21. DeAngelis LM, Yahalom J, Thaler HT, Kher U. Combined modality therapy for primary CNS lymphoma. *J Clin Oncol* 1992, **10**, 635–643.
22. Abrey LE, De Angelis LM, Yahalom J. Long-term survival in primary CNS lymphoma. *J Clin Oncol* 1998, **16**, 859–863.
23. Villá S, Viñolas N, Verger E, *et al*. Efficacy of radiotherapy for malignant gliomas in elderly patients. *Int J Radiation Oncol Biol Phys* 1998, **42**, 977–980.
24. 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**, 3563–3569.
25. Hao D, Di Francesco LM, Brasher PM, *et al*. Is primary CNS lymphoma really more common? A population-based study incidence, clinicopathological features and outcomes in Alberta from 1975 to 1996. *Ann Oncol* 1999, **10**, 65–70.
26. Fonseca R, O'Neill BP, Foote RL, *et al*. Cerebral toxicity in patients trated for small cell carcinoma of the lung. *Mayo Clin Proc* 1999, **74**, 461–465.
27. Brada M, Sharpe G, Rajan B, *et al*. Modifying radical radiotherapy in high grade gliomas; shortening the treatment time through acceleration. *Int J Radiation Oncology Biol Phys* 1999, **43**, 287–292.
28. Lafernaard FJ, Levendag PC, Nowak PJ, *et al*. Identification of prognostic factors in patients with brain metastases: a review of 1292 patients. *Int J Radiat Oncol Biol Phys* 1999, **43**, 795–803.
29. Aupérin A, Arriaga R, Pignon JP, *et al*. Prophylactic cranial irradiation for patients with small-cell lung cancer in complete remission. *N Eng J Med* 1999, **341**, 476–484.
30. Arriaga R, Le Chevalier T, Boric F, *et al*. Prophylactic crania! irradiation for patients with small-cell cancer in complete remission. *J Natl Cancer Inst* 1995, **87**, 184–190.
31. Gregor A, Cull A, Stephens RJ, *et al*. Prophylactic cranial irradiation is indicated following complete response to induction therapy in small cell lung cancer: results of a multicentre randomised trial. *Eur J Cancer* 1997, **33**, 1752–1758.
32. Fírvida JL, Viñolas N, Muñoz M, *et al*. Age: a critical factor in cancer management. A prospective comparative study of 400 patients. *Age and Ageing* 1999, **28**, 103–105.

Contra:

A.A. Brandes [a,*], A. Rigon [b], S. Monfardini [a]

[a] *Divisione di Oncologia Medica, Azienda Ospedale-Università, via Giustiniani 2, 35100 Padova, Italy*
[b] *Divisione di Radioterapia, Azienda Ospedale-Università, via Giustiniani 2, 35100 Padova, Italy*

1. Introduction

Although brain radiotherapy is a necessary treatment to prolong life expectancy in patients with primary or metastatic brain tumours, it has damaging effects that are poorly understood, especially in elderly patients, and mostly detrimental to the patients' quality of life. Whilst several reports adequately document brain injury from brain radiation therapy, the full impact of the problem is still not completely clear because the quality of life and mental status of the survivors have received less attention than the actual survival. If the treatment of patients with glioblastoma is palliative, concern about the effects of radiotherapy for anaplastic astrocytoma or brain metastasis of a well stabilised extracranial tumour in elderly patients becomes meaningful and every effort must be made to understand and prevent the potentially devastating long-term sequelae of such treatment.

2. Adverse effects of radiotherapy of the brain

The standard treatment of patients with high grade gliomas is radiotherapy at the dosage of 1.8–2.0 Gy/day given 5 days a week up to 59.4–60 Gy [1]; this treatment, however, is not free of damaging effects, especially when administered on the whole brain.

According to the time of appearance, the adverse effects of radiation can be divided [2,3] into: (a) Acute reactions, which occur during radiotherapy, and are correlated with time-dose fractions. 200 rad fractions with a total dose of 60 Gy are usually tolerated, even if cortiocosteroids are often required. These acute effects are considered reversible. (b) Early delayed reactions, which can appear a few weeks to several months after radiotherapy; these are characterised by somnolence and lethargy which can persist up to 14 days, but these signs generally improve after 4 weeks and disappear in 6–8 weeks. The predominant pathological finding is a loss of myelin probably due to a lack of replacement of mature oligodendrocytes with their slow turnover [2]. This causes long-term memory processing deficits because hippocampal, thalamic and neocortical connections are very sensitive to white matter damage due to subacute demyelination [4]. Eldor and colleagues [5] found that early delayed radiation injury is characterised by vascular damage; the initial site of damage appears to be the endothelial cell lining of the vessel wall, with nuclear and cytoplasmic swelling and formation of mural thrombi; these changes later evolve into thickening of the basement membrane and tunica media, uncontrolled proliferation of endothelial cells, and formation of platelet and fibrin thrombi [6]. This can lead to a total obliteration of the lumen of small blood vessels. In larger blood vessels, radiation has been

* Corresponding author. Tel.: +49-821-2970; fax: +49-821-2931.
E-mail address: brandes@ux1.unipd.it (A.A. Brandes).

0959-8049/00/$ - see front matter
PII: S0959-8049(99)00322-6

shown to enhance and accelerate the development of arteriosclerosis, probably due to its primary damage to the structural and functional integrity of the endothelial cell lining of the intima [3]. (c) Late delayed injury in the central nervous system (CNS) has not been studied as extensively as the early delayed lesions. These reactions can appear several months to years after radiotherapy, and are irreversible [7]. The injury is more present in the white matter, and can manifest as delayed radiation necrosis; indeed, in most cases, extensive areas of parenchymal necrosis were seen. Late delayed reactions may present with papilledema, progressive loss of vision, hemiparesis, dysphasia, focal seizures, dementia or hypothalamic insufficiency.

3. Clinical findings

Imperato and colleagues [8] studied a series of 160 consecutive patients with glioblastoma and anaplastic astrocytoma; 82% of them had radiotherapy. There were 9 long-term survivors; 2 became profoundly demented and died without evidence of tumour recurrence, 1 became moderately demented, 1 presented mild global dysfunction that prevented employment and 5 had significant neurological impairment.

Archibald and colleagues [4] evidenced that most long-term survivors (alive 18 months after diagnosis) of high grade glioma have significant cognitive difficulties; some patients will develop profound impairment years later, and only a few are capable of fully independent living. When predictable effective therapies for this cancer finally emerge, cognitive impairment resulting from treatment may become a significant medical and social problem, especially in elderly patients in whom the rate of radio-induced cognitive damage is much higher.

More rapidly growing tumours cause greater neuropsychological impairment [9], and it has been reported that high grade gliomas generally show more signs of frontal lobe dysfunction evidenced as long-term memory deficits [10]. In long-term survivors, memory impairment, other cognitive deficits, progressive global dementia, apathy and personality changes may be the outcome of treatment and consequent atrophy. A resulting functional encephalopathy, termed radiation encephalopathy, may resemble normal pressure hydrocephalus or leucodystrophy. This syndrome may be a consequence of increased permeability induced by radiotherapy, leading to the transudation of fluid into the interstitial spaces and thus, brain oedema that requires steroids for several months, with deterioration of the quality of life. Patients with leucoencephalopathy show ventricular enlargement, prominent sulci and hypodense white matter. The presence of hydrocephalus can be due to fibrosis of the leptomeninges or the arachnoid villi, and is responsible for alterations in gait, mentation, speech and sphincter control [6].

According to Marks and colleagues [11], radiation necrosis has an incidence of 5% in patients who received $\geqslant$4500 rad using 180 to 200 rad fractions, with a median time of onset of 14 months after radiotherapy. The radiation injury is a function of total radiation dose, fraction size, volume irradiated and duration of treatment [12]; radiologically, it can mimic tumour progression, but 28% of these patients subsequently improved without any further therapy [13].

4. Brain radiotherapy and aging

The CNS undergoes age-related regional losses of neurons in the cortex, cerebellum and hippocampus, as well as lipofuscin pigment accumulation; gradual losses of brain weight and cerebral blood flow occur. An Italian group [14] studied 5632 subjects aged 65–84 years, and found that the age adjusted prevalence rate of age-related cognitive disorders was 8.6%. Cognitive impairment is a frequent condition in the elderly and its incidence increases with age [15]. A Swedish group [16] conducted a 3 year follow-up study in 65 85-year-olds from a population-based 1902 sample; 29 persons were demented at 85 years of age; 7 developed dementia during follow-up, and only 29 remained non-demented. The dementia was mostly vascular, which is caused by cerebrovascular disorders and associated with degenerative changes in intracerebral capillaries and arterioles. These types of microvascular changes may lead to a dysfunction of the endothelial cells, with increased permeability and extravasion of serum proteins.

The elderly obviously appear to be more susceptible to radiation-induced brain atrophy and ultimately dementia, due to the presence of pre-existing vascular changes, and the higher incidence of diabetes mellitus that predisposes to vascular injury and atherosclerosis [17].

Stylopopulos and colleagues [18] showed that even glioma survivors older than 40 years of age presented a more rapid decline in clinical and cognitive status than younger patients. Maire and colleagues [19] reported a strong correlation between age and preservation of adult intellectual ability.

Asai and colleagues [20] studied 91 patients (59 with gliomas and 32 with metastatic brain tumours). Radiation therapy for high grade gliomas was delivered at a dose of 2 Gy/day, 5 days a week on limited fields plus a 2 cm margin, whilst for metastatic brain tumours whole-brain radiotherapy was given. Brain atrophy was observed in 56% of the patients, and was strongly correlated with age; in patients 50 years of age or older, the incidence was 72.9% whilst in patients younger than 50 years it was 39.2% ($P=0.005$). The incidence of

radiation-induced brain atrophy was correlated to the irradiation volume; it was noted in 73.3% of whole-brain irradiated patients, and in 47.5% of patients receiving regional irradiation ($P=0.025$). There was a significant difference in the incidence of dementia between the two groups, 75 versus 35.5% ($P=0.01$). Overall, dementia was observed in 48.9% of the patients, and was characterised in its mild form by amnesia and acalculia in the absence of urinary incontinence, and in its severe form by severe dementia and disturbance of consciousness. The average ages of the patients with dementia and normal mental function were 60.5 and 42.8 years of age, respectively, and the difference was significant ($P=0.001$). It is not surprising that dementia occur more frequently in older than in younger patients; radiation determines an occlusion of the microvasculature, resulting in an atherosclerotic-like disorder, and the damage is obviously enhanced in an already atherosclerotic brain [21].

5. Brain tumours in the elderly

In recent years, the incidence of both high and low grade gliomas in the elderly has increased. In slow growing tumours with a long life expectancy, the impact of radiotherapy must be carefully evaluated, as its risk–benefit ratio becomes increasingly unfavourable with increasing age [22].

In high grade gliomas, survival is clearly age-dependent [23,24], and several hypotheses have been advanced to explain the poor clinical course of elderly patients: (a) Increased peri- and postoperative morbidity and mortality as well as a diminished tolerance to therapy can be caused by the presence of concomitant diseases, such as hypertension, ischaemic heart disease, diabetes, prostate hypertrophy, chronic broncho-pulmonary disease and Parkinson's disease [25]. However, this theory does not explain why survival is also reduced in elderly patients without concomitant diseases [25]. (b) The preponderance of tumours have a high histological grade of malignancy. However, a reduced survival in this age class was also observed in patients with a disease having a lower grade of malignancy than glioblastoma [25]. (c) Genetic aberrations can determine a more aggressive tumour with less sensitivity to radio- and chemotherapy.

Using comparative genomic hybridisation to discern which genetic aberrations are associated with gliomas in old age, Kunwar and colleagues [26] found that in glioblastomas +7 (amplifications on chromosome 7) as well as −18q and −10 occurred more frequently ($P=0.005$ and 0.006 respectively) in older patients, whilst +17q, −Xp, −5q and −10q occurred primarily in younger patients ($P=0.05$). This study demonstrates that older patients have genetically different tumours from younger patients, thus implying that age influences the genetic pathways of tumour development amongst malignant gliomas. It was also observed that 65% of the +7 chromosomal alterations failed to respond to radiotherapy, so the poor clinical outcome of brain tumours in the elderly might be associated with a poor response to radiotherapy as well as to chemotherapy.

In their retrospective study to ascertain whether radiotherapy improves survival or neurological function in elderly patients with malignant supratentorial glioma, Meckling and colleagues [27] investigated 103 patients aged 70 years or over at the time of first presentation; for patients aged 80 years, no significant difference in distribution was found between those who received and those who did not receive radiotherapy ($P=0.61$). The study showed that patients >80 years of age with high grade brain tumour do not benefit from radiotherapy, whereas patients between 70 and 79 years of age with a neurological function score of 2 or more (ECOG classification) should be offered this option.

In a retrospective review of 113 patients with glioma, 19 of which were 70 years of age, Peschel and colleagues [28] found that 1 and 2-year survival rates were 18% and 0, respectively, in the older group versus 38 and 10% in younger age group; the differences were significant ($P=0.05$ and $P=0.01$). As the number of elderly patients were small, these investigators recommended prospective clinical trials in this age group to compare supportive care only versus standard radiotherapy, and to better define the role of high-dose radiation.

Villa and colleagues [29] studied 85 elderly patients with high grade gliomas and reported a total median survival time of 18 weeks; amongst the patients that completed the radiotherapy, this figure reached 55 weeks in those aged 65–70 years, and 34 weeks in patients >71 years old. The cases are highly selected; indeed, Pierga and colleagues [30] reported only 30 weeks survival in 30 consecutive patients aged >70 years who received radiotherapy and chemotherapy. Other schedules have been studied to improve the quality of life, and reduce radiotherapy damage.

In a series of 29 patients (age $\geqslant$65 years; mean age 65.9) with an initial performance status of $\leqslant$50 (mean: 43.3) Bauman and colleagues [31] administered a short course of whole-brain radiotherapy (30 Gy/10 fractions/2 weeks) and obtained a median survival of 6 months, suggesting that initial performance status could be used to select a subset of elderly patients who may benefit from a more intensive course of radiation.

Newall and colleagues [32] studied 18 patients aged over 60 years (age range: 63–75 years, performance status 50, range: 30–90), with a histological diagnosis of glioblastoma. The radiotherapy employed was opposed portals encompassing the whole brain to a midline dose of 3000 cGy in 10 fractions; both fields were treated

daily, and treatment was given on a 5-day per week schedule. Median survival was 44 weeks (range: 29–57). Amongst the patients with initial performance status $\leqslant 70$, median survival was 36 weeks. 15/18 patients had a functional improvement, and 3 of these were able to go on long journeys and resume part-time work. These results are as good or better than those reported in other studies [27], but they may have been somewhat biased by the large number of total and subtotal resections (17/18) and initial higher performance status of the patients (mean: 60, 10/18 patients had $\geqslant 50$). A regimen of surgery plus 2 or 3 weeks of radiotherapy appears to result in a survival duration equivalent to that achieved with long courses of radiotherapy; moreover, it is less time-consuming, less costly and probably less stressful to the patient.

However, it is not generally agreed to reduce radiotherapy in elderly patients. Indeed, Mohan and colleagues [33] report a median survival time of 4.5 months with radiotherapy $\geqslant 40$ Gy versus 7.3 months with $\geqslant 55$ Gy.

Data on the costs of this choice are not given; beside the economic burden for the patient, the quality of life offered to the patient must be considered; indeed, to obtain approximately a 3 month increase in survival, 1 month is spent undergoing the longer treatment.

6. Conclusion

Regarding the primary brain tumours, the natural history of low-grade astrocytoma and oligodendroglioma is longer than previously thought, and radiotherapy for these patients may have detrimental long-term side-effects. Accordingly, radiotherapy should be avoided in low grade gliomas. Regarding anaplastic astrocytoma and glioblastoma [34], it was shown that brain radiotherapy on limited fields does not have a detrimental effect on survival, because the incidence of distant recurrences is not higher than 4–5%. Thus, whole brain radiotherapy has been abandoned in favour of limited fields, that should be very limited in the elderly. In high grade gliomas, age, KPS and extent of resection were found to have prognostic value for survival. Analysis of the prognostic influence of some factors revealed that the median survival after minimal debulking was less than 26 weeks in patients with high grade gliomas and KPS < 60 and age > 60 years. The median survival of patients with high grade astrocytomas and best supportive care is 14 weeks; this means that in this group of patients with negative prognostic factors, the time advantage gained by radiotherapy is slightly higher than the time required for the treatment itself and, thus, it seems reasonable to avoid radiotherapy. In any case, intense radiotherapy should be avoided; however, in selected cases with small residual tumour and KPS > 70, a short radiation treatment may be considered, for instance 10 times 3 Gy over very limited fields in 2 weeks, five fractions a week [35]. In asymptomatic patients without residual disease after surgery, radiotherapy is often best avoided. The same guideline may apply in the presence of a large, inoperable mass.

In the chemosensitive metastatic tumours of the brain, chemotherapy can substitute for radiotherapy. If the tumour is chemoresistant, stereotactic radiotherapy without whole-brain irradiation can be considered. Radiotherapy should be avoided if multiple, in particular non-radiosensitive, lesions are present, and in patients with a low performance status and poor clinical condition; in these situations, a conservative approach with the best supportive care may guarantee the best quality of life.

References

1. Brandes AA, Soesan M, Fiorentino M. Medical treatment in high grade malignant gliomas in adults: an overview. *Anti Cancer Research* 1991, **11**, 719–728.
2. Sheline G, Wara W, Smith V. Therapeutic irradiation and brain injury. *Int J Rad Oncol Biol Phys* 1980, **6**, 1215–1228.
3. Hopewell JW. Radiation injury to the central nervous system. *Med Ped Oncol* 1998, **1**(Suppl.), 1–9.
4. Archibald Y, Lunn D, Ruttan L, *et al*. Cognitive functioning in long-term survivors of high grade glioma. *J Neurosurg* 1994, **80**, 247–253.
5. Eldor A, Fuks Z, Matzner Y, *et al*. Perturbation of endothelial functions by lonizing irradiation: effects on prostaglandins, chemoattractants and mitogens. *Semin Thromb and Hemost* 1989, **15**, 215–222.
6. DeAngelis L, Delattre JY, Posner J. Radiation-induced dementia in patients cured of brain metastases. *Neurology* 1989, **39**, 789–796.
7. Martins A, Johnston J, Henry J, *et al*. Delayed radiation necrosis of the brain. *J Neurosurg* 1977, **47**, 336–345.
8. Imperato JP, Paleologos N, Vick N. Effect of treatment on long-term survivors with malignant astrocytomas. *Ann Neurol* 1990, **28**, 818–822.
9. Salander P, Karlsson T, Bergenheim T, *et al*. Long-term memory deficits in patients with malignant gliomas. *J Neuro-Onc* 1995, **25**, 227–238.
10. Hom J, Reitam RM. Neuropsychological correlates of rapid vs slowly growing intrinsic cerebral neoplasms. *J Clin Neuropsychol* 1984, **6**, 309–324.
11. Marks J, Baglan R, Prassad S, *et al*. Cerebral radionecrosis: incidence and risk in relation to dose, time, fractionation and volume. *Int J Rad Oncol Biol Phys* 1980, **7**, 243–252.
12. Burger P, Mahaley M, Dudka L, *et al*. The morphologic effects of radiation administered therapeutically for intracranial gliomas. A postmortem study of 25 cases. *Cancer* 1979, **44**, 1256–1272.
13. Hoffman WF, Levin V, Wilson B. Evaluation of malignant glioma patients during the postirradiation period. *J Neurosurg* 1979, **50**, 624.
14. Di Carlo A, Baldereschi M, Maggi S. Prevalence and risk factors of age-related cognitive decline: The Italian longitudinal study on aging. *Neurology* 1998, **50**, Abstract 231.
15. Cohen HJ. Biology and aging as related to cancer. *Cancer* 1994, **74**, 2092–2100.

16. Skoog I, Wallin A, Fredman P. A population study on blood–brain-barrier function in 85-year-olds. Relation to Alzheimer's disease and vascular dementia. *Neurology* 1998, **50**, 966–971.
17. Crossen JR, Garwood D, Glastein E. Neurobehavioral sequelae of cranial irradiation in adults: a review of radiation-induced encephalopathy. *J Clin Oncol* 1994, **12**, 627–642.
18. Stylopopulos LA, George AE, De Leon MJ. Longitudinal CT study of parenchimal brain changes in glioma survivors. *Am J Neurorad* 1988, **9**, 517–522.
19. Maire JP, Coudin B, Guerin J. Neuropsychologic impairment in adults with brain tumors. *Am J Oncol* 1987, **10**, 156–162.
20. Asai A, Matsutani M, Kohno T, *et al*. Subacute brain atrophy after radiation therapy for malignant brain tumor. *Cancer* 1989, **63**, 1962–1974.
21. Murros K, Toole J. The effect of radiation on carotid arteries. *Arch Neurol* 1989, **46**, 449–455.
22. Brandes AA, Fiorentino MV. Treatment of brain tumors in the elderly. A review. *Oncology* 1998, **55**, 1–6.
23. Burger P, Green S. Patient age, histologic features, and length of survival in patients with glioblastoma multiforme. *Cancer* 1987, **59**, 1617–1625.
24. Corry J, Smith J, Wirth A, *et al*. Primary central nervous system lymphoma: age and performance status are more important than treatment modality. *Int J Rad Oncol Biol Phys* 1998, **41**, 615–620.
25. Ampil F, Fowler M, Kim K. Intracranial astrocytoma in elderly patients. *J Neuro-Oncol* 1992, **12**(2), 125–130.
26. Kunwar S, Bollen A, Prados M, *et al*. Age related genetic aoccur in malignant gliomas. *Proc Third Ann Mtg Soc Neuro-Oncol San Francisco*, 1998 (Abstract 118).
27. Meckling S, Dold O, Forsyth P, *et al*. Malignant supratentorial glioma in the elderly: is radiotherapy useful? *Neurology* 1996, **47**, 901–905.
28. Peschel R, Wilson L, Haffty B, *et al*. The effect of advanced age on the efficacy of radiation therapy for early breast cancer, local prostate cancer and grade III–IV gliomas. *Int J Rad Oncol Biol Phys* 1993, **26**, 539–544.
29. Villa S, Vinolas N, Verger E, *et al*. Efficacy of radiotherapy for malignant gliomas in elderly patients. *Int J Rad Oncol Biol Phys* 1998, **42**, 977–980.
30. Pierga JY, Hoang-Xuan K, Simon JM. Treatment of malignant gliomas in the elderly ($\geq$ 70 years). *Neurology* 1997, **48**, 27 (Abstract).
31. Bauman G, Gaspar L, Fisher B, *et al*. A prospective study of short-course radiotherapy in poor prognosis glioblastoma multiforme. *Int J Rad Oncol Biol Phys* 1994, **4**, 835–839.
32. Newall J, Ransohoff J, Kaplan B. Glioblastoma in the older patient: how long a course of radiotherapy is necessary? *J Neuro-Oncol* 1988, **6**, 325–327.
33. Mohan A, Suh JH, Phan JL, *et al*. Outcome in elderly patients undergoing definitive surgery and radiation therapy for supratentorial glioblastoma multiforme at a tertiary care institution. *Int J Rad Oncol Biol Phys* 1998, **42**, 981–987.
34. Wallner KE, Galicich JH, Krol G, *et al*. Patterns of failure following treatment for glioblastoma multiforme and anaplastic astrocytoma. *Int J Rad Oncol Biol Phys* 1989, **16**, 1405–1409.
35. Snijders-Keilholz A, Voormolen JH, Hermans J, *et al*. Should all patients with malignant astrocytoma have postoperative radiotherapy? *Acta Neuroch* 1991, **108**, 15.

Arbiter:

L.M. DeAngelis *

Department of Neurology, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10021, USA

The decision whether to administer radiotherapy to the brain of elderly patients harbouring intracranial neoplasms is an increasingly important issue. Cranial radiotherapy is the mainstay of treatment for both primary malignant and metastatic brain tumours. The most common primary brain tumour in the older age group is malignant glioma, particularly glioblastoma multiforme. There is significant epidemiological evidence that the incidence of this tumour is rising in general, particularly in the elderly population. This rising incidence is likely due to a combination of factors including improved neuro-imaging, a more aggressive diagnostic approach to new neurological symptoms in elderly patients, and a true change in the incidence of these diseases independent of better ascertainment [1,2]. With improved therapies leading to longer survival of patients with systemic cancer, there is an increased development of central nervous system (CNS) metastatic disease because a greater proportion of patients survive long enough to develop these intracranial complications [3].

Brandes and colleagues and Grau and Verger both acknowledge that the biology of malignant gliomas is more aggressive in older patients. In every single major prospective study of malignant gliomas, age is recognised as a critical and independent prognostic factor [1]. It is usually the most important prognostic factor, having a stronger impact on survival than either performance status or histopathology. It is very clear that these diseases have a different behaviour from the identical tumour in younger patients, and molecular pathology is beginning to categorise the genetic differences of malignant gliomas in the two age groups. Treatment of glioblastoma in the elderly rarely controls disease for longer than a few months. This is also true for whole-brain radiotherapy for brain metastases.

Neurotoxicity from radiation therapy has been divided into three different categories according to the temporal relationship of the neurological syndrome to the radiotherapy. Different syndromes are outlined in detail

* Tel.: +1-212-639-7123; fax: +1-212-717-3296.
E-mail address: deangell@mskcc.org (L.M. DeAngelis).

PII: S0959-8049(99)00320-2