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TOPIC REVIEW

The role of radiation therapy in treatment of adults with newly diagnosed glioblastoma multiforme: a systematic review and evidence-based clinical practice guideline update

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Abstract

Target population These recommendations apply to adult patients diagnosed with newly diagnosed glioblastoma.

Question 1 In adult patients (aged 65 and under) with newly diagnosed glioblastoma, is the addition of radiation therapy (RT) more beneficial than management without RT in improving survival?

Recommendations Level I: Radiation therapy (RT) is recommended for the treatment of newly diagnosed malignant glioblastoma in adults.

Question 2 In adult patients (aged 65 and under) with newly diagnosed glioblastoma, is the RT regimen of 60 Gy given in 2 Gy daily fractions more beneficial than alternative regimens in providing survival benefit while minimizing toxicity?

Recommendations Level I: Treatment schemes should include dosage of up to 60 Gy given in 2 Gy daily fractions that includes the enhancing area.

Question 3 In adult patients (aged 65 and under) with newly diagnosed glioblastoma, is a tailored target volume superior to regional RT for reduction of radiation-induced toxicity while maintaining efficacy?

Recommendation Level II: It is recommended that radiation therapy planning include 1–2 cm margin around the radiographically T1 weighted contrast-enhancing tumor volume or the T2 weighted abnormality on MRI.

Level III: Recalculation of the radiation volume during RT treatment may be necessary to reduce the radiated volume of normal brain since the volume of surgical defect will change during the long period of RT.

Question 4 In adult patients (aged 65 and under) with newly diagnosed glioblastoma, does the addition of RT of the subventricular zone to standard tumor volume treatment improve tumor control and overall survival?

Recommendation No recommendation can be formulated as there is contradictory evidence in favor of and against intentional radiation of the subventricular zone (SVZ)

Question 5 In elderly (age > 65 years) and/or frail patients with newly diagnosed glioblastoma, does the addition of RT to surgical intervention improve disease control and overall survival?

Recommendation Level I: Radiation therapy is recommended for treatment of elderly and frail patients with newly diagnosed glioblastoma to improve overall survival.

Question 6 In elderly (age > 65 years) and/or frail patients with newly diagnosed glioblastoma, does modification of RT dose and fractionation scheme from standard regimens decrease toxicity and improve disease control and survival?

Recommendation Level II: Short RT treatment schemes are recommended in frail and elderly patients as compared to conventional 60 Gy given in 2 daily fractions because overall survival is not different while RT risk profile is better for the short RT scheme.

Sponsored by the American Association of Neurological Surgeons and Congress of Neurological Surgeons Joint Section on Tumors.

Reviewed for evidence-based integrity and endorsed by the American Association of Neurological Surgeons and Congress of Neurological Surgeons.

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Level II: The 40.05 Gy dose given in 15 fractions or 25 Gy dose given in 5 fractions or 34 Gy dose given in 10 fractions should be considered as appropriate doses for Short RT treatments in elderly and/or frail patients.

Question 7 In adult patients with newly diagnosed glioblastoma is there advantage to delaying the initiation of RT instead of starting it 2 weeks after surgical intervention in decreasing radiation-induced toxicity and improving disease control and survival?

Recommendation Level III: It is suggested that RT for patients with newly diagnosed GBM starts within 6 weeks of surgical intervention as compared to later times. There is insufficient evidence to recommend the optimal specific post-operative day within the 6 weeks interval to start RT for adult patients with newly diagnosed glioblastoma that have undergone surgical resection.

Question 8 In adult patients with newly diagnosed supratentorial glioblastoma is Image-Modulated RT (IMRT) or similar techniques as effective as standard regional RT in providing tumor control and improve survival?

Recommendation Level III: There is no evidence that IMRT is a better RT delivering modality when compared to conventional RT in improving overall survival in adult patients with newly diagnosed glioblastoma. Hence, IMRT should not be preferred over the Conventional RT delivery modality.

Question 9 In adult patients with newly diagnosed glioblastoma does the use of radiosensitizers with RT improve the efficacy of RT as determined by disease control and overall survival?

Recommendation Level III: Iododeoxyuridine is not recommended to be used as radiosensitizer during RT treatment for patients with newly diagnosed GBM

Question 10 In adult patients with newly diagnosed glioblastoma is the use of Ultrafractionated RT superior to standard fractionation regimens in improving disease control and survival?

Recommendation There is insufficient evidence to formulate a recommendation regarding the use of ultrafractionated RT schemes and patient population that could benefit from it.

Question 11 In patients with poor prognosis with newly diagnosed glioblastoma is hypofractionated RT indicated instead of a standard fractionation regimen as measured by extent of toxicity, disease control and survival?

Recommendation Level I: Hypofractionated RT schemes may be used for patients with poor prognosis and limited survival without compromising response. There is insufficient evidence in the literature for us to be able to recommend the optimal hypofractionated RT scheme that will confer longest overall survival and/or confer the same overall survival with less toxicities and shorter treatment time.

Question 12 In adult patients with newly diagnosed glioblastoma is the addition of brachytherapy to standard fractionated RT indicated to improve disease control and survival?

Recommendation Level I: Brachytherapy as a boost to external beam RT has not been shown to be beneficial and is not recommended in the routine management of patients with newly diagnosed GBM.

Question 13 In elderly patients (> 65 year old) with newly diagnosed glioblastoma under what circumstances is accelerated hyperfractionated RT indicated instead of a standard fractionation regimen as measured by extent of toxicity, disease control and survival?

Recommendation Level III: Accelerated Hyperfractionated RT with a total RT dose of 45 Gy or 48 Gy has been shown to shorten the treatment time without detriment in survival when compared to conventional external beam RT and should be considered as an option for treatment of elderly patients with newly diagnosed GBM.

Question 14 In adult patients with newly diagnosed glioblastoma is the addition of Stereotactic Radiosurgery (SRS) boost to conventional standard fractionated RT indicated to improve disease control and survival?

Recommendation Level I: Stereotactic Radiosurgery boost to external beam RT has not been shown to be beneficial and is not recommended in patients undergoing routine management of newly diagnosed malignant glioma.

Keywords Radiation · Glioma · Glioblastoma · Treatment · Clinical practice guidelines · Evidence based

Abbreviations

AHRT	Hypofractionated accelerated RT
ART	Accelerated radiation therapy
Bx	Biopsy
CD	Complete response
CFRT	Conventional fractionated radiation therapy
CGE	Cobalt grey equivalent
CTV	Clinical tumor volume
EBRT	External beam radiation therapy
FRT	Fractionated radiation therapy
FSRT	Fractionated stereotactic RT
GBM	Glioblastoma multiforme
GTR	Gross total resection

GTV	Gross tumor volume
IMRT	Intensity modulated radiation therapy
MST	Median survival time
NTR	Near total resection
OS	Overall survival
PD	Progressive disease
PR	Partial response
PFS	Progression free survival
PTV	Planning target volume
RT	Radiation therapy
SD	Stable disease
SRT	Stereotactic radiation therapy
STR	Subtotal resection
SVZ	Subventricular zone
TM	Tumor mass
TMZ	Temozolomide
TTP	Time to progression
WBRT	Whole brain radiation therapy

Introduction and rationale

With an annual incidence of 3.2 per 100,000, glioblastoma (GBM) remains the most common malignant primary brain tumor [1]. Multiple randomized controlled trials have defined radiation therapy (RT) as a corner stone of adjuvant treatment of newly diagnosed GBM for improving overall survival (OS) and progression free survival (PFS) (Reviewed in [2]). In 2005, Stupp et al., published the results of the European Organization for Research and Treatment of Cancer—National Cancer Institute of Canada (EORTC-NCIC) 22981/26981, setting the standard of care for treatment of newly diagnosed GBM [3]. They demonstrated that temozolomide added to 60 Gy fractionated RT improves survival in these patients. Multiple other studies have been published since then, and all seem to confirm their conclusions.

The previous evidence-based clinical practice guidelines endorsed by the Joint Guidelines Committee of the American Association of Neurological Surgeons and the Congress of Neurological Surgeons have addressed the role of RT in treatment of newly diagnosed GBM [2]. The purpose of the current review is to update the clinical evidence on the role of RT in management of all aspects of newly diagnosed GBM with particular attention to address questions such as, the best volume of RT, the dose and further evaluate the utility of other schemes such as hypofractionated, ultrafractionated or accelerated hyperfractionated RT, the utility of stereotactic radiosurgery (SRS) and brachytherapy.

Methods

Writing group and question establishment

The evidence-based clinical practice guideline taskforce members and the Joint Tumor Section of the American Association of Neurological Surgeons (AANS) and the Congress of Neurological Surgeons (CNS) have prioritized an update of the guidelines for management of newly diagnosed glioblastoma. The writers represent a multi-disciplinary panel of clinical experts encompassing neurosurgery, neuro-oncology, and radiation oncology. Together, they were recruited to develop this update on the evidence-based practice guidelines for newly diagnosed glioblastoma (GBM) in adults. The methodology and findings of the previous guidelines were reviewed, and additional questions were developed to incorporate recent literature addressing practice patterns in management of GBM patients.

Literature review and eligibility criteria

A National Library of Medicine (PubMed), Embase, Elsevier Database and Cochrane Central Register of Controlled Trials comprehensive systematic literature review from January, 1st 2005 to October 31st, 2018 performed using glioblastoma (GBM) and radiation therapy (RT) search terms. Literature search was performed introducing these terms: [(Glioma OR Glioblastoma) AND (Radioactive OR radiosurgery OR radiation OR radiotherapy)]. This was limited to Humans (MeSH), adults AND English Literature. For the literature to be included only studies published in full as peer reviewed papers were considered. Furthermore, they had to meet the following criteria:

Inclusion criteria

- Be published in English language.
- Involve only patients with newly diagnosed WHO grade 4 glioma (glioblastoma) or provide results for newly diagnosed glioblastoma patients that can be separated from a mixed cohort.
- Involve adult patients (age over 18) or provide isolated results for adult patients in a mixed cohort.
- Fully published, peer-reviewed articles.
- The number of study participants with newly diagnosed glioblastoma was at least 5 for each study arm.
- Use of radiation therapy after diagnosis of glioblastoma had been made.
- Supratentorial glioblastoma only.

The search criteria were developed and performed by two independent reviewers. Citations were independently reviewed and included if they met the a priori criteria for

relevance. No discrepancies in study eligibility were noted. Corresponding full-text PDFs were obtained for all citations meeting the criteria and reviewed. Data was extracted by the first reviewer and verified by another, all of which were compiled into evidence tables. The tables and data were reviewed by all of the authors. Articles not meeting the selection criteria were removed.

Data collection process

After an extensive search, 4383 articles were found. By reviewing the abstracts and titles, we excluded all articles referring to other gliomas, those focusing on the use of chemotherapy and articles referring to infratentorial or spine glioblastoma. One-hundred-forty-five articles underwent full text review. Only 59 articles met all of our stringent inclusion criteria reported above and were used in formulating these evidence-based clinical guidelines (Tables 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14). The articles that were reviewed in the previous guidelines published in 2008 are not reported in our tables and the readers are encouraged to review them in Buatti et al. [2] The majority of the articles that underwent full text review was excluded because they discussed radiation therapy on recurrent glioblastoma and/or discussed the use of radiation therapy in high-grade gliomas where the results were not separable for anaplastic gliomas and glioblastomas. The remainder was excluded because they lacked significance for our topic. Three reviewers evaluated search-returned citations via an initial title/abstract screen for relevance based on the above pre-determined criteria separately and compared the results. If there was any discrepancy for inclusion or non-inclusion to full text review, the majority decision prevailed.

Both the quality of the evidence and the eventual strength of the recommendations generated by the evidence were graded according to a three-tiered system for assessing studies addressing therapeutic value as approved by the American Association of Neurological Surgeons and Congress of Neurological Surgeons (AANS/CNS) Joint Guidelines Committee (https://www.cns.org/guidelines/guideline-procedures-policies/guideline-development-methodology).

Scientific foundation

Classification of evidence and recommendation levels

The writers independently reviewed the qualifying studies, determined the strength of the evidence provided, and classified it. The information was classified according to the criteria described in the introduction. Briefly, evidence from well-designed randomized controlled clinical trials with clear mechanisms to limit bias were designated as class I. When one or more publications yielded this information a level I recommendation could be formulated. Level II recommendations were based upon studies that were randomized and controlled studies, but with design flaws leading to potential bias and limiting the paper's conclusions. Class II data also was represented by well performed non-randomized cohort studies, and case–control studies. Level III recommendations were reserved for single surgeon, single institutional case series, comparative studies with historical control, and randomized studies with significant flaws with limited power and compromised statistical analysis. Additional information on study classification and recommendation development can be found at https://www.cns.org/guidelines/guideline-procedures-policies/guideline-development-methodology.

Study selection and characteristics

Our search criteria yielded a total of 145 publications for full text review, which were reviewed by two authors independently. Among these, 59 studies met all outlined selection criteria and specifically focused on radiation therapy for GBM.

Assessment for risk of bias

Our search generated a list of abstracts, which were screened, and those articles that addressed our identified questions underwent full independent review by the authors. Reviewers were critical in their assessment, specifically in regard to trial design, such as randomization of treatment, blindness, prospective character, size of study population, baseline characteristics between study groups which could account for survivorship bias, selection bias, and appropriate statistical analyses of reported data.

Summary of prior recommendations

Multiple randomized controlled trials have confirmed RT to be the corner stone of adjuvant treatment for newly diagnosed GBM. Buatti et al. [2], on the first evidence-based clinical guidelines published in 2008, recommended RT in treatment of newly diagnosed GBM in adults with schemes to include a dosage of up to 60 Gy given in 2 Gy daily fractions that included the enhancing area (Level 1 Recommendation). Their recommendations were based on 6 randomized controlled trials (RCT) and one meta-analysis. Patient in these trials underwent RT in addition to chemotherapy and/or surgical intervention. When compared with the group of patients that did not receive RT, but received only chemotherapy and/or surgical intervention the former patients did better in terms of median survival [2]. The authors of the previous guidelines recommended the dose up to 60 Gy in 2 Gy daily fractions based on the results of

4 RCT where the dose recommended was compared with different higher or lower doses. Patient that received the dose recommended had higher median survival with lower side effects. They recommended a hypo-fractionated scheme for patients with poor prognosis and limited survival. This recommendation was based on 2 RCT and 2 prospective non-randomized trials where patients with poor prognosis that underwent RT with shorter overall treatment time had equivalent life expectancy when compared to conventional RT regimen [2]. The authors did not find any evidence to recommend a role for hyper-fractionation and accelerated fractionation. Similarly, they did not find consistent evidence to create recommendations for brachytherapy or stereotactic radiosurgery (SRS) as a boost to external beam radiation therapy (EBRT) as adjuvant therapy for newly diagnosed GBM based on randomized controlled studies that studied conventional RT for the time with addition of brachytherapy or SRS. According to Buatti et al., these studies did not demonstrate a survival benefit in patient with newly diagnosed GBM when brachytherapy or SRS were added to the conventional therapy. For more details, the reader is encouraged to read the paper by Buatti et al. [2].

Question 1: What is the role of radiation therapy in the management of adult patients (aged 65 and under) with newly diagnosed glioblastoma?

In the recent past, other studies have confirmed the value of RT for newly diagnosed GBMs. Rusthoven and colleagues [4], queried SEER database for adult patients with high-grade glioma treated during 1998–2007 (Table 1). They found 12,115 that were diagnosed with GBM. Adjuvant RT was used in 81.7% of GBM cases. Median OS of patients that received RT after surgical resection was 11 months versus 4 months for patient that did not received RT. RT was associated with a 10% OS advantage at 2 years, inducing the authors to conclude that adjuvant RT is associated with substantial improvement in survival among patients with GBM. This study was a retrospective review and studied patients that were treated at a time when the standard combination of adjuvant TMZ and RT treatment had not been widely adopted, but again, confirms the importance of adjuvant RT in treatment of newly diagnosed GBM.

Synthesis of results

Since the last published guidelines [2], we found only one specific retrospective study that has shown that adjuvant RT after surgical resection or biopsy improves OS and PFS [4] (Table 1). This study was classified as Level III evidence. This study, although retrospective in nature, confirmed once again that RT is recommended as adjuvant treatment for newly diagnosed GBM without changing the recommendation endorsed in Buatti et al. [2]. Their level I recommendation was based on 6 randomized controlled studies and 1 meta-analysis study. Three of these studies were classified as class I evidence. In these studies patients were randomized in different arms, where chemotherapy alone was compared to RT alone or a combination of the chemotherapy and radiation. On the meta-analysis pooled data detected significantly higher survival benefit favoring post-operative RT. On another study patients were randomized to receive chemotherapy alone or chemotherapy with RT. The later had significantly higher survival. On 2 other study, patients were randomized to receive chemotherapy alone, RT alone, chemotherapy and RT. Patients that received RT with chemotherapy had higher survival. All these studies showed that patients that underwent RT had higher overall survival than patients that did not receive RT. (All reviewed in [2].)

Question 2: What is the appropriate dose of radiation therapy for the treatment of newly diagnosed glioblastoma in adult patients?

Badiyan et al. [1], published a retrospective review of 209 patients with newly diagnosed GBM that received RT in combination with TMZ. RT planning was performed using Gross Total Volume (GTV-1) (residual contrast enhanced mass of surgical cavity) and GTV-2 incorporating the edema surrounding the residual tumor on T2 FLAIR sequences. The respective Clinical Total Volumes (CTVs) were contoured by adding 1 cm margin around each GTV and the Planning Target Volume (PTV) was planned by expanding by 0.3–0.5 cm the respective CTVs. The dose prescribed was 60–70 Gy divided in 2–2.4 Gy/fraction. Different groups of patients received different RT regimens (Table 2). In the multivariate analysis they found that only age and amount of surgical resection were associated with improvement of OS and PFS. The authors concluded that dose-escalation above 60 Gy with concurrent TMZ does not seem to improve clinical outcomes for patients with newly diagnosed GBM. This is a retrospective study with multiple variables and excessive number of treatment schedules/protocols and as such yielded class III information.

Tsien and colleagues [5] studied in a prospective non-randomized trial on the feasibility and value of RT dose escalation to the tumor bed by limiting the RT dose to normal tissue using intensity modulated radiation (IMRT). All 35 patients underwent chemoradiation within 5 weeks of the surgery. The RT was delivered to 2 different PTV. GTV was defined as the residual gross tumor including resection cavity. GTV was expanded by 1.5 cm to form the CTV. CTV and GTV were expanded respectively by 0.5 cm to generate PTV1 and PTV2. IMRT was used to deliver 60 Gy in 30 fractions to PTV1 and simultaneous higher dose (66–81 Gy)

Table 1 Information and summary of the articles that were included and used to answer the questions on the value of Radiation Therapy in treatment of patients with newly diagnosed GBM

Author/year/PMID	Study description	Data class	Conclusion
Rusthoven et al./2014 [4] PMID 25585784	*Study design:* retrospective review *Patient population:* Adult patients with newly diagnosed High Grade Glioma *Description:* Authors queried SEER database for adult patients with newly diagnosed High Grade Glioma during 1998–2007 that had undergone surgical resection. Performed a comparative evaluation of overall survival (OS) and case-specific survival (CSS) for patients treated with and without adjuvant RT	III	*Results* 14,461 cases of high-grade glioma of which 12,115 were GBM OS for GBM was 10 months and CSS 10 months Adjuvant RT was used in 81.7% of GBM cases Median OS for RT patients was 11 months vs 4 months for patient that did not receive RT RT was associated with a 10% OS advantage at 2 years 2-year/5-year CSS rates of 18%/6% vs 9%/4% ($p < 0.01$) No significant interactions were observed between RT and extent of resection *Authors conclusions*: Adjuvant RT was associated with substantial improvements in survival among patients with GMB in univariate and multivariate models *Comments* Database review. Authors did not consider genetic subclassification of these tumors to compare it with the patient survival. Authors did not explain the reason why the comparison patients did not receive RT

AHRT hypofractionated accelerated RT, *ART* accelerated radiation therapy, *Bx* biopsy, *CD* complete response, *CFRT* conventional fractionated radiation therapy, *CGE* cobalt grey equivalent, *CTV* clinical tumor volume, *EBRT* external beam radiation therapy, *FRT* fractionated radiation therapy, *FSRT* fractionated stereotactic RT, *GBM* glioblastoma multiforme, *GTR* gross total resection, *GTV* gross tumor volume, *IMRT* intensity modulated radiation therapy, *MST* median survival time, *NTR* near total resection, *OS* overall survival, *PD* progressive disease, *PR* partial response, *PFS* progression free survival, *PTV* planning target volume, *RT* radiation therapy, *SD* stable disease, *SRT* stereotactic radiation therapy, *STR* subtotal resection, *SVZ* subventricular zone, *TM* tumor mass, *TMZ* temozolomide, *TTP* time to progression, *WBRT* whole brain radiation therapy

Table 2 Information and summary of the articles that were included and used to answer the questions on the dose of radiation therapy for newly diagnosed GBMs

Author/year/PMID	Study Description	Data class	Conclusion
Badiyan et al. (2014) [1] PMID 25257812	*Study design:* retrospective review of case series *Patient population:* 209 patients with newly diagnosed GBM that receive RT with TMZ *Description:* Patients with GBM, KPS > 60, Age < 70 All patients underwent maximal safe resection or biopsy only All patients received daily 75 mg/m^2 TMZ for 6–7 weeks concurrent with RT then maintenance TMZ 150–200 m^2/day for 5 days every 28 days 42 patients were treated on various clinical trials External beam RT RT planning: GTV-1 = residual contrast enhancement of surgical cavity; GTV-2 = edema on T2 FLAIR; CTV-1 = 1 cm expansion of GTV-2; PTV = 0.3–0.5 cm expansion of the CTV; Dose prescribed was 60–70 Gy in 2–2.4 Gy per fraction; EDQ2 = equivalent doses 2 Gy/fraction for patients receiving hypofractionated RT 81 received standard-dose RT: 60 Gy in 2 Gy fractions to PTV-1 128 received dose-escalated RT to median PTV-1 dose 63 Gy (range 61–72 Gy). EDQ2 of 66 Gy (range 61–72 Gy) with median EQD2 of 64 Gy 33 patients received EQD2 > 66 Gy; 102 received hypofractionated RT (daily does > 2 Gy/day); 32 received dose-escalated RT with sequential boost (using 3D-CRT or IMRT) and 96 received dose-escalated RT with simultaneous integrated boost using IMRT	III	*Results* Median OS was 16.1 months 2-year/5-year OS was 32% and 13% respectively Median PFS was 7 mo 2-year/5-year PFS was 10% and 5% respectively Actuarial 5-year OS and PFS rates for Dose-Escalated RT versus Standard-Dose RT were 12.4% vs 13.2% (p = 0.71) and 5.6% vs 4.1% (p = 0.54) respectively In multivariate analysis only age (HR 1.04; p < 0.00009 and 1.03; p < 0.00001) and amount of surgical resection (HR 0.56; p < 0.008 and 0.52; p < 0.00005) were associated with improvement of OS and PFS For patients with favorable prognostic factors (underwent GTR/NTR), Dose-Escalation RT 5-year OS rate of 23.1% vs Standard-Dose RT 19.2% (p = 0.27) and 5 –year PFS of 12.3% vs 6.1% (p = 0.15) respectively For patients age < 50, Dose-Escalated RT as compared with Standard-Dose RT: 5-year OS 30.1% vs 26.7% (p = 0.85) and 5-year PFS rates of 13.6% vs 13.2% (p = 0.64) respectively At least 3 patients had symptomatic radiation necrosis (2 receive EQD2 of 64 Gy and 1–60 Gy) *Authors conclusions*: Dose-escalation above 60 Gy with concurrent TMZ does not seem to improve clinical outcomes for patients with newly diagnosed GBM *Comments* Retrospective study
Tsien et al. (2012) [5] PMID 22065084	*Study design:* prospective not-randomized trial *Patient population:* 38 adult patients with newly diagnosed GBM that underwent chemoradiation within 5 weeks of surgery *Description:* Radiation: GTV = Residual tumor/resection cavity (MRI with contrast) CTV = GTV + 1.5 cm volume expansion PTV1 and PTV2 = CTV and GTV + 0.5 mm volume expansion respectively IMRT 60 Gy in 30 fractions to PTV 1 and simultaneous higher dose (66–81 Gy) to PTV2 Chemotherapy: Concomitant TMZ 75 mg/m^2 daily for 6 weeks 4 weeks following RT TMZ 200 mg/m^2 days 1–5 every 28 days cycle (6–12 cycles) Response was defined by using Macdonald criteria	III	*Results* Median PFS 9 months, median OS 20.1 months Median follow up of 54 months, 7 were alive and 3 without evidence of disease progression No statistically significant relationship between RT dose and PFS or OS (> 0.5) Younger age (< 0.03), resection (p < 0.03) and RTOG RPA class 3 (p < 0.0003) were associated with improved survival Recurrence patterns: 16 were central, 2 in field, 8 marginal and 2 were distant Median Survival 20.1 months Change in pattern of failure with higher RT doses suggest improved efficacy Late CNS toxicity was observed with doses > 75 Gy Toxicities: Acute: 3 grade 5 hematologic toxicities (1 sepsis (75 Gy), 1 thrombocytopenia with pancytopenia (75 Gy), 1 anaplastic anemia (81 Gy); Late: 3 Grade 3 CNS toxicities (75–81 Gy) and 1 with Grade 3 Otitis *Authors conclusions*: GBM patients can safely receive standard TMZ with 75 Gy in 30 fractions delivered using IMRT. Median OS of 20.1 months is promising *Comments* There was no statistically significant relationship between RT dose and PFS or OS. Small prospective non-randomized study. Considered level III evidence

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to PTV 2. Patients received concomitant TMZ (75 mg/m^2 daily for 6 weeks) then after 4 weeks they received 200 mg/m^2 daily for 5 days every 28 days cycles). Median PFS was 9 months and median OS was 20.1 months. No statistically significant relationship between RT dose and PFS or OS was found. The authors reported that young age, amount of resection and RTOG RPA class 3 were associated with improved survival. Late toxicity was observed with doses higher than 75 Gy. Although this study did not demonstrate superiority of the dose escalation, it did confirm the safety and tolerability of delivering higher radiation doses with concurrent TMZ at a maximum of 75 Gy. This was prospective study, but not randomized and with a limited number of patients. Hence the data from this study was classified as class III.

The study that changed the treatment paradigm of GBM was the phase 3 randomized controlled trial by Stupp et al. [3]. In this study, the investigators from 85 worldwide centers studied 573 patients with a median age of 56 years of age who were randomized after surgery to receive RT alone, a total of 60 Gy fractionated in 2 Gy/day 5 days a week for 6 weeks or RT concomitant with TMZ. The second group underwent RT with the same dose as the first group but in addition during the radiation they received oral TMZ (75 mg/m^2/day 7 days a week for the duration of the RT treatment) then after 4 weeks break the patients continued to receive TMZ (150 mg/m^2/day, day 1 through 5 in a 28 day cycle and then 200 mg/m^2/day, day 1 through 5 for cycles 2 through 6). Median OS was 12.1 months and 14.6 months for patients in RT alone group and RT plus TMZ group respectively. Two-year survival for RT and TMZ group was 26.5% and 10% for RT alone group. The authors concluded that the addition of TMZ to RT for newly diagnosed GBM resulted in clinically meaningful and statistically significant survival benefit with minimal additional toxicity. While the goal of this study was to prove that chemoradiation is better than RT alone, it did set the standard dosing for RT to 60 Gy divided in fractions of 2 Gy/day for 5 days a week for a total of 6 weeks for the group of patients that are similar to those enrolled in the trial. This study did not compare 2 different RT doses and as such was not considered for defining our recommendations in regard to the dose of RT for newly diagnosed GBM. However, it is a reminder for us that the standard dose of 60 Gy used in this trial is the standard dose used world-wide for newly diagnosed GBM today. This same dose has been recommended by Buatti et al. in the previous recommendations based on two RCT and two non-RCT [2].

Synthesis of results

We found 1 retrospective study that described that 60 Gy administered in 2 Gy daily fractions was the best treatment dosage in terms of tolerability and survival [1]. One prospective non-randomized study showed that doses higher than 60 Gy given in 2 Gy daily fractions while well tolerated did not increase OS or PFS [5]. In view of all these studies, the recommendation remained unchanged regarding dosage of adjuvant RT in patients with newly diagnosed GBM. As such level I recommendation of Buatti et al. [2], that the dosage of 60 Gy divided in 2 Gy fractions for 5 days/week be used in the majority of patients with newly diagnosed GBM has not changed (Table 2). Buatti et al., based their recommendations in 4 studies, 3 of which were classified as class I. In one of these class I studies, patients were randomized to receive 45 Gy versus 60 Gy. On the other one patients were randomized in 4 groups. One group received 60 Gy to whole brain. The second group received 60 Gy to whole brain plus 10 Gy boost. The third group received 60 Gy plus carmustine and the fourth group received 60 Gy plus semustine and dacarbazine. On the 3rd study, patients were randomized in 3 groups. The first group received 60 Gy whole brain RT, the second received 70 Gy (60 Gy to whole brain and 10 Gy boost) and the third group received 60 Gy to whole brain plus chemotherapy. They found that increase of the dose above 60 Gy with the boost did not increased survival rate. Patients receiving 60 Gy did significantly better than the patient receiving only 45 Gy. (Reviewed in Buatti et al.)

Question 3: What is the optimal target volume for radiation therapy?

McDonald and colleagues [6], retrospectively reviewed a cohort of 62 adult patients with median KPS > 90% with newly diagnosed GBM. All patients underwent surgical resection (Table 3) and 60 received concurrent and adjuvant TMZ and 2 patients received concurrent arsenic trioxide. Radiation therapy was initiated within 2–4 weeks after surgery. The entire hyperintense area on MRI FLAIR sequences was considered for GTV. Initial CTV was drawn by expanding the GTV by 0.5 cm margin and initial PTV by expanding by 0.3–0.5 cm the margin around CTV. After that they created a boost GTV by using pre- and post-surgery T1W enhancing region on MRI. The boost CTV was created by expanding the boost GTV margin by 0.5 cm and a boost PTV by expansion of the CTV margin by 0.3–0.5 cm. Fourteen patients received 46 Gy at 2 Gy per fraction on initial PTV followed by additional 14 Gy at 2 Gy per fraction on Boost PTV for a total of 60 Gy. Forty-eight patients received 54 Gy at 1.8 Gy per fraction followed by additional 6 Gy at 2 Gy per fraction on Boost PTV for a total of 60 Gy. Median OS was 20 months and the authors did not find a difference in survival between patients treated with sequential boost technique and those with SIB technique. The median time to progression was 7 months (range 5–28 months). The authors concluded that treatment margins for GBM can be reduced and a PTV boost margin of 2.5 cm may not be required.

Table 3 Information and summary of the articles that were included and used to answer the questions on the target volume of radiation therapy

Author/year/PMID	Study description	Data class	Conclusion
McDonald et al. (2011) [6] PMID 20399036	*Study design:* retrospective review of case-cohort *Patient population:* 62 adult patients (median KPS > 90%) with newly diagnosed GBM *Description:* All patients underwent surgical intervention: - Biopsy (11 patients) - Surgical resection (30 GTR, 21 STR) Chemotherapy: 60 received concurrent and adjuvant TMZ and 2 concurrent arsenic trioxide RT initiated within 2–4 weeks after surgery GTV = Hyperintense signal on MRI FLAIR Initial CTV = GTV + 0.5-cm margin (excluding ventricles and bone) Initial PTV = 0.3–0.5-cm margin around CTV Boost GTV was created by using pre- and post-surgery T1W-enhancing region on MRI Boost CTV = Boost GTV + 0.5-cm margin Boost PTV = Boost CTV + 0.3–0.5-cm margin - 57 patients: IMRT - 6 patients: 3D-CRT - 14 patients: Initial PTV received 46-Gy at 2-Gy per fraction followed by additional 14-Gy at 2-Gy per fraction on Boost PTV for total of 60-Gy - 48 patients—Initial PTV received 54-Gy at 1.8-Gy per fraction followed by additional 6-Gy at 2-Gy per fraction on Boost PTV for total of 60-Gy	III	*Results* The 1-year OS was 65% Median OS was 20 months No difference in survival between patients treated with sequential boost technique and those with SIB technique Median time to progression was 7-months (5–28 months) 2 patients lost in follow up and 5 did not complete RT treatment course 32 recurrences were central, 6 were infield, 2 marginal and 1 distant relative to the 60-Gy Isodose line *Authors conclusions*: The data support the concept that the treatment margins for GBM can be reduced and a PTV boost margin of 2.5-cm may not be required *Comments* Retrospective study and limited number of patients. There is no control group and authors did not report the toxicities and rate of radiation necrosis
Kim et al. (2013) [7] PMID 23960453	*Study design:* Retrospective Case-cohort *Patient population:* 19 adult patients with newly diagnosed GBM *Description:* 19 patients with GBM underwent surgical GRT (Verified by MRI) and post-operative RT First simulation CT was performed at 3–4 weeks post-operatively and the second simulation CT for shrink-filed technique was performed in the 5th week GTV1 = Surgical defect on the first simulation CT (sim-CT1). CTV = GTV1 + 2 cm margin; PTV = CTV + 0.5 cm margin Dose to PTV was 50-Gy (daily fraction of 2-Gy). Following this, the shrink-field technique was performed for 10-Gy boost RT utilizing GTV2 (Surgical defect on second CT) Two techniques: 1. Boost RT (RTP1) CTV was GTV1 + 0.5 cm margin 2. Boost RT (RTP2) CTV2 was GTV2 + 0.5 cm margin Volumes of GTV1 and GTV2 were compared Boost RTs were compared as well Total RT dose was 60-Gy (50-Gy + 10-Gy Boost)	III	*Results* Defect volumes on CT0, GTV1 and GTV2 were 19.6–198.5 mL, 12.3–142.1 mL, 7.9–96.3 mL respectively Ration of volume reduction from GTV1 to GTV2 were -2.7–45.8 mL and -9.9–71.9% respectively Overall, surgical defect volumes were reduced from the surgical cavity on CT0 to GTV2 by 9–79.7%. ($p < 0.001$) RTP1 was significantly reduced in boost RTP2 In 5 patients, a 95% isodose curve in boost RTP1 did not completely cover CTV2 (missed target volume in 26.#%) *Authors conclusions*: The application of volume-adapted replanning during RT may decrease the irradiated volume of normal brain and prevent a radiation target miss for boost RT *Comments* Retrospective study. Did not study if change in RT volume for the boost RTP made any difference in terms of OS and PFS

AHRT hypofractionated accelerated RT, *ART* accelerated radiation therapy, *Bx* biopsy, *CD* complete response, *CFRT* conventional fractionated radiation therapy, *CGE* cobalt grey equivalent, *CTV* clinical tumor volume, *EBRT* external beam radiation therapy, *FRT* fractionated radiation therapy, *FSRT* fractionated stereotactic RT, *GBM* glioblastoma multiforme, *GTR* gross total resection, *GTV* gross tumor volume, *IMRT* intensity modulated radiation therapy, *MST* median survival time, *NTR* near total resection, *OS* overall survival, *PD* progressive disease, *PR* partial response, *PFS* progression free survival, *PTV* planning target volume, *RT* radiation therapy, *SD* stable disease, *SRT* stereotactic radiation therapy, *STR* subtotal resection, *SVZ* subventricular zone, *TM* tumor mass, *TMZ* temozolomide, *TTP* time to progression, *WBRT* whole brain radiation therapy

Table 4 Information and summary of the articles that were included and used to answer the questions on the radiation of subventricular zone

Author/year/PMID	Study description	Data class	Conclusion
Elicin et al. (2014) [9] PMID 24668610	*Study design:* Retrospective review of case series *Patient population:* Adult patients with newly diagnosed GBM *Description:* 60 patients diagnosed with GBM and treated at a single institution They all underwent surgery (26 GTR and 34 STR/biopsy) and chemoradiation CTV = Resection cavity including residual tumor on T1 with Gadolinium plus a 2 cm margin including edema on T2W Dose: 60 Gy in 2 Gy daily fractions presecribed to PTV SVZ volume = 3-5 mm thick strips lateral to lateral ventricles. (cSVZ = contralateral SVZ; bSVZ = bilateral SVZ; iSVZ = ipsilateral SVZ)	III	*Results* Median follow up were 24.5 months Median PFS and OS of whole cohort were 9.5 and 19.27 months Tumor in contact with SVZ = 32 patients and non in contact 28 patients Significant relation of cSVZ dose > 59.2% with poor PFS (10.37 vs 7.1 months, p = 0.009) in univariate analysis, but it was not significant in multivariate analysis overall cSVZ > 59.2 was a significant prognostic factor for poor PFS in age > 54, male gender, subtotal resection/biopsy only, positive SVZ contact and KPS > 90 groups cSVZ > 59.2 Gy was associated with poor OS in Subtotal resection/biopsy subgroups iSVZ > 62.25 Gy was associated with poor PFS in the subgroup of KPS > 90 and SVZ without tumoral contact *Authors conclusions*: High dose radiation of SVZ has negative impact on OS and PFS in patients with newly diagnosed GBM *Comments* Retrospective study with small sample size
Chen et al. (2013) [10] PMID 23540348	*Study design:* Retrospective review of case-cohort *Patient population:* 116 adult patients with newly diagnosed GBM *Description:* GTV1 = T1W tumor volume after gadolinium plus T2 FLAIR surrounding the area PTV1 = GTV1 plus 1- to 1.5-cm margin PTV1: Treated to 46-Gy in 23 fractions GTV2 = T1W tumor volume after gadolinium PTV2 = GTV2 cone-down volume plus 1- to 1.5-cm margin PTV2: Treated to an additional 14-Gy in 7 fractions SVZ was included in the radiation field no purposefully Ipsilateral, contralateral and bilateral SVZs were retrospectively contoured and SVZ was defined as a 5-mmmargin along the lateral wall of the lateral ventricles Surgery: 12%—biopsy, 53%—STR and 35%—GTR Ipsilateral, contralateral and bilateral contoured volume was 7.05 cm^3, 7.91 cm^3 and 14.8 cm^3 respectively. Median ipsilateral, contralateral, bilateral SVZ doses: 48.7-Gy, 34.4-Gy, 41.5-Gy	III	*Results* Direct contact of tumor with lateral ventricles was not prognostic for PFS or OS Subgroup GTR: Mean iSVZ dose of > 40-Gy significantly improved OS (17.5 months vs 15.6 months, p = 0.027) and PFS (15.1 months vs 10.3 months) Subgroup STR and Biopsy: iSVZ did not significantly improved OS nor PFS cSVZ and bSVZ radiation did not improve OS and PFS 7/23 patients that received < 40-Gy on iSVZ, experienced decrease in KPS 22/93 that received > 40-Gy on iSVZ, experienced decrease in KPS. These though did not significantly correlate with changes in KPS *Authors conclusions*: Higher radiation dose to the iSVZ was associated with improvement in PFS and OS in patients with GBM without negatively impacting KPS *Comments* Retrospective study. SVZ irradiation was not intentional and as such the doses and the volume of irradiation are not uniform

Table 4 (continued)

Author/year/PMID	Study description	Data class	Conclusion
Lee et al. (2013) [8] PMID 23462418	*Study design:* Retrospective review of case-cohort *Patient Population:* 173 adult patients with newly diagnosed GBM treated in 2 institutions that had received radiation dose of ≥ 59.4-Gy *Description:* SVZ was segmented as 3- to 5 mm lateral margin of the lateral ventricles based on the original treatment CTV = (at 1st center) Edema on T2W imaging, resection cavity and any residual post-operative enhancing area plus 2 cm surrounding area. Area received a cone-down dose of 60-Gy CTV = (at 2nd center) Resection cavity plus enhancement and 2 cm, and post-operative edema, T2W was included iSVZ and cSVZ dosimetry and volume were reviewed	III	*Results* Of 173, 21 received > 59.4-Gy to the iSVZ, the rest ≤ 59.4-Gy Median PFS and OS, respectively in the entire cohort were 10.4 months and 19.6 months Patients with high dose in iSVZ had a significant improvement in PFS (12.6 vs 9.9 months, p = 0.042) in univariate analysis In multivariate analysis, iSVZ radiation did not affect PFS when controlled for amount of resection and age *Authors conclusions*: There was an association between high iSVZ, radiation dose and PFS *Comments* Retrospectively reviewed study. SVZ radiation was not intentional and as such not standardized
Gupta et al. (2012) [11] PMID 22555992	*Study design:* Retrospective case-cohort *Patient population:* 40 patients with newly diagnosed GBM that received RT to SVZ after surgery *Description:* All patients completed post-surgery RT All patients received concomitant TMZ (75 mg/m^2/day) during RT and adjuvant therapy 150–200 mg/m^2/day for 5 days every 4 weeks. 2 patients did not receive adjuvant TMZ Mean RT volume: ipsilateral SVZ was 5.6 cc and Controlateral SVZ was 6.4 cc Median mean doses were: ipsilateral SVZ: 59.9-Gy, contralateral SVZ: 57.9 and combined SVZ: 57.9 20 patients received low median dose to SVZ and 20 received high median dose to SVZ	III	*Results* For entire patients population: Median PFS was 11 months and OS 17 months Controlateral SVZ: - PFS for those receiving Higher than median dose RT (HRT) was 10 months and Lower Dose (LRT) Not Reached (p = 0.02) - OS 14 months (HRT) vs not reached (LRT) (p = 0.05) Ipsilateral SVZ: - PFS: 10 vs 11 mo; p = 0.92 HRT vs LRT - OS: 15 vs 17 mo; p = 0.95, HRT vs LRT Combined SVZ: - PFS: 10 vs 14 mo; p = 0.06 HRT vs LRT - OS: 14 months vs Not reached; p 0.22 HRT vs LRT *Authors conclusions*: Irradiation of SVZ may influence survival of patients with GBM *Comments* Retrospective study evaluating the doses that SVZ received. SVZ were not specifically targeted during RT. Data not conclusively support authors conclusions that SVZ radiation increases survival
Foro Arnalot et al. (2017) [12] PMID 28389881	*Study design:* Retrospective review *Patient population*: 65 patients with newly diagnosed GBM *Description*: Evaluated patients that received incidental RT to (75 percentile) ipsilateral, contralateral and bilateral SVZ: 57.30, 48.8, 52.7 Gy respectively All received Surgery, RT and TMZ	III	*Results* Median PFS and OS was 11.5 ± 9.96 and 18.8 ± 18.5 mo Patients that received > 48.8 Gy in contralateral SVZ had a better PFS than the others (HR 0.46; 95% CI 0.23–0.91 p = 0.028). OS was not significantly different *Author's conclusions* High-dose incidental radiation in the contralateral SVZ was associated with a significant improvement in PFS but not OS *Comments* Retrospective review. SVZ radiation was not intentional

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Table 5 Information and summary of the articles that were included and used to answer the questions on the value of Radiation Therapy in Elderly

Author/year/PMID	Study description	Data class	Conclusion
Keime-Guibert et al. (2007) [13] PMID	*Study design:* Randomized Controlled Study *Patient population:* Elderly patients (> 70 years of age) with newly diagnosed GBM *Description:* 81 patients with newly diagnosed GBM KPS ≥ 70 All patients underwent surgical resection then randomized to Supportive Care (n = 42) or Supportive care in combination with RT (n = 39) - Surgery: biopsy (supportive care n = 22 and RT n = 20), GTR (Supportive care n = 13 and RT n = 12), STR (Supportive care n = 7, RT n = 7) - RT: 1.8 Gy fraction/day, 5 days/week, total 50 Gy CTV = Area residual enhancement plus 2 cm surrounding margin	I	*Results:* 10% survival at the median follow up of 21 weeks 53% of relative reduction risk of death for patients of RT group Median survival benefit was 12.12 weeks Median survival was 29.1 weeks for RT + supportive care vs 16.9 weeks for Supportive care group Median PFS was 14.9 weeks for RT group and 5.4 weeks for Supportive care group Survival benefit of RT was independent of extent of surgery KPS decline overtime with no significant difference between groups Performance status, quality of life and neuropsychologic evaluation did not significantly differ for both groups Toxicity: abnormal sleepiness after RT (n = 1). Corticosteroid toxicity: Diabetes in supportive only group (n = 7) and in RT (n = 2), Myopathy: Supportive group (n = 3) and RT group (n = 6) *Authors conclusions:* Addition of Adjuvant RT to supportive care in patients older than 70 years of age prolongs survival and does not reduce health-related quality of life or cognitive function *Comments:* This is RCT. Class I evidence
Babu et al. (2016) [14] PMID 26452121	*Study design:* Retrospective chart review *Patient population:* Elderly patients (65 and older) with newly diagnosed primary GBM *Description:* 120 patients with median age of 71 years All underwent surgical resection: 76 GTR and 44 STR. 3 patients underwent re-resection TMZ and RT (Standard): 110 patients RT alone: 1 Bevacizumab (Initial/before progression): 22; after progression 22 Other chemo mostly after progression: Lomustine, Irinotecan, Etoposide, Immunotherapy, Carmustine wafer, SRS	III	*Results* Median survival was 12 months 26.7% survived above 2 years Patients 75 years of age or older had worst prognosis (7.9 vs 15.1 months) Patients with KPS > 90 had 21.8 months survival, KPS 80 12.2 months, KPS < 80 7.2–7.4 months GTR had median survival of 14.1 mo; STR had a survival of 9.6 months (p = 0.038) Bevacizumab use improved survival (20.1 months vs 7.9 months) *Authors conclusions*: GTR and use of standard chemotherapy and RT increases survival in elderly patients *Comments* Retrospective review of charts. Add information that standard chemo and RT could be used even in elderly patients

Table 5 (continued)

Author/year/PMID	Study description	Data class	Conclusion
Abdullah et al. (2015) [15] PMID 25978638	*Study design:* Retrospective Review *Patient population:* Elderly patients (80–93 years of age) with newly diagnosed GBM (n = 58) *Description:* Only patients that underwent GTR were included Majority had KPS of 70 or 80 No adjuvant therapy (n = 38) RT only (n = 10) Chemo and RT (n = 10)	III	*Results* Median OS was 4.2 months (0.2–72 months) Higher KPS associated with better OS ($p < 0.05$) OS for patients not undergoing adjuvant therapy was 96.5 days, RT alone 200 days and RT with chemotherapy 351 days ($p < 0.05$) Statistically significant correlation between lack of EGFR expression and survival ($p < 0.05$, 276 vs 104 days) There was association between lack of p53 expression and survival ($p < 0.001$ 97 vs 330 days) *Authors conclusions* Patients with high pre-operative KPS, post-operative adjuvant therapy and lack of protein expression of EGFR and p53 have better overall survival *Comments* Retrospective study. Authors did not report the type, dose and length of radiation and/or chemotherapy administered. Authors did not report the results of multivariate analysis
Niyazi et al. (2012) [16] PMID 22231634	*Study design:* Retrospective review of case-cohort *Patient population:* 43 elderly patients (> 70 years of age) diagnosed with GBM *Description:* - Surgery: 34 Biopsy, 7 GTR, 2 STR - Chemotherapy: Concomitant TMZ with RT (18 patients), 75 mg/m^2/day for the duration of RT - RT: Conventional RT, 60-Gy over 6 weeks. Once daily dose of 2-Gy in 30 fractions GTV was contrast-enhancing lesion on T1W. CTV was GTV + 2 cm surrounding it including the edema PTV is CTV + surrounding 5 mm margin	III	*Results* Median follow up was 157 days (range 51–1257) Median PFS was 192 days Median OS was 264 days 1-year PFS was 16.8% and OS 32.6% 2-year PFS was 10.1% and OS 14.5% Median survival in RT only group was 314 days and in RT + TMZ group was 192 days Subgroup analysis: High age, low KPS and TMZ use was significantly associated with increased risk of death Patients with KPS 80, median survival was 437 days for RT + TMZ and 323 for RT only ($p = 0.716$) *Authors conclusions*: RT only is better than RT with concomitant TMZ in elderly patients with low KPS *Comments* Retrospective study

Table 5 (continued)

Author/year/PMID	Study description	Data class	Conclusion
Scott et al. (2011) [17] PMID 20675068	Study design: retrospective review of SEER database *Patient population:* 2836 elderly patients (> 70 years of age) with diagnosis of GBM *Description:* Patient were divided in 4 groups: - No treatment: 384 patients - Surgery alone: 635 patients - RT alone: 508 patients - Combination surgery and RT: 1.309 patients For patients that underwent surgery: 1944 underwent surgical resection (735 GTR and 1209 STR) and the rest biopsy - 71% of patients with STR and 68% of patients that underwent biopsy received RT	III	*Results* Radiotherapy was associated with significant increase survival as compared to no treatment ($p < 0.0001$) Surgery was associated with significant increase in survival as compared to no treatment ($p < 0.0001$) Combination therapy patients: Median survival was 8 months Radiation alone: 4 months Surgery alone: 3 months No treatment: 2 months ($p < 0.001$) Median OS was 7 months (combination RT + Surgery), 4 months (RT only), 2 months (Surgery only) and 1 month (no treatment) *Authors conclusions*: In this population, after adjusting for all confounding factors, RT confers an advantage regarding cancer-specific survival and OS. Thus age shouldn't be a factor in withholding treatment *Comments* Retrospective review of database. Non-randomized study
Marijnen et al. (2005) [18] PMID 15885825	*Study design:* Retrospective review *Patient population:* 202 patients ≥ 18 years with GBM & KPS > 40 *Description:* GTR, STR, or biopsy RT = 2 Gy fractions (60 Gy total); poor performance status received 30 Gy in 10 fractions on a whole brain field, or no RT	III	*Results* Median OS = 8.0 mo; total group, 13.9 mo; RPA III (n = 17), 10.6 mo RPA IV (n = 87), 3.8 mo; RPA V (n = 60), 2.1 mo; RPA VI (n = 38) Median OS = 3.6 months to ≥ 70 years, 8.1 months; 50–70 years, 11.0 months to < 50 In each separate RPA group, $OS_{\geq 70years} \approx OS_{50\text{-}70years}$ Irradiated patients (66%) survived significantly longer than non-irradiated patients: 10.6 vs 1.9 months ($p < 0.0001$) In RPA group V the median survival for irradiated patients was 9.4 vs 2.1 months for non-irradiated patients In a multivariate analysis, RT remained the only prognostic factor for survival (HR 8.9, $p < 0.001$) *Authors conclusions*: Prognosis for patients above 70 years of age is not different from younger patients, when analyzed for separate RPA groups. For patients with a poor prognosis (i.e. RPA group V), radiotherapy improves survival significantly *Comments* Retrospective study

Table 5 (continued)

Author/year/PMID	Study description	Data class	Conclusion
Combs et al. (2008) [19] PMID 17967509	*Study design:* Single institution retrospective review *Patient population:* 43 patients 65 years or older with primary GBM *Description:* Postoperative radiotherapy was applied with a median dose of 60 Gy, in a median fractionation of 5 × 2 Gy/week. Thirty-five patients received concomitant TMZ at 50 mg/m^2, and in 8 patients 75 mg/m^2 of TMZ was applied. Adjuvant cycles of TMZ were prescribed in 5 patients only	III	*Results:* Median OS = 11 months in all patients Actuarial OS = 48% @ 1 year, 8% @ 2 years Median OS = 18 mo; GTR, 16 mo; STR, and 6 mo; biopsy Median PFS = 4 months Actuarial PFS = 41% @ 6 months, 18% @t 12 mo Radiochemotherapy was well tolerated in most patients and could be completed without interruption in 38 of 43 patients. Four patients developed hematologic side effects greater than Common Terminology Criteria Grade 2, which led to early discontinuation of TMZ in 1 patient *Authors conclusions*: Radiochemotherapy is safe and effective in a subgroup of elderly patients with GBM and should be considered in patients without major comorbidities *Comments* Retrospective single institution review. No comparison arm

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Table 6 Information and summary of the articles that were included and used to answer the questions on the dose of radiation therapy in elderly and/or frail patients with GBM

Author/year/PMID	Study description	Data class	Conclusion
Roa et al. (2015) [20] PMID 26392096	*Study design:* Prospective randomized trial non inferiority study *Patient population:* Patients with newly diagnosed GBM Definitions: Frail patients: > 50 years old with KPS 50–70% Elderly and frail: > 65 years old with KPS 50–70% Elderly: > 65 years old with KPS 80—100% *Description:* 98 patients were recruited, 2 were lost in f/u and not included in analyses 2 arms with different RT protocols All patients underwent surgery - Biopsy: 4 arm I and 9 arm II - PR: 34 arm I and 30 arm II - GTR: 8 arm I and 8 arm II RT: PTV equaled CTV (Tumor volume + 2 cm margin) + 0.5 cm margin - Arm I: 25 Gy in 5 daily fractions of 5 Gy over 1 week - Arm II: 40.05 Gy in 15 daily fractions of 2.67 Gy over 3 weeks	II	*Results* Median OS was 7.9 months for arm I and 6.4 months for arm II (p = 0.988) Median PFS was 4.2 months for arm I and 4.2 months for arm II (p = 0.716) Mean global QoL scores at baseline were 42.6 and 51.2 for arm I and arm II respectively Mean global QoL scores at 4 weeks post-treatment were 49.6 and 49.7 for arm I and II respectively Mean QoL scores at 8 weeks after treatment for arm I and arm II were 51.3 and 54.9 respectively *Authors conclusions*: The trial support the non-inferiority of short RT treatment for elderly and frail patients with newly diagnosed GBM *Comments* The authors do not report whether these patients received chemotherapy or not. The authors use 2 different schemes of short RT and do not compare them with the standard RT. This in our opinion is a class 2 even though a RCT because it only compares 2 short RT regimens and does not compare short regimen with the conventional RT
Minniti et al. (2015) [23] PMID 25442339	*Study design:* retrospective study *Patient population:* 243 patients of age > 65 years with newly diagnosed GBM *Description:* 4–6 weeks after diagnosis, patients received: - 40-Gy delivered in 15 fractions with concomitant daily TMZ (n = 127) or - 60 Gy in 30–33 daily fractions of 1.8–2 Gy with concomitant daily TMZ (n = 116) Adjuvant TMZ was given 4 weeks after cessation of RT (5 days every 28 days cycle for 6–12 cycles) 49% of Standard-course therapy and 39% of patients on short-course RT received salvage therapy after progression	III	*Results* Median OS was 12 months and 12.5 months respectively for Standard and Short-course RT (p = 0.5) 12 and 24 months survival was similar (50% and 18% for standard and 54% and 12% for Short-course RT) Median PFS was 5.6 and 6.7 respectively (p = 0.5) 12 months PFS rates were 23% and 20% respectively (standard and short-course RT) 28 patients (standard RT) and 11 patients (short-course RT)—worsened neurological status 40% (n = 51) in standard RT and 14% (n = 16) in short-course RT experienced grade 2–3 neurological toxicities (p = 0.01) TMZ caused grade 3–4 hematologic toxicities in 4 patients, (standard RT n = 3 and short course RT, n = 1) *Authors conclusions*: Short-course RT seems a reasonable option for treating older patients with GBM enabling similar benefits but better toxicity profile than standard RT *Comments* Retrospective multi-institutional study

Table 6 (continued)

Author/year/PMID	Study description	Data class	Conclusion
Biau et al. (2017) [24] PMID 29212499	*Study design:* Retrospective review Patient population: 104 patients > 70 years of age with newly diagnosed GBM *Description*: - Surgery: 5 (5%) GTR, 9 (9%) PR, 90 (86%) Biopsy - Adjuvant therapy: CRT (60 Gy, 30 Fractions) + TMZ: 33 patients HFRT (40 Gy, 15 Fractions) + TMZ: 37 patients HRT alone: 34 patients	III	*Results* Median OS of all patients: 5.2 months OS at 12, 18 and 24 months: 19%, 12%, 5% No statistical significance between CRT + TMZ and HFRT + TMZ (p = 0.22) HRT OS 3.9 months (p = 0.018) Multivariate analysis: GTR surgery, use of TMZ in conjunction with CRT or HFRT and RPA class were significant prognostic factors *Author's conclusions* Maximal surgical resection and HRT in conjunction with TMZ are recommended as standard treatment for elderly patients *Comments* Patients with HRT alone were much older than the others and with lower KPS
Bracci et al. (2016) [25] PMID 27311728	*Study design:* Retrospective review of patient cohort *Patient population*: 21 patients of age 80 years and above with newly diagnosed GBM *Description*: - Surgery: 14 (66.6%) biopsy, 5 (23.8%) STR, 2 (9.5%) GTR - RT: 40.05 Gy in 15 fractions within 6 weeks of surgery Chemotherapy: TMZ concurrent daily 75 mg/m^2 (only 47% of patients) and adjuvant per Stupp protocol 150 mg/m^2/day for 5 days every 28 days	III	*Results* Median OS was 7.5 mo 1-year and 2-year OS were 39.5% and 6.6% respectively Median PFS were 5.8 mo 1-year and 2-year PFS were 15.2% and 0% Multivariate analysis, hospitalization was the only significant predictor of OS and PFS Use of concurrent TMZ vs no use did not provide any significant difference in terms of survival *Author's conclusions* Patients > 80 years of age should be considered for management based on RT and Chemotherapy *Comments* Retrospective review with small number of patients
Wang et al. (2016) [26] PMID 26952813	*Study design:* Retrospective review of cohort of patients *Patient population*: 184 patients > 60 years of age with newly diagnosed GBM *Description*: - RT: Group 1: 60 Gy in 30 fractions (158 patients) Group 2: 40.05 Gy in 15 fractions (26 patients) - Concurrent and Adjuvant TMZ 75 mg/m^2/daily and 150 mg/m^2/daily for 5 days every 28 95% in group 1 and 100% in group 2 - Surgery GTR/STR: 140 (88%) group 1; 24 (92%) group 2 GTR: 81 group 1 and 18 group 2 STR: 19 group 1 and 3 group 2 Unknown: 40 group 1 and 3 group 2 Biopsy 18 group 1 and 2 group 2	III	*Results* OS for both treatments was not significantly different (430 days vs 475 days). (p = .550) OS for patients receiving TMZ showed no significant difference (p = .707) Multivariate analysis, factors that remained significant are: age > 70 years, KPS < 70, extent of surgery and radiation planning technique *Author's conclusions* Elderly patients may benefit from hypofractionated therapy *Comments* Retrospective review of patient cohort

Table 6 (continued)

Author/year/PMID	Study description	Data class	Conclusion
Minniti et al. (2013) [22] PMID 23642624	*Study design:* Prospective phase II trial with primary end point, OS and secondary end points PFS, toxicity and Health related QOL (HRQOL) *Patient population:* 71 patients of age > 70 years with newly diagnosed GBM *Description:* After diagnosis, patients received 40-Gy delivered in 15 fractions with concomitant daily TMZ followed by adjuvant TMZ 4 weeks after chemoradiation HEQOL were assessed using EORTC QOL Questionnaire Core-30 (QLQ-C30) and EORTC Quality of Life Questionnaire Brain Cancer Module (QOL-BN20) Questionnaires were filled out right before chemoradiation, after chemoradiation and every 8 weeks after it until disease progression Mini-Mental Status Examination (MMSE) was used to assess neurocognitive function and administered immediately before RT and a month after and then every 3 cycles of chemotherapy 65 questionnaires were completed at baseline and only 12 at 1 year	II	*Results* Median OS was 12.4 months Median PFS was 6 months MGMT methylation status was the strongest significant independent prognostic factor for OS (Median OS rates were 15.9 months in methylated and 8.8 in unmethylated patients ($p = 0.0001$) Global health improved over time, mean score differed by 9.6 points between baseline and 6 months follow-up ($p = 0.03$) Social functioning and cognitive functioning, mean scores improved, with maximum difference of 10.4 and 9.5 points between baseline and 6 months follow-up ($p = 0.01$ and $p = 0.02$) respectively Motor dysfunction improved over time ($p = 0.02$) No significant changes for communication deficits ($p = 0.4$) and Insomnia ($p = 0.2$) Tendency toward improvement for emotional functioning ($p = 0.1$) and physical functioning ($p = 0.09$) Fatigue worsened overtime with a difference in mean score of 5.6 points between baseline and 4-months follow-up MMSE score improved or remained stable during 12-month follow-up in 89% of patients free of disease progression Decrease of MMSE was noticed in 11% of patients without disease progression *Authors conclusions*: Baseline HRQOL after a short course of RT in elderly patients with newly diagnosed GBM did not deteriorate overtime and in some instances improved until disease progression *Comments* Although a prospective trial, the authors report on HRQOL in elderly patients that underwent short course of RT without randomization. Further QOL was a secondary end-point of this trial. Classified as class II data

Table 6 (continued)

Author/year/PMID	Study description	Data class	Conclusion
Fariselli et al. (2013) [27] PMID 23625362	*Study design:* Retrospective single-center review of charts *Patient population:* 33 patients older than 70 years of age (70–82), with post-operative KPS ≥ 70 diagnosed with GBM *Description:* All patients underwent surgical resection (16 GTR, 13 STR, 4 stereotactic biopsy) 2 course hypofractionated accelerated RT (ART) was started 2–4 weeks post-surgery Total dose of 45-Gy and administered in 2 cycles (split in 2 cycles (15 days), 2.5-Gy/fraction, 3 daily fractions (inter-fraction rest time of 4 h for 3 consecutive days/cycle.) PTV = contrast-enhanced tumor excluding edema, plus 1-cm margin Macdonald's criteria were used to evaluate the response At progression, 7 patients received BCNU 150 mg/m^2 every 8 weeks, 2–4 cycles	III	*Results* 1 patient experienced grade 3 toxicity: cognitive disturbance No radiation necrosis occurred KPS at 3 months after RT was stable in 18 patients (73%), improved in 6 (24%) and worsened in 1 (3%) 1/7 of patients that received salvage chemotherapy experienced grade hematological toxicity Median PFS was 6 months Median OS was 8 months (2–24 months) Median survival rate at 1 year of 9 patients (27%) 2 patients had a survival of 21 and 23 months and 1 of 24 months On multivariate analysis, type of surgery was confirmed as the only significant factor on OS and GTR was independently associated with increased OS [HR 0.159; 95% CI 0.04–0.59; p = 0.006] *Authors conclusions*: RT is beneficial in the elderly patient population. Overall treatment time can be considerably shortened without a detrimental effect on clinical outcome *Comments* Retrospective review of a single center without control arm
Malmstrom et al. (2012) [21] PMID 22877848	*Study design:* Prospective randomized controlled trial *Patient population:* Adult patients (older than 60 years of age) with newly diagnosed GBM *Description:* 291 patients (age > 60 years) in 28 European centers were randomized after surgical intervention in a ration of 1:1:1 in blocks of nine to receive temozolomide, hypofractionated RT, or standard RT in some centers and in a ration of 1:1 in blocks of 8 to receive temozolomide or hypofractionated RT TMZ (119 [93 + 26] patients): PO in 200 mg/m^2 daily day 1–5 every 28 days Hypofractionated RT (123 [98 + 25] patients): 34-Gy in 10 fractions of 3.4-Gy 5 days/week over 2 weeks. Multiple field technique was used Standard RT (100 patients): 60-Gy administered in 30 fractions of 2-Gy 5 days/week for 6 weeks	II	*Results* Multivariate analysis showed prognostic value for performance score, surgical resection vs biopsy and age (> 70 vs 60–70) Fewer patients in standard therapy group were able to complete RT More patients in the TMZ group received second line treatment than did those in the RT groups (38/93 vs 29/98 vs 27/100) although not significant Survival was better in TMZ group vs standard RT No difference in survival between hypofractionated RT vs standard RT Survival was not different in 60–70 years of age group Survival was better with TMZ and with hypofractionated RT than with standard RT in older than 70 years of age group Median survival was similar for TMZ and hypofractionated RT groups Common adverse events: Seizures, fatigue, thromboembolic events Nausea and vomiting, more frequently in TMZ group Grade 3–5 infections were similar among all groups On TMZ group: MGMT promoter methylated tumors had better survival than those with unmethylated MGMT promoter status On RT groups, MGMT promoter status did not affect survival *Authors conclusions*: For patients older than 70 years, TMZ or hypofractionated RT over 2 weeks might be a valid alternative to standard RT. MGMT promoter methylation status might be a useful biomarker to help in treatment decision *Comments* RCT. Power of the study was lower than first calculated, hence classified as level II evidence. Further, combination of RT with chemo was not investigated

Table 6 (continued)

Author/year/PMID	Study description	Data class	Conclusion
Minniti et al. (2012) [28] PMID 22079725	*Study design:* phase II prospective open-label single-arm study *Patient population:* 71 adult patients above 70 years of age with newly diagnosed GBM *Description:* Patients > 70 years of age, KPS ≥ 60, underwent surgery, focal RT with concomitant TMZ, followed by adjuvant TMZ - Surgery: 35 patients GTR, 27 PR, 9 biopsy - RT within 4 weeks of surgery: 40-Gy in 15 fractions of 2.66-Gy. GTV = resection cavity and residual enhancing tumor. CTV = adding 2 cm margin around GTV. PTV = CTV was expanded by 4 mm - Chemotherapy: Concomitant TMZ 75 mg/m^2/day daily for the duration of RT. Adjuvant therapy was delivered for 5 days every 28 days for 12 cycles (150 mg/m^2/day first cycle and then 200 mg/m^2/day after) MacDonald criteria for neuroradiographic response were used PFS and OS were stratified by age (≥ 75 and < 75 years of age)	II	*Results* Median OS was 12.4 months Median PFS was 6 months The 1- and 2-year OS rates = 58% and 20% The 1- and 2 year PFS rates = 20% and 5% 61 patients experienced recurrence: within the treated volume 53 and outside or distant from targeted volume in 8 Univariate analysis, KPS, extent of resection, RPA class, and MGMT methylation status were associated with significant increase in OS Multivariate analysis, KPS > 70 and MGMT methylation status were significant for OS MGMT methylation status was associated with significant better PFS (10 months in methylated tumors and 4 in unmethylated, p = 0.0001) with 1- and 2-year PFS of 37% and 7% Toxicities: Grade 2 thrombocytopenia 1 patient. 10 patients had Grade 3 or 4 thrombocytopenia, 3 had Grade 3 neutropenia, 16 had Grade 3 or 4 lymphocytopenia. Grade 2 or 3 fatigue in 7 patients during RT and in 12 during adjuvant TMZ. Nausea and skin rash in 8 and 3 patients. 1 patient had pneumonia and 4 thromboembolic events. Grade 2 confusion in 4 patients. 3 patients had delayed Grade 3 cognitive disability *Authors conclusions*: Combination of abbreviated course of RT with concomitant and adjuvant TMZ is well tolerated and may prolong survival in elderly patients with GBM, especially in those with methylated MGMT promoter *Comments* Phase II prospective not randomized study. Hence considered as class II. There is no comparative arm
Idbaih et al. (2008) [29] PMID 19046921	*Study design:* Retrospective review of charts of case-cohort *Patient population:* 28 elderly patients (≥ 70 years of age) with newly diagnosed GBM *Description:* RT: After surgery, patient underwent RT: 40-Gy in 15 fractions over 3 weeks (2.67-Gy/per day/5 days) 17 received adjuvant chemotherapy: - 7 received TMZ only - 7 received TMZ and after failure, received nitrosurea or carboplatin) - 3 received 3 lines of therapy (TMZ, nitrosurea and carboplatin)	III	*Results* 2 patients did not finish RT secondary to tumor progression induced neurological deterioration Median follow up was 58.6 weeks Median PFS was 21.6 weeks Median OS was 50.6 weeks 13 patients had died of tumor progression at the time of analysis Patients with KPS ≥ 90 had a significantly longer survival (p = 0.029) Extent of resection and age (< 75 or ≥ 75) and RPA class did not significantly influence the OS *Authors conclusions*: Short term RT is an effective and safe alternative for selected (KPS ≥ 70) elderly patients with GBM *Comments* Retrospective review. Small group of patients. No report whether Chemotherapy influenced the OS

Table 6 (continued)

Author/year/PMID	Study description	Data class	Conclusion
Mak et al. (2017) [31] PMID 28440040	*Study design:* Retrospective review of National Cancer Data Base *Patient population*: 4598 patients with newly diagnosed GBM age ≥ 70 years *Description*: Patients diagnosed between 1998–2011 Surgical intervention followed or not by chemotherapy and radiation Radiation: - Short-course RT: 34–42 Gy in 2.5–3.4 Gy fractions = 304 patients - Long course RT: 58–63 Gy in 1.8–2.0 Gy fractions = 4294 patients	III	*Results* - Short Course RT vs Long Course median age: 78 vs 75 ($p < 0.0001$) - Short Course RT had worst Charlson-Deyo comorbidity scores ($p < 0.0001$), less likely to receive chemotherapy ($p < 0.0001$) Median OS: 4.9 months (Short Course) vs 8.9 months (Long Course) ($p < 0.0001$) *Author's conclusions* Hypofractionated Short Course RT was associated with worst prognosis in patients > 70 years of age *Comments* Evaluation of database. Patients that underwent Short Course RT were less likely to receive surgical intervention or chemotherapy and had worse comorbidity scores
Guedes de Castro et al. (2017) [30] PMID 28602417	*Study design:* Post Hoc analysis of data from Phase III randomized control non-inferiority trial *Patient population*: Elderly and frail patients with newly diagnosed GBM: age > 65 98 patients total for the original trial 61 patients for this post hoc analysis, 2 patients were lost in follow up (1 for each arm): - Arm 1: 26 - Arm 2: 35 *Description*: Patients randomly assigned to 2 groups for radiation therapy: 1. Short-course RT (Arm 1): 25 Gy in 5 fractions delivered in 1 week 2. Common Course RT (Arm 2): 40 Gy in 15 fractions delivered in 3 weeks Patients in the original trial were stratified by age < 65 and ≥ 65, KPS and extent of surgery No patient received TMZ during randomization Patients for the post-hoc analysis were age ≥ 65 and stratified per KPS, 50–70 vs 80—100 Received RT within 2 weeks of randomization	III	*Results* All elderly patients: - Median OS arm 1 vs arm 2: 6.8 months vs 6.2 months ($p = .936$) respectively - Median PFS arm 1 vs arm 2: 4.3 months vs 3.2 months ($p = .706$) respectively Elderly and non-frail patients (KPS 80–100): - Median OS arm 1 vs arm 2: 8 months vs 8 months ($p = .904$) Elderly and frail patients (KPS 50–70): - Median OS arm 1 vs arm 2: 7.5 months vs 6.7 months ($p = .890$) *Author's conclusions* Short-course RT of 25 Gy in 5 fractions is an acceptable treatment options for patients ≥ 65 years of age and with poor performance status or those with contraindication to TMZ *Comments* This is a post-hoc analysis of a randomized controlled trial, as such classified as Class III recommendation

AHRT hypofractionated accelerated RT, *ART* accelerated radiation therapy, *Bx* biopsy, *CD* complete response, *CFRT* conventional fractionated radiation therapy, *CGE* cobalt grey equivalent, *CTV* clinical tumor volume, *EBRT* external beam radiation therapy, *FRT* fractionated radiation therapy, *FSRT* fractionated stereotactic RT, *GBM* glioblastoma multiforme, *GTR* gross total resection, *GTV* gross tumor volume, *IMRT* intensity modulated radiation therapy, *MST* median survival time, *NTR* near total resection, *OS* overall survival, *PD* progressive disease, *PR* partial response, *PFS* progression free survival, *PTV* planning target volume, *RT* radiation therapy, *SD* stable disease, *SRT* stereotactic radiation therapy, *STR* subtotal resection, *SVZ* subventricular zone, *TM* tumor mass, *TMZ* temozolomide, *TTP* time to progression, *WBRT* whole brain radiation therapy

Table 7 Information and summary of the articles that were included and used to answer the questions on the timing of radiation therapy after diagnosis

Author/year/PMID	Study description	Data class	Conclusion
Adeberg et al. (2015) [32] PMID 26223282	*Study design:* Retrospective review *Patient population:* Adult patients with newly diagnosed GBM *Description:* 50 patients that underwent 3 prospective studies were compared with a reference group of 127 cases that received RT and TMZ only Surgery: all patients (GTR only n = 18) RT: 60 Gy, 2 Gy fractions/day, 5 days/week for 6 weeks Chemo: 3 different trials: Temsirolimus (n = 19), Enzastaurin (n = 13) and Cilengitide (n = 18) Median delay for study patients was 35 days (18–49 days) versus reference-sample patients, 27 days (5–98)	III	*Results* Median OS for the patients was 16.2 months (2–56 months) non significantly different from the reference group (18.2 months, p = 0.64) Median PFS was 6.9 vs 6.3 months (p = 0.20) Study medication and degree of resection between the groups did not affect the results Significant decrease in PFS and OS if RT was performed earlier than 24 days *Authors conclusions*: Delay of adjuvant RT does not impact survival. Initiation of RT earlier than 24 days after surgery has negative impact on OS *Comments* Complex study design. Retrospective in nature. The authors do not consider specific time-frames between surgery and RT, but only consider the median delay (27 vs 35). Selection bias that patients that started therapy earlier could have had worst tumor
Han et al. (2015) [33] PMID 25856113	*Study Design:* Retrospective Review *Patient population:* 198 adult patients with newly diagnosed GBM enrolled in 4 different trials of RT with chemotherapy plus an experimental agent *Description* All patients underwent surgical resection, Biopsy (n = 33), partial resection (n = 95), gross total resection (n = 67) All patients underwent RT + TMZ + experimental agent: - Group 1: < 30 days from diagnosis (n = 100) - Group 2: 30–35 days (n = 48) - Group 3: > 35 days (n = 50) RT + TMZ: Standard Stupp protocol	III	*Results* Earlier RT + TMZ in patients that had undergone biopsy or PR or younger OS and PFS was better in group 2 (p = 0.002 and p = 0.06 respectively) compared to Group 1 OS and PFS was worst in group 3 when compared to group 2 *Authors conclusions* In multivariate analysis, time interval to chemoradiation (30–34 days) remained a statistically significant factor for OS with trends toward significant PFS. Delay after this time interval shows poorer survival *Comments* Retrospective review. Patients that had delayed adjuvant therapy more often had GTR. This could bias these patients toward longer survival because of the surgery
Sun et al. (2015) [34] PMID 25768833	*Study design:* Retrospective review of TCGA database *Patient population:* 218 patients with newly diagnosed GBM *Description:* All patients underwent surgery: Biopsy, STR or GTR All patients underwent standard Chemoradiation (Stupp protocol) within 7–232 days post-surgery Patients were divided in 3 groups depending on the timing of adjuvant chemoradiation: - Group 1: less then 20 days - Group 2: 21–27 days - Group 3: 28–35 days - Group 4: 36 days or longer Median delay was 27 days	III	*Results* Median PFS for delay < 27 days was 7.2 months and > 27 was 7.8 days (p = 0.840) PFS for delay less then 42 days or more than 42 days was not significant Median OS for delay < 27 days was 15.9 months and > 27 was 14.9 (p = 0.180) Differences between 2 extreme groups (1 and 4) was not significant Median OS for delay < 42 days and > 42 days was significantly different (15.9 months vs 12.9 months, p = 0.022 and HR of death of 1.835) *Authors conclusions* Significant delay of longer than 6 weeks may negatively affect OS but not PFS *Comments* The data was collected from the TCGA database which intent is not to collect data on imaging and outcome, but genetics of the tumor. No data is available to understand the tumor burden on patients that underwent earlier chemotherapy as compared to those that underwent later

Table 7 (continued)

Author/year/PMID	Study description	Data class	Conclusion
Spratt et al. (2014) [35] PMID 24190580	*Study design:* Retrospective review of cohort group *Patient population:* Adult patients with newly diagnosed GBM *Description:* 345 patients underwent surgical resection/biopsy, chemotherapy and RT Timing of post-operative RT was determined by subjective evaluation of clinical urgency and complexity Different radiation techniques and doses were used Interval from Surgery to RT/Chemo was segregated in 3 groups, < 2 weeks, 3–5 weeks and > 6 weeks	III	*Results* 83.8% (n = 289) were treated with IMRT with median dose of 60 Gy STR was performed in 52.5%, GTR in 30.4% and biopsy alone in 17.1% Interval from surgery to RT was 6.1% (21 patients) < 2 weeks, 62.3% (215) 3–5 weeks and 31.6% (109) > 6 weeks post-surgery Median OS for the entire cohort was 12.2 months The 1-year actuarial OS was 43.1, 53.3 and 64.3% for < 2 weeks, 3–5 weeks and > 6 weeks But the Cox regression multivariate model demonstrated a significant detriment in delaying post-operative RT after adjusting for known prognostic factors (< 2 weeks as reference); 3–5 weeks (HR 2.80 [0.72–10.89] p = 0.14), and > 6 week (HR 3.76 [1.01–14.57] p = 0.05) Higher doses of RT, IMRT technique and greater extent of surgery were significantly associated with improved OS *Authors conclusions*: There is a survival detriment with delaying RT post-surgery greater than 6 weeks *Comments* Retrospective analysis. It is not entirely explained why patients were treated at different times and why they received different doses
Valduvieco et al. (2013) [36] PMID 22855197	*Study design:* Retrospective review of case cohort Patient population: 107 adult patients with newly diagnosed GBM that underwent complete surgical resection followed by RT RT Description: All underwent GTR followed by RT Tumor volume included a safety margin of 2 cm. 60-Gy over a 6 weeks course (2-Gy/day) 86 patients received chemotherapy, Before 2005, BCNU (200 mg/m^2 × 6 weeks) after they received TMZ	III	*Results* Median OS was 16.8 months (13.1–20.5 months) On Univariate analysis, age (p = 0.036), KPS (p = 0.031), additional treatment with chemotherapy (p < 0.0001), and initiation of RT before 42 days (p = 0.009) had prognostic influence on survival On multivariate analysis, higher KPS, delay in initiation of RT of < 42 days and complementary Chemotherapy were independently associated with longer OS *Authors conclusions*: In patients with complete surgical resection, initiation of RT within 6 weeks was an independent predictor of longer survival *Comments* Retrospective non-randomized study with internal control only. Does not report the difference that delay in RT can have in patients that do not receive chemotherapy versus those that do receive chemotherapy

Table 7 (continued)

Author/year/PMID	Study description	Data class	Conclusion
Randolph et al. (2016) [38] PMID 27816029	*Study design:* Retrospective review of charts *Patient population*: 161 patients with newly diagnosed GBM *Description*: Surgical intervention: - Biopsy 36 (22.4%) - STR 45 (28%) - GTR 80 (49.7%) RT 60 Gy in 2 Gy daily fractions Chemotherapy: - Concurrent 115 (71.4%) - Non concurrent 46 (28%) - Temodar 107 (93%) Median time from surgery to RT: - For GTR and STR patients = 28 days For biopsy = 20 days	III	*Results* Median PFS was 6.8 mo PFS for GTR compared to biopsy or STR: 7.8 months vs 5.3 and 5.5 respectively ($p = 0.005$) PFS for starting RT < 28 days vs > 28 days: 6.7 months vs 6.9 months ($p = 0.07$) Only for biopsy and STR patients, PFS < 28 days vs > 28 days: 4.2 months vs 6.7 months ($p = 0.006$) Median OS was 12.2 mo OS for GTR vs STR vs Biopsy alone: 15.6 vs 11.0 vs 8.3 months ($p = 0.0002$) Delay of RT > 28 days was not significant (12.2 months vs 12.2 months) For Biopsy and STR patients, < 28 days vs > 28 days OS: 7.8 months vs 12.3 months ($p = 0.005$) For GTR patients there was no significant difference (17.7 s 12.2 months, $p = 0.58$) *Author's conclusions* 28 days delay of RT after surgery is not inferior to starting treatment in less than 28 days *Comments* Retrospective review
Wang et al. (2016) [39] PMID 26440447	*Study design:* Retrospective review of patient cohort *Patient population*: 447 adult patients with newly diagnosed GBM *Description*: - Surgical intervention: GTR 203, STR 46, Biopsy 68 - TMZ: 274 patients - RT dose < 36 Gy: 46 patients 36–54 Gy: 44 patients > 54 Gy: 357 patients - < 21 days post-surgery: 152 patients - 21–32 day post–surgery: 151 - > 32 day post-surgery: 144	III	*Results* Significant differences between the groups in terms of age, KPS, extent of surgery, RP class and RT technique Median OS for all was 371 days Kaplan–Meier OS: - < 21 days: 374 days - 21–32 days: 465 days - > 32 days: 478 days ($p = 0.004$) 1-year OS was 51.4%, 64.4% and 61.4% respectively *Author's Conclusions* In univariate analysis there was better prognosis for patient starting RT > 21 days post-surgery. In Multivariate analysis, there was no significant difference *Comments* Retrospective analysis with multiple variables that were different from a group to the other. Bias that patients with worst KPS, biopsy alone or older were treated with RT in < 21 days

Table 7 (continued)

Author/year/PMID	Study description	Data class	Conclusion
Noel et al. (2012) [40] PMID 22660920	*Study design:* Retrospective review of case-cohort *Patient population:* 400 adult patients with GBM *Description:* Surgery: 143 had biopsy, 90 PR, 164 GTR, 3 unknown RT: Median dose of 60-Gy in all patients Adjuvant chemotherapy: 268 patients of 316 who received concomitant treatment Median waiting times to RT measured: - First Symptoms to RT (338 patients) 77 d - Pathology to RT (359 patients) 36 d - Multidisciplinary Meeting to RT (179 patients) 32 d - CT for delineation to RT (313 patients) 12 d - Surgery to RT (400 patients) 41 d Number of patients receiving RT after surgery: - < 4 weeks surgery: 65 - > 5 weeks: 80 - 6 weeks: 79 - 7 weeks: 75 - ≥ 8 weeks: 101	III	*Results* Median survival was 409 days 12-, 18-, 24-month OS was 56.3, 33.7, 27.6% respectively No correlation was found between time interval to RT and survival Multivariate analysis, independent prognostic factors of overall survival were age ($p \leq 0.0001$) and degree of surgical resection, and type of surgery ($p = 0.0006$) *Authors conclusions*: Waiting time until RT after diagnosis did not affect patient outcome *Comments* Retrospective study of a dyshomogenous population. It was not reported whether patients that received biopsy only had a worse prognosis and therefore received RT earlier than patients that underwent GTR. Thus, this is class III data
Blumenthal et al. (2009) [41] (PMID 19114694)	*Study design:* Retrospective review of RTOG Database *Patient population:* 2855 adult patients with GBM that had been enrolled in different RTOG trials *Description:* 2855 patients with newly diagnosed GBM that had been enrolled in various RTOG trials from 1974–2003 (before Stupp trial) Different RT regimens according to the different RTOG trial protocols with median total dose of 60 Gy and ranging from 1.7 to 86 Interval from surgery to the start of RT: < 2 weeks: 756 patients 2–3 weeks: 805 patients 3–4 weeks: 757 patients 4–6 weeks: 537 patients	III	*Results* Median survival was: < 2 weeks: 9.2 months 4–6 weeks: 12.5 months (p, 0.0001) Multivariate analysis of OS showed that time to radiation and RPA stage are statistically significant factors with respect to OS *Authors conclusions*: Waiting time between 4 and 6 weeks for RT after diagnosis did show better OS *Comments* Retrospective study of a dyshomogenous population. Thus, this is class III data

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As this was a retrospective study without a control group it represents class III data.

Kim et al. [7], retrospectively studied 19 adult patients with GBM who underwent GTR and post-operative RT. The purpose of their study was to evaluate changes in treatment volume according to changes in surgical defect volume during RT and determine the effects of volume-adapted re-planning for RT. First simulation CT (simCT) was performed at 3–4 weeks post-operatively and the second simCT for shrink-filed technique was performed in the 5th week. Planning Tumor Volume (PTV) was the sum of Clinical Tumor Volume (CTV) plus 0.5 cm margin. Total RT dose was 60 Gy. Fifty Gy was given to the PTV based on the first simCT and then a 10 Gy boost was given to Gross Tumor Volume (GTV) plus 0.5 cm margin based on the first simCT for one group and for the other group GTV was recalculated based on the second simCT. They reported that overall surgical defect volumes were reduced from the surgical cavity on the first simCT. They concluded that volume-adapted re-planning during RT might decrease the irradiated volume of normal brain and prevent a radiation target miss for boost RT. The authors did not report the effect this technique had on OS, PFS or KPS. This study provides class III data.

Synthesis of results

There are no recent studies that fulfilled our inclusion criteria that compared different volume calculations for Whole Brain Radiation Therapy (WBRT) as it relates to OS and PFS. However, the majority of the studies reviewed, used PTV for planning purposes by adding 1–2.5 cm margin to the GTV that include the post-operative enhancing mass or the FLAIR on T2W images. There was one retrospective study, classified as class III study in which the authors recommended that PTV boost margin of 2.5 cm may not be required [6]. As such our recommendation remain the same with the level II recommendation from Buatti et al., that literature supports limited radiation fields for newly diagnosed GBM [2]. After a full literature review, Buatti et al., found only 2 class 2 studies that compared whole brain radiation therapy with more limited–around the enhancing tumor area–RT. In those studies, according to Buatti et al., the treatment regimen did not differ statistically in terms of overall survival. As such recommendation was made in favor of more limited field of radiation [2].

We found one retrospective study that evaluated changes of the volume of the surgical defect during RT [7]. This was a retrospective study. From this study we can recommend that since changes of the volume of surgical defect will change during the 6 weeks of RT, recalculation of the radiation volume may be necessary to reduce the radiated volume of normal brain.

Question 4: Is there any additional benefit that derive from radiation of the subventricular zone?

It has now been widely accepted that neural stem cells reside in the subventricular zone (SVZ) [8]. It is thought that these cells could be contributing to the cancer stem cells and tumor progression. Conversely other studies have demonstrated that SVZ cells do not have any proliferative or tumor triggering effect [9]. Further, it has been postulated that immune-reactive cells and inflammatory response cells may be residing in SVZ [9]. From these considerations, another emerging concept in RT for GBM has been whether or not radiation of the SVZ would impact survival. A series of publications meeting inclusion criteria, noted below, provide class III data on the topic. (Table 4).

Elicin and colleagues [9] retrospectively reviewed the radiation plans of 60 patients that underwent RT for GBM after surgical resection and/or biopsy. Patients received 60 Gy in 2 Gy daily fractions prescribed to PTV. They considered the SVZ volume strips of 3–5 mm lateral to the lateral ventricles. In 32 patients the tumor was in contact with SVZ. They found that RT of > 59.2 Gy of contralateral SVZ was a significant prognostic factor for poor PFS in age older than 54, male gender, subtotal resection/biopsy only and tumor being in contact with SVZ. The same dose was associated with poor OS in patients that had undergone subtotal resection or biopsy only. Radiation of ipsilateral SVZ with doses > 62.25 Gy was associated as well with poor PFS in the subgroup of KPS > 90 and tumor without contact with SVZ. The authors concluded that radiation of SVZ has a negative impact on OS and PFS for these patients. This was a retrospective study where radiation volumes had not been drawn taking in consideration specifically the SVZ.

In a similar study, Chen et al. [10], reviewed the RT dose distribution in the SVZ in 116 patients with newly diagnosed GBM. Subventricular zone was not intentionally included/excluded from the radiation field. Median ipsilateral, contralateral and bilateral mean SVZ doses were 48.7 Gy, 34.4 Gy and 41.5 Gy respectively. They found that direct contact of tumor with lateral ventricles was not prognostic for PFS or OS. Radiation of SVZ was associated with improvement in survival only for patients that had undergone gross total resection (GTR) (OS 17.5 months versus 15.6 months, $p = 0.027$ and PFS 15.1 months versus 10.3 months) leaving us wonder whether it was the surgical resection that influenced the survival rather than the SVZ radiation. They concluded that higher radiation dose to the ipsilateral SVZ was associated with improvement in PFS and OS in patients with GBM without negatively impacting KPS. This is retrospective study where the irradiation of SVZ was not intentional and as such doses and volumes were not uniform. Further, improvement in OS was seen only in patients that had undergone GTR.

Table 8 Information and summary of the articles that were included and used to answer the questions on the schemes of radiation therapy

Author/year/PMID	Study description	Data class	Conclusion
Chen et al. (2013) [42] PMID 23786946	*Study design:* Retrospective cohort study *Patient population:* 54 patients with newly diagnosed GBM Description: All patients underwent surgery (12—GTR; 22—STR; 18—PR; 2—Biopsy) 88.9% underwent concurrent chemoradiation within 1 month GTV1 = Any FLAIR or T2 abnormality CTV is expansion by 2 cm PRV = Adding 0.5 cm expansion to CTV GTV2 = Fields were shrunk to exclude edema Boost PTV = adding 2 cm to GTV2 - IMRT was delivered to 21 patients - 3D-CRT was delivered to 33 patients Median dose of radiation was 60-Gy (range 32.0–62.4) divided in 1.8–2.2-Gy daily fractions TMZ was delivered concomitantly with RT (75 mg/m^2/day for 7 days per week for duration of RT After 4-week break, all patients received 6–12 cycles of TMZ, 5-days schedule (150–200 mg/m^2/day) every 28 days, except 16 patients Median follow-up was 13 months (4–52) Rate of follow up was 93%	III	Results The use of IMRT resulted in significantly lower maximum dose to both lens No significant difference was observed in brainstem or optic nerve max dose 1-year OS was 79.6% and PFS was 48.7% 1-year OS was 89.6% vs 75.8% for IMRT and 3D-CRT, respectively (p = 0.795) 1-year PFS was 61% vs 45.5%, for IMRT and 3D-CRT respectively (p = 0.867) 32 patients had recurrence, 5 were undetermined, 16 had local recurrence, 9 had distant recurrences and 2 had both IMRT group: 2 patients had grade I/II toxicities, 3 late grade I/II neurotoxicities; and 1 developed pseudoprogression 3D-CRT group: 1 patient developed grade III acute neurotoxicities, 5 were diagnosed with pseudoprogression *Authors conclusions*: Delivering standard radiation doses by IMRT did not improve survival or decrease toxic effects of treatment in this series as compared to 3D-CRT Comments Retrospective study. It did not show any benefit of IMRT over 3D-CRT

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Table 9 Information and summary of the articles that were included and used to answer the questions on the radiosensitizer compounds for GBM during RT

Author/year/PMID	Study description	Data class	Conclusion
Goffman et al. (1992) [43] PMID 1310102	*Study design:* Phase I/II Study *Patient population:* 45 patients (23–75 year-old) w/ KPS = 80 and confirmed GBM *Description:* Radiosensitizer–IdUrd, IV 1,000 mg/m^2/day, 14 day in $RT_{initial}$ 1,000 mg/m^2/day, 14 day in $RT_{cone\text{-}down}$ RT–CT and MR for tumor definition V_{target} initial = abnormality + 5 cm (2 × 150 cGy)/d V_{target} cone-down = abnormality + 2 cm (2 × 125 cGy)/day Later in the study: (2 × 150 cGy)/d after 4500 cGy, for $dose_f$ = 70–75 Gy In the earlier phases of the study, a break of 7 to 10 days was given before cone down; in the later phases of the study, this requirement was dropped, but virtually all patients required at least a few days' break because of scalp reaction and need for recovery of blood cell counts	III	*Results* The results do not indicate a significant benefit for use of sensitizers, as compared with other contemporary and aggressive types of radiation treatment MST = 11 months 2-year AS = 9% As yet, there are no survivors at 3 years. Tumor biopsies at craniotomy showed relatively low sensitizer incorporation *Authors conclusions*: The failure of radiosensitizers combined with RT to show major benefit may be due to patient selection but appears also to be related to the combined problems of poor drug penetration/uptake into tumor, tumor-cell heterogeneity, and a high inherent cellular radioresistance of GBM *Comments* Not randomized phase I/II study, hence classified as class III

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Table 10 Information and summary of the articles that were included and used to answer the questions on the ultrafractionated RT

Author/year/PMID	Study description	Data class	Conclusion
Beauchesne et al. (2016) [45] PMID 26501997	*Study design:* Phase II prospective non-randomized trial Patient Population: 40 adult patients with newly diagnosed, unresectable GBM (6 patients were excluded from final analysis) Description: All patients had biopsy only - RT: Ultrafractionated focal irradiation: 3 daily doses of 0.75-Gy at least 4 h apart, 5 days/week for 6–7 consecutive weeks, 90 fractions for a total of 67.5-Gy RT was delivered to the GTV with 2.5 cm margin for CTV - Chemo: Patients received standard concomitant and maintenance TMZ as per Stupp protocol Tumor progression was defined according to Macdonald criteria. Results were compared to patients that underwent biopsy only from EORTC/NCIC 26981–22981/CE.3 trial	III	*Results* At 4 years, 3 were alive (8.8%) Median OS was 16 months 2-year survival was 32.4%, 3-years was 17.2% Median PFS rate at 6 months was 76.5% 4 complete responses and 7 partial responses As compared to the EORTC/NCIC RT trial, there was a significant improvement in PFS and OS in Ultra-RT patients Toxicity: Fatigue grade II in 30 patients, Headache grade I in 6, skin reaction grade I in 10, alopecia grade II in 20 *Authors conclusions*: Ultrafractionated-RT is feasible, well tolerated and shows improved outcome in patients with not resectable GBM Comments Still a small group of patients compared to a different trial control with different selection criteria
Beauchesne et al. (2010) [44] PMID 20511183	*Study design:* Phase I/II prospective non-randomized trial *Patient population:* 27 adult patients with newly diagnosed, unresectable GBM (Only 22 completed the full course) *Description:* All patients had biopsy only RT: Ultrafractionated focal irradiation: 3 daily doses of 0.75-Gy at least 4 h apart, 5 days/week for 6–7 consecutive weeks, 90 fractions for a total of 67.5-Gy RT was delivered to the GTV with 2.5 cm margin for CTV Tumor progression was defined according to Macdonald criteria At progression, 16 of 21 patients received fotemustine as first-line salvage chemotherapy, 1 patient underwent partial surgical resection and 1 underwent SRS Results were compared to patients that underwent biopsy only from EORTC/NCIC 26981–22981/CE.3 trial: Combination of standard RT with concomitant and maintenance TMZ)	III	*Results* At 4 years, 2 were alive Median OS was 9.5 months 2-year survival was 15.5% as compared to EORTC/NCIC trial where patients that received only RT had a median OS of 7.9 months and 2-year survival of 4.6% OS rate at 6, 12, 18 and 24 months was, 74, 29, 19, 15% respectively Median PFS rate at 6, 12, 18 and 24 months was 45, 13, 6 and 6%, respectively As compared to the EORTC/NCIC RT trial, there was a significant difference in Ultra-RT trial, but no difference could be detected with respect to OS Toxicity: Fatigue grade II in 20 patients, Headache grade I in 2, skin reaction grade I in 11, alopecia grade II in 12 *Authors conclusions*: Ultrafractionated-RT is feasible, well tolerated and could improve outcome in patients with not resectable tumors *Comments* Small group of patients compared to a different trial control with different selection criteria

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In another study, Lee et al. [8], reported on 173 patients with newly diagnosed GBM treated in 2 institutions that had received > 59.4 Gy. SVZ was segmented as 3–5 mm lateral margin of the wall of the lateral ventricle based on the original treatment plan. Twenty-one patients received > 59.4 Gy to the ipsilateral SVZ (iSVZ) and the rest < 59.4 Gy. Median PFS and OS, respectively in the entire cohort were 10.4 months and 19.6 months. Patient with high dose in iSVZ had a significant improvement in PFS (12.6 versus 9.9 months, $p = 0.042$) in univariate analysis. In multivariate analysis, iSVZ radiation dose did not affect PFS when controlled for amount of resection and age. The authors concluded that there was an association between high iSVZ radiation dose and PFS, although this was not shown in the

Table 11 Information and summary of the articles that were included and used to answer the questions on the hypofractionated therapy

Author/year/PMID	Study description	Data class	Conclusion
Navarria et al. (2018) [46] PMID 29291951	*Study design:* Retrospective review of single institution Patient population: 267 adult patients with newly diagnosed GBM Description: (After maximal safe resection of the tumor, RT was given with TMZ): 1. Before propensity analysis: 169 adults in CFRT and 98 in HFRT - 60 Gy with 2 Gy daily fractions for 30 consecutive days - 60 Gy with 4 Gy daily fractions for 15 days 2. After propensity analysis: 82 patients for each group: CFRT and HFRT	III	*Results:* Before propensity analysis, patient in both groups differed in KPS and EOR. After propensity analysis they matched - Prior to propensity analysis: *OS*: 15.2 months for CFRT group and 15.9 for HFRT *1, 2, 3-year OS*: 66.9 ± 3.6%; 25 ± 3.4% and 12 ± 2.6% for CFRT group and 71.4 ± 4.6%, 31.7 ± 4.9% and 18.3 ± 5.0% for HFRT (p value = 0.4) *PFS*: 10.7 months for CFRT group and 10 months for HFRT group - After propensity analysis: *OS*: 17.9 months for CFRT group and 16.7 for HFRT group *1, 2, 3-year OS*: 75.6 ± 4.7%, 32.7 ± 5.2% and 15.5 ± 4.1% for CFRT group and 75.6 ± 4.7%, 33.3 ± 5.4% and 18.9 ± 5.6% for HFRT (p value = 0.8) *PFS:* 12.3 months for CFRT and 10.0 months for HFRT group Toxicities appear to be comparable *Authors conclusions:* short course of radiation therapy would seem comparable to CFRT in terms of outcome and less burdensome *Comments:* Retrospective analysis
Azoulay et al. (2015) [47] PMID 25927334	*Study design:* Retrospective review in a population-based cohort *Patient population:* 276 Adult patients with newly diagnosed GBM *Description:* - Surgery: maximal safe resection in all - RT: PTV40: GTV/Cavity + 1.5 cm margin received 40 Gy in 20 fractions PTV60: GTV/Cavity + 0.5 cm margin received 60 Gy in 20 fractions Conventional RT 60 Gy in 30 fractions (ConvRT): n = 147 Hypofractionated RT with 60 Gy in 20 fractions (HF60): n = 86 Hypofractionated RT with 40 Gy in 15 fractions (HF40)—in patients over 70 years of age or with KPS < 70: n = 43 - Chemotherapy: TMZ concomitant and adjuvant as first treatment	III	*Results* For whole population, median OS was 13.7 months and median PFS 8.8 months ConvRT, Median survival was 16 mo HF60, median survival was 15 mo HF40, median survival was 8 mo 2-years OS was 23.1% for ConvRT and 19.7% for HF60 For 65 year and older patients, median OS was 10 months in ConvRT, 9.13 HF60 (p = 0.357) and 7.6 months for HF40 (p = 0.0049) PFS was 9 months for ConvRT and HF60, compared to 5.4mo in HF40 (p = 0.0002) In multivariate analysis, no significant difference in outcome when compared ConvRT and HF6, but significant worst outcome for HF40 *Authors conclusions*: Moderate hypofractionated RT is associated with comparable outcome to conventional RT regimen for newly diagnosed GBM *Comments* Retrospective study. Does not report the toxicities

Table 11 (continued)

Author/year/PMID	Study description	Data class	Conclusion
Arvold et al. (2015) [48] PMID 25841623	*Study design:* Retrospective Review of case series *Patient population:* 135 Patients older than 65 years of age with newly diagnosed GBM *Description:* Surgery: Biopsy/STR or GTR HRT: 40 Gy in 15 daily fractions of 2.67 Gy Standard: 60 Gy in 33 fractions of 1.8 Gy or 60 Gy in 30 fractions of 2 Gy per fraction Chemotherapy: Standard Stupp protocol TMZ for 5 to 11 cycles HRT = 9 patients, HRT + TMZ = 34, Standard RT = 35, Standard RT + TMZ = 57 HRT and HRT + TMZ patients were 10 year older than the Standard Therapy patients	III	*Results* Median OS was 10.2 months HRT alone—shorter OS HRT + TMZ, Standard RT, Standard RT + TMZ was not significantly different In multivariate analysis: Older age, lower KPS, multifocal disease, HRT without TMZ and Standard RT without TMZ were significantly associated with lower OS as compared to Standard RT + TMZ HRT + TMZ—no significant differences in survival compared to SRT + TMZ *Author conclusions* There is no difference in survival between HRT + TMZ and SRT + TMZ for elderly patients *Comments* Class III study
Lim et al. (2015) [49] PMID 24705988	*Study design:* Retrospective review *Patient population:* 33 patients with poor prognostic features (ECOG ≥ 3, biopsy only or rapid progression after surgery) or age > 70 with newly diagnosed GBM *Description:* - Surgery: All patients, Resection or Biopsy (n = 16) - Adjuvant therapy (within 4 weeks post surgery): - TMZ (stupp protocol) - Hypofractionated RT: 30–45 Gy in 10–15 fractions of 3 Gy on 5 days/week GTV = Lesion on T1W with contrast or surgical cavity CTV = 0.5–1.5 cm margin around GTV PTV = 0.3 cm margin around CTV Salvage surgery and/or chemotherapy was delivered to some patients at recurrence	III	*Results* Median OS was 10.6 months and median PFS 7.5 mo 1-year OS and PFS were 42.4 and 32.3% respectively In multivariate analysis, poor pre- and post-RT performance status and post-surgery progression were independent predictive factors of OS For PFS, post-surgery progression was independent predictive factor Grade 2 CNS toxicity (n = 5), Grade 3 Hematologic toxicity (n = 1) 26 patients showed stable to improved QoL (ECOG Scores) *Authors conclusions* Hypofractionated concurrent RT with TMZ would be a treatment option for high-risk patients with GBM *Comments* Retrospective review without a control group. A feasibility study

Table 11 (continued)

Author/year/PMID	Study description	Data class	Conclusion
Iuchi et al. (2014) [50] PMID 24495592	*Study design:* Prospective single institution study *Patient population:* 46 adult patients with pathologic confirmed diagnosis of GBM *Description:* Surgery: All patients underwent surgical resection Radiation: IMRT: 8 fractions over 10 days, total dose of 68-Gy in 8.5-Gy fractions to PTV1; 40-Gy in 5.0-Gy fractions to PTV2, and 32-Gy in 4.0-Gy to PTV3 GTV = enhancing tumor + surgical cavity PTV1 = GTV + 5 mm margin PTV2 = PTV 1 + 15 mm margin PTV3 = Region with hyperintensity signal on FLAIR Chemo: All patients underwent concurrent and adjuvant TMZ (75 mg/m^2 for 42 days then 150–200 mg/m^2 orally for 5 days every 28 days)	III	Results Progression of enhancing lesions at tumor site was seen in 19 patients: 13 as tumor progression and 6 as radiation necrosis (using Met-PET) 2- and 5-year local PFS was 63.9% and 57.5% respectively Distant failure was observed in 10 patients, dissemination occurred in 21, primary failure in 11 and CSF in 14. The median time to failure was 9.7 months after treatment TMZ was withdrawn in 10 patients due to grade 3 skin rash, grade 3 pneumonitis, grade 3 fatigue, grade 3 bone marrow suppression and performance deterioration Median OS was 20 months 1-, 2-, 3- 4-, 5-year survival rates were 69.6%, 42.8%, 26.5%, 13.3% and 6.6% respectively Radiation necrosis was observed in 20 patients around the tumor bed and in SVZ Radiation necrosis at SVZ was associated with prolonged survival: OS 36.2 vs 13.3 months; p = 0.0001) *Authors conclusions*: Hypofractionated high-dose IMRT with concurrent and adjuvant TMZ altered dominant failure pattern from localized to disseminated Comments Prospective study, but not randomized and did not compare Hypofractionated IMRT with other forms of radiation

Table 11 (continued)

Author/year/PMID	Study description	Data class	Conclusion
Ciammella et al. (2013) [51] PMID 23453151	*Study design:* Retrospective review of case-cohort *Patient population:* adult patients with newly diagnosed GBM, KPS ≥ 60 and surgical cavity plus T1W enhancing residual ≤ 6 cm *Description:* Surgery: All underwent maximum safe surgical resection (GTR 38 patients, PR 14, biopsy 15) Radiation: Hypo-fractionated IMRT started within 6 weeks of surgery, at 25-Gy delivered in 5 fractions in one week (5-Gy per fraction) at 70% isodose GTV = Contrast enhanced lesion. CTV = GTV expanded uniformly by 1.5 cm to encompass any T2W abnormality. PTV = CTV expanded by 5 mm margin. IMRT plans were generated to deliver 25-Gy as a minimum dose to PTV and higher dose, 35.7-Gy to GTV Chemotherapy: Adjuvant TMZ (150 mg/m^2/day) was started within 4 weeks after the end of RT: 5 days every 28 days for 6–12 cycles Used McDonnald radiologic criteria for response/relapse	III	*Results* Median time of starting RT after surgery was 32 days (28–49) RT: Min and max dose were 25-Gy–35.7-Gy Median follow-up of 14.9 months (3–62 months) Median OS was 13.43 months The 6-months, 1-, 2- and 3-year OS was 91%, 53%, 24% and 12% respectively Median PFS was 7.9 months The 6-months, 1-, 2- and 3-year PFS rates of 73%, 29.42%, 9% and 6% respectively Mean time at progression disease after RT was 6.1 months (0–43.2 months) Recurrence occurred in-field in 33 patients (56%), at RT field margin in 19 patients (32%) and out-field in 7 (12%) No grade 3 or 4 toxicity was observed Post treatment median KPS was 90 (80–100); Improved in 43, stable in 14 and worst in 10 patients Late grade 1 and 2 toxicities included fatigue (30%), nausea (10%), insomnia (2%), headache (15%) and anorexia (35%) Toxicity during TMZ was mild: Grade 3 neutropenia, thrombocytopenia and anemia occurred in 7, 2 and 1 patient, respectively. No grade 4 In multivariate analysis, extent of resection was the only independent predictive factory (< 0.005) Patterns of recurrence correlated with OS (< 0.001) and PFS (< 0.004) with mean time to progression of 5.6 and 13.5 months respectively and median survival of 12.3 and 18.8 months respectively *Authors conclusions*: Hypo-fractionated radiation therapy can be used in patients with GBM, resulting in favorable overall survival and low toxicity Comments Retrospective review. Authors do not compare the outcomes of hypo-fractionated therapy with the standard therapy

Table 11 (continued)

Author/year/PMID	Study description	Data class	Conclusion
Reddy et al. (2012) [52] PMID 22483738	*Study design:* Prospective phase II trial Patient population: 24 adult patients with newly diagnosed GBM, KPS > 60. Surgical cavity plus T1W enhancing residual tumor on MRI had to be < 6 cm in diameter *Description:* Surgery: 11 patients GTR, 10 NTR, 3 PR or biopsy RT: GTV = Contrast-enhancing residual tumor plus entire surgical cavity CTV = T2W abnormality on MRI PTV1 = GTV plus a 5-mm margin PTV2 = CTV plus a 5-mm margin 60-Gy in 6-Gy fractions was prescribed to PTV1 30-Gy in 3-Gy fractions was prescribed to PTV2 1 fraction of hypo-IMRT daily, 5 days/week Chemotherapy: TMZ with hypo-IMRT (75 mg/m^2 starting on the first day of RT for 28 days) and adjuvant TMZ after RT (150–200 mg/m^2 daily for 5 days every 28 days for 6 cycles)	III	Results Median follow-up was 14.8 months (2.7–34.2 months) 4 patients were alive at 20.6 months No grade 3 or 4 acute or late nonhematologic toxicities observed Acute grade 1 or 2 toxicities = fatigue (67%), headache (46%), nausea (25%), insomnia (8%), confusion (4%), partial seizure (13%), anorexia (21%) Grade 3 or 4 hematologic toxicities = anemia (4%), Leukopenia (17%), neutropenia (17%), thrombocytopenia (13%) 6 patients underwent re-operation at 10.3 months for recurrence Median OS was 16.6 months (4.1–35.9 months) Authors conclusions: Hypofractionated IMRT with concurrent TMZ is safe Efficacy appeared to be comparable to that with standard therapy *Comments* Hypofractionated IMRT is safe. Small group of patients and not comparative study. Not able to conclude on the efficacy of this type of treatment
Terasaki et al. (2011) [53] PMID 20640480	*Study design:* prospective non-randomized trial. (Pilot trial) *Patient population:* 26 adult patients (KPS ≥ 50) with newly diagnosed GBM *Description:* All patients underwent maximum surgical resection (8 GTR and 16 PR) Hypofractionated RT (45-Gy in 15 fractions over 3 weeks) with concomitant TMZ started within 3 weeks after surgery GTV = enhancing tumor side post surgery CTV = Adding 2 cm margin to GTV PTV = adding 5 mm margin to CTV Minimum and maximum absorbed dose was planned to be between 95 and 105% TMZ dose: 75 mg/m^2/day, 7 days a week for 21 days (duration of RT). Then after 4 weeks of break, 150–200 mg/m^2/day for 5 days every 28 day cycles for up to 12 cycles Response was evaluated by MacDonnald criteria	III	*Results* PFS at 6-months was 65% Median PFS was 9.6-months Median OS was 15.6 months Univariate analysis: Age (< 50 p = 0.04), degree of surgery (p = 0.03) and KPS at baseline (≥ 70; p = 0.02) were significant prognostic factors Stratified analysis, extent of resection > partial resection: Median OS was 20 months Multivariate analysis no factors were significant for improvement of OS Toxicities: RT/TMZ concomitant: 10 patients had Grade 2 neutropenia, 2 had grade 2 radiation-induced dermatitis, 10 experienced fatigue, 8 had grade 2 headaches, 12—grade 1 anorexia, 12—grade 1 nausea. During TMZ maintenance: 3 had grade 4 neutorpenia, 1 had grade 4 thrombocytopenia *Authors conclusions*: The survival rates of hypofractionated RT with standard TMZ regimen are comparable with those achieved with standard RT schedules and acceptable toxicity *Comments* Although prospective study, there is no randomization and the comparison is made with historical controls. The number of patients in the trial is small

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Table 12 Information and summary of the articles that were included and used to answer the questions on the brachytherapy for newly diagnosed GBM

Author/year/PMID	Study description	Data class	Conclusion
Waters et al. (2013) [55] PMID 23673513	*Study design:* Prospective not-randomized trial *Patient population:* 11 adult patients with GBM *Description:* After surgical resection, GliaSite (n = 9) or MammoSite (n = 2) device was implanted in the resection cavity GTR—9 patients, STR—2 3–8 days post-op the GliaSite balloons were filled with Iotrex solution with pre-caluclated dose of 60-Gy to a depth of 1 cm from balloon surface. For MammoSite, the dose was prescribed to 1 cm margin from the balloon surface and HDR source was moved into the treatment position Skin dose was maintained below 12-Gy One patient received 45-Gy because of the proximity of the lesion to the optic apparatus 4 weeks after brachytherapy, patients received EBRT to 46-Gy to the T2W hyperintense region + 2 cm margin on MRI followed by 14-Gy boost to the T1-Enhancing volume All patients received TMZ 150–200 mg/m^2/day for 5 days each 28 days cycle Follow up MRIs were performed every 1–3 months Results were compared with historical controls	III	*Results* Interval development of new contrast-enhancing lesions was seen in 2 of 9 patients (22%).[images were available only for 9 of 11 patients] All patients had evidence of tumor recurrence following EBRT and TMZ (2–17 months) Median PFS after surgery was 10 months Median survival was 15.6 months 2-year OS was 42.4% There was a trend towards improved 6 months PFS of brachytherapy patients when compared with historical controls There 2 cases of grade 2 toxicities (Generalized seizure in 1 patient and left hemiparesis in another one that resolved with dexamethasone) *Authors conclusions*: This case series demonstrates the safety of immediate post-operative brachytherapy when applied prior to RT and TMZ *Comments* 11 patients compared to historical controls. Did not show improvement in PFS, but only a trend
Matsuda et al. (2011) [56] PMID 21427185	*Study design:* Retrospective review of case-cohort *Patient population:* 67 consecutive patients with newly diagnosed GBM *Description:* Patients underwent surgery: 13 GTR, 47 PR and 7 Biopsy Silicon tubes were inserted around the boundary between eloquent and non-eloquent tissue RT: - 35 patients: Standard therapy, daily CRT (1.8–2.0-Gy) to total overall dose 60–60.2-Gy - 32 patients: High-Dose particle radiotherapy (HDT): Boron Neutron Capture Therapy (BNCT) or Photon Therapy (PT): - 15 patients had BNCT. It was given to patients with: Supratentorial unilateral tumor, no deeper than 7 cm with KPS > 50: (GTV and CTV-1 = residual contrast-enhancing volume. CTV-2 and CTV-3 = GTV + 2 or 3 cm margin, respectively) Average of 30-Gy single session and additional fractionated photon irradiation totaling 30-Gy were given to GTV - 17 patients had PT. It was used in supratentoral tumors with maximum post-operative tumor diameter of < 4 cm, KPS > 60: (GTV and CTV-1 = residual contrast-enhancing volume. CTV-2 = GTV + 1 cm margin and CTV-3 = GTV + FLAIR area. PTV = CTV + 5 mm margin 50.4-Gy in 28 fractions were delivered to PTV in the morning Chemotherapy: 47 patients: Procarbazine, nimustine (ACNU) and Vincristine in combination with CRT For elderly patients only ACNU was used ACNU was used in combination of HDT	III	*Results:* Median OS for all patients: 17.7 months The 1- and 2-year survival rates were 67.2% and 33.7% Median PFS was 7.8 months 1-year and 2-year PFS rates were 32.6 and 18.4% respectively Median OS for HDT was 24.4 months and for CRT was 14.2 months Median OS was 18.5 months in patients > 65 years of age compared to 16.8 in younger patients (p = 0.871) Acute Toxicities in BNCT: mild erythema (common), transient orbital swelling (1 patient). No late toxicities were observed Acute Toxicities in PT: radiation dermatitis (common), rash (1 patient), headache (5 patients). Late Toxicities: radiation necrosis and leukoendephalopathy (1 patient each) *Authors conclusions*: Patients receiving HDT showed longer survival times than those treated with CRT *Comments* Retrospective study. Patients undergoing HDT were more likely to have undergone GTR surgery and have a better preoperative PS, although the authors denied that these confounding factors were significant in their findings. Patients were not randomized to whether undergo HDT or not

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Table 13 Information and summary of the articles that were included and used to answer the questions on the accelerated hyperfractionated GBM

Author/year/PMID	Study Description	Data class	Conclusion
Fariselli et al. (2017) [57] PMID 28708230	*Study design:* Prospective single arm open label phase II trial *Patient population:* 35 patients age 18–65 years diagnosed with GBM *Description:* All patients underwent surgical resection (23 radical surgery and 12 non radical) Split 2 cycles course of hypofractionated accelerated RT (AHRT) was started within 40 days post-surgery Total dose of 60-Gy was administered with fractions of 2 Gy, 3 times a day with 4 h interruptions in between same day fractions, in 5 consecutive days 2 different cycles divided by 28 days All patients received concomitant TMZ in 3 single administrations 1 h before every single fractions of RT Macdonald's criteria were used to evaluate the response for 12 patients and for the others it was not used	III	*Results* 1 patient experienced grade 4 thrombocytopenia and neutropenia 4 and 11 patients had grade 2 and 1 hematologic toxicity respectively 6 patients had grade 1 leukopenia 12 had radiologic images of radiation necrosis vs recurrence 5 patients underwent surgical intervention for neurological deterioration and 4 had radiation necrosis and 1 had GBM (grade 4 radiation necrosis) Median PFS was 6 months Median OS was 22 months (95% CI 17–27) OS at 12, 18 and 24 months were 82%, 59%, 44% respectively Radiation necrosis was significant prognostic factor *Authors conclusions*: Aggressive treatment schedule needs further exploration. The high rate of necrosis versus local control rate needs further investigation *Comments* Class III because the study was a single arm open label trial. Intention was to evaluate tolerability and efficacy of a different radiation schedule
Fariselli et al. (2013) [27] PMID 23625362	*Study design:* Retrospective single-center review of charts *Patient population:* 33 patients older than 70 years of age (70–82), with post-operative KPS $\geq$ 70 diagnosed with GBM *Description:* All patients underwent surgical resection (16 GTR, 13 STR, 4 stereotactic biopsy) Split-course hypofractionated accelerated RT (AHRT) was started 2–4 weeks post-surgery Total dose of 45-Gy and administered in 2 cycles (split in 2 cycles (15 days), 2.5-Gy/fraction, 3 daily fractions (inter-fraction time of 4 h for 3 consecutive days/cycle PTV = contrast-enhanced tumor excluding edema, plus 1-cm margin Macdonald's criteria were used to evaluate the response At progression, 7 patients received BCNU 150 mg/m^2 every 8 weeks, 2–4 cycles	III	*Results* 1 patient experienced grade 3 toxicity: cognitive disturbance No radiation necrosis occurred KPS at 3 months after RT was stable in 18 patients (73%), improved in 6 (24%) and worsened in 1 (3%) 1/7 of patients that received salvage chemotherapy experienced grade hematological toxicity Median PFS was 6 months Median OS was 8 months (2–24 months) Median survival rate at 1 year of 9 patients (27%) 2 patients had a survival of 21 and 23 months and 1 of 24 months On multivariate analysis, type of surgery was confirmed as the only significant factor on OS and GTR was independently associated with increased OS [HR 0.159; 95% CI 0.04–0.59; p = 0.006] *Authors conclusions*: RT is beneficial in the elderly patient population. Overall treatment time can be considerably shortened without a detrimental effect on clinical outcome *Comments* Retrospective review of a single center without control arm

Table 13 (continued)

Author/year/PMID	Study Description	Data class	Conclusion
Buckner et al. (2006) [58] PMID 16921039	Study design: Phase III trial Patient population: 451 patients with newly diagnosed GBM (401 eligible) *Description:* After surgery, patients were randomly assigned to treatment: Arm A (BCNU plus standard RT) BCNU: 200 mg/m^2/d IV @ d1 every 8 weeks, six cycles SRT: 1.80 Gy/day × 36 days (64.8 Gy) Arm B (BCNU plus ART) BCNU: 200 mg/m^2/d IV @ d1 every 8 weeks, six cycles ART: 2 × 1.60 Gy/day × 15 days (48.0 Gy) Arm C (cisplatin plus BCNU plus standard RT) BCNU: 50 mg/m^2/d IV, d1–d3 every 8 weeks, cycles 1 and 2 200 mg/m^2/d IV @ d1 every 8 weeks, cycles 3–6 CDDP: 30 mg/m^2/d IV, d1–d3 & 29–31 every 8 weeks, cycles 1 and 2 SRT: 1.80 Gy/day × 36 days (64.8 Gy), cycle 2 arm D (cisplatin plus BCNU plus ART) BCNU: 50 mg/m^2/day IV, d1–d3 every 8 weeks, cycles 1 and 2 200 mg/m^2/d IV @ d1 every 8 weeks, cycles 3–6 CDDP: 30 mg/m^2/day IV, d1–d3 & 29–31 every 8 weeks, cycles 1 and 2 ART: 2 × 1.60 Gy/day × 15 days (48.0 Gy), cycle 2	III	*Results* Frequent toxicities: myelosuppression, vomiting, sensory neuropathy, and ototoxicity and were worse with cisplatin. There was no difference in toxicity between SRT and ART Median OS = 10.1 mo: arms A and B, 11.5 mo: arms C and D 2-year survival rates = 11.5%: arms A and B, 13.7%: arms C and D (p = .19) Median OS = 11.2 mo; arms A and C, 10.5 mo; arms B and D 2-year survival rates = 13.8%—arms A and C, 11.4%—arms B and D (p = .33) *Authors conclusions*: Cisplatin administered concurrently with BCNU and RT resulted in more toxicity but provided no significant improvement in survival. Standard RT and ART produced similar toxicity and survival *Comments:* RCT. However, does not compare the standard Stupp protocol with this new radiation scheme. As such is classified as level III data

AHRT hypofractionated accelerated RT, *ART* accelerated radiation therapy, *Bx* biopsy, *CD* complete response, *CFRT* conventional fractionated radiation therapy, *CGE* cobalt grey equivalent, *CTV* clinical tumor volume, *EBRT* external beam radiation therapy, *FRT* fractionated radiation therapy, *FSRT* fractionated stereotactic RT, *GBM* glioblastoma multiforme, *GTR* gross total resection, *GTV* gross tumor volume, *IMRT* intensity modulated radiation therapy, *MST* median survival time, *NTR* near total resection, *OS* overall survival, *PD* progressive disease, *PR* partial response, *PFS* progression free survival, *PTV* planning target volume, *RT* radiation therapy, *SD* stable disease, *SRT* stereotactic radiation therapy, *STR* subtotal resection, *SVZ* subventricular zone, *TM* tumor mass, *TMZ* temozolomide, *TTP* time to progression, *WBRT* whole brain radiation therapy

multivariate analysis. Further this is a retrospective analysis and SVZ radiation was not intentional and as such not standardized.

In their retrospective study on the radiation of SVZ for GBM in 40 patients, Gupta and colleagues [11], found that irradiation of SVZ may influence survival of patients with GBM. Twenty patients had received a low dose to SVZ instead the other 20 had received a high median dose. For the entire patient population, median PFS was 11 months and OS was 17 months. From the results it appears that patients that received lower dose of radiation on SVZ experienced a longer PFS and OS (Table 1). Needless to mention that this was a retrospective study, where SVZ irradiation was not intentional.

In a recent study, Foro Arnelot et al. [12], performed a retrospective review of 65 patients that had undergone RT and had received incidental RT to ipsilateral, contralateral and bilateral SVZ. They noticed that only patients that received > 48.8 Gy in contralateral SVZ had a better PFS than others (HR 0.46; 95% CI 0.23–0.91 p = 0.028). OS did not change.

Synthesis of results

The question regarding radiation of the SVZ was not explored by Buatti et al. [2]. We did not find any studies where SVZ, believed by some to be the area of maintenance of the glioma stem cells and by others area of deposit of immune reactive cells, was irradiated intentionally to improve OS and/or prolong PFS. There was one retrospective study where radiation of SVZ showed a negative impact on OS and PFS (Table 4) [9]. Another study showed that patients that received lower doses of RT to SVZ experienced longer survival [11]. Two other studies showed that higher irradiation doses at SVZ or contralateral SVZ improved OS and PFS [10, 12]. However, in one of these latter studies, patients with better OS and PFS were those that had received GTR of the tumor confounding their findings. Then another study showed a benefit of irradiation of SVZ in univariate analysis but failed to show any benefit on the multivariate analysis [8]. In summary, the studies reporting on irradiation of the SVZ are contradictory. As such no recommendation can be given on this regard. Further randomized controlled studies when SVZ is intentionally included in the radiation field should be done to address this interesting topic.

Table 14 Information and summary of the articles that were included and used to answer the questions on the Stereotactic Radiation therapy in treatment of newly diagnosed GBM

Author/year/PMID	Study description	Data class	Conclusion
Einstein et al. (2012) [59] PMID 22445005	*Study design:* Prospective phase II trial *Patient Population:* 35 adult patients with newly diagnosed GBM *Description:* Majority of patients underwent STR 46% received concurrent TMZ MRS post-operatively with 10 × 10x15 mm voxel size and the entire T2W abnormal area was analyzed All patients underwent GammaKife SRS within 5 weeks of surgery Highlighted voxels on the MRS scan within 2-cm of the contrast-enhancing lesion were targeted with a single 8-mm isocenter to the 50% isodose 15-Gy for diameters 3–4 cm, 18-Gy for 2–2.9 cm and 24-Gy for diameters < 2 cm Within 2 weeks after SRS, conformal RT: 60-Gy total, with 2-Gy fractions/day for 5 days/week Treatment volume = Residual contrast enhancing tumor plus surrounding edema on post-operative MRI plus 2-cm margin If no edema, a 2.5-cm margin surrounding the T1W enhancing tumor was added	III	*Results* Median survival: 15.8 months Univariate analysis significant prognostic factors: age, initial surgery type, concurrent chemotherapy and RTOG RPA class Patients > 60 year-of-age had medial OS 11 months vs 22 months for < 60 years-of-age GTR or STR had a median survival of 17 months, vs 6 months for those with biopsy only Median survival for non-chemotherapy patients was 11 months vs 20.8 months for those treated with chemotherapy Compared to RTOG historical controls, median survival was > 22 months vs 17.9 months for RTOG RPA Class 3, 18.7 vs 11.1 months for Class 4; 12.9 vs 8.9 months for Class 5 Compared to EORTC chemo/RT trial data, median survival was 22 vs. 21.4 months for Class 3; 18.7 vs. 16.3 months for Class 4; 12.9 vs. 10.3 months for Class 5 Overall median survival of chemotherapy patients was 20.8 months vs. 14.6 months for EORTC chemo/RT patients Grade 3 and 4 toxicity was reported 9 (26%) of patients *Authors conclusions*: MRS-targeted SRS directed only to areas of high biologic activity combined with conformal RT is feasible with acceptable toxicity. The survival is higher than historical controls *Comments* Phase II study. Compared to historical controls only. Classified as class III
Kong et al. (2006) [60] PMID 18503347	Study design: Retrospective review *Patient population:* 19 patients with unresectable GBMs Description: Gamma Knife Surgery (GKS) + RT = 10 Mean age = 53 years Pre-treatment KPS = 80 (60–100) Median marginal dose = 12 Gy (9–16 Gy) RT alone = 9 Mean age = 56 years Pre-treatment KPS = 90 (50–100) Total dose = 60 Gy (2 Gy × 30)	III	Results Mean follow-up duration = 7.2 months Median OS: 52 weeks (95% CI 22–110.6 weeks)—GKS, 28 weeks (95% CI 22.5–33.5 weeks)—RT Not statistically significant (p = 0.0758) PFS at 3 mo = 75%—GKS, 45%—RT (p = 0.082) Post-treatment KPS: ≥ pre-treatment—GKS, < pre-treatment by 20 + points in six of nine patients—RT (p = 0.004) *Authors conclusions*: Gamma Knife surgery prior to radiotherapy may be helpful in preserving patients' daily activities in the adjuvant management of unresectable GBM *Comments* Retrospective review. Unclear why some patients received SRS and Conventional RT and some others received conventional RT alone

Table 14 (continued)

Author/year/PMID	Study description	Data class	Conclusion
Cardinale et al. (2006) [61] PMID 16750317	*Study design:* Phase II trial *Patient population:* 76 patients > 18 yo w/ post-op enhancing tumor + tumor cavity diameter ≤ 60 mm *Description:* EBRT = 2 Gy/day, d1–d5: weeks 1 and 2, d1–d4: weeks 3–5, d1–d3: week 6 (50 Gy total) FSRT = 5–7 Gy/day, d5: weeks 3–5, d4: wk6 BCNU: 80 mg/m^2 IV, d1–d3 (w/in 1 month post-RT) every 8 weeks, 6 cycles	III	*Results* Toxicity included: 3 Grade 4 chemotherapy, 3 acute Grade 4 radiotherapy, and 1 Grade 3 late Median OS = 12.5 months. No survival difference is seen when compared with the RTOG historical database Patients with GTR (41%) had a median OS of 16.6 months vs. 12.0 months for historic controls with GTR (p = 0.14) *Authors conclusions:* FSRT boost trial for GBM was feasible and well tolerated. There is no significant survival benefit using this dose-intense RT regimen. Subset analysis revealed a trend toward improved outcome for GTR patients suggesting that patients with minimal disease burden may benefit from this form of accelerated RT *Comments* Only post-hoc analysis showed a trend towards improved outcome

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Question 5: Is radiation therapy beneficial to elderly and/or frail patients with newly diagnosed RT?

The protocol designed and implemented in the Stupp et al. study [3] that was published in 2005 has become the standard of care and used widely by the neuro-oncology community for treatment of newly diagnosed GBM. Nevertheless, the maximal age of patients included in this study was 70 years of age with WHO performance status of 2 or better. As such there has been a need to define the treatment paradigm for patients that did not qualify for the Stupp study due to their age and/or performance status. (Table 5).

We found one randomized controlled trial that studied the effects of RT in patients older than 70 years of age [13]. Keime-Guibert et al. carried out a multi-institutional trial that randomized 81 patients over 70 years of age with newly diagnosed GBM in two groups after surgical intervention. The first group received supportive care only and the second group received fractionated RT (1.8 Gy/day 5 days/week for 6 weeks for a total of 50 Gy) in addition to supportive care. They found that median survival for patients in the second group was significantly longer than in the first group, 29.1 weeks versus 16.9 weeks respectively. The reported PFS was 14.9 weeks for the RT group and 5.4 weeks for the supportive care group. Further the authors noted that the performance status, cognition and quality of life were not worse for patients that received RT. The trial was closed early after preliminary evaluation showed a significant benefit of RT. In the end it was concluded that addition of adjuvant RT to supportive care in patients older than 70 years of age prolongs survival and does not reduce health-related quality of life. Given the study design it provides class I evidence.

There are additional studies that provide class III data reaching the same conclusions.

Babu and colleagues [14] reviewed retrospectively the treatment of 120 elderly patients (aged 70 and older) with newly diagnosed primary GBM. The majority of the patients underwent GTR (n = 76) and almost all the patients (n = 110) received standard chemotherapy and RT with TMZ and 6 weeks of EBRT. Several of these patients received other chemotherapy treatment after recurrence and few (n = 22) received bevacizumab. Median overall survival was reported to be 12 months and approximately 26.7% of patients were alive after 2 years. Patients 75 years of age and older had a worst prognosis (p > 0.0001). KPS was a significant variable in the survival with patients with KPS > 90 surviving significantly longer than those with KPS < 80. The authors concluded that elderly patients aged 70 and older tolerate surgical resection and standard chemoradiation well and experience an increase in long-term survival. This study was a retrospective chart review and did not have a control arm.

In a retrospective review Abdullah and colleagues [15] reported on the survival of 58 octogenarian patients with

newly diagnosed GBM. All patients underwent a GTR of the tumor. Majority of patients did not undergo adjuvant therapy. Ten patients underwent RT alone and ten other patients underwent chemotherapy and radiation. Best survival was seen in the group that underwent chemoradiation (351 days) and the group that underwent RT alone (200 days) as compared to the group that did not receive adjuvant therapy (96.5 days, $p < 0.05$). Other variables that were associated with significantly better survival were lack of EGFR expression and lack of p53 expression. These authors did not report whether in multivariate analysis the administration of adjuvant therapy still conferred a better survival in this group of patients. Further, the authors did not report the type, dose and length of adjuvant therapy.

In another study, Niyazi et al. [16], retrospectively reviewed treatment received by 43 patients age 70 years and older. The majority of patients underwent biopsy alone. All patients received conventional RT of 60 Gy over 6 weeks. Only 18 patients received concomitant TMZ with RT. Median PFS was 192 days and median OS was 264 days. Median survival in RT only group was 314 days and in RT and TMZ was 192 days. For patients with KPS > 80, median survival was 437 days for the group that received concomitant RT and TMZ and 323 for patient that received RT alone ($p = 0.716$). They concluded that RT alone is better than RT with concomitant TMZ in elderly patients with low KPS.

Scott and colleagues [17] reviewed treatment received and associated outcome in patients with age 70 years and older on the SEER database. They identified 2836 elderly patients with newly diagnosed GBM. Patients were divided in 4 groups: (1) no treatment (n = 384), (2) surgery alone (n = 635), (3) RT alone (n = 508) and (4) Combination of surgery followed by RT (n = 1309) patients. They reported that RT alone and surgery alone were associated with significant increase in survival as compared to no treatment. Multivariate analysis showed that RT significantly improved cancer-specific survival after adjusting for all other parameters such as surgery, tumor size, location, etc. All patients that underwent treatment of any sort fared better than patients that did not received any treatment at all. They concluded that age shouldn't be a factor in withholding treatment for patients with newly diagnosed GBM. The authors did not specify the type of radiation received with doses and volumes.

Marijnen and colleagues [18], studied retrospectively 202 adult patients with GBM and KPS > 40. The majority of patients received 60 Gy divided in 2 Gy fractions per day. Patients with poor performance status received 30 Gy in 10 fractions on a whole brain field or did not received RT at all. For the total group, median OS was 8 months. In each separate RPA group, overall survival for patients older than 70 years of age was similar to that of patients between the ages of 50 to 70. Furthermore, they reported that irradiated patients with poor KPS and RPA V survived longer (9.4 months) than patients that were not irradiated in this same group (2.1 months). According to the authors, in a multivariate analysis, RT remained the only prognostic factor for survival in these patients ($p < 0.001$). They concluded that prognosis for patients above 70 years of age is not different from that of younger patients, when analyzed for separate RPA groups. For patients with a poor prognosis (i.e. RPA group V), RT improves survival significantly. This is a retrospective study. Further the authors did not specify why certain patients with low performance status received RT, even though a reduced dose, and others were not considered for RT at all.

Combs et al. [19], published a single institution retrospective review of 43 patients older than 65 years of age with primary GBM. Postoperative RT was applied with a median dose of 60 Gy in a median fractionation of 5 × 2 Gy/Week. Thirty-five patients received concomitant TMZ (50 mg/m^2) and 8 patients received 75 mg/m^2. Adjuvant cycles of TMZ were prescribed in 5 patients only. They reported a median OS of 11 months. Chemoradiation was well tolerated in most of the patients. They concluded that chemoradiation is safe and effective in elderly patients with GBM and should be considered in patients with no major comorbidities.

Synthesis of results

There was one randomized controlled trial that found that RT in elderly patients is better than supportive care alone and it prolongs PFS [13]. Other six retrospective studies indicated as well that RT in elderly and/or frail patients (KPS > 40) confers better survival [14–19]. In summary, all the above-cited studies found that age should not be a determinant in withholding adjuvant RT. Based on the result of a prospective randomized study [13], we can state that there is class I data to recommend RT in elderly patients with newly diagnosed GBM.

Question 6: What is the optimal dose of RT for elderly and frail patients?

In a prospective randomized non-inferiority trial, Roa et al. [20], evaluated the effect of 2 different RT doses in elderly and frail patients (see Table 6 for definition) with newly diagnosed GBM (Table 6). Ninety-eight patients (two were lost in follow up), after undergoing surgical intervention were divided into two arms for RT. Arm 1 received 25 Gy in 5 daily fractions of 5 Gy over 1 week and arm 2 received 40.5 Gy in 15 daily fractions of 2.67 Gy over 3 weeks. Median OS and PFS were not significantly different. The mean global quality of life scores (QoL) at 4 weeks post treatment was not significantly different. At 8 weeks post treatment QoL improved as compared to pre-treatment scores. The authors concluded that this trial supports the use

of short RT treatment for elderly and frail patients. Since different regimens of chemotherapy were given, this may impair our full understanding whether these 2 regimens are interchangeable. Although a prospective RCT, due to these confounders we classified this study as Class II for the purpose of our recommendations.

Malmstrom and colleagues [21], in a prospective randomized controlled trial assessed the optimal palliative treatment in patients older than 60 years of age with newly diagnosed GBM. Patients (n = 291) were randomized across three treatment groups TMZ, hypofractionated radiotherapy (34 Gy in 10 fractions of 3.4 Gy 5 days/week over 2 weeks) and standard RT (60 Gy administered in 30 fractions of 2 Gy 5 days/week for 6 weeks), and 51 other patients were randomized in 2 groups, TMZ and hypofractionated RT only. Multivariate analysis showed prognostic value for performance score, the degree of surgical resection and age. They reported that survival was better in TMZ group as compared to standard RT. There was no difference in survival seen between hypofractionated RT versus standard RT. Survival was better with TMZ and with hypofractionated RT than with standard RT alone. The authors concluded that for patients older than 70 years of age, TMZ or hypofractionated RT over 2 weeks might be a valid alternative to standard RT. They did not investigate the combination of RT with TMZ as in the previous 2 mentioned studies. The authors reported that the power of the study was lower than they expected, as such has been classified as providing class II data. While very complex design with 4 groups, this study does help in concluding that in elderly patients hypfractionated RT is a valid alternative to standart RT.

Minniti et al. [22], reported data from a prospective non-randomized phase II trial with primary end point OS and secondary end points PFS, toxicity and health related quality of life (HRQOL). They evaluated 71 patients of age greater than 70 years with newly diagnosed GBM. After the diagnosis, patients received 40 Gy delivered in 15 fractions (2.66 Gy/fraction) with concomitant daily TMZ followed by adjuvant TMZ 4 weeks after chemoradiation. Median OS was 12.4 months and PFS was 6 months. MGMT methylation status was the strongest significant independent prognostic factor for OS. The authors reported that global health, social functioning and cognitive functioning improved. There was a tendency toward improvement for emotional and physical functioning as well. They concluded that baseline HRQOL after short course of RT in elderly patients did not deteriorate overtime and in some instances improved until disease progression. This was classified as a class II data due to the non-randomization.

In a retrospective chart review, Minniti and colleagues [23] from 3 different institutions, reported on 2 different regimens of adjuvant RT in elderly patients with newly diagnosed GBM. Half of the patients received standard chemoradiation, with TMZ and 1.8–2.0 Gy of daily fractions for 30–33 days for a total of 60 Gy. The other half received a total of 40 Gy delivered in 15 fractions. The authors reported that mean PFS, mean OS, 12 months PFS were not different for the 2 groups. Nevertheless, they found that cognition after therapy was worse after standard therapy. The authors suggested that short-course RT is a reasonable option for treating older patient with GBM. As a retrospective study, there could be a bias toward the patients' selection for any of the specific treatment option.

In a retrospective review of 104 patients older than 70 years of age with newly diagnosed GBM, Biau et al. [24], compared adjuvant treatment with standard RT (60 Gy in 30 daily fractions and TMZ), versus high fraction radiation therapy (HFRT) 40 Gy divided in 15 fractions and TMZ, versus HFRT alone. They did not find a statistical significance between the 3 type of treatments. In multivariate analysis, gross total resection (GTR) surgery, use of TMZ in conjunction with conventional RT (CRT) or HFRT and RPA class were significant prognostic factors. They concluded that maximal surgical resection and HFRT in conjunction with TMZ are recommended as standard treatment for elderly patients.

In another retrospective study, Bracci et al. [25], reported treatment of 21 patients older than 80 years of age with surgical intervention, 14 patients with biopsy, 5 with subtotal resection and 2 with GTR. They all received 40.05 Gy in 15 fractions within 6 weeks of surgery and concurrent TMZ. Median OS was 7.5 months, median PFS were 5.8 months. They concluded that these patients should be considered for management based on RT and chemotherapy. This was a very small retrospective study with only 21 patients.

Wang et al. [26], conducted a retrospective review on 184 patients older than 60 years of age. The majority of patients, 158 of them received conventional RT, 60 Gy in 30 fractions. The rest, 26 patients, received 40.05 Gy in 15 fractions. The majority of these patients underwent surgical resection consisting in GTR or subtotal resection (STR) and then received concurrent and adjuvant TMZ. Overall survival for both treatments was similar.

In another study, Fariselli et al. [27], retrospectively reviewed their experience at a single-center. Thirty-three patients older than 70 years of age with post-operative KPS $\geq$ 70 underwent split-course hypofractionated accelerated RT (HART) that was started 2–4 weeks after the surgery. Total dose received was 45 Gy administered in 2 cycles, 2.5 Gy per fraction in 3 daily fractions with interfraction time of 4 h for 3 consecutive days/cycle. One patient experienced grade 3, cognitive toxicity. KPS at 3 months was stable in 18 patients, improved in 6 and worsened in 1. They reported that median OS was 8 months and median survival rate at 1 year of 27%. Their conclusion was that RT is beneficial in the elderly patient population and using

HART, the treatment time can be considerably shortened without detrimental effect on clinical outcome and with low toxicity.

In another earlier publication, Minniti et al. [28], had reported a phase II prospective open-label single-arm study on the efficacy of combined chemotherapy with TMZ and RT in 71 adult patients of age older than 70 years with newly diagnosed GBM. RT was administered within 4 weeks of surgery: 40 Gy in 15 fractions of 2.66 Gy. PTV was delineated based on the adding 2.4 mm margin around the resection cavity and residual enhancing tumor. Median OS was reported to be 12.4 months and PFS was 6 months. The 1- and 2-year OS rates were 58% and 20% respectively. Sixty-one patients experienced recurrence within and outside the treated volume (n = 53) and distant from the targeted volume (n = 8). In the multivariate analysis they found that KPS > 70 and MGMT methylation status were the only significant prognostic factors that increased OS. Toxicities were described as grade 2 and 3 thrombocytopenia, grade 3 neutropenia, grade 3 or 4 lymphocytopenia. Grade 2 confusion (n = 4) and grade 3 cognitive decline (n = 3) were observed as well. The authors concluded that a combination of abbreviated course of RT with concomitant and adjuvant TMZ is well tolerated and may prolong survival in elderly patients with GBM, especially those with MGMT status and KPS > 70.

Idbaih et al. [29], retrospectively reviewed a cohort of 28 elderly patients (> 70 years of age) with newly diagnosed GBM. After surgery all patients underwent RT, 40 Gy in 15 fractions over 3 weeks (2.67 Gy/day/5 days). Seventeen patients received adjuvant chemotherapy. Median PFS was 21.6 weeks and median OS was 50.6 weeks. Patient with KPS > 90% had a significantly longer survival. They concluded that short term RT is an effective and safe alternative for selected (KPS > 70) elderly patients with GBM. This was another retrospective study with a small group of patients.

Guedes de Castro et al. [30], in 2017 performed a post-hoc analysis on a subset of data from a phase III randomized control non-inferiority trial of the International Atomic and Energy Agency. They reviewed results of 61 patients older than 65 years of age and compared two RT schedules, 25 Gy in 5 fractions delivered in 1 week and 40.05 Gy in 15 fractions delivered in 3 weeks. None of these patients received TMZ during the trial. Patients in this post-hoc analysis were stratified per KPS, 50–70 versus 80–100. All patients received RT within 2 weeks of randomization. There was no difference in median OS for frail patients treated with 25 Gy in 5 fractions (7.5 months vs 6.7 months, p = 0.890). They concluded that a short-course of 25 Gy in 5 fractions is an acceptable treatment option for patients older than 65 years of age and with poor performance status, or for those patients with contraindication to TMZ. This was post-hoc analysis of a randomized controlled trial and as such was classified as class III.

Contrary to all the above-mentioned studies, Mak et al. [31], after retrospectively reviewed data from National Cancer Database arrived at the conclusion that Hypofractionated short course of RT (HFRT) for patient older than 70 years of age is associated with worse prognosis. They reported that median OS for the HFRT was 4.9 months versus 8.9 months in the patients treated with conventional RT. We want to underline the fact that the authors stated that patients that underwent HFRT were less likely to receive surgical intervention or chemotherapy and had worst comorbidity scores. Furthermore, while 4294 patients in their study received conventional RT, only 304 patients had received HFRT. These could explain their conclusions that are in contrast with the majority of publications on this matter.

Synthesis of results

We found 1 randomized prospective trial that did not find any difference in terms of OS and PFS between standard, 60 Gy for 30 days, and short-course RT of 34 Gy for 10 days in elderly patients (Table 6) [21]. Another prospective non-inferiority trial studied 2 different short RT schedules for elderly patients and showed that short RT is beneficial for this group of patients [20]. There was another prospective single arm open label study that showed that short-course of RT benefits elderly patients in terms of survival, cognition and quality of life [22]. We found 6 retrospective review trials that showed that elderly patients benefit from a short treatment protocol, 40.05 Gy administered in 15 fractions [23–25, 27–29]. Based on these results we have class II data to recommend short RT for elderly and frail patients and we have class III data that shows that the best schemes and dosage for treatment of elderly patients is 40.05 Gy administered in 15 fractions. However, there is class II data that shows that 40.05 Gy administered in 15 fractions and 25 Gy administered in 5 fractions of 5 Gy/daily are interchangeable [20]. Further, based on one post-hoc analysis of data from a randomized control study, short course RT with 25 Gy in 5 fractions did not show any difference in survival for elderly patients with low KPS when compared with 40.05 Gy administered in 15 fractions and as such this scheme can be considered for these patients [30]. In addition, in another study, short-course RT of 34 Gy for 10 days was used and showed good results in elderly patients [21]. In view of these studies while short-term RT is a good treatment option for elderly and frail patients, the optimal dose and treatment scheme is difficult to be defined.

Question 7: What is the best timing to start RT after diagnosis for patients with newly diagnosed GBM?

Timing of when to start adjuvant therapy after surgical intervention has been another controversial issue (Table 7). The ideal time interval has not been determined yet. Intuitively, accounting for the aggressive growth of residual GBM after surgical resection, it is preferred that adjuvant therapy be started as soon as possible. Nevertheless, we need to give time to the patients for post-surgical recovery, wound healing, and as well reduction of cerebral edema and tissue hypoxia to resolve after intervention for the RT to be efficacious.

Adeberg et al. [32], retrospectively reviewed the result in a cohort of 50 patients with newly diagnosed GBM that had participated in 3 different trials (EORTC 26082-22081 (n = 19), H6Q-MC-S039 (n = 13) and EORTC 26071-22072 (n = 18)) and compared them with 127 patients that underwent standard chemoradiation with TMZ. The median delay for the study patients was 35 days (range 18–49) and for the reference group was 27 days (range 5–98). The median OS and PFS did not significantly differ for the 2 groups. The authors reported that patients that started chemoradiation earlier than 24 days after surgery had worst OS and PFS. They concluded that delay in starting adjuvant RT does not impact survival and that starting adjuvant RT should be delayed for more than 24 days after the surgery for better outcomes. This was a complex study design with arbitrarily assigning patients to study group and reference group respectively. Further, the authors, when studying the effect of delay in starting treatment, did not discuss the time difference specifically, but consider the median (27 versus 35 days). In reality, there were patients in the reference groups that had a delay that lasted more than 3 months (98 days) while the patients in the study group had a shorter delay (range 18–49 days). The authors suggested that initiation of adjuvant therapy should be delayed at least for 24 days after surgical intervention. Regarding these results, it is unclear whether patients that received adjuvant RT earlier were judged by the clinicians to have a worse tumor and that is why they had a worse prognosis instead of the timing of RT having any impact on survival.

In a similar study design, Han et al. [33], retrospectively reviewed the impact of timing of adjuvant therapy on the survival of 198 patients with newly diagnosed GBM. After surgical intervention, patients underwent RT and TMZ followed by Enzastaurin, Erlotinib and Bevacizumab and erlotinib. They divided patients in three groups based on the timing of adjuvant therapy after surgery, within 30 days, 31–34 days and more than 35 days. The authors reported that patients in group 2 did significantly better than the other patients and patients in the 3rd group did the worst. It appears that delaying the adjuvant therapy for 4 weeks can increase survival. It is not surprising though that this group of patients was the one that achieved GTR during the surgery. This could bias the results in favor of this group. The same bias could be assumed to be confounding the results on all these retrospective studies that have tried to evaluate the timing of chemoradiation post-surgery.

Sun et al. [34], reviewed the outcomes of patients from The Cancer Genome Atlas (TCGA) database that had been treated after 2005 according to the Stupp protocol and for which the time to RT from diagnosis was known. Only 218 patients fulfilled their criteria. Patients had undergone standard chemoradiation 7–232 days post-surgery. The authors found that there was no difference in PFS for patients that received chemoradiation earlier or later. They found a significant difference in OS for patients that received chemoradiation earlier than 42 days post-surgery (15.9 months vs 12.9 months, p = 0.022). The same possible bias of the differences in the extent of surgical resection and timing of adjuvant therapy applies to this study as well. Patients that had larger and/or not surgically resectable tumors could have undergone adjuvant therapy earlier than the other patients. Further the purpose of the TCGA database is not to give data on patients' prognosis based on the treatment regimens but collects genetic data on different tumors from academic centers and as such may not be the best database to serve the purpose of this study. In addition, some patients received RT 232 days post-surgery, increasing the concerns that these patients may have received RT at recurrence and the diagnosis was not a newly diagnosed GBM.

In a retrospective review of 345 patients with newly diagnosed GBM, Spratt et al. [35], attempted to analyze whether a delay in adjuvant therapy after surgical resection had an impact on survival. Interval from surgery to radiation therapy and chemotherapy was segregated in 3 groups, less than 2 weeks, 3–5 weeks and greater than 6 weeks. In univariate analysis, the 1-year actuarial OS was 43.1, 53.3 and 64.3% respectively for those that received adjuvant therapy 2 weeks, 3–5 weeks and greater than 6 weeks after surgical diagnosis. However, the Cox regression multivariate analysis model demonstrated a significant detrimental effect in delaying post-operative RT after adjusting for known prognostic factors such as RPA class, extent of surgery, KPS, etc., (< 2 week group as reference); 3–5 weeks (HR 2.80 [0.72–10.89}, p = 0.14), and > 6 weeks (HR 3.76 [1.01–14.57], p = 0.05). Their data did not support an OS benefit when delaying RT and they demonstrated that there is a detriment with delaying RT post-surgery for more than 6 weeks. This was a retrospective study where the patients in different groups were not matched.

Valduvieco et al. [36], reviewed the data on 107 adult patients with newly diagnosed GBM that underwent complete surgical resection followed by RT. The dose used was 60 Gy over a 6 weeks course with 2 Gy/day fractions.

Median OS was 16.8 months and they reported that on multivariate analysis, higher KPS, early initiation of RT in less than 42 days after surgery and complementary chemotherapy were independently associated with longer OS. They concluded that even with complete surgical resection, initiation of RT within 6 weeks was an independent predictor of longer survival.

Lai et al. [37] studied a representative group of 1375 elderly patients (age > 65) through a review of SEER cancer registry to determine whether the timing of cranial radiation has an impact on survival. They reported a median survival of 9.3 months for patients that underwent GTR, 8 months for those that underwent STR and 5–6 months for those that underwent biopsy alone. Median time to RT for the surgical group was 16 days and only 10 days for the biopsy group. They found in multivariate analysis that time to radiation was not a significant prognostic factor. Further they reported that age older than 70 years was a poor survival determinant. They concluded that initiation of cranial radiation within 6 weeks of surgery/biopsy has an equivalent survival effect in elderly patients with GBM. When delay is necessary the upper limit of 6 weeks may serve as the latest time point for starting RT.

On the contrary, in a recent study, Randolph et al. [38], retrospectively reviewed outcomes in a cohort of 161 patients with newly diagnosed GBM. Eighty patients underwent GTR of the tumor, 45 underwent STR and 36 patients, biopsy alone. Overall PFS was 6.8 months. PFS was better for patients that underwent GTR as compared to biopsy or STR, 7.8 months, 5.3 months and 5.5 months respectively ($p = 0.005$). For patients that underwent biopsy or STR alone, when RT was started in less than 28 days OS was 7.8 months while for the patients that underwent RT after 28 days it was 12.3 months ($p = 0.005$). For patients that underwent GTR, OS was not significantly different whether RT was started in less or more than 28 days after surgical intervention (17.7 months vs 12.2 months, $p = 0.58$). The authors concluded that for patients that undergo GTR, 28 days delay of RT after surgery is not inferior to starting treatment in less than 28 days. This was a retrospective review and there is the possibility of the bias that patients that started RT in less than 28 days and especially those that underwent less than GTR had worst prognosis to start with.

In another similar retrospective review, Wang et al. [39], reported the results of survival on a cohort of 447 patients with newly diagnosed GBM. The majority of the patients ($n = 357$) received > 54 Gy RT. They stratified the patients based on the time to the start of the RT after surgical intervention, less than 21 days post-operatively (152 patients), between 21 and 32 days ($n = 151$) and more than 32 days ($n = 144$). Overall survival was 374 days for the first group, 465 days for the second group and 478 days for the group that received RT more than 32 days after surgical intervention ($p = 0.004$). The authors reported than in unilateral analysis there was better prognosis for patients starting RT more than 21 days post-surgery, however in the multivariate analysis, there was no significant difference. There is the possibility that these results suffer from the bias of patient selection. Patients with worse KPS values underwent biopsy alone or were older and as a consequence were able to start RT earlier.

Noel and colleagues [40], after retrospectively reviewing 400 patients with newly diagnosed GBM, concluded that the time until RT after diagnosis did not affect patient outcome. They had 65 patients that underwent radiation in less than 4 weeks after diagnosis, 80 that received RT 5 weeks after surgery, 79 patients at 6 weeks, 75 at 7 weeks and 101 patients received radiation more than 8 weeks after diagnosis. Median survival was 409 days for all patients. On multivariate analysis, they found age, degree of surgical resection and type of surgery performed to be the only independent prognostic factors for overall survival. This was a retrospective study of a dyshomogenous population and there was no mention of the reasons why such a difference in timing of initiation of RT after diagnosis was present.

Blumenthal et al., retrospectively reviewed the data from 2855 patients with newly diagnosed GBM that had been enrolled in various Radiation Therapy Oncology Group (RTOG) trials [41]. They divided the patients in different groups based on the timing from surgery to RT. They found that median OS for the group that underwent RT in less than 2 weeks after surgery was 9.2 months and for the group that underwent RT 2–3 months after surgery median OS was 10.8 months as compared to 11.7 months for the group that received RT between 3 and 4 weeks after surgery and 12.5 months for those that received RT 4–6 weeks after surgery. In multivariate analysis they found that RPA and timing of RT after surgery were the only significant variables with impact on median OS. They concluded that short delay after surgery is better than early RT. As the other studies these authors failed to compare directly groups based on their extent of surgical resection or tumor residual post-surgery. The bias that patients with larger tumor residual underwent RT earlier remains. However these authors did not include in this study any patients that received radiation 6 weeks after surgical intervention amid the idea that delay of chemotherapy and RT after 6 weeks can be detrimental.

Synthesis of results

Timing of the RT post-surgical intervention is still controversial. We found several retrospective studies that have studied the best timing for RT after surgery, and there were no prospective studies (Table 7). Few of these studies reported that adjuvant RT is best if started within 6 weeks after surgical intervention [35–37, 41]. Six other studies

reported that delaying RT after surgery does not give worse results [32–34, 38–40]. All the above studies are retrospective and could be biased by patients' selection as it pertains to the feasibility of surgical intervention and degree of resection, and the timing of RT. Furthermore, these last studies did not report how long the delay from surgical intervention to RT can last and still be able to provide good outcomes. These studies evaluate the difference in time of starting RT between groups of patients that started RT before or after 28 days, or between 18–49 days and 50–98 days, or in less than 30 days, or more than 35 days, etc. They do not specify a cut off day after which RT post-surgery is deleterious or not-efficacious. At this point we can only state that starting RT before the sixth week after surgery is recommended. Further prospective randomized studies are needed to define the best interval to start adjuvant RT after surgical intervention.

Question 8: What is the best treatment technique for patients with newly diagnosed GBM?

On the basis of computer planning studies, Intensity Modulated Radiation Therapy (IMRT) has shown better planning target volume coverage and better sparing of regions at higher risk. It appears that IMRT may also be a good planning and radiation technique for GBM, so as to reduce radiation doses on healthy cerebral tissue.

Chen et al. [42], retrospectively reviewed their experience with 54 patients that had undergone IMRT (n = 21 patients) or 3D Conformal Radiation Therapy (3D-CRT) (n = 33 patients) for newly diagnosed GBM. Median dose of radiation was 60 Gy divided in 1.8–2.2 Gy daily fractions. They reported that the use of IMRT resulted in significant reduction of dose to both lenses, but no difference was observed in brainstem or optic nerve maximum dose. There was no significant difference in 1-year OS and PFS between the 2 groups. They concluded that delivering radiation doses by IMRT did not improve survival or decrease toxic effects of RT treatment in comparison to 3D-CRT. (Table 8).

Synthesis of the results

There was only one study that has reported on the difference between IMRT and 3D conformal radiation therapy. This study did not find any difference in OS and PFS for these patients. Based on this one study, we cannot give any recommendations in regard to the technique for delivering RT, IMRT vs conventionalin patients with newly diagnosed GBM.

Question 9: Is the use of radiosensitizers beneficial for patients with GBM?

Radiosensitizers are chemical products that when administered to the patients together with RT would make tumor cells more sensitive to the radiation. The previous guidelines from Buatti et al., did not have any recommendations in regard to the radiosensitizers [2]. We found an article published in 1992 by Goffman et al. [43], that fulfilled our criteria. This was a phase I/II trial that evaluated the benefits of a radiosensitizer use during RT in 45 patients with newly diagnosed GBM (Table 9). The radiosensitizer under consideration was iododeoxyuridine (IdUrd). IdURD was administered intravenously, 1000 mg/m^2/day for 14 days during the initial RT and 1000 mg/m^2/day for 14 days during cone-down RT. The initial RT volume was based on the tumor definition on CT and MRI plus 5 cm margin. The dose was 2 times 150 cGy/day. The target volume for the cone-down RT was contoured by adding 2 cm margin around the abnormality seen on MRI or CT. Virtually all patients required at least a few days break between initial RT and cone-down RT. The authors did not find a major benefit from using this particular radiosensitizer at these dosages. They concluded that the failure of this radiosensitizer combined with RT might be related to the combined problems of poor drug penetration/uptake into tumor, tumor-cell heterogeneity and a high inherent cellular radio-resistance of GBM.

Synthesis of the results

At this time, no recommendations can be given as it relates to the use of radiosensitizers during RT for GBM treatment. Further studies should explore new substances and their benefits as sensitizers during RT.

Question 10: Is ultrafractionated radiation therapy useful in treatment of newly diagnosed GBM?

Non-traditional radiation schemes are considered those that do not follow the Stupp protocol of 60 Gy fractionated in a daily rate of 2 Gy. Such protocols aim to reduce the time of delivering the 60 Gy, to reduce the dose and administer it over a different time span or to allow for increase of the dose of RT. Ultrafractionated radiation therapy aims to give slightly higher than the standard 60 Gy, but with a more concentrated schedule delivering the fractions multiple times a day.

Beauchesne et al. [44], reported results of a phase I/II prospective nonrandomized trial of an ultrafractionated RT schedule in 27 patients with unresectable GBM (Table 10). All patients underwent biopsy only and after that, they received ultrafractionated focal radiation, consisting in 3 daily doses of 0.75 Gy at least 4 h apart, 5 days/

week for 6–7 consecutive weeks for a total of 67.5 Gy. RT was delivered to gross total volume (GTV) enlarged by 2.5 cm. The authors did not specify what they considered as GTV, contrast enhancing tumor or FLAIR signal. Only 22 patients were able to complete the entire course of therapy. The authors reported that median OS was 9.5 months, and at 4 years 2 patients were alive. The 2-year survival was reported to be 15.5%. OS was 74%, 29%, 19% and 15% at 6, 12, 18 and 24 months respectively. Toxicity was encountered as fatigue in 20 patients, headache in 2, skin reaction in 11 and alopecia in 12. They concluded that ultrafractionated RT is feasible, well tolerated and could improve outcome in this group of patients. This was a phase I/II trial and not comparative study, furthermore the authors did not report the reason why these tumors were defined as unresectable and they did not report the volume of these tumors. As such, while a very interesting study, the results do not help in defining any recommendations in regard to ultrafractionation and specifically who are the patients that could benefit from this different schedule.

After the above publication of EORTC/NCIC 26981-22981/CE.3 trial, these same authors performed a second phase II study where patients with newly diagnosed unresectable GBM (n = 40) underwent ultrafractionated RT and this time in combination with TMZ (concurrent and post-radiation maintenance) [45]. Six patients were excluded for various reasons and ultimately only the data for 34 patients were included [45]. This time the authors showed a significant difference in OS and PFS for these patients as compared to the first EORTC/NCIC 26981-22981/CE.3 trial patient group. This was a non-randomized trial. Furthermore, in this trial the patients were admitted for the entire duration of their radiation treatment (6 weeks), which adds to the cost of the RT.

Synthesis of results

Only two studies from the same group of authors were found to have explored the utility of ultrafractionated RT for newly diagnosed GBM. These two studies are prospective phase I/II trials without a comparative arm, however, both articles are published by the same authors and as such those results have not been reproduced by other authors [44, 45]. Furthermore, the toxicities are higher than with conventional therapy. These authors do not give any specifics on who are the patients that should be considered for this modified radiation schedule. While no definitive recommendations can be given in regard to ultrafractionation, this regimen is worth exploring further in patients with unresectable GBM.

Question 11: Is there a role for hypofractionated radiation therapy in treatment of newly diagnosed GBM?

Hypofractionated RT is another non-traditional radiation scheme that aim to deliver a reduced total dose of radiation (less than the standard 60 Gy) in a shorter amount of time.

Several groups have studied non-traditional fractionation schemes (Table 11). In a recent retrospective review of single institution experience, Navarria et al. [46], analyzed the results of 267 adult patients who after having received the maximal safe resection of the tumor underwent RT with TMZ. They compared 2 groups. Group 1 received 60 Gy with 2 Gy daily fractions for 30 consecutive days and the other group received 60 Gy with 4 Gy daily fractions for 15 days. Some of the patients were reviewed before a propensity analysis and others after. For the former, OS was 15.2 months for conventional RT and 15.9 months for hypofractionated radiation therapy (HRT). PFS was similar as well. Even after the propensity analysis when patients from both groups the difference in OS and PFS was not significant (17.9 months for hypofractionated and 16.7 months for the conventional therapy and PFS was 12.3 months and 10.0 respectively). The authors concluded that the results of short course of radiation therapy would seem comparable to conventional RT.

In a retrospective review, Azoulay and colleagues [47] reported the results of a population-based cohort study of 276 adult patients with newly diagnosed GBM. All patients underwent maximal safe surgical resection or biopsy. After surgery, 147 patients received conventional RT, 60 Gy divided in 30 fractions to the planned tumor volume (PTV), 86 patients received HRT, 60 Gy divided in 20 fractions and then 43 patients (age over 70 years or patients with KPS < 70) received HRT with 40 Gy in 15 fractions. All patients received concomitant and adjuvant TMZ as first treatment. Patients of the 3rd group were less likely to undergo surgical resection. For the whole population, median OS was 13.7 months and median PFS was 8.8 months. For the patients that received conventional RT median survival was 16 months, PFS was 9 months and 2-year OS was 23.1%. For the patients that received HRT 60 Gy, median survival was 15 months, PFS 9 months and 2-year OS was 19.7%. There were no significant differences between these 2 groups. There was a significant difference between these 2 groups and the 3rd group in terms of median survival (8 months) and PFS (5.4 months). However, the patients in this 3rd group were older, with lower KPS and more likely to have received biopsy instead of maximal surgical resection. The authors concluded that moderate HRT at 60 Gy in 20 days is associated with comparable outcome to conventional RT regimen for newly diagnosed GBM. This regiment would reduce the length of radiation. The authors

did not report whether the toxicities were comparable for both groups.

In a retrospective review, Arvold and colleagues [48] compared 4 different treatment schemes in a group of 135 elderly patients (age older than 65 years of age) with newly diagnosed GBM. After undergoing biopsy/STR or GTR, patients underwent HRT therapy alone, HRT in conjunction with TMZ, standard RT (SRT) alone or SRT in conjunction with TMZ (Details in Table 11). In multivariate analysis they found that older age, lower KPS, multifocal disease and RT without chemotherapy (either HRT or SRT) were associated with significantly lower OS when compared to RT with TMZ. They concluded that there is no difference in survival between HRT and SRT for elderly patients. The number of patients for each group was small and this was a retrospective study. Further the study suffers from the bias that patients with worst KPS or poorer general status did not receive chemotherapy.

Lim and colleagues [49] evaluated the use of HRT on patients with high risk GBM (see Table 5). Thirty-three patients underwent HRT with TMZ. The authors compared their results with historical controls. Median OS was 10.6 months and median PFS was 7.5 months. They reported low rate of toxicities and concluded that hypofractionated concurrent RT with TMZ would be a treatment option for patients with GBM and poor prognostic features.

Iuchi et al. [50], reported the result of a prospective non-randomized single institution study on 46 adults with newly diagnosed GBM that were treated with HRT schedule. All patients underwent surgical resection and after that they underwent IMRT RT, 8 fractions over 10 days for a total dose of 68 Gy in 8.5 Gy fractions to PTV-1, 40 Gy in 5.0 fractions to PTV-2 and 32 Gy in 4.0 Gy to PTV-3 (see Table 11 for the definitions). All patients underwent concurrent and adjuvant TMZ. The PFS at 2 and 5-years was 63.9% and 57.5% respectively. Distant failure was observed in 10 patients and primary failure in 11 patients. The reported median OS was 20 months. Radiation necrosis was observed in 20 patients around the tumor bed and in SVZ. The authors concluded that hypofractionated high dose IMRT with concurrent and adjuvant TMZ altered dominant failure pattern from localized to disseminated.

Ciammella et al. [51], reported a retrospective review of adult patients with newly diagnosed GBM with KPS > 60 and surgical cavity plus residual enhancing tumor of less than 6 cm that after undergoing surgical resection received hypo-fractionated IMRT. Radiation was started within 6 weeks of surgery at 25-Gy delivered in 5 fractions in one week (5-Gy per fraction) at 70% isodose. Patients received adjuvant TMZ (150 mg/m^2/day 5 days every 28 days cycles that was started within 4 weeks after the end of RT. Median OS was 13.4 months (range 3–62 months) and median PFS was 7.9 months. Median time to progression was 6.1 months (range 0–43.2 months). Recurrence occurred in-field in 33 patients, at the margin in 19 patients and out of field in 7. Post-treatment median KPS improved in 43 patients, remained stable in 14 and worsened in 10 patients. The authors concluded that HRT could be used in patients with GBM resulting in favorable OS and low toxicity. This is a retrospective review and the authors do not compare the outcomes of hypo-fractionated therapy with the standard therapy.

Reddy et al. [52], reported the result of a phase II trial where they studied 24 patients with newly diagnosed GBM that after surgery underwent hypofractionated IMRT. Median OS was reported to be 16.6 months. There was no grade 3 or 4 acute or late non-hematologic toxicities observed, but there were acute grade 3 or 4 hematologic toxicities observed (Table 5). The authors concluded that hypofractionated IMRT with concurrent TMZ is safe and the efficacy appears to be comparable to that of the standard therapy.

Terasaki et al. [53], who performed a prospective non-randomized pilot study of HRT, where they prospectively followed 26 adults with newly diagnosed GBM. All patients underwent maximum safe surgical resection. After surgical resection, patients underwent HRT (45 Gy in 15 fractions over 3 weeks) with concomitant TMZ started within 3 weeks after surgery. The minimum and maximum absorbed doses were planned to be between 95 and 105%. The PFS at 6 months was reported to be 65%. Median PFS was 9.6 months and median OS was 15.6 months. Several toxicities were reported as well, and the authors concluded the efficacy of their regimen was similar to standard radiation therapy regimens (Table 5).

Synthesis of results

In summary, several studies have evaluated the efficacy and safety of hypofractionation in patients with newly diagnosed GBM (Table 11). The schemes of fractionations have been diverse. In the majority of these studies, HRT appeared to be safe and with no major toxicities as compared to the standard therapy. One advantage of hypofractionatied RT seems to be the reduction of time of treatment. Nevertheless, these studies have used different hypofractionated schemes and as such a specific fractionation scheme for best results needs to be defined in further prospective randomized trials for the general adult population. In conclusion, the level I recommendation for HRT remains the same as in the first published guidelines [2], that it may be used in elderly and patients with poor prognosis (KPS > 40) with newly diagnosed GBM. This recommendation was born from review of class I data published by Roa et al., in 2004 [54]. In a randomized prospective clinical trial, the authors recruited 100 patients over age 60. One group received standard RT

(60 Gy in 30 fractions over 6 weeks and the other received 40 Gy in 15 daily fractions over 3 weeks. Median survival for the first group was 5.1 months and for the second group it was 5.6 month (p = 0.57). Six-month survival was 44.7% and 41.7% respectively. They concluded that there was no significant difference between the two treatments in this patient population. Hence, it is reasonable to consider the HRT in patients older than 60 years of age.

Question 12: Is there a role for brachytherapy in treatment of patients with newly diagnosed GBM?

Brachytherapy is an RT technique that utilizes the placement of radioactive material in or around the tumor bed to increase or boost the delivery of local radiation. In the previous guidelines, Buatti et al. [2], did not recommend brachytherapy in the routine management of newly diagnosed GBM.

Waters et al. [55], reported the results of a prospective non-randomized trial with 11 adult patients with newly diagnosed GBM (Table 12). After surgical resection, GliaSite (n = 9) or MammoSite (n = 2) were implanted in the resection cavity. Three to eight days later the balloons were filled with enough Iotrex solution to provide a dose of 60-Gy to a depth of 1 cm from balloon surface. One patient received 45-Gy because of the proximity of the lesion to the optic apparatus. Skin dose was maintained below 12-Gy. Four weeks after brachytherapy, patient received EBRT to 46-Gy to the T2W hyperintense area plus 2 cm surrounding it. This was followed by 14-Gy boost to the T1W enhancing volume. The results were compared with historical controls. All patients had evidence of tumor recurrence following EBRT and TMZ (at 2–17 months). Median PFS after surgical intervention was 10 months and median OS was 15.6 months. The 2-year OS was 42.4%. There were 2 cases with grade 2 toxicities (seizure and left hemiparesis) observed. The authors concluded that this case series demonstrated the safety of immediate post-operative brachytherapy when applied prior to RT and TMZ. This study did not show any improvement in PFS or OS, and authors were only able to evaluate the safety of brachytherapy for a very small cohort of patients.

In another study, Matsuda and colleagues [56], reviewed their experience with 67 consecutive patients with newly diagnosed GBM. All patients underwent surgical resection or biopsy. Silicon tubes were inserted around the boundary between eloquent and non-eloquent tissue. Standard therapy was administered to 35 patients (total dose 60–60.2 Gy, 1.8–2.0 Gy/daily fractions). Thirty-two patients received High dose particle radiotherapy (HDT) with boron neutron capture therapy (BNCT) or photon therapy. BNCT was given to patients with supratentorial unilateral tumor no deeper than 7 cm with KPS > 50. An average dose of 30 Gy in single session was given to the CTV-2 and CTV-3. An additional photon irradiation totaling 30 Gy was given to GTV. Photon therapy with a dose of 50.4 Gy in 28 fractions to the PTV in the morning was administered to 17 patients with supratentorial tumors that had a maximum post-operative tumor diameter of less than 4 cm and KPS > 60. Forty-seven patients received procarbazine, nimustine and vincristine in combination with Conventional RT (CRT). Median OS for all patients was 17.7 months. The 1 and 2-year survival rates were 67.2% and 33.7%. Median PFS was 7.8 months. Median OS for HDT patients was 24.4 months and for CRT was 14.2 months. Although not statistically significant, median OS was better for patients older than 65 years of age (24.4 months) as compared to the younger patients (16.8 months). There were some acute toxicities that were observed as well. The authors concluded that patients that received HDT had longer survival than patients that received CRT. This is a retrospective study. The authors reported that patients that underwent HDT were more likely to have undergone GTR surgery and had a better performance status, although they denied that these confounding factors were significant in their findings.

Synthesis of results

In summary, we found only 2 studies (Table 12) that fulfilled our criteria where brachytherapy was used for treatment of newly diagnosed GBM. One of the studies did not show any difference in PFS or OS. The other one did not report survival benefits of brachytherapy when compared to conventional therapy, however those patients did undergo GTR surgery. No definitive recommendations can be given as it pertains to the brachytherapy after reviewing these 2 studies. Randomized controlled trials are needed to be able to define its role in treatment of newly diagnosed GBM. The recommendations regarding brachytherapy remain the same as in the Buatti et al. [2]. Two randomized studies, one matched control study and a series of retrospective studies were used by Buatti et al., [2] to build the recommendations on brachytherapy. Despite promising results in few of the retrospective studies, they found 2 RTC that failed to demonstrate a survival advantage for brachytherapy in newly diagnosed GBM. One study randomized 140 patients to EBRT versus EBRT and brachytherapy of Iodine-125 implants. They did not report a statistical survival benefit. (Reviewed in [2]). The other study reviewed by Buatti et al., was a randomized multi-center comparison of surgery, EBRT and BCNU (n = 137) versus same regimen with addition of brachytherapy of I-125 (n = 299). The authors reported that addition of brachytherapy did not add any long-term survival benefits. (Reviewed in [2]).

Question 13: Is there a role for accelerated RT in patients with newly diagnosed GBM?

Accelerated RT or hyperfractionated accelerated RT aims to deliver the same standard dose fractionated but delivering it multiple times a day for a shorter period of time.

In 2017, Fariselli and colleagues [57] published the results of a prospective single arm open label phase II trial of 35 adult patients (age 18–65) with newly diagnosed GBM (Table 13). After surgical intervention, the patients received 2 cycles of accelerated RT (AHRT). This was started within 40 days after the surgery. The total dose of 60 Gy was administered with fractions of 2 Gy, 3 times a day every 4 h in the same day, in 5 consecutive days. Patients received 2 different cycles divided by an interval of 28 days. All patients received TMZ in 3 single administrations 1 h before every single fraction of RT. Twelve patients experienced radiation necrosis. Five patients experienced neurological deterioration and underwent surgical intervention. Four of these patients had radiation necrosis confirmed on the pathology report. Median PFS was 6 months and median OS was 22 months. They concluded that aggressive treatment schedules need further exploration.

On a prior report, Fariselli et al. [27], had explored the same AHRT technique but delivering only a total of 45 Gy to 33 patients older than 70 years of age. As discussed in one of the previous sections, the median PFS was 6 months and OS was 8 months. On the multivariate analysis, the extend of resection was confirmed as the only significant factor that influenced OS, and specifically GTR was independently associated with increase OS [HR 0.159; 95% CI 0.04–0.59; p = 0.006]. None of the patients experienced radiation necrosis. They concluded that accelerated hyperfractionated RT scheme is beneficial to elderly patient population and overall treatment time can be considerably shortened without a detrimental effect on clinical outcome.

Buckner et al. [58], reported the result of a phase III randomized controlled trial of 451 patients with newly diagnosed GBM. After surgical resection, patients were randomly assigned to 4 groups. First group (A) received BCNU and standard for the time RT, 1.80 Gy/day for 36 days at a total dose of 64.8 Gy; group B, received BCNU and AHRT, 2 times 1.6 Gy per day for 15 days for a total dose of 48.0 Gy; Group C received cisplatin plus BCNU and standard RT as group A; and group D received cisplatin and BCNU and AHRT with the same dose as group B. There were no differences noted in toxicity between patients that received CRT or ART. When compared, median overall survival for patients in group A and B that received same chemotherapy regimen was 10.1 months and for group C and D was 11.5 months (not statistically significant). When compared, group A and C that received same standard RT with groups B and D that received same AHRT regimen had similar median OS, 11.2 months and 10.5 months respectively. The authors concluded that CRT and AHRT produced similar toxicity and survival. Being a RCT, this report provides class I data that AHRT is not worse than CRT. To be noted is the fact that with AHRT smaller RT doses are being administered and in a shorter period of time. It remains to be evaluated weather AHRT is better than the standard therapy when given together with TMZ, now the standard chemotherapeutic of choice and whether this regimen reduces costs and has similar toxicity pattern as the standard RT.

Synthesis of results

In summary, one study did not show that hyperfractionated and accelerated schemes (AHRT) have any significant difference in OS and PFS when compared to the standard RT schemes [57]. That study showed that majority of patients experienced radiation necrosis and some of them so severe that they had to undergo surgical intervention when the total RT dose was the standard 60 Gy. However, there were other 2 studies that showed that this scheme could be beneficial for the elderly if lower total RT dose is used (45 Gy for one study [27] and 48 Gy in the other study [58]) One of those studies [58] was a randomized controlled trial and in theory provides level I evidence; however, they did not use the AHRT with the current drug of choice for newly diagnosed GBM, temozolomide. Hence, we will consider this recommendation as a level III if the total RT dose administered is lower than 60 Gy (45 Gy or 48 Gy).

Question 14: Is there a role for stereotactic radiosurgery in treatment of patients with GBM?

As it pertains to stereotactic radiosurgery (SRS) for GBM, there have been several studies that have evaluated this modality mostly as a boost in addition to the CRT (Table 14).

Einstein et al., [59] performed a prospective non-randomized phase II trial enrolling 35 patients with newly diagnosed GBM. The majority of patients underwent subtotal resection. With the discretion of the neuro-oncologist, 46% patients received concurrent TMZ. All patients underwent GammaKnife stereotactic radiosurgery (SRS) within 5 weeks post-surgery. Patient underwent Magnetic Resonance Spectroscopy (MRS) and the highlighted voxels within 2 cm of the contrast-enhancing lesions were targeted with a single 8-mm isocenter to the 50% isodose. The doses used were 15 Gy for diameter 3–4 cm, 18 Gy for lesions 2–2.9 cm and 24 Gy for diameters less than 2 cm. Within 2 weeks after SRS, patients underwent CRT, 60 Gy total with 2 Gy fractions/day for 5 days/week. Median survival was 15.8 months. Median survival for patients older than 60 years of age was 11 months and 22 months for younger patients. When compared to EORTC trial patients, the

survival in this trial was longer. The authors concluded that MRS targeted SRS directed only to areas of high biologic activity combined with CRT is feasible with acceptable toxicity and the survival is higher than the historical controls.

Kong et al. [60], retrospectively reviewed 19 patients with unresectable GBM. Ten of these patients underwent RT and SRS (GammaKnife) with a median marginal dose was 12 Gy (9–16 Gy). Nine patients underwent RT alone, 60 Gy fractionated at 2 Gy/day for 30 days. They reported an OS of 52 weeks for patients undergoing RT and SRS and 28 weeks for those that received RT alone ($p=0.0758$). PFS at 3 months was 75% for patients that underwent Gammaknife radiation and 45% for the others ($p=0.082$). The authors concluded that GammaKnife prior to RT might be helpful in preserving patient's ability to perform the activities of daily living. This was a retrospective review and groups may have not been homogenous. OS and PFS differences were not statistically significant. There is no rationale for explaining how SRS helped post-treatment KPS.

In another study, Cardinale et al. [61], reported the results of RTOG 0023, a phase II trial where they studied 76 patients with newly diagnosed GBM. The patients underwent first RT, 2 Gy/day 5 days/week for the first 2 weeks, then 4 days a week for the following 3 weeks and then for 3 days a week on the next 2 weeks for a total of 50 Gy. Then the patients underwent fractionated conformal SRS boost, 5–7 Gy/day once a week for 4 weeks. The cumulative dose of RT was 70 or 78 Gy in 29 treatments over 6 weeks. After the RT course patients received BCNU at 80 mg/m^2 for 3 days every 8 weeks for 6 cycles. Median OS was 12.5 months. No survival difference was seen when compared with the RTOG historical database. The authors concluded that a fractionated SRT boost trial for GBM was feasible. The authors also concluded that there was no significant survival benefit using this dose-intense RT regimen. Only a post-hoc analysis showed a trend towards improvement of outcome in patients that have undergone gross total resection.

Synthesis of results

We did not find any new RCT evaluating the role of SRS for treatment of GBM that fulfilled our criteria (Table 14). The 3 new studies that we found were published in 2006 and 2012. They were not RCT. One study found that when compared to historical controls the integration of SRS with standard RT may be beneficial [59]. This was classified as class III evidence due to comparison with historical control. Another retrospective study of only 19 patients that had undergone non-homogenous treatment protocols, concluded that SRS could impart benefits to patients with newly diagnosed GBM [60]. There was a phase II study published during this period that did not find SRS to add any benefit to the treatment of patients with GBM [61]. From these studies only in one of them 46% of the patients were treated with standard Stupp protocol in addition to SRS. Unfortunately, the results of treatment in these patients was not reported separately. In summary, two studies, classified as class III found some benefit on using SRS for treatment of GBM and one study did not find any benefit. Buatti et al. [2], in the previous guidelines based their recommendation that SRS is not recommended in the routine management of newly diagnosed GBM on an RCT, class I data that prospectively evaluated patients that underwent either EBRT alone with BCNU ($n=97$) or BCNU with EBRT plus SRS ($n=99$). Median survival was not statistically significant. Since we did not find any RCT, level I data to contradict their conclusion we concur with the recommendations given on the previous guidelines.

Conclusions

Review of recent literature support the previous guidelines class I recommendations that RT plays an important role in treatment of GBM with the standard dose of 60 Gy fractionated in 2 Gy per day for 5 days a week. The area of radiation should include a 1–2.5 cm margins added to the residual enhancing area. Radiation therapy should not be excluded as a treatment option in elderly patients and in patients with low performance status. These patients may benefit from RT with a reduced dose and length of time such as hypofractionated schemes or accelerated hyperfractionated schemes. There have been no studies that have compared hypofractionated schemes with accelerated hyperfractionated schemes for us to recommend one versus the other. Patients benefit more when radiation therapy is started within 6 weeks from the diagnosis. SRS as it pertains to their routine use in newly diagnosed GBM has not been shown to infer further benefit and as such is not recommended.

Key issues for future investigation

There is class I evidence for use of RT in addition to chemotherapy as adjuvant treatment in patients with newly diagnosed GBM. Dosage of 60 Gy fractionated in 6 weeks is being used as standard therapy. New dosages and schemes that could shorten the length of RT, such as hypofractionated and accelerated hyperfractionated schemes, should be evaluated in randomized controlled trials (RTC) to find the best short RT schemes that will reduce toxicity and time of treatment without detriment to the PFS and/or OS. The benefits or risks of radiation of SVZ need further evaluation in RCT. Timing of when to start RT after diagnosis and/or surgical resection needs further study in RCT. Since we have entered a new era of molecular based classification of

gliomas, future studies should address new RT schemes and dosages based on gliomas differences in molecular markers.

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Compliance with ethical standards

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