Radiotherapy For Malignant Gliomas in the Elderly

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ABSTRACT

While fractionated external beam radiotherapy remains the principal treatment in patients with histologically verified malignant glioma, its use in older patients and in patients with adverse prognostic features has not be subject to randomised studies. Hypofractionated partial brain irradiation offers a short, well tolerated treatment with a palliative benefit for patients with predicted median survival of < 6 months. To assess its true efficacy in terms of survival and quality of life gain requires a formal randomised comparison with supportive care either alone or in combination with palliative chemotherapy and with radical radiotherapy. On present evidence, palliative radiotherapy remains the appropriate treatment for this group of patients but the final choice should be based on patients wishes moderated by the clinician's perception of the gain of treatment.

INTRODUCTION

The incidence of malignant glioma increases after the age of 45[1] and peaks between 65 and 84 years of age.[2] Oncologists are therefore frequently faced with a decision on the choice of treatment in older patients. The decision to proceed with radiotherapy (RT) should be based on evidence of survival and quality-of-life (QOL) benefit for RT in malignant glioma, on evidence of favorable differential effect of RT in patients with poor prognostic features, and on information of the comparative effectiveness of other treatment strategies.

RADIOTHERAPY IN ELDERLY PATIENTS WITH MALIGNANT GLIOMA

Two large, randomized studies performed in the 1970s have compared RT with supportive care alone. They demonstrated 6-month survival benefit at a median time point for the whole population of patients studied.[3,4] The 2 × 2 design in the study by Walker et al[3] also compared chemotherapy alone versus no specific treatment without the addition of RT; chemotherapy with carmustine demonstrated little impact on survival. The studies showing benefit for RT were carried out at a time when QOL assessment was not routinely performed. However, they reported improvement or stabilization of performance status (PS) using the Karnofsky PS scale in patients who received RT. On this basis, RT has become accepted as the treatment of choice in patients with histologically verified malignant glioma. On present evidence, of all treatments tested, RT offers the greatest survival benefit.

Differential Effect of Radiotherapy Based on Age and Prognosis

All studies assessing the influence of prognostic factors on survival record age as an independent determinant of prognosis. The effect of age on survival is shown in Figure 1 derived from MRC data [5] Most prognostic factor analyses are derived from large multicenter trials where older patients, usually those beyond 65 or 70 years of age, are underrepresented as they are generally excluded from studies of increased treatment intensity. The prognosis of patients aged over 70 is therefore not fully defined.

Although age is an independent predictor for survival and the factor with the largest impact on outcome, it is the combination of age, PS, and tumor histology that best separates patients into identifiable prognostic groups. The Medical Research Council (MRC) Risk Adaptive Prognostic Index shows the distribution of patients into 4 prognostic groups (Table 1).[5] Patients > 60 years of age with World Health Organization PS of ≥ 2 (patients with marked disability)

have a median survival of only 5 months, with < 5% surviving 2 years (Figure 2). Overall, this category is similar to the Radiation Therapy Oncology Group recursive partitioning analysis Class VI that is also primarily defined by age, histology, and PS[6,7]. I It should be noted that the trials from which these data are derived excluded patients > 70 years of age.

When deciding on treatment for patients with an adverse prognosis, it is the differential effect of RT on prognostic subgroups that needs to be considered. The initial trials testing the effectiveness of RT did not stratify patients by age, and data had not been analyzed retrospectively to assess if RT had a differential effect on individual age groups.[3,4] The only available information comes from a small phase III study that randomized 171 patients following surgery to chemotherapy alone or chemotherapy followed by conventional external beam RT.[8] As expected, there was a significant survival benefit in favor of RT. The study was retrospectively stratified by age, and the magnitude of benefit appeared smaller in patients ≥ 50 years of age. These are the only data that suggest a lesser magnitude of benefit for radical RT in older patients. However, the potential bias of retrospective stratification and the small size of the cohort that seriously underpowered the study do not provide confidence in the results. In addition, it is not clear how many patients > 65 or 70 years of age were included in this study and the information about the effect of RT on older patients therefore remains incomplete.

When deciding on radical treatment, it is important to balance the beneficial effects and the risks of therapy. The side effects of RT are traditionally classified into acute and late effects. Because patients with adverse prognosis have a median survival of ≤ 6 months, consideration of late effects of RT are of little relevance. The major acute effects of radiation are tiredness and lethargy that last for weeks or months following a radical course of treatment.[9] Some have considered this a reason not to offer treatment.[9]

Tailoring Therapy to Prognosis

The optimum conventional external beam RT is a 6-week course of treatment to a dose of 60 Gy in 30 daily fractions.[10,11] There is no evidence that dose intensification with hyperfractionation[12] or accelerated fractionation[13] offers survival benefit, although shortening the treatment time by giving RT twice a day shortens the treatment episode. In the MRC adverse prognostic group (group 3 in Table 1 and Figure 2) the median survival is approximately 5 months. The treatment episode, which includes a minimum of 2 weeks of preparation and ≥ 4 weeks of recovery from the post-treatment effects, therefore takes up one third of the remaining lifespan measured at the median time point. In this palliative setting it is therefore appropriate to reduce the intensity and duration of treatment.

A variety of short low-dose, palliative RT regimens have been tested that include 30 Gy in 10 fractions and 30 Gy in 6 fractions given over a period of 2 weeks.[14] Median survival in a cohort of patients treated at The Royal Marsden Hospital with the latter regimen was approximately 6 months. Direct comparison to historical controls is difficult particularly as the outcome in the Marsden cohort was based on the intent-to-treat population (all patients considered for RT even if they did not receive it) and the study entered older and disabled patients not generally included in large multicenter trials. The treatment was well tolerated with only minimal time spent receiving therapy (only 6 visits over a period of 2 weeks). The beneficial effect of RT tested in terms of functional benefit using the Barthel Index (a measure of activities of daily living) showed improved or stable function in 78% of surviving patients on completion of treatment and in approximately 51% of surviving patients at 3 months after treatment.[14]

Short palliative RT is one of the three principal management options in patients with poor-prognosis malignant glioma. The others are supportive care alone and radical RT. There are no randomized studies comparing the different management approaches in the group of

patients with adverse prognostic factors. The only available comparison of supportive care with radical RT is from the randomized trials of the 1970s (previously discussed).

We attempted to compare the outcome of patients treated with palliative RT at the Royal Marsden with those treated by radical RT (controls). Control patients were matched for age and PS from the MRC database of patients receiving radical RT to 60 Gy in 30 fractions.[15] While the results suggest a small survival benefit for radical RT, the matching was not perfect and it is likely that the group of patients receiving palliative RT represented a population not normally selected for treatment in large, randomized studies from which the matched control population was obtained. Matching can only account for imbalances in known, objective prognostic factors, which typically account for < 50% of variation in patient outcome. These factors may not capture important, but less quantifiable, prognostic indicators that oncologists apply (perhaps subconsciously) when determining the treatment approach for individual patients or that patients exhibit by their treatment preference. The apparent small survival gain in favor of radical RT, therefore, most likely represents a selection bias rather than real evidence for benefit for more intensive RT in poor-prognosis patients.

It is important to consider both the relative and absolute effects of treatment. In the MRC randomized trial of 45 Gy versus 60 Gy, the relative benefit to the 60Gy group, as demonstrated by the survival hazard ratio (0.75), did not differ substantially across prognostic groups.[10] However, the same relative effect produces substantially different absolute effects. Though the overall median survival was increased from 9 months to 12 months, the same hazard ratio applied to a group with a median survival of only 5 months which translates to an absolute increase in median survival of only 6 weeks.

Even if there is a potentially shorter survival gain for palliative compared with radical RT, in the context of a median life expectancy of < 6 months it is the “quality of survival” or “quality-adjusted survival” that is important.[16] There are no published data assessing the effect of RT on

quality-adjusted survival in poor-prognosis glioma patients. However, the short exposure to low-intensity treatment is largely without the severe exhaustion experienced following radical RT, and the treatment episode itself is much shorter. It is therefore likely that, even if survival was marginally shorter, the quality-adjusted survival between the two treatment approaches may be equivalent to or even in favor of less-intensive treatment.

While a randomized trial of radical versus palliative RT is desirable, the opinion among many oncologists is that it is not appropriate to offer a radical 6-week course of intensive treatment to patients with a median life expectancy of < 6 months. I It is also unlikely that elderly patients with severe disability would be entered into such trials. This type of study would only be feasible if it also included patients with more favorable prognosis, and information on the benefit of radical RT compared to shorter, lower-dose treatment for such patients is already known.[10]

A more appropriate randomized study for a poor-prognosis group of patients would be a comparison between supportive care alone and palliative RT. It is difficult to enter patients who have a relatively sudden and unexpected serious illness into randomized studies with a “no treatment” arm described as supportive care alone. As a more acceptable alternative, patients in the supportive care group may be offered simple chemotherapy. On the basis of present evidence of randomized studies of RT versus chemotherapy,[3] chemotherapy with nitrosoureas and other alkylating agents such as temozolomide cannot be considered an effective alternative to RT even though phase II studies of selected patients suggest some efficacy for chemotherapy largely using a surrogate endpoint of response.

CONCLUSION

Currently, RT remains the primary treatment option in patients with malignant glioma. In the absence of randomized studies assessing the differential effect of RT on patients with adverse prognosis, the choice of treatment is based on the clinician's perception and the patient's wishes. The alternatives for poor-prognosis patients based on age and PS are supportive care alone, palliative hypofractionated RT, and radical RT. Only future randomized trials will provide objective data to allow for a rational choice based on survival and quality-adjusted survival. However, the final choice must be based on the patient's wishes, with the knowledge and perception of the personal gain from the individual management options.

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FIGURE LEGENDS

Figure 1.—Actuarial survival probability of the MRC cohort of patients with malignant glioma plotted by age. MRC = Medical Research Council.

Figure 2.—Actuarial survival probability of the MRC cohort of patients with malignant glioma plotted by prognostic group. MRC = Medical Research Council.

Table 1. MRC Risk Adaptive Prognostic Groups in Patients With Malignant Glioma Treated With Surgery and Conventional Radiotherapy

Group	Age, years	Histology	WHO PS
0	≤ 45	AA	Any
1	≤ 45	GBM	Any
2	> 45 and ≤ 60	Any	Any
	> 60	Any	0 or 1
3	> 60	Any	≥ 2

MRC = Medical Research Council; WHO PS = World Health Organization performance status; AA = Anaplastic astrocytoma; GBM = Glioblastoma multiforme.
Data from Stenning SP, et al.[5]