

Currently, older age is among the most significant prognostic factors associated with poor prognosis in GBM patients. Recently, Scott et al. retrospectively analyzed a total of 437 patients aged 70 years and older with newly diagnosed GBM to identify specific prognostic factors. They show extent of resection, age and KPS as significant variables for four subgroups of prognostic factors [A previous recursive partitioning analysis of prognostic factors for GBM including 832 patients of all ages demonstrated that patients aged >65 years had the worst prognosis, independent of the extent of surgical resection or performance status . Other authors studied prognostic factors in 676 GBM patients of all ages and showed no evidence of interactions between the effects of RT and patient age .

Moreover, emerging data on biological features between primary and secondary glioblastoma further suggest that tumors in older patients may be more aggressive [31, 41]. However, in the opinion of a number of authors, this data could be affected by an initial selection bias in overall populations as well as in elderly populations

Finally, older age may be associated with a poor prognosis, but elderly patients may achieve improved survival by means of surgery and/or adjuvant or alternative treatments. Indeed, Keime-Guilbert's randomized controlled study showed prolonged survival in patients >70 years (70 years old or older) with a KPS \geq 70, treated with 50 Gy vs. supportive care [Scott reported an OS of 17.1 months for GBM patients with good KPS who received surgery and chemoradiotherapy, with a standard fractionated RT [46]. Short-course RT has also been investigated for patients older than 65–70 years, with interesting results on survival and without increased toxicity In a randomized trial, Roa [44] reported no significant change in median overall survival (mOS) when comparing standard fractionated RT (30 frx2 Gy, 60 Gy in 6 weeks) to hypofractionated RT (15 frx2.66 Gy, 40 Gy in 3 weeks) for GBM patients older than 60 years (mean age 71 years). The mOS was 5.6 months and 7.3 months for the conventional and hypofractionated therapy groups, respectively. The impact of altered RT fractionation in patients aged 70 years have also been evaluated in the past in a number of trials with a mOS between 4 and 8 months .These studies suggest that hypofractionated RT may be a reasonable alternative schedule for elderly GBM patients.

Therefore, the optimal treatment schedule for elderly patients has yet to be determined

Nevertheless, the choice of hypofractionation aims to minimize the effect of tumor repopulation and may increase tumor destruction by means of the greater dose per fraction . Moreover, it is common knowledge that DNA repair is increased after irradiation , and that ionizing radiation-induced cognitive impairments depend on radiation dose, but more directly on the limited capacity of the DNA DSB repair system . Although different altered schedules of irradiation have been used over the years, there is a lack of data on toxicity and molecular effects, mainly on cellular repair mechanisms.

The other important question of whether the short OS in elderly GBM patients may be prolonged by chemotherapy as an alternative, or in addition to RT has not yet been answered satisfactorily: in the NOA-08 and Nordic trial, chemotherapy alone was compared with RT alone, with different results (similar efficacy in the Nordic trial, but not in the NOA-08); differences in patient features and chemotherapy schedule are probably at the basis of these discrepant results. However, two recent studies reported on the benefit of multimodality therapy in elderly GBM patients, showing an OS of as long as 17.2 months and an odds ratio for death as low as 0.45 ($p < 0.0001$) [26], respectively.

In this context, the ongoing EORTC trial, which is currently under investigation in our daily practice, will clarify whether concomitant and adjuvant temozolomide to hypofractionated radiotherapy could be a correct choice for elderly people with primary GBM.