Managing the Elderly Patient

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Abstract

Glioblastoma multiforme (*GBM*) is a devastating disease at any age. However, GBM has traditionally been associated with particularly poor outcomes in *elderly* patients, with reported median survival time of just a few months typical in many case series. The reasons for this are not entirely clear, but it has been suggested that the elderly are generally frailer and less able to cope with the *toxicity* associated with standard treatment approaches to GBM, notably *surgery* and *radiotherapy*. This may explain why single-modality therapy or best supportive care only becomes increasingly common with advancing age. More recently, however, there has been speculation that GBM may be a biologically more aggressive disease in the elderly and perhaps inherently more resistant to radiation. This has yet to be confirmed but has provoked interest in understanding precisely why age has such a negative effect on survival at a time when a significant increase in numbers of elderly GBM patients is predicted due to an aging population. Interestingly, since the introduction of the Stupp protocol, which promotes the use of *chemoradiotherapy* post surgical resection, several reports have emerged indicating that elderly patients can tolerate aggressive multimodality therapy with impressive median survival times of over a year in some cases. However, it is important to point out that *patient selection* is likely to be critical and the results in these series cannot be extrapolated to the general elderly population. Unsurprisingly, the gold standard treatment of GBM in the elderly has yet to be determined.

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As such, a number of *clinical trials* have been developed to specifically answer this question in patients over the age of 70, a group that has previously been excluded from pivotal trials in GBM. It is hoped that these studies will pinpoint clinical and/or molecular *prognostic factors* that will guide treatment of the individual elderly patient with the optimal combination of therapy.

Keywords
Glioblastoma multiforme (GBM) • Elderly • Toxicity • Surgery • Radiotherapy • Chemoradiotherapy • Patient selection • Clinical trials • Prognostic factors

Introduction

Glioblastoma (GBM) is an incurable and devastating malignancy, the incidence of which increases with age. Despite a modest improvement in overall survival from this disease in the past 20 years, stemming from advances in diagnostic and therapeutic techniques, the median survival of patients with GBM remains poor and is at best 14–18 months [1, 2]. Elderly patients, however, fare even worse and it has long been recognized that age is the single most important prognostic factor in GBM. Why this should be the case has been the subject of much debate for many years and, indeed, remains a controversial issue today. It has been suggested that the inferior outcomes seen in older patients are simply a result of less aggressive treatment or withholding treatment, most likely due to concerns over ability to cope with therapy and/or fear of inducing significant toxicity. A number of large population-based studies certainly concur with this viewpoint and demonstrate different patterns of care in elderly GBM patients compared with younger adults. As researchers achieve a greater understanding of the molecular basis of primary brain tumors, however, evidence is emerging that GBM may be a biologically different disease in the elderly. This may explain, or at least partly explain, why the prognosis in elderly patients is poor even in the context of multimodality therapy. Unsurprisingly, the gold standard treatment of GBM in the elderly has yet to be determined. Important factors have been the tendency for key studies in GBM to be limited to patients below a certain age and the culture of nihilism that has surrounded the management of these patients in many centers. There is now a call for a consensus approach to the management of GBM in the elderly, especially as the population is aging and clinicians are facing the prospect of treating a progressively older cohort of patients.

Definition of Elderly

The treatment of cancer in the elderly is of increasing importance in oncology. However, the definition of "elderly" can vary from study to study and from clinician to clinician. Historically, the term "elderly" was linked to the age of eligibility for retirement benefits, typically 65 years. Accordingly, a cutoff of 65 years has traditionally been the norm for geriatric medicine. As the life expectancy of the population continues to increase, however, a new definition of elderly may need to be sought. Some authors have advocated a distinction between the "young old" (65–74 years), the "older old" (75–84 years), and the "oldest old" (>85 years) [3]. In keeping with the changes in population dynamics, some recent GBM studies have included patients up to the age of 70 years rather than 65 years, most notably the pivotal Stupp trial [1, 2]. Until a revised definition has been agreed, there will continue to be discrepancies in establishing the upper age limits for clinical trials in GBM. For the purposes of this review, the term "elderly" refers to patients aged 65 years and above.

Epidemiology of GBM in the Elderly

Approximately 50 % of cases of GBM occur in patients aged >65 years [4]. While this proportion is likely to rise because of the aging population, there has been speculation that the actual incidence of GBM in the elderly is also increasing. In 1990 the National Cancer Institute published a report detailing a marked increase in the incidence of primary brain tumors in the elderly, including GBM [5]. This apparent increase was later attributed to an improvement in cancer detection, owing to more widespread use of imaging in older patients [6]. This explanation has not been universally accepted, especially as another series has also illustrated an increase in the age-adjusted incidence of GBM [7]. It is important to remember that discrepancies in local practice may mean that a rise in the number of cases may not necessarily be reflected in referral patterns to all tertiary treatment centers. Conversely, as public expectations of healthcare provision continue to rise, more patients may be referred who would previously have been managed conservatively.

Pathology of GBM in the Elderly

The last 10–15 years has seen many exciting molecular developments in brain tumor pathology, most notably the discovery of the prognostic and predictive power of loss of heterozygosity of 1p19q in oligodendroglioma [8–13] and the prognostic value of methylation of the O6-methylguanine-DNA methyltransferase (MGMT) promoter in GBM [14]. It has been suggested that these and other markers of glioma biology may be affected by age. Indeed, GBMs arising in the context of a previously diagnosed lower-grade glioma (secondary GBM) have a better prognosis than primary GBM, and the incidence of secondary GBM decreases with age. This correlates with the observation that the IDH-1 mutation that is commonly found in low-grade gliomas is not detected in the elderly [15] and has been proposed as a possible explanation for the poorer outcomes seen in older patients. However, secondary GBMs account for no more than 10 % of all cases [16], so this hypothesis is unlikely to account for the overall disparity in survival between younger adults and the elderly. Furthermore, a relatively recent analysis showed no difference in the prognosis of primary versus secondary GBMs once age-adjusted analysis was performed [16].

Following on from these findings, a potential correlation between age and biological aggressiveness in primary GBMs has been investigated in a number of clinicopathological series. Initial studies focused primarily on markers of proliferation and/or histological features and generated either negative or conflicting results [17–20]. Recently there has been interest in more sophisticated chromosomal/molecular analysis, particularly the significance of epidermal growth factor receptor (EGFR) amplification and MGMT methylation. The data regarding patterns of EGFR expression and outcome in GBM according to age is confusing (reviewed in [21]), but there is some evidence to suggest that MGMT may influence prognosis in older as well as younger adults. This will be discussed in more detail in the next section.

The Effect of Age on Prognosis in GBM

The single most important prognostic factor in GBM is age. Survival in GBM begins to decline at the age of 45 and decreases dramatically thereafter [16, 22]. Patients over the age of 65 have a 2-year survival of less than 5 % in historical series compared to over 20 % in patients below 50 years. Data from numerous retrospective, prospective, and epidemiological studies corroborate these findings [16, 23, 24]. In both the original and the recently updated Radiation Therapy Oncology Group (RTOG) recursive partitioning analyses (RPA) for patients with high-grade glioma, age over 50 years was the clinical factor with the greatest predictive significance for survival [25, 26]. However, determining an exact cutoff age above which prognosis is so poor as to justify the withholding of treatment is difficult. Recommendations vary according to the statistical model applied and do not take into account

variability between patients. Indeed, a recent case series reported good outcomes in a small number of GBM patients treated aggressively who were all over the age of 80 years [27].

If selected elderly patients can respond favorably to treatment for GBM, why is the general prognosis reported for larger elderly cohorts so poor? It is unlikely that there is a single answer to this question and the evidence to date suggests that the reasons for adverse outcomes in this group are multifactorial. One of the major discriminators of prognosis in the RPA analyses was performance status [25, 26], and it is not entirely surprising to find that elderly patients with GBM tend to have a poorer level of functioning, both physically and cognitively. This can be at least partly explained by medical comorbidities, the incidence and severity of which increase with advancing age. However, it has also been suggested that older patients present with larger tumors [28], possibly as a result of age-related cerebral atrophy providing increased scope for tumor growth prior to the development of raised intracranial pressure. Tumor size has previously been correlated with reduced survival in both low-grade and high-grade gliomas [29, 30]. An example of GBM arising in the brain of an elderly patient is shown in Fig. 11.1. Regardless of whether the patient's poor performance status is attributable to tumor burden or comorbid medical conditions, frail patients have limited physiological reserve and are less likely to tolerate surgical and oncological interventions. Yet, not all elderly patients are frail and infirm. It is unclear why fit older patients still fare worse than their younger counterparts. Three main reasons have been put forward: reluctance to treat the elderly patient, increased resistance to chemotherapy and/or radiotherapy, and heightened treatment-related toxicity.

Age and Patterns of Care in GBM

It is widely recognized that older age may be an obstacle to receiving optimal medical care, particularly in oncology. Studies in women with breast cancer, for example, have demonstrated that elderly patients have reduced access to informational support at first diagnosis [31] and that this discrepancy follows through to lower referral rates to hospice/palliative medicine services at the end of life [32]. It is therefore important to question whether patterns of care differ between younger and older patients with GBM and, if so, whether the disparities are large enough to influence survival outcome. To this end, a number of large epidemiological studies comprising several 1,000 patients with GBM have been published. To date there is no evidence to support the existence of either a delay in diagnosis in the elderly [33–35] or a prolongation in the time between diagnosis and treatment [34]. This indicates that the elderly are not disadvantaged at the points of diagnosis or initiation of treatment.

The current standard of care for GBM, as established in the National Cancer Institute of Canada (NCIC) and the European Organization for the Research and Treatment of Cancer (EORTC) collaborative trial, is maximal surgical debulking followed by concurrent chemoradiotherapy and maintenance of temozolomide for 6 months [1, 2]. However, several large population-based analyses indicate that the probability of receiving multimodality therapy is reduced with increasing age and, in fact, patients over the age of 65 are significantly more likely to receive no treatment at all [16, 33, 34, 36–44]. For example, in a review of 715 adult GBM cases in Zurich, Switzerland, Kita et al. noted that best supportive care was often the only treatment offered to older patients and this increased with advancing age. Here, 27 % of patients aged 55–64 received supportive care only, compared with 44 % of those aged 65–74 and 75 % of those aged over 75 years [40]. In the case of elderly patients who do receive treatment, surgery rates are generally much lower, and they are more likely to have a biopsy as opposed to a definitive surgical procedure [36, 38]. Radiotherapy rates are also notably lower in elderly cohorts: approximately 65 % in patients over 70 [39] compared with over 90 % in younger adults [44]. A population-based study of over 3,000 GBM patients in Ontario, Canada, demonstrated that increasing age was also associated with lower mean radiation dose [38]. The most recently published United States-based

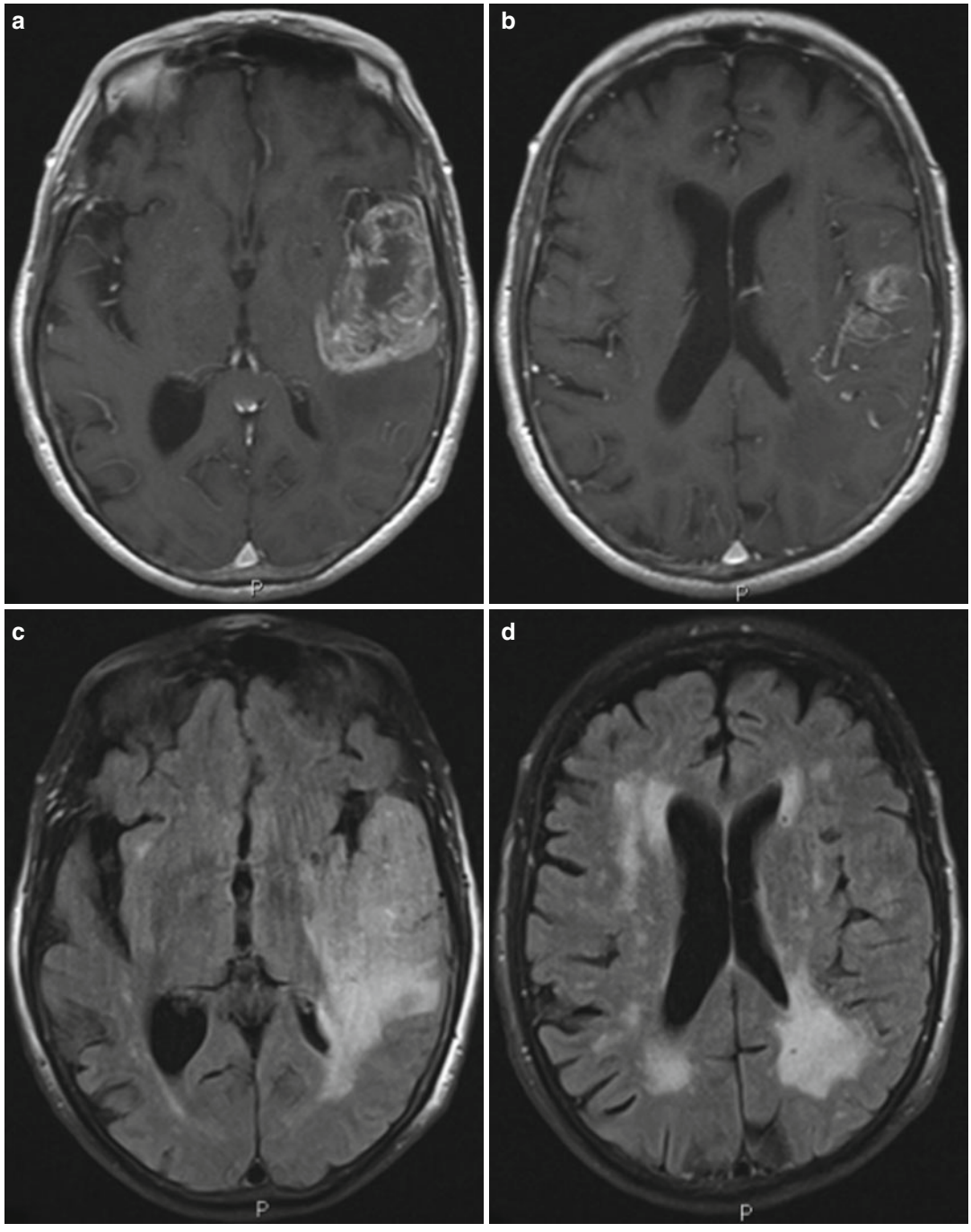

Fig. 11.1 Appearance of glioblastoma in an elderly brain. Contrast-enhanced T1-weighted (**a** and **b**) and FLAIR (**c** and **d**) MR images of the brain of an 81-year-old lady with presumed glioblastoma of the left parietal lobe. Note the presence of cerebral atrophy and abnormalities on FLAIR sequence suggestive of ischemic changes in the normal brain

Surveillance, Epidemiology and End Results (SEER) Program analysis, which reported on almost 3,000 patients over the age of 70 years treated between 1993 and 2005, demonstrates that this pattern of less aggressive treatment is not changing over time. While a higher proportion of patients in this study received some type of treatment, this was mainly single modality; less than half were treated with both surgery and radiotherapy [39]. Given that the addition of temozolomide chemotherapy to radiation has only become standard practice within the last 5 years, accurate data on patterns of care with respect to the use of chemotherapy are not yet available.

As these large studies were predominantly conducted in North America, it is important to consider the possibility that a financial barrier to medical treatment may exist for some patients. However, the SEER database is linked to Medicare, the health insurance provider for well over 90 % of elderly patients in the United States [45], so it is unlikely that discrepancies in treatment according to age are due to disparities in access to healthcare. This is reinforced by the findings of the Swiss cohort where 82 % of patients below the age of 65 years received active treatment (surgery followed by radiotherapy, surgery alone, or radiotherapy alone) as opposed to 47 % of patients above the age of 65 years despite the fact that Switzerland has a sophisticated healthcare system with unrestricted access [40]. Similarly, the German study by Lutterbach et al. remarked that access to healthcare was not determined by age [34].

These studies undoubtedly provide a valuable insight into the lower uptake (or offering) of treatment with advancing age and emphasize that this is a worldwide phenomenon. However, it is difficult to conclude that "inadequate treatment" is entirely responsible for poorer survival. This is especially relevant as not all groups collected data on survival. Interpretation of the data is also limited by lack of information on performance status and/or medical comorbidity. Another major drawback of these studies is that variations in referral patterns to tertiary treatment centers mean that they might not have included all patients with GBM. Thus, the proportion of patients receiving no treatment may actually be underestimated. In summary, there are clear age-related differences in the management of GBM patients, and this is probably reflected in the poorer outcome seen in elderly GBM patients, but it is highly likely that additional factors are also involved.

Age and Treatment Resistance in GBM

A factor that has been mooted as a potential reason for lower rates of radiotherapy uptake in the elderly is the apparent shortened survival advantage when compared with adult GBM patients [46–48]. While this difference could be partly explained by death due to other causes, it has also been suggested that age may influence the radiosensitivity of primary brain tumors. Some groups have attempted to address this by quantifying the radiological response of GBM to radiotherapy in younger versus older adults [49–51]. Using a simple assessment scale in patients who had measurable disease, age was found to be a predictor of poorer radiological response to radiation, although most of the imaging techniques would now be considered outdated. In addition, both performance status and extent of surgical resection were independent prognostic factors, which suggests inherent selection bias. It seems unlikely that age itself is a pivotal factor in determining responsiveness to ionizing radiation, but an association between intrinsic biological factors and age is plausible. Tumor radiosensitivity is complex and depends on myriad molecular characteristics and DNA repair mechanisms, many of which are altered in GBM. Until there is proof that GBM in the elderly represents a different biological spectrum of disease from that of younger patients, however, the view of age as a surrogate for radioresistance must remain speculative.

Since the introduction of the Stupp protocol, there has been further debate about treatment resistance in the elderly. This stems from historical reports that glioma cell lines from older patients are less chemosensitive [52, 53], although the agents tested were nitrosoureas rather than

temozolomide. Following the emergence of MGMT methylation status as a predictor of response to temozolomide, a number of groups have tried to establish whether epigenetic silencing of this gene varies with age, since lower levels of MGMT methylation could perhaps explain the poorer outcome in elderly patients treated with this regimen. Intriguingly, recent data suggests that there are no significant differences in the proportion of MGMT-methylated tumors in older versus younger patients [27, 54–58]. In addition, a recent case series of 83 patients over the age of 70, all of whom received treatment with concurrent chemoradiotherapy for GBM, supports the importance of MGMT as a clinical marker in elderly patients as well as younger adults [55]. Here, MGMT-methylated patients had a median survival of 15 months and a 2-year survival of 28 %. Unmethylated patients had a much poorer outcome with a median survival of 10 months and 2-year survival of only 10 %. If these findings are confirmed in a larger series, it seems less likely that GBM in the elderly population is a biologically different disease from that seen in younger patients. It may be the case, however, that additional cytogenetic or molecular aberrations have yet to be identified, especially in unmethylated GBMs, which probably represent a heterogeneous group of tumors.

Age and Treatment Toxicity in GBM

Cancer treatment in the elderly is fraught with risks. Patients are typically frailer and less capable of tolerating radical procedures such as surgery. For instance, there is a higher risk of surgical complications and a tendency to require a longer hospital stay following surgery, which increases the risk of hospital-acquired infections [59]. There may be alterations in drug metabolism due to changes in body weight, liver mass, and the oxidative system. This in turn can affect the distribution and absorption of anesthetic agents, antibiotics, and anticonvulsants, not to mention chemotherapy. In addition, elderly patients are more likely to be subject to polypharmacy, which increases the risk of drug-drug interactions. Chemotherapy-related toxicity is often more pronounced. Hematological toxicity in particular is increased, possibly due to compromised stem cell reserve [60], and there is an elevated risk of neutropenia along with the associated infectious complications, hospitalizations, and mortality rates [61].

It is also well recognized that elderly patients generally cope less well with radiotherapy. Many anecdotal reports indicate that the elderly are more likely to suffer from radiation-related fatigue and somnolence in the short term. Unfortunately, most studies performed in this age group do not include late toxicity as an endpoint, mainly because most of these patients do not live long enough to develop neurological sequelae. It is therefore difficult to gauge the precise effects of radiotherapy on the elderly brain. There are certainly biological reasons why radiation might be more toxic in this population, most notably higher rates of cerebrovascular disease and diabetes. Small vessel damage is thought to be an important contributor to late radiation toxicity, particularly the most critical sequelae of brain irradiation: cerebral necrosis. While it is reasonable to predict that preexisting vasculopathy and/or hypertension would exacerbate and/or accelerate this process, there is little concrete scientific data to support this. Certainly, the lack of relevant animal models has hindered efforts to elucidate the mechanisms and risk factors that combine to produce late radiation toxicity in the brain. Although age and radiation necrosis cannot be definitively linked, it has been documented that age is a significant risk factor for the development of both cerebral atrophy and encephalopathy [62–64]. This probably explains the global neurocognitive decline that can follow brain irradiation in the elderly. Again, it is unclear whether vascular risk factors predispose for this phenomenon. Of note, it typically takes at least 6–9 months and often up to 1–2 years for these clinical effects to become apparent [62, 65, 66] so it could be argued that trying to gain a greater understanding of late radiation effects in the elderly is not necessary given the predicted short survival. Clearly, the risks of acute and subacute side effects still remain important issues when considering management of the elderly patient. However, if the

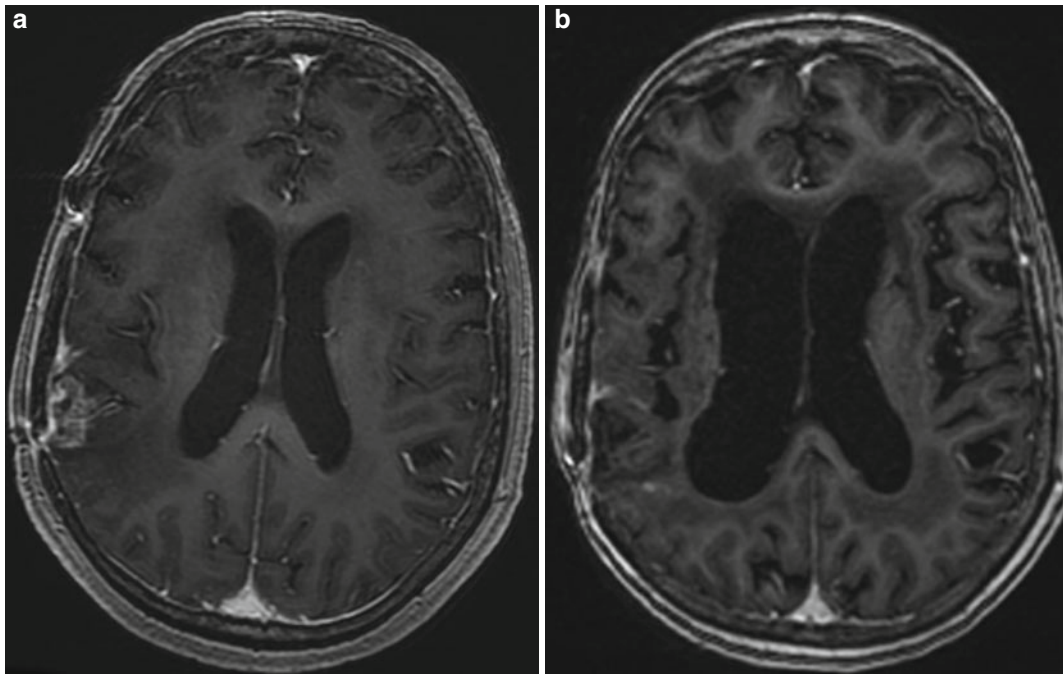

Fig. 11.2 Treatment-related effects in an elderly brain. Contrast-enhanced T1-weighted MR images of a 64-year-old lady with histologically confirmed glioblastoma of the right parietal lobe, prior to radical chemoradiotherapy (**a**) and 5 years post treatment (**b**). Of note, there is no evidence of tumor recurrence, but gross cerebral atrophy is present corresponding to a clinical picture of dementia and incontinence, presumed secondary to treatment

median overall survival for certain subgroups of elderly patients is pushed out beyond 6–9 months, minimizing late radiation effects will become a more pressing issue. An example of significant late radiation toxicity in a long-term survivor of GBM is demonstrated in Fig. 11.2.

Management of GBM in the Elderly Patient

GBM is a symptomatic disease associated with headaches, progressive loss of neurological function, and deterioration in cognitive abilities. Multimodality treatment of GBM is lengthy and potentially toxic, but equally treatment can improve survival and relieve some of the aforementioned symptoms of the disease. The key to successfully managing the elderly patient with GBM is to balance tumor-related symptomatology with the risks of treatment-related toxicity. This is likely to vary from patient to patient depending on their performance status, comorbid medical conditions, and expressed wishes. Accordingly, treatment of the elderly should encompass a broad spectrum, from best supportive care to maximal surgical debulking plus chemoradiotherapy. It must always be remembered, however, that quality of life is of paramount importance especially as the anticipated survival for most of these patients is likely to be a matter of months.

Surgery

Surgery is a critical aspect of the management of patients with GBM, as it delivers diagnostic information while simultaneously providing rapid relief of mass effect. In addition, the act of cytoreduction is thought to improve tolerance to adjuvant therapy. Firm evidence in support of this statement may be lacking, with the exception of a study that demonstrated a higher response rate to

chemotherapy (and improved survival) following surgical debulking in the recurrent disease setting [67], but it is generally accepted that this is the case. It has already been outlined that surgical resection rates are generally lower in the elderly, and it has been suggested that less aggressive treatment may contribute to the poorer outcome seen in this patient population. The two are not necessarily linked, not least because the precise role of surgery in terms of survival has been a contentious issue for many years. Systematic reviews have repeatedly found no convincing evidence of a survival advantage of surgical resection over a biopsy (reviewed in [68]). However, a significant number of prospective and retrospective studies have indicated that maximal resection is associated with a longer survival (reviewed in [68]), and it has been argued that earlier studies used less effective surgical techniques. There is increasing consensus that more extensive surgery, in combination with increasingly sophisticated imaging techniques, can offer a survival advantage. What is more, it has very recently been suggested that maximal debulking can also increase the efficacy of adjuvant therapies [69]. So, if aggressive surgical resection can alleviate disease-related symptoms, increase tolerance to radiotherapy, and potentially improve survival and/or effectiveness of adjunctive therapies, why is this not offered routinely to elderly patients?

The most plausible explanation is the generally frailer and comorbid condition of older patients with newly diagnosed GBM [36, 38, 40]. The elderly are more likely to have concomitant cerebrovascular and systemic disease and poor physiological reserves. These factors can have a marked impact on surgical morbidity and mortality. Interestingly, elderly GBM patients are more likely to present with symptoms of cognitive dysfunction than their younger counterparts [33], which in itself is associated with a higher rate of perioperative complications [70]. In a German series of 44 patients with a primary brain tumor (all aged >80 years), 43 % of patients improved after surgery and 34 % remained stable. However, over 20 % of patients deteriorated and the overall perioperative mortality was 11 % [71]. By contrast, Kelly et al. found that postoperative mortality was only slightly higher than biopsy-related mortality, at 2.5 % vs. 2.2 % [72], although the latter study analyzed a younger age group (>65 years as opposed to >80 years). There is no denying that surgery can have profound negative effects in the elderly. Equally, significant improvements in functional status and quality of life following surgery have been documented by a number of sources indicating that its use can be justified in the elderly [72–74]. The same cannot be said for radiotherapy: poor performance status pre-irradiation predicts for poor performance status postirradiation [75].

Another possible explanation for less aggressive surgery (or no surgery) in older patients may be the dearth of definitive randomized phase III evidence of a survival benefit, particularly as the accumulating data in this field is largely based on studies of younger adults. To this end, researchers have attempted to address the question of whether surgical resection improves survival specifically in the elderly. This has been performed mainly through case series and by subgroup analysis on the data from the large population-based cohorts, although a small single-institution randomized trial was undertaken in Finland in the 1990s [76]. However, performance status is an important potential confounding factor in studies of therapeutic management of elderly GBM patients, and the results must be interpreted with caution. Patients undergoing surgery are likely to be healthier, and they may have more localized and/or superficial lesions that may be biologically more favorable. Moreover, the rate of adjuvant therapy (and in particular data regarding completion of adjuvant therapy) is not always clear. The fact that virtually all of these studies, with the exception of the Finnish trial, are retrospective adds to the complexity of the available evidence and hints at inherent selection bias.

The Finnish group examined a total of 23 patients with malignant glioma aged over 65 years and randomly assigned patients to biopsy only or surgical resection followed by radiotherapy +/− chemotherapy (a further seven were excluded due to low-grade malignancy or benign pathology). The median survival time was significantly longer in patients who underwent surgical resection

Table 11.1 Surgical resection versus biopsy in elderly GBM patients

Group	Age	*N*	Median OS (months)	OS benefit?
Randomized data				
Vuorinen 2003 [76]	≥65	23	Resection 5.6 Biopsy 2.8	✓
Retrospective series				
Kelly 1994 [72]	≥65	128	Resection 6.8 Biopsy 3.8	✓
Mohan 1998 [78]	≥70	102	Maximal resection 17.3 Subtotal resection 7.2 Biopsy 3.4	✓
Chaichana 2011 [79]	≥65	80	Maximal resection 4.9 Subtotal resection 5.7 Biopsy 4.0	✓
Ewelt 2011 [80]	≥65	103	Maximal resection 13.9 Subtotal resection 7.0 Biopsy 2.2	✓
Zachenhofer 2011 [77]	≥65	20	Maximal resection 8.2 Subtotal resection 7.8 Biopsy 7.8	✗

N number of patients, *OS* overall survival

compared with patients who underwent biopsy alone (5.6 months vs. 2.8 months, respectively) [76]. Of note, the median age was similar in both groups, but preoperative Karnofsky performance status (KPS) was higher in the craniotomy group [77] compared with the biopsy-only group [70]. While this unique study is a valuable contribution to the literature, it is too small to provide any definitive conclusions.

The small number of retrospective case series published to date has yielded inconsistent results, as shown in Table 11.1 [72, 76–80]. The first report, by Kelly et al., compared outcomes of surgical resection in 40 patients aged over 65 years with outcomes of biopsy only in a further 88 patients, a proportion of whom went on to have adjuvant treatment. Both groups had comparable median age of approximately 70 years and KPS approaching 85 %. Intriguingly, while the authors reported their findings as only a "modest improvement," survival was almost doubled in the group who had undergone surgical resection (6.3 months vs. 3.6 months) [72]. Mohan et al. also reported a significant impact on survival of complete versus partial resection versus biopsy in a study of GBM patients over the age of 65 (17.2 months vs. 7.2 months vs. 3.4 months, respectively) [78]. Interestingly, in 2011, there were three separate reports on the effect of extent of surgery in elderly GBM patients aged over 65 years. All three were retrospective, single-institution studies featuring between 20 and 103 patients. Both Chaichana et al. and Ewelt et al. reported a positive effect of surgical resection on overall survival as opposed to biopsy only, although the benefit was only several weeks in the former [79, 80]. The resected patient group in the Chaichana study was compared with a historical series of patients who had undergone biopsy only so matching for KPS index was permitted [79]. Conversely, the decision for resection was strongly based on KPS in the Ewelt cohort [80]. The third study did not show any advantage of surgery (either maximal resection or subtotal resection) over biopsy [77].

It is important to note that there were only 20 elderly patients in the Zachenhofer series, so it is perhaps not entirely surprising that the findings were negative [77]. Interpreting the results of such small studies can prove troublesome. However, it can also be difficult to dissect out meaningful results from the data produced by the larger population-based cohorts due to previously mentioned discrepancies in KPS level and surgical bias. For instance, Scott et al. remarked

that surgery was associated with increased cancer-specific survival compared with no treatment in their review of almost 3,000 elderly GBM patients, but the authors acknowledged that information on performance status was lacking [39]. Analysis of some smaller cohorts containing up to several 100 patients has demonstrated conflicting findings. For example, both Pierga et al. and Chang et al. reported a 5–6 month survival advantage for tumor resection versus no resection [81, 82]. Of note, both of these groups suspected that their findings were influenced by a strong selection bias [81, 82]. Conversely, surgery was not found to have any bearing on survival in other published series [75, 83].

Taken together, the limited data that is available suggests that surgical resection as opposed to biopsy alone is tolerated, at least in fit elderly patients with a KPS of ≥70 and an accessible lesion, and may be associated with a small survival advantage. Less-fit patients may also benefit symptomatically and functionally, and surgery may render a proportion of these patients suitable for adjuvant treatment, but the risks of surgery must always be carefully considered in the context of poor physiological condition and medical comorbidities. Technological developments such as functional magnetic resonance imaging (fMRI), intraoperative neurofunctional monitoring, and neuronavigation have rendered neurosurgical procedures safer and more effective. To what extent this will influence surgical management of the elderly patient, fit or unfit, has yet to be determined. It is possible that some centers that are currently reluctant to operate on the elderly may continue to refrain from radical procedures. In order to promote a more standardized approach to the elderly population, it will be necessary to pinpoint preoperative factors that influence survival. Chaichana et al. have provided some insight into identifying which patients are more likely to benefit from aggressive surgery [29]. Their retrospective review of over 100 patients with an average age of 73 years indicated that the presence of more than one risk factor had a significantly negative impact on survival. The risk factors comprised KPS <80, chronic obstructive pulmonary disease, motor deficit, language deficit, cognitive deficit, and tumor size larger than 4 cm. While the authors accept that this study did not allow for the effect of adjuvant therapy and requires prospective evaluation, it is an interesting exploration of the potential value of prognostic factors and may be the first step in developing a surgical algorithm for the management of GBM in the elderly.

Radiotherapy

Robust evidence of a survival benefit following aggressive surgery in the elderly GBM patient has yet to be shown, but the survival advantage of postoperative treatment, in the form of radiotherapy, has been demonstrated. While a number of retrospective case series hinted at the value of radiotherapy in this context, there is now randomized phase III data available to substantiate this [48]. Historical series using a variety of dose/fractionation schedules illustrated a median survival of 4–12 months, as shown in Table 11.2 [72, 78, 83–90], although it should be noted that survival of over 9 months was only elicited in studies with fewer than 30 patients [87, 90]. In addition, several of these case series included anaplastic astrocytoma as well as GBM [83–85, 88]. This may have resulted in an overestimation of the actual survival time. In order to accurately assess the effect of radiation on survival, Keime-Guibert et al. randomized 81 elderly patients over the age of 70 with newly diagnosed anaplastic astrocytoma or GBM to radiotherapy plus best supportive care or best supportive care alone in the postoperative setting; surgical resection and biopsy were both permitted. The trial was discontinued at the first interim analysis because the radiotherapy arm was found to be significantly more effective. The median survival was 29.1 weeks for patients undergoing radiotherapy as opposed to 16.9 weeks for those patients in receipt of best supportive care only. This was in spite of the lower radiation dose applied in this study (50.4 Gy in 28 fractions) in contrast to the standard dose/fractionation regimen for GBM (60 Gy in 30 fractions). The authors did not report any difference in health-related quality of life or

Table 11.2 Summary of radiotherapy trials in elderly patients with GBM

Group	Age	*N*	Fractionation	Median OS (months)
Randomized data comparing surgery and radiotherapy with surgery alone				
Keime-Guibert 2007 [48]	≥70	81	50.4/28	Surgery + RT 7.3 Surgery 4.3
Historical radiotherapy case series in the elderly				
Ampil 1992 [84]	≥65	21	60/33	4.0
Kelly 1994 [72]	≥65	96	NR	4.2
Hoegler 1997 [83]	≥70	23	37.5/15	8.0
Mohan 1998 [78]	≥70	58	Various	7.3
Villa 1998 [85]	≥70	85	60/30	4.2
Jeremic 1999 [86]	≥60	44	45/15	9.0
Brandes 2003 [87]	≥65	24	59.4/33	11.2
Glantz 2003 [88]	≥70	54	60/33	4.1
Muacevic 2003 [89]	≥65	123	60/30	5.6
Idbaih 2008 [90]	≥70	28	40/15	11.7
Scott 2011 [99]	≥70	206	Various	4.5

N number of patients, *OS* overall survival, *NR* not reported, *RT* radiotherapy

cognitive status between the treatment groups, indicating that radiotherapy was well tolerated in this patient population. Indeed, no severe adverse events were recorded, and only 6 patients (15 %) did not complete the course of radiotherapy.

Even in the face of a 3-month survival advantage from radiation, it is clear from the various SEER analyses and other population-based studies that radiotherapy treatment is not always delivered to elderly patients. This is most likely due to concerns over patient frailty and ability to cope with a protracted course of treatment. However, it is important to consider the possibility that clinicians may have an age cutoff above which they feel radiation is not applicable due to poor tolerability and/or minimal perceived benefit. The patients themselves may decline treatment over fears of excessive toxicity and negative impact on their quality of life. For many elderly patients, the prospect of 2–3 weeks of radiotherapy planning followed by 6 weeks of radiotherapy treatment with daily hospital visits is daunting. In reality the length of treatment-free survival may amount to no more than a number of weeks, and this must be taken into account when selecting and counseling potential treatment candidates.

It is for these reasons that hypofractionated radiotherapy has been advocated in the elderly and/or frail patient with GBM. Hypofractionation has the advantage of reducing the time frame (and potentially reducing the morbidity) of treatment while maintaining comparable survival outcomes to more lengthy conventional radiotherapy. The most commonly studied regimen in the management of GBM is 40 Gy in 15 fractions. Radiobiologically, this dose should provide similar tumor control to 60 Gy in 30 fractions. While increasing the dose of radiation per fraction does pose an increased risk of neurotoxicity, it has already been pointed out that the most critical toxicities typically occur at least 6–9 months post treatment, if not longer [62, 65, 66]. Thus, patients with an expected prognosis of well under 1 year are unlikely to be at high risk of experiencing problems relating to radiation necrosis. However, as both old age and large fraction size are known risk factors for radiation-induced encephalopathy [63, 64], a hypofractionated regimen may exacerbate this particular outcome. Although the literature in this field suggests a significant time to onset in excess of 1 year, there are many anecdotal reports of generalized neurocognitive decline in elderly patients similar to that seen with encephalopathy at earlier time points.

In terms of effectiveness, single-arm historical case series of hypofractionated regimens, including 40 Gy in 15 fractions, did not demonstrate

Table 11.3 Hypofractionated radiotherapy compared with standard fractionation in GBM

Group	Age	*N*	Fractionation	Median OS (months)	Outcome of hypofractionation
Randomized data					
Roa 2004 [96]	≥60	100	60/30	5.1	Equivalent
			40/15	5.6	
Nonrandomized data					
Bauman 1994 [94]	All ages	92	>50	10	Inferior
			30/10	6	
			No RT	1	
Ford 1997 [91]	All ages	59	60/30	4	Equivalent
			36/12		
Mohan 1998 [78]	≥70	102	≥55	7.3	Inferior
			<45	4.5	
			No RT	1.2	
Hulshof 2000 [92]	All ages	155	66/33	7	Equivalent
			40/8	5.6	
			28/4	6.6	
McAleese 2003 [95]	All ages	136	60/30	7.5–9.5	Inferior
			30/6	5	
Lutterbach 2005 [93]	≥60	96	60/30	5.6	Equivalent
			42/12	7.3	

N number of patients, *OS* overall survival

inferior survival in elderly populations [83, 86, 90], as already shown in Table 11.2. At the same time, various hypofractionated schedules have been analyzed in comparison with standard fractionation approaches up to a total dose of 66 Gy in a combination of retrospective and prospective studies, as outlined in Table 11.3 [77, 91–96]. Three studies illustrated equivalent survival with hypofractionated and conventional regimens [34, 91–93]. However, only Lutterbach et al. specifically looked at "elderly" patients, although this is debatable as the age cutoff was 60 years [93]. Both Ford et al. and Hulshof et al. included younger patients in their analyses, albeit in the case of Hulshof et al., almost one half of the 155 patients were aged over 60 years [91, 92]. Three further series demonstrated a worse outcome in the hypofractionated arms [78, 94, 95]. It should be noted that while Mohan et al. included only patients aged over 70 [78], the other groups had wider entry criteria and accepted younger patients provided that their KPS level was sufficiently low (either aged 50–70 years with KPS 50–90 or any age with KPS <50) [94, 95]. Hence, a proportion of patients selected for short-course radiotherapy in the two latter-mentioned studies were generally frail and deemed not fit for long-course treatment. It is likely that a significant number of these patients had a poorer prognosis at the outset and this may have skewed the results. Both groups used matched controls as part of their analyses, but attempting to retrospectively match patients is not always accurate.

To answer this clinical question in a more controlled way, a randomized phase III trial was established. Two regimens were tested in 100 patients over the age of 60: 40 Gy in 15 fractions versus the standard 60 Gy in 30 fractions [96]. The median survival for both groups was comparable (5.6 months vs. 5.1 months, respectively) suggesting that hypofractionated radiotherapy in elderly patients with GBM is equivalent to conventional radiotherapy. However, this trial has been subject to a number of criticisms. Firstly, whether the age of 60 is a valid threshold for the term "elderly" is controversial. Secondly, the patients in this study were of relatively poor performance status and had not been optimally debulked. Thirdly, late neurological toxicity was not assessed, although this was probably irrelevant as

Table 11.4 Chemoradiotherapy versus radiotherapy in elderly GBM patients

Group	Age	Chemotherapy	Sequencing	*N*	Median OS (months)
Mohan 1998 [78]	≥70	BCNU, PCV	Adjuvant	16	RT + chemo 8.0
				86	RT 4.9
Pierga 1999 [81]	≥70	BCNU, PCV	Adjuvant	12	RT + chemo 13.5
				18	RT 6.3
Brandes 2003 [87]	≥60	PCV, TMZ	Adjuvant	54	RT + chemo 14.9
				24	RT 11.2
Patwardhan 2004 [98]	≥59	BCNU, TMZ, Gliadel	Adjuvant	9	RT + chemo 13.6
				6	RT 5.5
Kimple 2010 [97]	≥70	Etoposide, TMZ, irinotecan	Concurrent + adjuvant	14	RT + chemo 11.6
				4	RT 6.5
Scott 2011 [99]	≥70	CCNU, TMZ, carboplatin	Concurrent + adjuvant	29	RT + chemo 13.3
				45	RT 7.2

N number of patients, *OS* overall survival, *RT* radiotherapy, *TMZ* temozolomide

survival rates were just under 6 months. Nonetheless, hypofractionated regimens, particularly 40 Gy in 15 fractions and 30 Gy in 6 fractions, have become standard practice in many centers for the treatment of elderly and/or frail patients who are unlikely to tolerate a conventional course of treatment.

Chemoradiotherapy

In 2005, a new standard of care for GBM was defined in a phase III trial, which demonstrated that the addition of concurrent and adjuvant temozolomide chemotherapy to radical radiotherapy was associated with significantly superior survival [1]. The caveat is that this trial had an upper age limit of 70 years. However, combining chemotherapy with radiotherapy in the elderly has been widely practiced using a number of cytotoxic drugs given concomitantly and/or in the adjuvant phase. Nitrosoureas and temozolomide are the predominant cytotoxic agents, although platinum, topoisomerase inhibitors, and even targeted therapies have also been employed. Results of several case series have tended to show a superior outcome with chemoradiotherapy compared with radiotherapy alone, as illustrated in Table 11.4 [78, 81, 87, 97–99]. Median overall survival reached over a year in some cases, although it is very likely that only the fittest patients who had also undergone optimal debulking were selected for triple-modality treatment, which may have significantly influenced the outcome.

Many centers have a policy of restricting the Stupp protocol to patients aged below 70 years, so data on the safety and effectiveness of this regimen in older patients is limited. However, a handful of single-institution series published recently have documented outcomes and toxicity in elderly cohorts [54, 55, 57, 100–103]. This data is shown in Table 11.5 [2, 54, 55, 57, 100–103]. As with the earlier chemoradiotherapy series featuring an array of drugs and/or scheduling, median survival times of over 1 year have been reported. It is important to point out that the definition of "elderly" in these published series varies between 60 years and 70 years, and again, it is extremely likely that the patients in these case series were selected on the basis of general fitness. In fact, several groups remarked that combination treatment appeared to be most advantageous in patients with higher KPS [100, 101]. Interestingly, a trend benefit analysis of the original Stupp data by age showed a decreasing benefit with increasing age, with hazard ratios of 0.63 for patients aged 50–60 years (P <0.05), 0.72 for patients aged 60–65 years (P = 0.096), and 0.80 for patients aged 65–70 years (P = 0.34) [104].

An important question if chemoradiotherapy is to become more common practice in elderly patients is whether this regimen will be tolerated. This is relevant both in the short term, due to the acute toxicity of chemotherapy and potential

Table 11.5 Stupp protocol-based chemoradiotherapy studies in elderly GBM patients

Group	Age	*N*	Median OS (months)	1	2	3	G3/G4 toxicity
Combs [a]2008 [100]	≥65	43	11	88 %	12 %	NR	Combined 9 %
Minniti 2008 [101]	≥70	32	10.6	94 %	NR	NR	Concomitant 6 % Adjuvant 27 %
Sjiben 2008 [57]	≥65	19	8.5	NR	NR	NR	Combined 42 %
Brandes 2009 [54]	≥65	58	13.7	100 %	NR	NR	Concomitant 19 % Adjuvant 46 %
Stupp 2009 [2]	60–70	83	10.9	NR	NR	NR	NR
Fiorica 2010 [102]	≥65	42	10.2	69 %	52 %	14 %	Concomitant 5 % Adjuvant 7 %
Gerstein 2010 [103]	≥65	51	11.5	59 %	20 %	NR	Combined 41 %
Minniti 2011 [55]	≥70	83	12.8	NR	NR	NR	Combined 27 %

N number of patients, *OS* overall survival, *1* patients completing CRT, *2* patients commencing adjuvant temozolomide, *3* patients completing 6 cycles of adjuvant temozolomide, *NR* not reported
[a]50 mg/m^2 temozolomide during concomitant phase in this study

exacerbation of acute radiation toxicity, and also in the long term especially if prolonged survival reveals excess late radiation effects. Age is a known risk factor for reduced chemotherapy tolerance. The pharmacokinetics of individual agents should always be borne in mind when administering chemotherapy to elderly patients. Fortunately, temozolomide is metabolized by nonenzymatic processes that are less subject to variability between individuals [105], and it has a relatively favorable toxicity profile [106]. It does, however, cause noncumulative myelosuppression, particularly thrombocytopenia. Although this section focuses on the adverse effects of chemotherapy, it is also important to point out that elderly patients often have a degree of mucosal atrophy and reduced gastrointestinal motility. Hence, absorption of oral chemotherapy agents such as temozolomide may be impaired [107], and the effectiveness of this regimen may be compromised.

Examination of toxicity in the recently published elderly Stupp protocol data sets indicates that the incidence of grade 3 or 4 events is extremely variable. While Combs et al. and Fiorica et al. report levels of severe toxicity at less than 10 % [100, 102], a significantly higher level of grade 3 or 4 events of approximately 40 % has been reported by three other groups [54, 57, 103]. Notably, just over 80 % of patients in the cohort reported by Combs et al. received 50 mg/m^2 of daily temozolomide at the outset during the concurrent phase as opposed to the standard dose of 75 mg/m^2 which may have contributed to the lower levels of toxicity in this series [100]. Most of the described toxicity was hematological, and this probably explains why adjuvant chemotherapy was not given in the majority of patients, although it is often difficult to elicit this information from the published material. In fact, most of the studies provided relatively clear information on the percentage of patients who completed concomitant chemoradiotherapy without a dose reduction and/or stopping chemotherapy, but not the percentage of patients who (i) commenced adjuvant chemotherapy or (ii) completed 6 cycles of adjuvant chemotherapy, as illustrated in Table 11.5. Two pertinent questions stem from this missing data. Firstly, is this regimen as well tolerated in elderly patients as some authors would lead us to believe if very few patients can actually complete? Secondly, is concomitant chemotherapy the key active component, and is there any additional benefit from adjuvant temozolomide in the elderly?

In relation to the first question, significant toxicity has certainly been documented [54, 57, 103], and this has already been alluded to. After hematological toxicity, neurological sequelae were the next most common problem. It is concerning that a prospective phase II study of concurrent

temozolomide in patients over the age of 65 reported grade 2 deterioration in mental status in 31 % and grade 3 deterioration in a further 25 %, leading to significant disability [108]. Moreover, grade 3 leukoencephalopathy occurred in 6 %. Of note, the median interval between start of treatment and development of neurological toxicity was 6 months in this study, whereas time to progression was 9.5 months, indicating a correlation with treatment rather than disease progression. In another series, 25 % of patients experienced grade 3 or grade 4 deterioration in mental state during or just after radiotherapy, and the rate of grade 3 encephalopathy was 10 % [54]. Hence, the neurological and neurocognitive sequelae of combined treatment may be profound. Any responses to the second question would be speculative and likely to remain so for some time, as there are no plans to compare concomitant versus concomitant plus adjuvant chemotherapy in the near future.

On balance, the reported series to date suggest that there is a potential benefit of aggressive multimodality therapy in the elderly, but caution should be exercised because (i) this benefit is likely to be smaller compared with younger patients, (ii) the treatment may be considerably more toxic, and (iii) patient selection is crucial. Should this type of approach become more commonplace, then the issue of pseudoprogression is likely to be raised. At present it is unknown whether this phenomenon is any more or less common in the elderly. The only confirmed risk factor is MGMT status [109]. As yet, there is no definitive evidence that methylation of MGMT in GBM varies significantly with age [27, 54–58]. It may be the case that the aging cerebral vasculature may be more subject to radiation-induced disruption and dysfunction, in which case a higher incidence of pseudoprogression is a distinct possibility in the elderly. If so, will the degree of pseudoprogression be more profound? This is potentially concerning as it has been proposed that severe cases of pseudoprogression may predispose to necrosis [110]. The elderly may therefore be at higher risk of toxicity from combined chemoradiotherapy, both in the short term and in the long term. Conversely, pseudoprogression is thought to perhaps indicate improved clinical outcome [109, 111–113], but clinicians might be more likely to pull out of treatment earlier in an elderly patient with a scan suggestive of progression. Hence, some older patients with a response to treatment may be denied ongoing effective therapy. There is no doubt that this is an interesting topic for future study, and as the significance of this phenomenon becomes clearer, it is likely that imaging and/or markers of pseudoprogression will be incorporated into clinical trials of multimodality therapy.

Chemotherapy Versus Radiotherapy

While there has been a recent flurry of publications advocating aggressive multimodality therapy in the elderly [55, 99–102], it is interesting that the most up-to-date clinical trials featuring elderly GBM patients have focused on de-intensification protocols, mainly comparing radiotherapy with chemotherapy. This is not an entirely new concept as a number of phase II studies and retrospective series using temozolomide as an alternative to radiotherapy have previously been reported. These demonstrated median survival durations of just over 6 months, with acceptable toxicity [88, 114–117]. In some cases, imaging was used to evaluate measurable disease, and partial responses or stable disease was elicited in up to 70 % of patients [115–117]. Certainly, there are advantages of opting for chemotherapy over radiotherapy as this allows patients to be treated at home for the most part, only attending hospital for a clinic visit every 4 weeks (if following the standard 28-day cycle of temozolomide). On the other hand, careful blood monitoring is required and compliance may be an issue, especially if there is evidence of cognitive deficit.

The Nordic Brain Tumor Study Group randomized 342 patients over the age of 60 years to conventional radiotherapy (60 Gy in 30 fractions), hypofractionated radiotherapy (34 Gy in 10 fractions), or temozolomide (200 mg/m^2 daily for 5/28 days for 6 cycles). Preliminary results suggest that the three arms are equivalent, although evaluation is confounded by crossover from radiotherapy to temozolomide and vice versa. However,

the median overall survival was relatively short across the various arms (6–9 months), despite the fact that 60 years was the minimum age and 75 % had a good performance status of 0–1 [118]. Meanwhile, the Neuro-Oncology Working Group of the German Cancer Society (NOA) conducted a two-arm study to investigate the efficacy of chemotherapy versus conventional radiotherapy alone. NOA-08 randomized 412 patients, all over the age of 65 years, to 60 Gy in 30 fractions or temozolomide (100 mg/m^2 daily, 1 week on/1 week off, until progression). Early results indicate that radiation may have on advantage for radiation over chemotherapy although, once again, median overall survival rates were disappointing at less than 9 months; survival was measured at 293 days in the radiotherapy arm versus 245 days in the chemotherapy arm [119]. Another drawback of the chemotherapy arm in this trial was the prospect of remaining on treatment until disease progression or death. This would probably be unappealing to the majority of elderly patients.

At present, there is no substantive data to support the use of temozolomide over radiation in the elderly GBM patient although chemotherapy remains a viable alternative in patients who refuse radiotherapy.

Intracavitary Chemotherapy

GBM is a unique disease in that chemotherapy can be safely applied into the surgical cavity at the time of debulking. Gliadel wafers are biodegradable polymers containing 3.85 % carmustine. Compared with surgery alone, implantation of these wafers at the time of repeat surgery may prolong survival [120], but this practice remains controversial and does not form part of routine treatment at many centers. There is also data to suggest that this approach may be beneficial at the time of first surgery [121, 122], although this is based on patients of all ages. Chaichana et al. have recently published the findings of a sizeable case–control study of elderly patients aged over 65 [123]. Altogether, 88 patients had intracavitary carmustine wafers inserted at initial surgery, and half of these patients were matched with controls who had not undergone implantation. Reassuringly, there was no increase in perioperative morbidity and mortality in the carmustine wafer cohort. In terms of efficacy, a survival advantage of 2–3 months was demonstrated for the carmustine group. However, this study was not a randomized controlled trial, and as such intracavitary treatment cannot be considered standard practice. Nonetheless, this approach merits further investigation as it may be considerably less toxic and better tolerated than the Stupp protocol in elderly patients.

Best Supportive Care

GBM is undoubtedly a devastating disease, characterized by progressive loss of neurological function and changes in cognitive ability and personality. Indeed, a proportion of sufferers will be unsuitable for any oncological treatment at the outset due to significant disability. For these patients, best supportive care is of paramount importance. Steroids can relieve some of the pressure symptoms associated with tumor growth. However, the use of glucocorticoids must be considered in the context of their potentially devastating side effects such as emotional lability, insomnia, proximal myopathy, weight gain, immunosuppression, venous thrombosis, and hyperglycemia. It is imperative that the patient is closely monitored in the community, especially if there is a history of heart failure and/or diabetes. The use of analgesia and anticonvulsants may also be required with subsequent risks of toxicity and drug-drug interactions. Patients often require extensive physical assistance and close supervision which can result in marked personal and economic stresses on the caregiver. Early contact with hospice and/or community palliative medicine team is advised as well as information on support groups for both the patient and the carer.

Recurrent Disease

As the median survival of elderly GBM patients is just a few months and a significant number do not receive any treatment at the outset, there is virtually no data on how best to manage the

elderly patient with recurrent disease. The decision to treat should be centered around the individual patient, and various factors must be taken into account, including performance status, response to initial therapy, time since diagnosis, and whether the recurrence is local or diffuse. Therapeutic options are similar to those of the general adult population and include further surgery, systemic chemotherapy with temozolomide or nitrosoureas, targeted agents such as vascular endothelial growth factor receptor (VEGFR) inhibitors, and radiotherapy. However, re-irradiating the aging brain of an elderly patient would be a daunting prospect for most radiation oncologists. The former options are therefore more likely to be carried out in clinical practice.

Future Perspectives

The numbers of elderly GBM patients are ever increasing, but these patients have largely been excluded from the pivotal, practice-changing trials. It has now been recognized by the neuro-oncology community that the optimal management of GBM in older patients needs to be determined. Realistically, this could be achieved in one of two ways: either by including all age groups in future clinical trials or alternatively devising separate trial protocols for those aged over 65 years (or perhaps over 70 years). As elderly patients are generally frailer and less able to tolerate traditional oncological therapies, it seems reasonable to consider them as a separate group and devise protocols accordingly. Indeed, there has already been some progress in this direction, as shown by the temozolomide versus radiotherapy studies that had a minimum age criteria of 70. Some would say, however, that fit elderly patients are being undertreated by this approach and that triple-modality therapy should be an option. The NCIC and EORTC have recognized this and designed a randomized trial that compares radiotherapy alone with radiotherapy plus concurrent and adjuvant temozolomide for up to 1 year in the over 65 age group. The radiotherapy regimen in this study is 40 Gy in 15 fractions over 3 weeks, based on the Roa data that showed equivalence to 60 Gy in 30 fractions over 6 weeks [96]. The primary objective of this trial is to assess the impact of concomitant therapy on survival. Toxicity data will be particularly interesting, especially as chemotherapy is being combined with a higher dose of radiation per fraction than in the Stupp protocol. The only other prospective studies to date examining the effect of multimodal treatment in the elderly have been small single-institution trials that focused on hypofractionated radiotherapy followed by adjuvant chemotherapy as opposed to a concomitant regimen [124, 125]. Of note, in both of these studies, the median survival was around 9 months, yet chemotherapy was planned for up to 12 months. It is unclear why the NCIC-EORTC groups opted for 12 months of treatment, given that a substantial proportion of their patients are unlikely to be alive at this point. Whether this length of treatment is acceptable and/or appropriate for the majority of elderly patients will only be realized when the final data is available for survival and quality of life analysis.

The NCIC-EORTC trial has incorporated molecular analysis into the protocol, and it is hoped that this additional information will help select out those patients who are most likely to benefit from multimodality therapy. It has already been mentioned that MGMT status appears to be as common in elderly GBM patients as in their younger counterparts and may have prognostic value in the elderly despite their overall poorer outcome [55]. Some investigators have proposed that the negative effect of age can be counteracted by methylation of MGMT [126], although there is no substantive evidence to support this. Clearly, this area requires further clarification and large-scale prospective evaluation such as that provided by the NCIC-EORTC study is key. It is increasingly likely that more GBM studies in the future will include molecular testing, comprising not only MGMT analysis but also a more rigorous examination of the various genetic alterations and/or molecular signaling pathways that might contribute to clinical outcomes, with the ultimate aim of developing a more individualized approach to therapy. To this end, a number of targeted agents are currently under investigation

in GBM, but the possibility of individualized treatment, particularly in the elderly population, is some way off.

The most widely studied targeted agent in GBM is bevacizumab, a humanized monoclonal antibody that inhibits VEGF activity. Although this agent is not yet widely available, it is licensed for use in the recurrent setting in some parts of the world. This is based on phase II data demonstrating an increase in 6-month progression-free survival when bevacizumab was administered in combination with irinotecan [127, 128]. Although elderly patients were not excluded from these trials, the median age in both studies was less than 55, suggesting a higher proportion of younger patients. Intriguingly, a retrospective analysis of a single-institution study showed that patients over the age of 55 gained the most benefit from single-agent bevacizumab in the context of recurrent disease [129]. Antiangiogenic treatment may be a useful therapeutic tool in the elderly, but this premise is based on very preliminary data. Further work is required to establish whether VEGF inhibition has a role in the management of primary and/or recurrent GBM in the elderly, either alone or in combination with radiotherapy and/or chemoradiotherapy. Although targeted agents are generally not as toxic as traditional oncological therapies, VEGF inhibitors are not without adverse effects. Indeed, there is some evidence from other tumor types to suggest that toxicity is more pronounced in the elderly when bevacizumab is combined with chemotherapy [130]. A number of other targeted agents are also under investigation; many of these are tyrosine kinase inhibitors directed against growth factor receptors including, but not necessarily exclusive to, VEGF. Even if some of these agents prove too toxic to be combined with standard concomitant therapy, especially in the elderly, they may have a role either in combination with radiotherapy or as single-agent treatment in frail patients, provided that there is sufficient evidence of efficacy.

DNA repair is an important mechanism of radiation resistance, and a number of novel agents are available that target components of the DNA damage response. Of the compounds under development, the most advanced are inhibitors of poly(ADP-ribose) polymerase (PARP), some of which have been used as single agents in the treatment of BRCA-mutated breast and ovarian cancer, with remarkable success and minimal toxicity [131, 132]. A large body of preclinical data has also established PARP inhibitors as effective radiosensitizers and early-phase clinical trials in combination with radiotherapy are now underway [133]. Of particular relevance to the treatment of GBM, the radiosensitizing effects of PARP inhibitors are observed only in actively replicating cells [134]. Since the cells of the normal brain are non-replicating, this raises the prospect of tumor-specific radiosensitization for GBM. As single-agent PARP inhibitors such as olaparib are extremely well tolerated, these compounds may be particularly well suited to the treatment of elderly GBM patients, in combination with either radical or short-course radiotherapy [135].

While there is currently much interest in trying to develop new therapeutic targets in GBM, it is important to remember that the most critical component of management is radiotherapy. Numerous studies have not demonstrated a benefit of dose escalation, so there is little to be gained by further exploration of this route, especially in elderly patients where this is concern about the tolerability of radiation. This does not mean that there is no room for improvement in terms of delivery of radiotherapy to older patients. The advent of intensity-modulated radiotherapy (IMRT) has provided radiation oncologists with a greater ability to sculpt the dose around a target volume. IMRT is often used to spare a specific organ at risk, such as the spinal cord or optic chiasm, and has the advantage of delivering a highly conformal, homogeneous dose to the target volume while simultaneously sparing normal tissue. Hence, techniques such as IMRT may be of particular benefit in elderly patients, by minimizing radiation dose to normal brain and improving tolerance to treatment. An example of a more favorable dose distribution using IMRT compared with conventional radiotherapy is illustrated in Fig. 11.3.

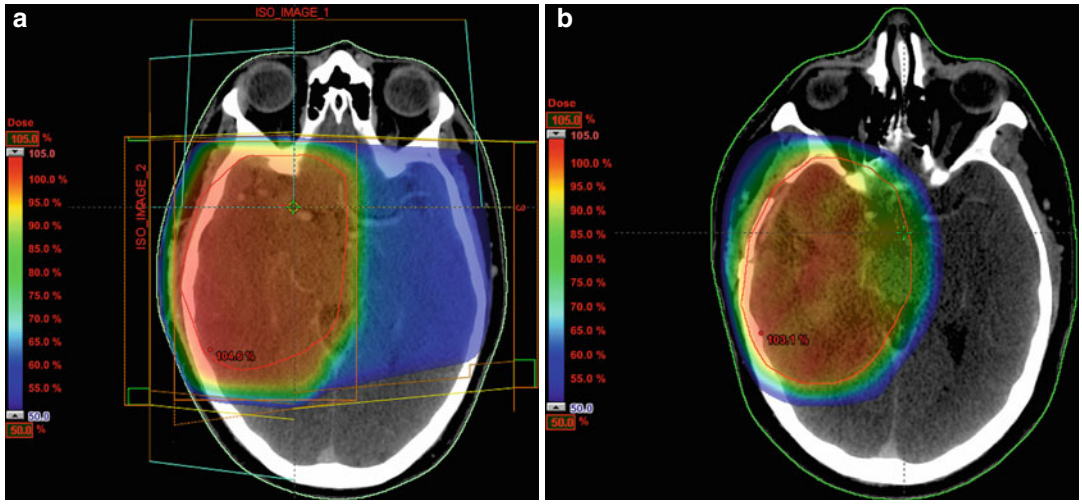

Fig. 11.3 Normal brain sparing with intensity-modulated radiotherapy (IMRT). Contrast-enhanced computed tomography (CT) planning images of two patients with right temporal lobe tumors treated with radical chemoradiotherapy using different techniques: conventional 3-field arrangement (**a**) and IMRT (**b**). The PTV in each case is indicated in *red*, and color dose wash demonstrates the 50 % isodose (*blue* shading). Note the improved sparing of surrounding normal brain in the IMRT-treated case

Conclusion

Managing elderly GBM patients effectively can be challenging, as they are often frailer and less able to tolerate standard multimodality therapy. However, a subgroup of elderly patients is less impaired in terms of neurological function and performance status and can cope with "aggressive" management. Underpinning the use of multimodality treatment is debulking surgery. Recent reports are challenging the widely held view that elderly patients do not tolerate neurosurgical intervention, and evidence is emerging that tumor resection can improve performance status in this patient group. A more interventional neurosurgical approach brings a number of potential benefits: (i) rapid and effective relief of raised intracranial pressure and possible improvement in performance status, (ii) high-quality tissue for diagnosis and molecular classification that might help to predict prognosis and guide nonsurgical treatment, (iii) the potential for use of local cytotoxic agents, and (iv) a possible improvement in tolerance of subsequent radiotherapy and/or chemotherapy. While not all of these statements are yet supported by high-level evidence, it is the opinion of the authors that selected elderly patients will derive significant, cumulative benefits from more aggressive neurosurgical management. Still, it is important to be mindful that even the fittest elderly GBM patients may not necessarily derive the same survival advantage as younger patients. Ultimately, the key to successful management of GBM in the elderly population is to differentiate between those patients who are most likely to benefit from multimodality therapy and those who would be better served by de-intensification protocols. Currently, elderly patients constitute approximately half of all patients with GBM, and this proportion is likely to increase significantly over the coming years. It is therefore imperative that we achieve a greater understanding of how to select patients for the various treatment approaches appropriately. Hopefully the implementation of carefully designed clinical trials in the elderly will identify prognostic factors, clinical and/or molecular, that will guide treatment with the optimal combination of conventional and novel therapies.

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