicity associated to WBRT appears to become a problem when survival increases, but also because neu-

Table 4 Incidence of leukoaraiosis and/or leukoencephalopathy on MRI in patients with melanoma brain metastasis (BM) with survival superior to 3 months after WBRT

Case	Age	Gender	Survival (months)	MRI Grade (Zimmerman [13])	MRI Grade evolution of leukoencephalopathy
1	67	Male	4	Leukoaraiosis Grade II 19 months pre-WBRT	Grade III in 2 months
2	81	Male	31	Leukoaraiosis Grade I 21 months pre-WBRT	Grade II in 9 months and Grade III in 13 months
3	59	Male	45	Leukoaraiosis Grade I at diagnosis of BM	Grade II in 5 months and Grade III in 11–16 months
4	63	Male	11	Leukoencephalopathy Grade I 8 months post-WBRT	Grade IV in 3 months
5	47	Male	14	Leukoencephalopathy Grade I 10 months post-WBRT	Grade II in 3 months

roimaging has improved and awareness among physicians is higher [9]. Different definitions such us "diffuse radiation injury", "radiation-induced dementia", "radiation or treatment-induced leukoencephalopathy", "subacute brain atrophy after radiotherapy" or "radiation neurotoxicity" have been used [9, 17–20]. The clinical pattern is characterised by recent event memory loss and learning difficulties. Moreover, a severe intellectual deterioration culminating in a state resembling akinetic mutism has been described [18, 21].

White matter changes are more sensitively imaged by MRI than CT [22]. MRI allows the evaluation of

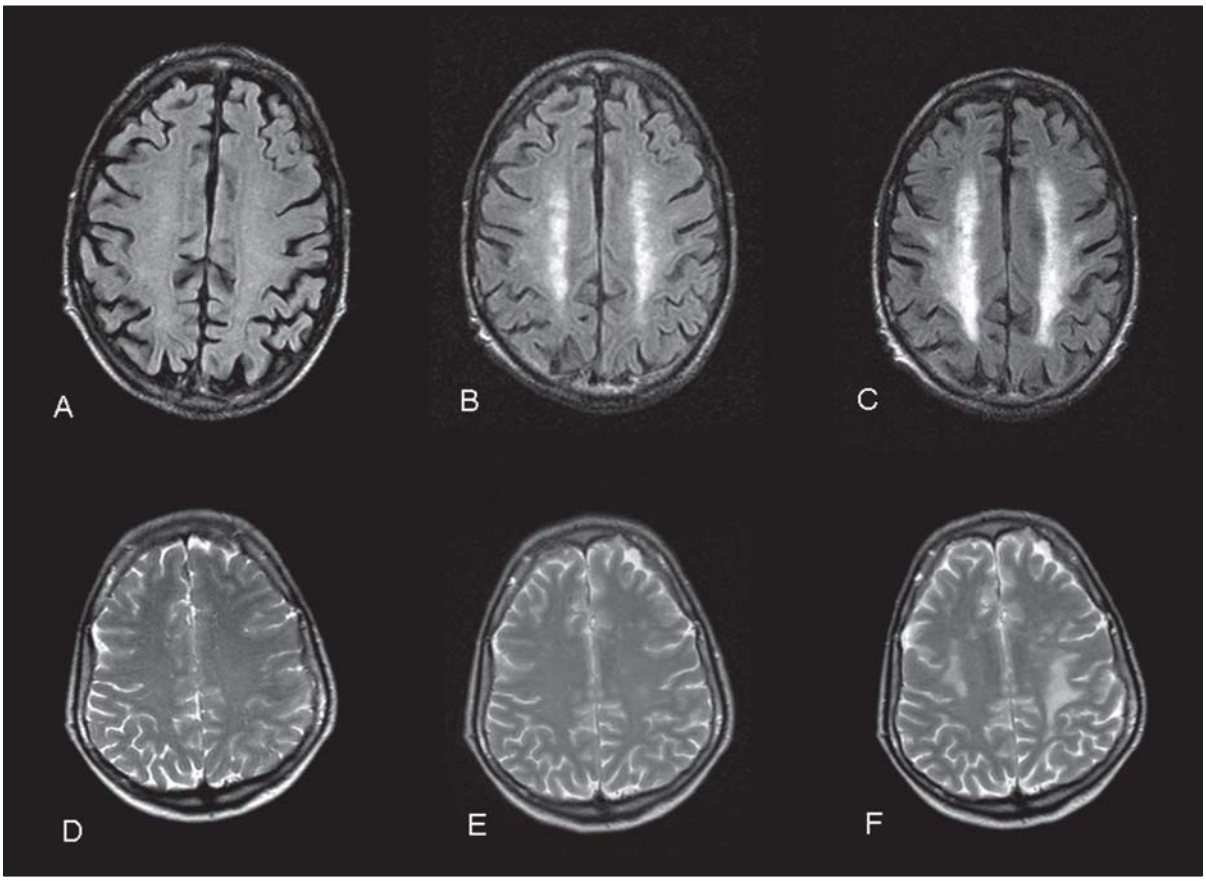

Fig. 2 Case 2 (A–C) (radiation dose 30 Gy/10 fr and TMZ). Axial FLAIR magnetic resonance image: **A** before WBRT shows slight bilateral hyperintensity of semioval centres (grade I); **B** nine months after WBRT shows serious bilateral symmetrical hyperintensity of both semioval centre (grade II); **C** 15 months after treatment shows increased bilateral symmetrical hyperintensity of semioval centres (grade III). Case 5 (D–F) (radiation dose 20 Gy/5 fr and TMZ). Axial T2-weighted fast spin-echo (FSE) MRI: **D** previous WBRT does not show abnormalities; **E** 10 months after WBRT shows incipient bilateral asymmetrical hyperintensity of both semioval centres (grade I); **F** 13 months after treatment shows worsening with bilateral and increased asymmetrical hyperintensity of semioval centres (grade II)

severity degrees of cortical atrophy, which is the main abnormality characteristic, and the presence of a bilateral increase in T2-weighted image throughout the white matter. The relationship of late adverse effects to radiation dose, fraction size, overall treatment time and patient age in patients with brain metastases has not been clearly defined. The true incidence of treatment-related side effects of cranial irradiation in adults who survive more than three months without brain tumour growth or recurrence has been significantly underestimated. DeAngelis et al. [18] studied a large group of patients with brain metastases from different primary tumours treated with WBRT and identified an incidence of "clinical" radiation-induced dementia of 1.9% (7/370). The diagnosis of brain metastases was performed by CT or MRI, without reference to how many patients presented previous cerebral white matter changes consistent with leukoaraiosis. Regine et al. [23], in a prospective randomised study, observed that progression of brain metastases was a much greater cause of neurocognitive dysfunction than WBRT. More recently, Shibamoto et al. [24] studied the incidence of brain atrophy and dementia after WBRT (40±10 Gy boost) and observed that dementia after WBRT without tumour recurrence was infrequent. In the present series three out of the five patients (60%) with leukoencephalopathy presented brain metastases recurrence.

Wassenberg et al. [25] observed that pre-existing white matter abnormalities and age older than 60 years may predispose to radiation-induced white matter lesions in primary central nervous system lymphoma patients. These results are consistent with our findings as 58% of patients older than 65 years showed a significantly higher risk of presenting white matter changes, like previous leukoaraiosis in developing leukoencephalopathy after WBRT. In the present study, we found a 24.3% incidence of leukoaraiosis and 5.4% MRI leukoencephalopathy changes after WBRT. Vascular risk factors are associated with neurotoxicity and can interact synergically with cranial radiation leading to enhanced neurotoxicity. Sixty-six percent (n=29) of patients were treated with TMZ, but up to now no references have been found concerning neurotoxicity related to TMZ. As stated by Gruss et al. [26], toxic leukoencephalopathy and mental deterioration after WBRT with 2.5 Gy fractions, five times a week, up to a total dose of 40 Gy and three additional boosts of 2 Gy followed by fotemustine has been reported in a patient who survived more than 2.5 years.

Fisher et al. [20], in a study of patients with primary central nervous system lymphoma treated with WBRT, observed a delay but not prevention of neurotoxicity in those patients treated with hyperfractionation schedule. Among our patients, the small patient group with survival superior to 3 months does not permit the evaluation of the clinical relevance of the dose per fraction.

In conclusion, despite advances in oncology, brain metastases remain incurable, with a MST of 4 months. Given this situation, improvement in the quality of life is a well known measure of therapeutic success rather than gaining survival time with debilitating symptoms. Radiation-induced leukoencephalopathy is greater in patients with pre-existing leukoaraiosis. Because of the potential of long-term survival in a small subset of patients with brain metastases and the risk of radiation-induced dementia, neurotoxicity reduction in patients with leukoaraiosis should be an important goal of further studies.

References

1. Madajewicz S, Karakousis C, West CR et al (1984) Malignant melanoma brain metastases. Review of Roswell Park Memorial Institute experience. Cancer 53:2550–2552
2. Chao JH, Phillips R, Nickson JJ (1954) Roentgen-ray therapy of cerebral metastases. Cancer 7:682–689
3. Carella RJ, Gelber R, Hendrickson F et al (1980) Value of radiation therapy in the management of patients with cerebral metastases from malignant melanoma: Radiation Therapy Oncology Group Brain Metastases Study I and II. Cancer 45:679–683
4. Buchsbaum JC, Suh JH, Lee S-Y et al (2002) 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 94:2265–2272
5. Franke W, Neumann N, Richter-Hintz D et al (2000) Temozolomide – A promising agent in the therapy of brain metastases in malignant melanoma. In: American Society of Clinical Oncology 36th Annual Meeting, New Orleans, 20–23 May. Prog Proc Am Soc Clin Oncol 19: 575
6. Biasco G, Pantaleo MA, Casadei S (2001) Treatment of brain metastases of malignant melanoma with temozolomide. N Engl J Med 345:621
7. Conill C, Puig S, Toscas I, Castel T (2002) Complete response of cerebral metastatic melanoma after a combined treatment of radiotherapy and temozolomide. Med Clin (Barc) 119:758–759
8. Conill C, Fernandez-Ibiza J, Malvehy J et al (2004) Temozolomide in patients with melanoma brain metastases treated with whole brain irradiation. Med Clin (Barc) 122:413–415
9. Crossen JR, Garwood D, Glastein E, Neuwelt EA (1994) Neurobehavioral sequelae of cranial irradiation in adults: a review of radiation-induced encephalopathy. J Clin Oncol 12:627–642
10. Karnofsky DA, Abelmann WH, Craver LF, Burchenal JH (1948) The use of nitrogen mustards in the palliative treatment of cancer. Cancer 1:634–656
11. Conill C, Verger E, Salamero M (1990) Performance status assessment in cancer patients. Cancer 65:1864–1866
12. Gaspar LE, Scott Ch, Murray K, Curran W (2000) Validation of the RTOG recursive partitioning analysis (RPA) classification for brain metastases. Int J Radiat Oncol Biol Phys 47: 1001–1006
13. Zimmerman RD, Fleming CA, Lee BCP et al (1986) Periventricular hyperintensity as seen by magnetic resonance: Prevalence and significance. AJNR Am J Neuroradiol 7:13–20
14. Tsuruda JS, Kortman KE, Bradley WG et al (1987) Radiation effects on cerebral white matter: MR evaluation. AJR Am J Roentgenol 1987; 149:165–71
15. Vigliani MC, Duyckaerts C, Hauw JJ et al (1999) Dementia following treatment of brain tumors with radiotherapy administered alone or in combination with nitrosourea-based chemotherapy: a clinical and pathological study. J Neuro-Oncol 41:137–149
16. Corn BW, Yousem DM, Scott CB et al (1994) White matter changes are correlated significantly with radiation dose. Cancer 74:2828–2835
17. Asai A, Matsutani M, Kohno T et al (1989) Subacute brain atrophy after radiation therapy for malignant brain tumor. Cancer 63:1962–1974
18. DeAngelis LM, Delattre JY, Posner JB (1989) Radiation-induced dementia in patients cured of brain metastases. Neurology 39:789–796
19. Hochberg FH, Slotnick B (1980) Neuropsychologic impairment in astrocytoma survivors. Neurology 30:172–177
20. Fisher B, Seiferheld W, Schultz Ch et al (2005) Secondary analysis of Radiation Oncology Group Study (RTOG) 9310: an intergroup phase II combined modality treatment of primary central nervous system lymphoma. J Neuro-Oncol 74:201–205
21. Johnson BE, Becker B, Goff WB et al (1985) Neurologic, neuropsychologic, and computed tomography scan abnormalities in 2 to 10-year

survivors of small cell carcinoma lung cancer. J Clin Oncol 3:1659–1667
22. Curran WJ, Hecht-Leavitt C, Schut L et al (1987) Magnetic resonance imaging of cranial radiation lesions. Int J Radiat Oncol Biol Phys 13:1093–1098
23. Regine WF, Scott C, Murray K, Curran W (2001) Neurocognitive outcome in brain metastases patients treated with accelerated-fractionation vs. accelerated-hyperfractionated radiotherapy: an analysis from Radiation Therapy Oncology Group Study 91-04. Int J Radiat Oncol Biol Phys 51:711–717
24. Shibamoto Y, Baba F, Oda K et al (2006) Incidence of brain atrophy and dementia after whole-brain radiotherapy in patients with brain metastases: a prospective study. Int J Radiat Oncol Biol Phys 66[Suppl 1]:S86–S87
25. Wassenberg MW, Bromberg JE, Witkamp TD et al (2001) White matter lesions and encephalopathy in patients treated for primary central nervous system lymphoma. J Neurooncol 52: 73–80
26. Gruss C, Geissler A, Schalke B et al (2002) Severe neurological disabilities after complete remission of advanced malignant melanoma following fotemustine therapy in combination with total brain irradiation. Melanoma Res 12:403–404