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Treatment of newly diagnosed glioblastoma in the elderly (Review)

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[Intervention Review]

Treatment of newly diagnosed glioblastoma in the elderly

Catherine Hanna[1], Theresa A Lawrie[2], Ewelina Rogozińska[3], Ashleigh Kernohan[4], Helen Bulbeck[5], Usama M Ali[6], Sarah Jefferies[7], Tomos Robinson[4], Robin Grant[8]

[1]Department of Oncology, University of Glasgow, Glasgow, UK. [2]The Evidence-Based Medicine Consultancy Ltd, Bath, UK. [3]Evidence-based Medicine Consultancy Ltd, Bath, UK. [4]Institute of Health & Society, Newcastle University, Newcastle upon Tyne, UK. [5]Director of Services, brainstrust, Cowes, UK. [6]Centre for Statistics in Medicine, University of Oxford, Luton, UK. [7]Department of Oncology, Addenbrooke's Hospital, Cambridge, UK. [8]Edinburgh Centre for Neuro-Oncology (ECNO), Western General Hospital, Edinburgh, UK

Contact address: Theresa A Lawrie, The Evidence-Based Medicine Consultancy Ltd, 3rd Floor Northgate House, Upper Borough Walls, Bath, BA1 1RG, UK. tesslawrie@gmail.com.

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ABSTRACT

Background

A glioblastoma is a universally fatal type of brain tumour for which the standard of care is maximum surgical resection followed by chemoradiotherapy, when appropriate. Age is an important consideration in this disease, as older age is associated with shorter survival time and a greater risk of treatment-related toxicity.

Objectives

1) To determine the most effective and best-tolerated approaches for the treatment of elderly people with newly diagnosed glioblastoma

2) To summarise current evidence for the incremental resource use, utilities, costs and cost-effectiveness associated with the different approaches.

Search methods

The search was conducted by the CGNOC Information Specialist on 13 June 2018 and topped up on 3 April 2019. Electronic databases searched included the Cochrane Central Register of Controlled Trials (CENTRAL), Embase, and Medline, and the NHS Economic Evaluation Database (EED) up to database closure. Clinical trial registries and selected neuro-oncology society conference proceedings from the passed five years were hand searched. Related articles feature of Pubmed and reference lists of included studies were used and scrutinised, respectively.

Selection criteria

Randomised trials (RCTs) of treatment interventions to improve health outcomes in elderly people with glioblastoma. We defined ‘elderly' as over the age of 70 years; however, we also include studies defining the ‘elderly' as over 65 years of age.

Data collection and analysis

Two review authors extracted data to a pre-designed and piloted data extraction spreadsheet. These were checked by a third author and differences resolved by discussion. Where sufficient data were available, treatment options were compared in a network meta-analysis (NMA) using Stata software (version 15.1). For outcomes with insufficient data for NMA, pairwise meta-analysis were conducted in RevMan. The GRADE approach for NMA and pairwise evidence was used to grade the relevant evidence, which was presented in summary of findings tables.

Main results

We included 12 RCTs involving approximately 1,818 participants. Six were conducted exclusively among elderly people (either defined as 65 years or older or 70 years or older) with newly diagnosed glioblastoma, the other six reported data for an elderly subgroup among a broader age range of participants. Most participants were capable of self-care. Study quality was commonly undermined by lack of outcome assessor blinding and attrition.

Seven trials contributed to a NMA for overall survival, with interventions including supportive care only (1 trial arm); hypofractionated radiotherapy (RT40; 4 trial arms); standard radiotherapy (RT60; 5 trial arms); temozolomide (TMZ; 3 trial arms); chemoradiotherapy (CRT; 3 trial arms); bevacizumab with chemoradiotherapy (BEV_CRT; 1 trial arm); and bevacizumab with radiotherapy (BEV_RT). Compared with supportive care only, NMA evidence suggested that all treatments apart from BEV_RT prolonged survival to some extent.

Overall survival

High-certainty evidence shows that CRT prolongs overall survival compared with RT40 (HR 0.67, 95% CI 0.56 to 0.80) and low-certainty evidence suggests that CRT may prolong overall survival compared with TMZ (TMZ vs CRT: HR 1.42, 95% CI 1.01 to 1.98). Low certainty evidence also suggests that adding BEV to CRT may make little or no difference (BEV_CRT vs CRT: HR 0.83, 95% CrI 0.48 to 1.44). We could not compare the survival effects of CRT with different radiotherapy fractionation schedules (60Gy/30 fractions and 40Gy/15 fractions) due to a lack of data. When treatments were ranked according to their effects on overall survival, BEV plus CRT ranked as the best treatment, CRT second, TMZ third, with supportive care only as the worst treatment. However, rankings do not take into account the certainty of the evidence, which was most robust for CRT without BEV.

One trial comparing tumour treating fields plus adjuvant chemotherapy (TTF_AC) with adjuvant chemotherapy alone could not be included in the NMA as participants were randomised after receiving concomitant chemoradiotherapy, not before. Findings from the trial suggest that the intervention probably improves overall survival in this selected patient population.

We were unable to perform NMA for other outcomes due to insufficient data. Pair-wise analyses were conducted for the following:

Quality of life

Moderate-certainty narrative evidence suggests that overall, there may be little difference in quality of life between TMZ and RT, except for discomfort from communication deficits, which are probably more common with RT (1 study, 306 participants, P=0.002). Data on quality of life for other comparisons were sparse, partly due to high drop-out rates, and the quality of the evidence tended to be of low or very low.

Progression free survival

High-certainty evidence shows that CRT increases time to disease progression compared with RT40 (HR 0.50, 95% CI 0.41 to 0.61); moderate-certainty evidence suggests that RT60 probably increases time to disease progression compared with supportive care only (HR 0.28, 95% CI 0.17 to 0.46) and that BEV_RT probably increases time to disease progression compared with RT40 alone (HR 0.46, 95% CI 0.27 to 0.78). Evidence for other treatment comparisons was of low or very low certainty.

Severe adverse events

Moderate-certainty evidence suggests that TMZ probably increases the risk of grade 3+ thrombo-embolic events compared with RT60 (RR 2.74, 95% CI 1.26 to 5.94; participants = 373; studies = 1) and also the risk of grade 3+ neutropenia, lymphopenia, and thrombocytopenia. Moderate-certainty evidence also suggests that CRT probably increases the risk of grade 3+ neutropenia, leucopenia and thrombocytopenia compared with hypofractionated RT alone. Adding BEV to CRT probably increases the risk of thrombo-embolism (RR 16.63, 95% CI 1.00 to 275.42; moderate-certainty evidence).

Economic evidence

There is a paucity of economic evidence regarding the management of newly diagnosed glioblastoma in the elderly. Only one economic evaluation on two short course radiotherapy regimen (25 Gy versus 40 Gy) was identified and its findings were considered unreliable.

Authors' conclusions

For elderly people with glioblastoma who are self-caring, evidence suggests that CRT prolongs survival compared with RT and may prolong overall survival compared with TMZ alone. For those undergoing RT or TMZ therapy, there is probably little difference in quality of life overall. Systemic anti-cancer treatments TMZ and BEV carry a higher risk of severe haematological and thromboembolic events. Current evidence provides little justification for using BEV in elderly patients outside of a clinical trial setting. Whilst the novel TTF device appears promising, evidence on quality of life and tolerability is needed in an elderly population. Quality of life and economic assessments of CRT versus TMZ and RT are needed. Economic evaluations should include indirect costs to patients and families.

PLAIN LANGUAGE SUMMARY

Treatment options for newly diagnosed glioblastoma in older people

What is the issue?

Glioblastoma is an aggressive type of brain tumour that can lead to death within months of diagnosis. The standard treatment recommended for people with newly diagnosed glioblastoma is to remove as much of the tumour as possible by operation, and then to give chemotherapy (an anti-cancer medicine called temozolomide[TMZ]) and radiotherapy (RT). TMZ is usually given at the same time as radiotherapy (concomitant chemotherapy), and also for about six months after radiotherapy (adjuvant chemotherapy). Together these treatments can be called chemoradiotherapy (CRT). However, not all people are fit enough to receive CRT, which can have serious side-effects.

Older people with glioblastoma survive for a shorter time and are more susceptible to side effects than younger people and it is not known whether the standard CRT or other treatment options are best in this age group. The term 'the elderly' in relation to glioblastoma commonly refers to people 70 years and older. In this review we evaluated evidence on different treatments that have been looked at in older people with newly diagnosed glioblastoma, to find out which treatments can help older people with glioblastoma live longer with the best quality of life and least side effects possible, and the cost of treatments in relation to their effectiveness.

How we conducted the review

We searched the literature to identify randomised trials that compared two or more treatments in the elderly with newly diagnosed glioblastoma. People in these studies had an equal chance of receiving one treatment or another treatment after surgical removal of their brain tumour. We also looked for studies on the cost-effectiveness of treatments. We defined 'the elderly' as 70+ years, but also included data from patients 65+ years old if studies did not give results for the 70+ age group. Cochrane methods to assess the quality of each study and collect the data were used. We did network meta-analysis (NMA), which allowed us to compare the effect of several different treatments directly and/or indirectly, where possible. When NMA was not possible, we used analysis methods that compared two treatments only (pairwise meta-analysis). We rated the certainty of the evidence using an established approach (GRADE) and presented the evidence in summary tables.

What we found

We found 12 studies in older people with glioblastoma evaluating different RT and CT options, supportive (palliative) care only, and other treatments added to RT and or CT, including a medical device that is worn on the head and emits an electric field (known as tumour treating fields). Most people enrolled in these studies did not have serious disabilities and were capable of self-care. We compared the relative effects of seven treatments on patients overall survival using NMA. All treatments tested in the NMA apart from one, in which an agent called bevacizumab (BEV) was added to RT, clearly prolonged survival to some extent compared with supportive care only. The strongest evidence we found showed that CRT leads to a longer survival time than short course RT only; but weaker evidence suggested that CRT also prolongs survival compared with TMZ only. When we ranked all treatments according to their effectiveness in prolonging survival time, the BEV after chemoradiotherapy (BEV_CRT) ranked highest; CRT ranked second and TMZ ranked third. Rankings do not take into account the certainty of the evidence, however, and the evidence for CRT was more certain than for BEV_CRT. In addition, evidence comparing the first two treatments suggested that adding BEV to CRT made little difference to overall survival time.

A study of tumour treating fields could not be included in the NMA because it was conducted among fitter elderly patients who had already received part of their CRT. Evidence from this study suggested that adding tumour treating fields after radiotherapy probably improves survival in this fitter group of patients.

With regard to quality of life, evidence suggested that the impact of TMZ and RT-only treatments is probably not very different, except for greater discomfort from communication deficits with RT. Quality of life evidence was hard to interpret for other treatment options because it tended to be limited by high drop-out rates, as people with GBM do not live very long and may not feel like filling out questionnaires when they feel unwell.

With regard to other outcomes, high-certainty evidence showed that CRT delays disease progression compared with radiotherapy only. Evidence also suggested that adding BEV to short course radiotherapy probably delays disease progression but may not improve overall survival. TMZ and BEV are more toxic to blood cells than RT and are associated with an increased risk of blood clots and blood vessel blockages (thrombo-embolism).

Our conclusions

For reasonably fit elderly people with glioblastoma, evidence suggests that CRT prolongs survival compared with RT or TMZ alone, and that any of these three treatment options might prolong survival compared with supportive care only. Serious adverse events affecting blood components are more common with anti-cancer medicines TMZ and BEV. There is not enough evidence on BEV to support its use in elderly people with GBM outside of a clinical trial setting. More research is needed on how different treatments affect quality of life and

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Summary of findings on overall survival comparing treatments to supportive care only

Estimates of effects, certainty assessment and rankings of different treatment options compared with supportive care only on overall survival in elderly people with glioblastoma

Patient or population: elderly people with newly diagnosed glioblastoma

Interventions: radiotherapy with 40Gy in 15 fractions (RT40); radiotherapy with 60Gy in 30 fractions (RT60); chemoradiotherapy (CRT); chemoradiotherapy plus bevacizumab (BEV_CRT); radiotherapy plus bevacizumab (BEV_RT); temozolomide (TMZ)

Comparison: Supportive care only

Outcome: Overall survival

All intervention options (7 RCTs; 1,540 participants in total)*	**Relative effect (network estimate) ** (95% CI)**	**Illustrative absolute relative risk of death at three months after diagnosis (95% CrIs) *** **	**Certainty of the evidence (GRADE)**	**Ranking¥**
Supportive care only*** (1 RCT, 81 participants)	**Reference comparator**	median survival time 3.9 months	Reference comparator	7.0 (worst)
RT60 (5 RCTs; 713 participants)	**HR 0.47** (0.29 to 0.76)	22% lower risk of death (9% to 32% lower risk)	⊕⊕⊕⊖ **Moderate[1]**	5.0
BEV_RT (1 RCT; 75 participants)	**HR 0.48** (0.23 to 1.00)	22% lower risk of death (0% to 36% lower)	Not graded[2]	4.7
RT40 (4 RCTs; 930 participants)	**HR 0.44** (0.25 to 0.77)	24% lower risk of death (9% to 34% lower)	⊕⊕⊖⊖ **Low[3]**	4.3
TMZ (3 RCTs, 538 participants)	**HR 0.42** (0.25 to 0.71)	25% lower risk of death (11% to 34% lower)	⊕⊕⊖⊖ **Low[3]**	3.8
CRT (2 RCTs; 635 participants)	**HR 0.30** (0.17 to 0.53)	32% lower risk of death (19% to 39% lower)	Not graded[2]	1.8
BEV_CRT (1 RCT; 73 participants)	**HR 0.25** (0.11 to 0.54)	34% lower risk of death (19% to 43% lower)	Not graded[2]	1.4

NMA-SoF table definitions

Estimates are reported as **HR**: Hazard Ratio. **CI**: credible interval.**NMA**: network meta-analysis

* This refers to the number of studies in the network evaluating the given intervention and the number of participants involved in these studies.

** All NMA effect estimates in this summary of findings table are derived 100% from indirect evidence, except for the comparison of RT60 versus supportive care, which was directly compared in one study. Where there was no common comparator for the comparison we did not grade the certainty of the evidence.

*** The assumed median survival time with supportive care only is based on Keime-Guibert 2007, which may be slightly underestimated in this older study, in which at least half the patients had a biopsy only (not maximal resection).

¥These rankings do not take into account the certainty of the evidence and should be interpreted with caution. The estimates of ungraded evidence are very uncertain.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Downgraded -1 as the evidence was derived from a single small study.
[2] There was no common comparator for the comparison (i.e. the intervention was not connected in a loop in the evidence network), therefore we did not grade the certainty of the evidence.
[3] Contributing direct evidence was of moderate or low certainty.
Abbreviations
BEV_CRT = chemoradiotherapy plus bevacizumab; CRT = chemoradiotherapy; RT40 = radiotherapy (40Gy in 15 fractions); RT60 = radiotherapy (60Gy in 30 fractions); SC = supportive care; TMZ = temozolomide; TTF_AC = tumour treating fields plus adjuvant chemotherapy)after concomitant CRT)

Summary of findings 2. Summary of findings on overall survival comparing treatments to hypofractionated radiotherapy

Estimates of effects and certainty assessments compared with hypofractionated radiotherapy (40 Gy/15 fractions) on overall survival in elderly people with newly diagnosed glioblastoma

Patient or population: elderly people with newly diagnosed glioblastoma

Interventions: chemoradiotherapy (CRT); chemoradiotherapy plus bevacizumab (BEV_CRT); radiotherapy plus bevacizumab (BEV_RT); temozolomide (TMZ)

Comparison: hypofractionated radiotherapy (RT 40)

Outcome: Overall survival

All intervention options **(7 RCTs; 1,540 participants in total)***	**Relative effect (network estimate) ** (95% CrI)**	**Certainty of the evidence (GRADE)**
RT 40 (4 RCTs; 930 participants)	**Reference comparator**	**Reference comparator**
BEV_RT (1 RCT; 75 participants)	**HR 1.08** (0.66 to 1.78)	⊕⊕⊖⊖ **Low[1]**
TMZ (3 RCTs, 538 participants)	**HR 0.95** (0.71 to 1.26)	⊕⊕⊖⊖ **Low[1]**
CRT (2 RCTs; 635 participants)	**HR 0.67** (0.56 to 0.80)	⊕⊕⊕⊕ **High**
BEV_CRT	**HR 0.56** (0.31 to 0.99)	⊕⊕⊕⊖ **Moderate[2]**

(1 RCT; 73 participants)	

For the comparison with standard radiotherapy (60 Gy/30 fractions) see Summary of findings 3.

NMA-SoF table definitions
Estimates are reported as HR: Hazard Ratio. CI: confidence interval. . For assumed median survival times and absolute effect estimates, please refer to Summary of findings for the main comparison.
NMA: network meta-analysis

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]Contributing direct evidence was of low certainty (study design limitations and imprecision).
[2]Contributing direct evidence was of high or moderate certainty.
y

Summary of findings 3. Summary of findings on overall survival comparing treatments to standard radiotherapy

Estimates of effects and certainty assessment compared with standard radiotherapy (60 Gy/30 fractions) on overall survival in elderly people with newly diagnosed glioblastoma

Patient or population: elderly people with newly diagnosed glioblastoma

Interventions: radiotherapy with 40Gy in 15 fractions (RT 40); chemoradiotherapy (CRT); chemoradiotherapy plus bevacizumab (BEV_CRT); radiotherapy plus bevacizumab (BEV_RT); temozolomide (TMZ);

Comparison: standard radiotherapy (RT 60)

Outcome: Overall survival

All intervention options (7 RCTs; 1,540 participants in total)*	**Relative effect (network estimate) ** (95% CrI)**	**Quality of the evidence (GRADE)**
RT 60 (5 RCTs; 713 participants)	**Reference comparator**	**Reference comparator**
RT 40 (4 RCTs; 930 participants)	**HR** 0.94 (0.72 to 1.23)	⊕⊕⊖⊖ **Low[1]**
BEV_RT (1 RCT; 75 participants)	**HR** 1.01 (0.58 to 1.79)	⊕⊖⊖⊖ **Very low[1,2]**
TMZ (3 RCTs, 538 participants)	**HR** 0.89 (0.71 to 1.11)	⊕⊖⊖⊖ **Very low[3]**
CRT (2 RCTs; 635 participants)	**HR** 0.63 (0.46 to 0.87)	⊕⊕⊖⊖ **Low**
BEV_CRT	**HR** 0.52 (0.28 to 0.98)	Not graded

(1 RCT; 73 participants)

NMA-SoF table definitions
Estimates are reported as **HR**: Hazard Ratio. **CI**: confidence interval. For assumed median survival times and absolute effect estimates, please refer to Summary of findings for the main comparison.
NMA: network meta-analysis

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Contributing direct evidence was of low certainty (study design limitations and imprecision).
[2] Downgraded for imprecision.
[3] Contributing direct evidence of very low certainty (imprecision, study design limitations and inconsistency).

Summary of findings 4. Summary of findings on quality of life

The effect of different treatment comparisons for newly diagnosed glioblastoma in the elderly on quality of life

Patient or population: elderly people with newly diagnosed glioblastoma

Interventions: One treatment option

Comparison: An alternative treatment option

Comparison	Narrative summary of evidence	No of studies (elderly participants)	Quality of the evidence (GRADE)	Comments
RT vs supportive care only	Evidence on relative HRQoL is very uncertain.	1 study (59 participants at 30 day and 26 at 135 day time-points, respectively)	⊕⊖⊖⊖ **Low[1,2]**	The study reported that global assessments of deterioration over time also did not differ significantly between the two groups. The drop-out rate was high and unbalanced so findings were difficult to interpret.
Hypofractionated RT vs standard RT (60Gy/30 fractions)	There may be little difference in HRQoL scores between hypofractionated and standard fractionation schedules in the 6 to 8 weeks following treatment.	2 studies (participants numbered 85 and 24, respectively, at the furthest time-point)	⊕⊖⊖⊖ **Low[1,2]**	One study compared a 25Gy schedule with a 40Gy schedule; the other compared a 40Gy schedule with a standard 60Gy schedule.

TMZ vs RT	No significant differences in global QoL scores at 3, 6, or 12 month measurements. However, there was a significant difference in discomfort from communication deficits, which were greatest for those receiving RT who died at between 6 and 12 months (p=0·002).	1 study (306 participants)	⊕⊕⊕⊖ **Moderate**[3]	Evidence was not downgraded for attrition because data were reported for 82% of participants in each group for this outcome.
CRT vs RT	Authors reported that quality of life was similar in the two treatment groups. See Comments.	1 study (562 participants; number with QOL data was unclear)	Not graded	Investigators noted that attrition impacted the quantity of data. They conducted analyses using time to deterioration (with deterioration defined as a 10-point decrease in the score on the function domain or a 10-point increase in the score on the symptom domain) and plotted QoL scores over time. They reported that "There were no other clinically important differences between trial groups, which supports our observation that quality of life was similar in the two treatment groups."
BEV_CRT vs CRT	This was reported for the overall trial but not for elderly subgroup specifically.	1 study (73 participants)	Not graded	The authors reported significantly delayed deterioration in HRQoL scores in favour of BEV_CRT across five main HRQoL domains (global health, communication, social functioning, motor function, physical functioning). When progression of disease was removed as a deterioration event, the time to clinically significant deterioration or death remained statistically significant for communication, social functioning and global health.
BEV_RT vs RT	Investigators reported that "before progression, no differences were detected for individual scales in a generalized linear mixed model, except for less favorable values in arm A (BEV) for global health (P=0.048) and pain (P=0.027)".	1 study (75 participants)	Not graded	In the publication, global health was reported in a forest plot along with individual HRQoL items, such as cognitive functioning, emotional functioning and pain, measured with EORTC QLQ-C30/BN20 scales. No other data were provided or obtained.
RIN_CRT vs control/CRT	This was reported for overall trial but not for elderly subgroup specifically.	1 study (174 participants)	Not graded	Investigators reported no significant differences between patients in their trial arms in any of the HRQoL measures.
TTF_AC vs CRT	This was reported for overall trial but not for elderly subgroup specifically.[4]	1 study (134 participants)	Not graded	There was no significant difference in HRQoL reported between the trial arms, except for itchy skin which was more prominent in the TTFields arm at 3,6 and 9 months (p=0.005, p=0008, p=0.04). There was no significant difference at 12 months.
IRI_BEV_RT vs CRT	This was reported for overall trial but not for elderly subgroup specifically.	1 study (34 participants)	Not graded	There was no significant difference between the treatment arms.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]Sparse data from single studies [-1]
[2] Serious risk of bias from attrition [-1]
[3] Downgraded because data were presented graphically and effects could not be estimated.
[4] In this trial (Stupp 2017a) TTF_AC was compared with adjuvant chemotherapy (TMZ) only, after both arms had received concomitant CRT.
Abbreviations: CI: Confidence interval; HR: Hazard Ratio; RT: radiotherapy; CRT: chemoradiotherapy; BEV_CRT: chemoradiotherapy plus bevacizumab; BEV_RT: radiotherapy plus bevacizumab; TMZ: temozolomide; TTF_AC: tumour treating fields with adjuvant chemotherapy (after concomitant CRT) (TTF_AC); RIN_CRT: rindopepimut after CRT; IRI: irinotecan

Summary of findings 5. Summary of findings on progression free survival

The effect of different treatment comparisons for newly diagnosed glioblastoma in the elderly on progression free survival

Patient or population: elderly people with newly diagnosed glioblastoma

Interventions: One treatment option

Comparison: An alternative treatment option

Progression free survival	Relative effect (95% CI)	No of studies (elderly participants)	Quality of the evidence (GRADE)	Comments
RT vs supportive care only	**HR** 0.28 (0.17 to 0.46)	1 study (81 participants)	⊕⊕⊕⊖ **Moderate**[1]	Median time to progression was 3.5 months in the RT arm vs 1.3 months in the supportive care arm of this study (Keime-Guibert 2007).
Hypofractionated RT vs standard RT (60Gy/30 fractions)	**HR** not reported	1 study (64 participants)	Not graded	This study (Roa 2015) reported that median progression free survival showed no statistically significant difference between arms (4.2 v 4.2 months in arms 1 and 2, respectively; P = 0.716).
TMZ vs RT	**HR** 1.15 (0.92 to 1.44)	1 study (373 particpants)	⊕⊕⊖⊖ **Low**[2,3]	No additional comments.
CRT vs RT	**HR** 0.50 (0.41 to 0.61)	1 study (562 participants)	⊕⊕⊕⊕ **High**	No additional comments.
BEV_CRT vs CRT	**HR** 0.78 (0.46 to 1.32)	1 study (73 participants)	⊕⊕⊖⊖ **Low**[1,2]	In this study (Avaglio 2014), BEV_CRT did not increase overall survival either relative to CRT alone for elderly patients.
BEV_RT vs RT	**HR** 0.46 (0.27 to 0.78)	1 study (75 participants)	⊕⊕⊕⊖ **Moderate**[1]	Despite delaying disease progression in this study (ARTE 2018), BEV_RT did not increase overall survival.
RIN_CRT vs CRT	Not reported separately for elderly subgroup.			
TTF_AC vs CRT	Not reported separately for elderly subgroup.			
IRI_BEV_RT vs CRT	Not reported separately for elderly subgroup.			

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]Sparse data from single studies [-1]
[2] Serious risk of bias from attrition [-1]
[3] Serious imprecision
Abbreviations: CI: Confidence interval; HR: Hazard Ratio; RT: radiotherapy; CRT: chemoradiotherapy; BEV_CRT: chemoradiotherapy plus bevacizumab; BEV_RT: radiotherapy plus bevacizumab; TMZ: temozolomide; TTF_AC: tumour treating fields with adjuvant chemotherapy (after concomitant CRT) (TTF_AC); RIN_CRT: rindopepimut after CRT; IRI: irinotecan

Summary of findings 6. Summary of findings on severe adverse events

The effect of different treatments for newly diagnosed glioblastoma on severe adverse events

Patient or population: elderly people with newly diagnosed glioblastoma

Settings: Any

Intervention: One treatment option

Comparison: An alternative treatment option

Comparison	Narrative summary of evidence	No of studies (elderly participants)	Quality of the evidence (GRADE)	Comments
RT vs supportive care only	Not reported.	NA	NA	
Hypofractionated RT vs standard RT (60Gy/30 fractions)	This outcome was only reported in one small study and there were no instances of grade 3 or higher treatment-related toxicity.	1 study (61)	Not graded	
TMZ vs RT	TMZ increases the risk of thrombo-embolic and haematological adverse events	1 study (373)	⊕⊕⊕⊖ **Moderate[1]**	
CRT vs RT	CRT increases the risk of haematological adverse events	1 study (562)	⊕⊕⊕⊖ **Moderate[1]**	
BEV_CRT vs CRT	BEV_CRT increases the risk of grade 3+ thrombo-embolic events.	1 study (73)	⊕⊕⊕⊖ **Moderate[1]**	Other adverse events data were not available for elderly subgroup specifically. For the larger study sample, Grade 3+ cerebral bleeding events (2.0% versus 0.9%) and wound healing events (3.3% vs 1.6%) were higher in the BEV plus CRT arm versus CRT alone. There were also higher rates of Grade 3+ thromboyctopenia (15% vs 9.8%) and infection rates (12.8% versus 7.8%) in the BEV)CRT arm.

BEV_RT vs RT	There was little or no difference in thrombo-embolic, haematological, and other severe adverse events reported	1 study (75)	⊕⊕⊖⊖ **Low**[1]	
RIN_CRT vs CRT	This was reported for overall trial but not for elderly subgroup specifically.	1 study (174 participants)	Not graded	The most common severe adverse events for the experimental (rindopepimut) versus control arm of the trial were: thrombocytopenia (9% vs 6%), fatigue (2% vs 5%), brain oedema (2% vs 3%), seizure (2% vs 2%) and headache (2% vs 3%). There was one death, secondary to pulmonary embolism, that was assessed as potentially related to the treatment in the experimental arm.
TTF_AC vs AC	This was reported for overall trial but not for elderly subgroup specifically.	1 study (134 participants)	Not graded	Overall, it was reported that there was no significant increase in rates of severe adverse events when TTF were added to adjuvant chemotherapy (48% vs 44%, p=0.58).
IRI_BEV_RT vs CRT	This was reported for overall trial but not for elderly subgroup specifically.	1 study (34 participants)	Not graded	Overall, rates of severe adverse events were 72% in the experimental arm and 84% in the CRT arm. In the experimental arm, severe vascular events were most common (11.8%) and two cerebral haemorrhages occurred (one fatal). For patients in the CRT arm, severe haematological toxicity was most common (18.2%).

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Downgraded -2 for sparse data from small single study and imprecision
Abbreviations: CI: Confidence interval; HR: Hazard Ratio; RT: radiotherapy; CRT: chemoradiotherapy; BEV_CRT: chemoradiotherapy plus bevacizumab; BEV_RT: radiotherapy plus bevacizumab; NA: not applicable; TMZ: temozolomide; TTF_AC: tumour treating fields with adjuvant chemotherapy (after concomitant CRT) (TTF_AC); RIN_CRT: rindopepimut after CRT; IRI: irinotecan

BACKGROUND

Description of the condition

Glioblastoma multiforme is a high grade, aggressive primary tumour of the central nervous system with a poor prognosis. The incidence of glioblastoma is increasing and this rise is most rapid in the elderly (Ferguson 2014). Use of the term 'the elderly' in relation to glioblastoma commonly refers to people 70 years and older (NCCN 2018). Age is an important consideration in the treatment of glioblastoma as it is a negative prognostic indicator (Lorimer 2017). A Surveillance Epidemiology and End Results (SEER) population analysis reported that for every year increase in patient age, there was a statistically significant decrease in survival (Thumma 2012). Median survival drops from about 12 to 18 months for younger people with glioblastoma, to three to six months for older age cohorts (Brodbelt 2015).

The molecular status of glioblastoma is also an important prognostic factor and several molecular subtypes of glioblastoma have been recognised (Lara-Velazquez 2017). One of the most important molecular signatures is O^6-methylguanine-DNA-methyltransferase (MGMT) promoter methylation, which has been shown to confer predictive and prognostic benefit (Malmstrom 2012; Yin 2014). Treatment for glioblastoma is not curative and the natural history of the disease is that patients will relapse after treatment and it will ultimately be a fatal condition (Louis 2016). Retrospective studies have shown that older people are less likely to get aggressive, multi-modality treatment (Iwamoto 2008; Lorimer 2017; Paszat 2001), but people with glioblastoma across all age groups who do get active treatment live longer (Brodbelt 2015). Direct healthcare costs for the management of malignant gliomas (malignant glioma encompasses anaplastic glioma, i.e. World Health Organization (WHO) grade 3 and 4) have been estimated at USD 32,764 per patient (2011 data; Raizer 2015).

Description of the intervention

The 'standard of care' of treatment for patients aged under 70 years of age with glioblastoma consists of surgery followed by radiotherapy (60 Gy in 30 fractions) with concomitant and adjuvant temozolomide (TMZ) chemotherapy (Stupp 2005; NCCN 2018). This management plan is less often used in the elderly for the following reasons:

- People over 70 years old were not included in the landmark trial (Stupp 2005), and a subsequent communication of the results of an exploratory subgroup analysis revealed that the survival benefit in this trial was not statistically significant for subgroup of people aged 66 to 70 years (Laperriere 2013).
- Shorter radiotherapy courses or chemotherapy alone can lead to better outcomes for the elderly than the standard course of radiotherapy. Patients rarely live long enough to develop late complications from radiation therapy, therefore larger fraction size may be justified to allow for a shortened course of treatment.
- Both chemotherapy and radiotherapy treatment toxicities are often greater in the elderly (Lawrence 2011; Sijben 2008).
- The shorter predicted survival time for older people with glioblastoma means that they might spend much of this time recovering from the six-week course of radiotherapy.

Small prospective (Vuorinen 2003), and retrospective studies (Chaichana 2011a; Chaichana 2011b), have shown that, for people aged 65 and over with glioblastoma, maximal debulking (resection) is associated with better survival and a trend to longer time remaining independent versus biopsy alone. Therefore maximal resection, if feasible, is the recommended primary approach to glioblastoma in the elderly (NCCN 2018). Depending on a person's performance status, radiotherapy or chemotherapy, or both, can then be added. As it remains unclear which treatment is best for glioblastoma in the elderly, participation in clinical trials is strongly encouraged (NCCN 2018). There is little evidence to guide treatment of recurrent glioblastoma in the elderly and approaches are based on retrospective studies (Socha 2016).

Treatment with either radiotherapy or chemotherapy

A randomised trial of radiotherapy (50 Gy delivered over a period of 5 to 6 weeks) versus best supportive care showed that radiotherapy conferred a 12-week survival benefit in older people with malignant glioma (Keime-Guibert 2007). Another randomised trial found that radiotherapy (60 Gy over a period of 6 to 7 weeks) was as effective as intensive ("dose-dense") adjuvant temozolomide chemotherapy alone (Wick 2012). There is increasing interest in using hypofractionated radiotherapy (radiotherapy delivered over shorter period of time, e.g. 34.0 Gy in 10 fractions over a period of two weeks) for older people with glioblastoma, as it has been found to have similar survival benefits compared to the standard regimen of 60 Gy in 30 fractions over a period of six weeks (Malmstrom 2012; Roa 2004).

Combination treatment

A randomised trial has shown that adding TMZ to hypofractionated radiotherapy for older people with glioblastoma confers a survival advantage compared to hypofractionated radiotherapy alone (Minniti 2012; Perry 2017), but not necessarily for those people with MGMT unmethylated tumours.

How the intervention might work

Surgery is an important step in the treatment of glioblastoma. Also, there is evidence that surgery improves one- and two-year survival rates compared to biopsy alone (Brown 2016). The extent of surgery can be divided into three main categories which have different definitions in the literature: 'maximal' debulking or gross total resection (GTR), subtotal resection (STR), and biopsy. The role of maximal debulking surgery is to minimise the tumour volume that remains to optimise the impact of subsequent treatment modalities, which are likely to be more effective against small volume tumours (Lara-Velazquez 2017).

Radiotherapy is delivered to the primary tumour or the surgical cavity with a margin to account for microscopic spread, patient movement, and set-up error (Niyazi 2016). One of the most important mechanisms of action of radiation therapy is the promotion of double strand breaks in DNA which, if left unrepaired, will result in cell death (Baskar 2014). DNA damage is more likely to occur in rapidly dividing cells, such as glioblastoma tumour cells, rather than normal brain which has a slower rate of cellular turn over. This provides the therapeutic index between the tumour and normal surrounding tissue.

Systemic chemotherapy can enhance the therapeutic effect of radiotherapy but is also an effective treatment on its own. The most widely used chemotherapy agent for newly diagnosed glioblas-

toma is TMZ, which acts as a DNA alkylating agent (Zhang 2012). Those tumours with MGMT-promoter methylation lack the MGMT enzyme which repairs the cytotoxic damage caused by TMZ, thereby making tumour cells more chemosensitive.

Why it is important to do this review

Previous research has demonstrated that increasing age has an important effect on overall survival and tolerability of treatment for patients with a diagnosis of GBM (Thumma 2012). Increasing age, regardless of performance status, has an important influence on treatment decisions made by clinicians (Palmer 2018), however there is still a lack of consensus on the optimal treatment options for the elderly subgroup of patients with GBM.

Is it recognised that treating older people with glioblastoma presents unique challenges and that the standard approach is not always appropriate. There have been several randomised trials in recent years that have tested therapeutic strategies specifically for older people with glioblastoma (e.g. Malmstrom 2012; Perry 2017; Roa 2004; Wick 2012). Other trials including younger people have also performed subgroup analysis to test if therapeutic benefit is maintained in older people. Due to the variation in age thresholds to define the 'elderly', performance status, treatment regimens, and molecular subtypes, it has been difficult to translate these individual studies into clinical practice. This is also because the focus of many intervention trials is on survival, which might not be the most important outcome to elderly people with glioblastoma; rather, the quality of the remainder of their life might be their most important consideration. As the median age of diagnosis is around 64 years of age (Ostrum 2015), a significant proportion of newly diagnosed patients fall into the 'elderly' category.

Selecting the appropriate management strategy for an elderly patient group is important from a quality of life perspective and also has significant resource implications (Raizer 2015). It has been estimated the average cost for a regimen of temozolomide to treat a person with newly diagnosed glioblastoma is USD 46,693 (USD in 2018 converted from NZD 2005) (Hamilton 2005). It is therefore important to understand the costs and benefits to avoid implementing costly and potentially toxic treatment for little clinical benefit.

Currently there is no clear consensus on how to apply the available evidence to guide treatment of the individual person seen in clinic. A systematic review and network meta-analysis of randomised trials would help to inform the best approach to the treatment of older individuals with newly diagnosed glioblastoma and help to identify research gaps.

OBJECTIVES

- To determine the most effective and best-tolerated approaches for the treatment of elderly people with newly diagnosed glioblastoma.
- To summarise current evidence for the incremental resource use, utilities, costs and cost-effectiveness associated with the different approaches.

METHODS

Criteria for considering studies for this review

Types of studies

- Randomised controlled trials (RCTs) for evidence on effectiveness and safety.
- Full economic evaluations (cost-effectiveness analyses, cost-utility analyses, and cost-benefit analyses) conducted alongside any study design and any model-based economic evaluations for economic evidence.

Types of participants

Elderly people undergoing treatment for histologically confirmed newly diagnosed glioblastoma. For the purpose of this Cochrane Review, we defined 'elderly' as 70 years and older; however, where investigators

defined the 'elderly' as over 65 years of age, we included these studies. We included studies of people of all ages that report subgroup findings for elderly people (over 65 or 70 years of age) provided the participants in the subgroup numbered more than 20. We also included the mixed data if it was clear that 80% or more of participants in the study were over the age of 65 years. Similarly, where the study population included both grade 3 or 4 gliomas (anaplastic astrocytomas or glioblastoma), we tried to obtain separate data for participants with glioblastoma; if this was not possible, we considered including the study if more than half the study population had glioblastoma.

Types of interventions

Interventions evaluated alone or in combination with each other versus any of the other interventions included the following.

- Radiotherapy (standard, hypofractionated, and other techniques).
- Chemotherapy (TMZ and other types).

We included all available regimens of radiotherapy and chemotherapy that have been evaluated in randomised trials. If we identified interventions in the included studies of which we were not aware, we considered including them after we assessed their comparability with those interventions named above. We excluded phase 1 and 2 studies of novel interventions that have been shown to be detrimental and have not been developed further.

It was not possible to create separate networks according to the type of surgical procedure (GTR, STR, and biopsy only). Within each networks we assumed that any participants within the network could be randomised to any of the interventions e.g. an elderly person with histologically confirmed glioblastoma could be equally likely to be randomised to standard radiotherapy, chemotherapy, any combination of these or supportive care.

Types of outcome measures

Primary outcomes

- Overall survival (time from randomisation to death from any cause).
- Quality of life (QoL), as measured using a standardised questionnaire, e.g. the European Organisation for Research and Treat-

ment of Cancer (EORTC) QLQ-C30 or QLQ-BN20 (specific for brain cancer), or the Functional Assessment of Cancer Therapy scale (FACT-G [general] or FACT-Br [specific for brain cancer]).

Secondary outcomes

- Progression-free survival (time from randomisation to disease progression or death from any cause).
- Severe adverse events, according to standardised scales, e.g. Common Terminology Criteria for Adverse Events (CTCAE).
- Cognitive impairment (objective or subjective), as measured by an overall cognitive function score, as a change-over-time score, or reported as individual cognitive function domains, e.g. verbal fluency, processing speed, memory, attention, and executive functioning, using a standardised measurement tool, e.g. Mini Mental State Exam (MMSE), EORTC, FACT.
- Functional impairment or disability, as measured by an overall ability score and/or as a change of ability over time score using a standardised measurement tool, e.g., Karnofsky Performance Status Scale, Neurological Functions Score, EORTC, FACT; or as a categorical outcome as defined by investigators.
- Fatigue, according to CTCAE, EORTC, or as defined by investigators.
- Economic outcomes:
  * Resource use for health care.
  * Health state utilities.
  * Costs of health care.
  * Incremental cost-effectiveness.

Search methods for identification of studies

Electronic searches

1. For studies on the effects of the interventions, we searched the following databases:

- The Cochrane Central Register of Controlled Trials (CENTRAL; latest issue), in the Cochrane Library.
- MEDLINE via Ovid (from 1946).
- Embase via Ovid (from 1980).

2. For economic evidence we searched the following databases:

- MEDLINE via Ovid (from 1946).
- Embase via Ovid (from 1980).
- NHS Economic Evaluation Database (EED).

The EED database was searched up to the end of December 2014 (when the last records were added to that database) and MEDLINE and Embase from 1 January 2015, as the NHS EED already included comprehensive searches of these databases prior to 2015. We also considered relevant grey literature (such as health technology assessments, reports, and working papers) for inclusion.

Please refer to Appendix 1 for the MEDLINE search strategy.

We did not apply language restrictions to any literature searches.

Searching other resources

We searched the following for ongoing trials:

- ClinicalTrials.gov (clinicaltrials.gov/).
- WHO International Clinical Trials Registry Platform (ICTRP) (apps.who.int/trialsearch/).

If ongoing trials that have not been published were identified through these searches, we approached the principal investigators to ask for an update on the trial status and any relevant unpublished data, if available.

We used the related articles feature of PubMed and handsearched the reference lists of included studies to identify newly published articles and additional studies of relevance. We also handsearched conference proceedings from 2014 to 2018 (5 years) of the British Neuro-Oncology Society, the Society of Neuro-Oncology, the European Association of Neuro-Oncology and the World Federation of Neuro-Oncology Societies conferences for relevant ongoing or unpublished studies.

Data collection and analysis

Selection of studies

For the results of search 1 (trials of effects of interventions), the Information Specialist at the Cochrane Gynaecological, Neuro-oncology and Orphan Cancer Group (CGNOC) downloaded all titles and abstracts retrieved by electronic searching to EndNote X8 and removed duplicates. Two review authors (TAL, CRH, or ER) independently screen the remaining records and excluded studies that clearly did not meet the eligibility criteria. For potentially eligible records, copies of the full texts were obtained and two review authors (TAL, CRH and ER) independently assessed them for eligibility. The respective review authors resolved any disagreements through discussion and, if necessary, consulted at least one other review author. We used Covidence to facilitate this study selection process and documented the reasons for exclusion of studies accordingly.

To inform the economic outcomes, full economic evaluations (cost-effectiveness analyses, cost-utility analyses, and cost-benefit analyses), we considered cost analyses and comparative resource-utilisation studies. Studies carried out alongside relevant RCTs and model-based studies were considered for inclusion. Two review authors (LV and AK) independently screened for eligible studies.

Data extraction and management

Two review authors (TAL, CRH, or ER) independently extracted data from included studies using a pre-designed data extraction form (Higgins 2011). We extracted the following data:

- Author contact details.
- Country.
- Setting.
- Dates of participant accrual.
- Funding source.
- Inclusion and exclusion criteria.
- Study design.
- Study population and baseline characteristics:
  * Number of participants enrolled.
  * Number of participants analysed.
  * Age.
  * Gender.

- Potential effect modifiers:
  - Molecular type of glioblastoma.
  - Performance status.
- Intervention details:
  - Type of intervention, dose, timing, and other regimen details.
  - Type of comparator.
- Risk of bias assessment (see below).
- Duration of follow-up.
- Primary outcome(s) of the study.
- Review outcomes:
  - For time-to-event outcomes (overall and progression-free survival) we extracted the hazard ratio (HR) with its 95% confidence interval for time points as reported by the study authors. We noted the definition of and procedure used to identify progression [check this]. Where reported, we also extracted dichotomous data for these outcomes at author specified time-points.
  - For dichotomous outcomes (e.g. serious adverse events), we extracted the number of participants in each treatment arm that experienced the outcome of interest and the number of participants assessed.
  - For continuous outcomes (e.g. QoL scores), we extracted the value and standard deviation of the outcome of interest and the number of participants assessed at the relevant time-point in each group. We also extracted change-from-baseline score data where reported and noted the type of scale used.
  - We extracted adjusted statistics where reported.
  - Where possible, all data extracted were those relevant to an intention-to-treat analysis, in which participants were analysed in the groups to which they were assigned.
  - We resolved differences between review authors by discussion or by appeal to a third review author when necessary.

Assessment of risk of bias in included studies

We assessed the risk of bias using Cochrane's 'Risk of bias' tool and the criteria specified in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). This included assessment of:

- Random sequence generation.
- Allocation concealment.
- Blinding of participants and healthcare providers.
- Blinding of outcome assessors.
- Incomplete outcome data (more than 20% missing data considered high risk).
- Selective reporting of outcomes.
- Other possible sources of bias, e.g. lack of a power calculation, baseline differences in group characteristics.

Two review authors (ER and CRH) independently assessed risk of bias and resolved any differences in opinion by discussion or by consulting a third review author (TAL). We summarised judgements in 'Risk of bias' tables along with the characteristics of the included studies and interpreted the results of meta-analyses in light of the overall 'Risk of bias' assessment. For more details about the 'Risk of bias' assessment see Appendix 2.

We assessed economic evaluation studies for bias in two stages. The first stage involved assessing risk of bias from the sources of the effectiveness data. In economic evaluations carried out alongside clinical trials we assessed these using the Cochrane 'Risk of bias' tool, as described above. If the economic evaluation was model-based, we used the ROBIS tool to assess bias in the effectiveness studies (Whiting 2016). The second stage involved assessing the risk of bias of the economic evidence (i.e. assessing the overall methodological quality). This was done using the CHEERS checklist (Husereau 2013).

Measures of treatment effect

Effectiveness data

- For time-to-event outcomes (e.g. overall survival), we extracted the hazard ratio (HR) with its 95% confidence interval (CrI).
- For continuous outcomes (e.g. QoL scores) we assumed that study authors would use different measurement scales, therefore, we planned to estimate the standardised mean difference (SMD) and its 95% CI using the pooled data. However, if the same measurement scale was used, we estimated the mean difference (MD) and its 95% CI. If studies did not report total values but, instead, reported change-from-baseline outcomes, we combined these change values with total measurement outcomes by using the (unstandardised) mean difference method in Review Manager 5 (RevMan 5) (RevMan 2014). We used subgroups to distinguish between MDs of change scores and MDs of final values, and pooled the subgroups in an overall analysis (Higgins 2011).
- For dichotomous outcomes, we calculated the effect size as a risk ratio (RR) with its 95% CI.

Economic data

Two review authors (AK and LV) independently extracted data from relevant economic studies and summarised this information in tables. We extracted data on the following:

- Type of evaluations.
- Sources of effectiveness data.
- Cost data.
- Sources of cost data.
- Sources of outcome valuations.
- Analytical approach.

Unit of analysis issues

Two review authors (TAL and ER) assessed unit of analysis issues according to Higgins 2011, and resolved any differences in opinion by discussion. These included reports where there are multiple observations for the same outcome (e.g. repeated measurements with different scales or at different time-points, recurring events). If meta-analysis was not feasible or meaningful, we extracted data from all scales or time-points and attempted to describe them narratively.

Multi-arm trials

We included multi-arm trials in this review. We treated multi-arm studies as multiple independent comparisons in pairwise meta-analyses and did not combine data from different arms. In the network meta-analysis we accounted for the correlation between the effect sizes derived from the same study (White 2015).

Dealing with missing data

We did not impute missing data. In the event of missing data, we wrote to study authors to request the data on primary outcomes and describe in the 'Characteristics of included studies' tables how any missing data were obtained.

Assessment of heterogeneity

Assessment of clinical and methodological heterogeneity

We assessed clinical heterogeneity between studies by comparing characteristics of included participants, and interventions in each meta-analysis of each comparison, by visual inspection of forest plots, by estimation of the percentage heterogeneity between trials which cannot be ascribed to sampling variation (Higgins 2003), by a formal statistical test of the significance of the heterogeneity (Deeks 2001), and, where possible, by subgroup analyses. If there was evidence of substantial heterogeneity, we investigated and reported the possible reasons for this.

Assessment of consistency across treatment comparisons

We examined the assumption of consistency by assessing the distribution of potential effect modifiers across the pair-wise comparisons (Cipriani 2013; Jansen 2013; Salanti 2012). The assumption would hold if the following were true:

- The common treatment used to compare different interventions indirectly was similar when it appeared in different trials.
- All pairwise comparisons did not differ with respect to the distribution of effect modifiers.

Assessment of statistical heterogeneity and inconsistency

Assumptions when estimating the heterogeneity

In standard pairwise meta-analyses, we estimated different heterogeneity variances for each pairwise comparison. In network meta-analysis, we assumed a common estimate for the heterogeneity variance across the different comparisons (White 2015).

Measures and tests for heterogeneity

We assessed the presence of statistical heterogeneity within the pairwise comparisons using the I2 statistic, which is the percentage of variability that cannot be attributed to random error (Higgins 2003).

Assessment of statistical inconsistency

We were not able to assess statistically the global agreement between the various sources of evidence in a network of interventions (consistency). However, we were able to apply a local approach using a node-splitting method (Dias 2010).

Assessment of reporting biases

In pairwise comparisons, if there were 10 or more studies included in meta-analyses, we had planned to investigate reporting biases (such as publication bias) using funnel plots. However, in none of the analyses were 10 or more studies included.

Data synthesis

Methods for direct treatment comparisons

Initially we performed standard pair-wise meta-analyses for each comparison using the random-effects model in Stata statistical software version 15.1 (STATA) and Review Manager software (RevMan 2014).

Methods for indirect and mixed comparisons

We conducted network meta-analyses within a frequentist framework using multivariate meta-analysis (White 2015) if we considered participants, comparisons, and outcomes to be sufficiently similar to ensure an answer that was clinically meaningful. We also used STATA commands for visualising and reporting network meta-analysis results (Chaimani 2015). If meta-analysis was not possible but limited data were available, we attempted to synthesize narrative summaries according to guidance in the Cochrane Handbook.

We summarized characteristics and results of included economic evaluations using additional tables, supplemented by a narrative summary that compared and evaluated methods used and principal results between studies. Unit cost data was also tabulated, when available. We reported the currency and price year applicable to measures of costs in each original study alongside measures of costs, incremental costs, and incremental cost-effectiveness by study. Where details of currency and price year were available in original studies, we converted measures of costs, incremental costs, and cost-effectiveness to (latest year) international dollars value using implicit price deflators for gross domestic product (GDP) and GDP Purchasing Power Parities (EPPI Centre Cost Converter 2016). Details of the methodological characteristics of individual included health economics studies was summarised in 'Characteristics of included studies' tables. All elements of the economics component of this review were conducted according to current guidance on the use of economics methods in the preparation and maintenance of Cochrane reviews (Higgins 2011; Shemilt 2018; Wijnen 2016).

'Summary of findings' tables and results reporting

Effectiveness summary of findings

We presented the primary outcomes in the summary of findings tables. Evidence for pairwise comparisons was assessed based on GRADEpro Guideline Development Tool (GDT) methods (GRADEpro 2015) (i.e. we assessed risk of bias, inconsistency, imprecision, indirectness and publication bias), whereas network evidence was assessed using the approach suggested by Puhan 2014 and advanced by Brignardello-Petersen 2018. Narrative evidence summaries were prepared if data could not be synthesised and assessed according to the GRADE approach suggested by Murad 2017. The certainty of pairwise and network evidence for each outcome was rated as 'high', 'moderate', 'low' or 'very low' as defined according to the GRADE approach:

- **High certainty**: We are very confident that the true effect lies close to that of the estimate of the effect;
- **Moderate certainty**: We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different;
- **Low certainty**: Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect; and
- **Very low certainty**: We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.

To assess the network evidence, we assessed the certainty of the direct evidence (if any), the indirect evidence (if estimable) and the network evidence in this order. Direct evidence was assessed using the standard (pair-wise) GRADE approach, but without assessing imprecision (i.e. we assessed risk of bias, inconsistency, indirectness and publication bias). Indirect evidence ratings, based on the certainty rating of the lower of the two arms forming the loop in the network diagram, were assessed when they contributed more than the direct evidence to the network estimates. The final step was to assess the certainty of the network effect estimate based on whether intransitivity was present (i.e. whether there were differences in study characteristics that may modify the effect in the direct comparisons that form the basis for the indirect estimate; Puhan 2014). The network estimate was assessed in the first instance as being equivalent to the higher of the direct and indirect estimates, and incoherence and imprecision were then considered, with downgrading by one level accordingly if serious. Where no direct evidence was available and when the treatments did not have a common comparator, we presented the network estimate but did not rate the certainty of the evidence. Where possible, we estimated the absolute effects of treatments relative to the effect of a given reference comparator based on an assumed risk, the source of which was stated. For median survival times, we based illustrative absolute effects on hazard ratios.

Summary of findings tables were designed following the approach suggested by Schunemann 2009 and by Yepes-Nuñez 2019. In Summary of Findings tables we provided justification for each assessment about the confidence in the estimates of effect (e.g. reasons for downgrading the certainty of the evidence), with confidence assessed as 95% credible intervals (CrI). Two review authors (TL and ER) independently assessed the certainty of the evidence. We resolved any differences of opinion by discussion. We interpreted the graded evidence based on the Cochrane Effective Practice and Organisation of Care (EPOC) Group's guidance (Cochrane EPOC 2015) and, for time-to-event evidence, on suggestions in Barraclough 2011.

Relative treatment ranking

We computed ranking of probabilities for all included treatments and obtained a treatment hierarchy using the surface under the cumulative ranking curve (SUCRA). For primary outcomes, we assessed the robustness of these findings in sensitivity analysis.

Economic evaluation summary of findings

For the economic evaluation studies, we presented the following findings in a table:

- Method of economic evaluation.
- Costs.
- Outcomes.
- Incremental cost effectiveness ratio.

Subgroup analysis and investigation of heterogeneity

For pairwise comparisons we assessed heterogeneity using the I^2 statistic that measures the percentage of variability that cannot be attributed to random error (Higgins 2003). We considered clinical heterogeneity and risk of bias in the interpretation of any heterogeneity. The certainty of the evidence was downgraded for heterogeneity where $I^2 \geq 60\%$.

Due to sparse structure of the network we assumed no substantial statistical heterogeneity and fitted a fixed effect model. However, we performed sensitivity analyses to examine the impact of our original assumptions by applying an alternative classification of radiotherapy with 50 Gy in one study (Keime-Guibert 2007); removing one of the arms from three-arm trial (RT40, Malmstrom 2012), and splitting the chemoradiotherapy node according to the radiation dose (40 Gy and 60 Gy).

For primary outcomes, we had planned to assess findings by the different age thresholds used by investigators to define the elderly and by MGMT methylation status; however, data were insufficient for these subgroup analyses.

Sensitivity analysis

We performed sensitivity analyses to investigate assumptions that we made to facilitate a connected network, including:

- pooling data from a study utilising a radiotherapy dose of 50Gy with studies utilising 60Gy or 40Gy dose schedules.
- pooling data from study arms utilising combined chemoradiation, where studies utilised 60Gy or 40Gy radiotherapy dose schedules.

We based these assumptions on calculations of the equivalent doses (EQD2) and biologically effective doses (BED) of the different radiotherapy schedules utilised in included studies (Table 1).

We also conducted sensitivity analysis to investigate the impact of a single three-arm study forming the only loop in the network and to justify the lack of assessment of inconsistency (see above).

RESULTS

Description of studies

Results of the search

Intervention studies

Searches conducted on the 13th June 2018 and the 3rd April 2019 led to the identification of 12 included studies (with 31 associated records) and two potentially eligible ongoing studies (with three associated records). We identified the following numbers of records through the first electronic database search:

- **Medline**: 1946 to May week 5 2018 – 930 records
- **Embase**: 1980 to 2018 week 24 – 848 records
- **Central**: Issue 5 2018 – 1571 records

The results of this initial search are summarised in Figure 1. Following de-duplication across the databases, the combined total yield was 2493 records. The Information Specialist at the Cochrane Gynaecological, Neuro-oncology and Orphan Cancer (CGNOC) Group ran these records through the Cochrane RCT Classifier', which uses machine learning to identify records that are likely to be RCTs. Following classification, 1462 records were identified as having more than a 10% likelihood of being an RCT, whilst 1031 references had less than a 10% likelihood of being an RCT. The Information Specialist then deduplicated the remaining 1462 records and sifted out the clearly irrelevant records (e.g. those that related to other types of cancers). Two study authors (CH, TL) independently screened the remaining yield of 990 records. Out of these, 12 studies (ARTE 2018; Avaglio 2014; GLARIUS 2016; Green 1983; Keime-Guibert 2007;

Malmstrom 2012; Perry 2017; Roa 2004; Roa 2015; Stupp 2017a; Weller 2017; Wick 2012) with 31 associated records were finally included (Figure 1). Additionally, one ongoing study was identified (NCT01602588).

Figure 1. Study flow diagram (search date 13 June 2018)

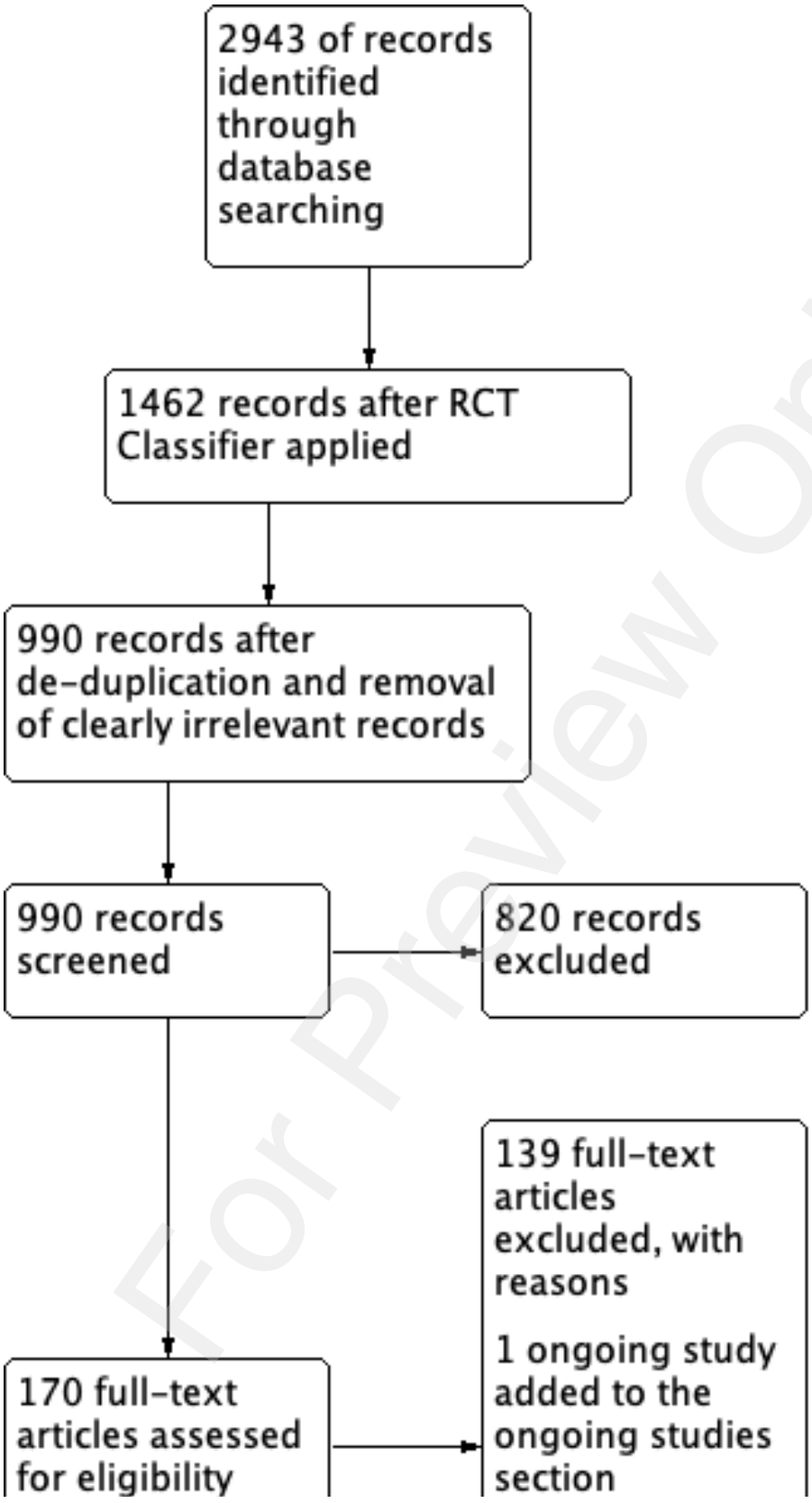
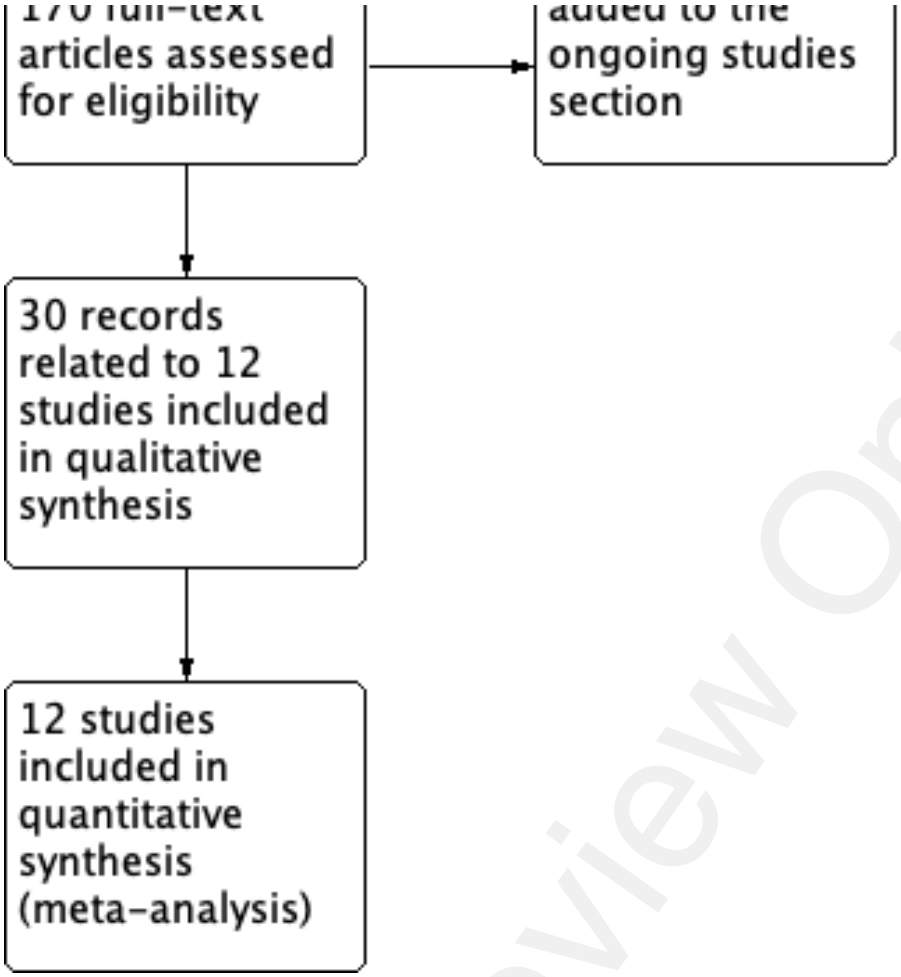


Figure 1. (Continued)



The top up search on 3rd April 2019 yielded 125 additional records to be screened on title and abstract. After deduplication and screening on title and abstract, six full text papers were retrieved. Three of these papers were additional publications related to two already included studies (Avaglio 2014; GLARIUS 2016), the other three were excluded with reasons. Additionally, searches of clinical trial registries and of relevant society conference proceedings from 2014 to 2018 identified one ongoing trial (NUTMEG 2018) and four potentially eligible records, respectively. The ongoing trial was added to the Ongoing studies section, including one conference abstract (NUTMEG 2018). The other three conference abstracts were classified as excluded studies. The results of the top-up search are summarised in Figure 2.

Figure 2. Study flow diagram (search date 3 April 2019).

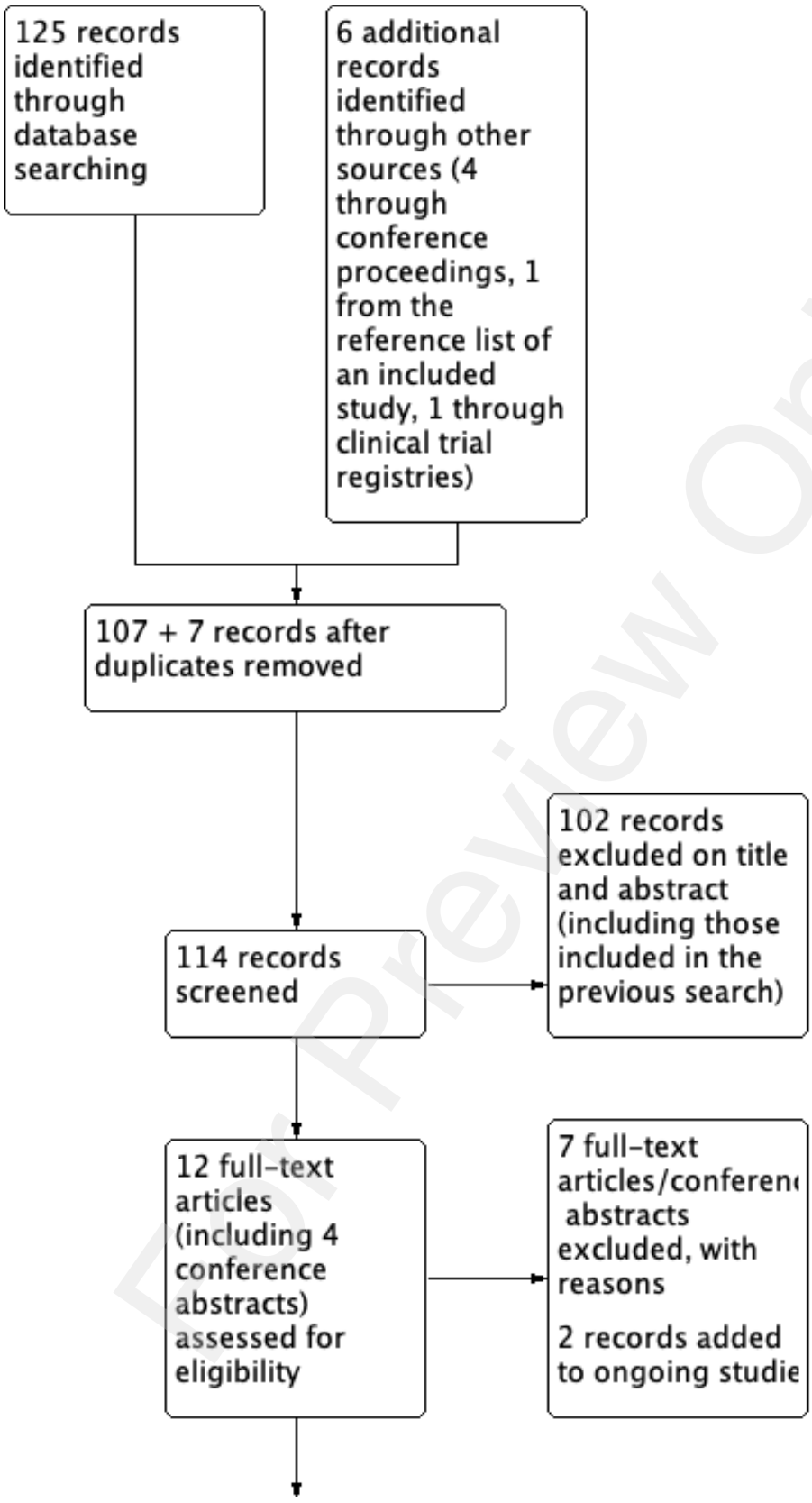
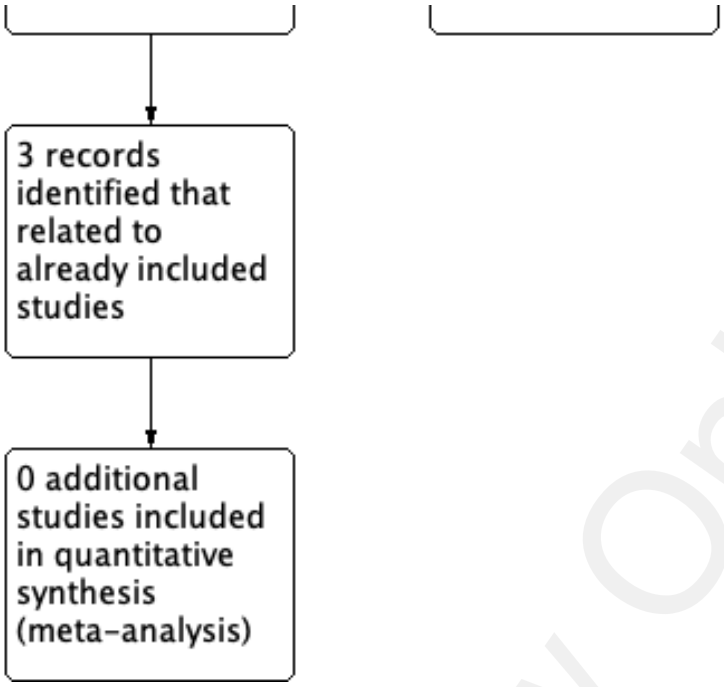


Figure 2. (Continued)



Economic studies

For economic studies, we identified the following numbers of records through electronic database searches conducted on the 13th June 2018:

- **Medline**: 1946 to May week 5 2018 – 113 records
- **Embase**: 1980 to 2018 week 24 – 151 records

Following deduplication across these databases, the total yield to be sifted was 101 records. The top up search conducted on the 3rd April 2019 yielded an additional 22 records. Five titles and abstracts were identified for full text screening (Ghosh 2018, Jiang 2017; Moroney 2017; Roussakou 2017; Waschke 2018), one of which (Ghosh 2018) was included.

Included studies

We included 12 RCTs, six were conducted exclusively among elderly people (either defined as 65 years or older or 70 years or older) with newly diagnosed glioblastoma (ARTE 2018; Keime-Guibert 2007; Perry 2017; Roa 2004; Roa 2015; Wick 2012). The other six RCTs included patients from a broader age range and reported some data separately for their elderly subgroup (Avaglio 2014; GLARIUS 2016; Green 1983; Malmstrom 2012; Stupp 2017a; Weller 2017), which we extracted for this review.

Numbers recruited and analysed:

Altogether, approximately 1818 elderly participants involved in the included studies contributed data to the review. In seven studies, the elderly participants analysed numbered less than 100. In five studies (Green 1983; Malmstrom 2012; Perry 2017; Stupp 2017a; Wick 2012), the number analysed was more than 100, equaling to 107, 123, 562, 134, and 373 participants , respectively.

Location of studies:

Six studies were conducted in the following individual countries: Canada (Roa 2004), France (Keime-Guibert 2007), Germany (Wick 2012; GLARIUS 2016), United States (Green 1983); Switzerland (ARTE 2018); the rest were multicountry studies (Avaglio 2014; Malmstrom 2012; Perry 2017;Roa 2015; Stupp 2017a; Weller 2017).

Dates of recruitment:

Accrual occurred before 1980 in one study (Green 1983) and between 1996 and 2001 in another (Roa 2004). In all other studies, accrual occurred from 2000 onwards.

Funding:

Seven studies were funded by pharmaceutical companies (ARTE 2018: Roche Pharmaceuticals; Avaglio 2014: Hoffmann-La Roche; GLARIUS 2016: Roche Pharmaceuticals; Malmstrom 2012: Merck; Perry 2017: Schering-Plough/Merck; Weller 2017: Celldex Therapeutics; Wick 2012: Merck, Sharp & Dohme; two of these (Malmstrom 2012; Perry 2017) also received grants from national cancer research funds. One study (Stupp 2017a) received funding from a medical device company, Novocure Ltd). The rest were funded by research grants from national cancer research funds or charities.

Characteristics of study participants

Age:

Eight studies defined older patients using an age threshold of 65 years, two studies (Avaglio 2014; Keime-Guibert 2007) used an age threshold of 70 years, and two studies recruited participants from 60 years of age (Malmstrom 2012; Roa 2004). One of the latter studies defined an older subgroup using a threshold of 70 (Malmstrom 2012), whereas the other did not define an older subgroup and presented all data together (Roa 2004). As the mean age of participants in the latter study was about 72 years with a standard deviation of about 5 years, the majority of participants in this study would have been over 65 years of age, but the exact proportion of the sample that this represents was unclear (see Risk of bias in included studies).

Gender:

Most studies had participant gender ratios of about 3 to 2 in favour of male participants; however, in two studies, the proportion of men and women was roughly equal (Roa 2015; Wick 2012).

Performance status:

Most studies required that participants have a certain performance status prior to enrolment and did not recruit participants that were not self-caring. Thus, participants of six studies specified Karnofsky performance scores (KPS) of 60 or more (ARTE 2018; Wick 2012), or 70 or more (GLARIUS 2016; Green 1983; Keime-Guibert 2007; Stupp 2017a), two studies specified an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2 (Perry 2017; Weller 2017), and two specified a World Health Organization (WHO) performance status of 0 to 2 (Avaglio 2014; Malmstrom 2012). Two studies, however, recruited participants with poorer peprformance status (minimum KPS of 50) (Roa 2004; Roa 2015), patients with a KPS of 50 require considerable assistance and frequent medical care (Table 2).

MGMT-methylation status:

Eight studies reported MGMT-methylation status of their participants: ARTE 2018; Avaglio 2014; GLARIUS 2016; Malmstrom 2012; Perry 2017; Stupp 2017a; Weller 2017; and Wick 2012. In the overall samples, the MGMT-methlyated status was represented by at least 21% of participants with these test results in ARTE 2018, 26% in Avaglio 2014; 47% in Malmstrom 2012, 46.6% in Perry 2017; 37% in Stupp 2017a, 34% in Weller 2017 and 20% in Wick 2012. In GLARIUS 2016, all participants had MGMT-unmethylated glioblastomas. For two studies in which the elderly were a subgroup (Malmstrom 2012; Weller 2017), MGMT-methylation status was reported for the broader sample and might not necessarily have reflected the MGMT-methylation status of the elderly subgroup relevant to this review.

Interventions and comparisons

Most studies (10) randomised participants to two treatment arms but one trial (Malmstrom 2012) had three treatment arms and one had four treatment arms (Green 1983). The majority of treatments offered to patients were either radiotherapy alone, systemic anti-cancer treatment (SACT) alone, or a combination of both. One trial (Keime-Guibert 2007) had a standard management arm of supportive care, and one RCT used a medical device, known as tumour treating fields (TTF), in combination with radiotherapy and temozolomide (Stupp 2017a) in its experimental arm. All studies randomised participants after diagnosis and before radiotherapy and/

or chemotherapy with the exception of Stupp 2017a and Weller 2017 which both randomised participants after chemoradiotherapy and before commencement on adjuvant TMZ.

In the trials that included elderly patients only (ARTE 2018; Keime-Guibert 2007; Perry 2017; Roa 2004; Roa 2015; Wick 2012), the reference treatment arms were radiotherapy alone (60Gy in 30 fractions [Roa 2004; Wick 2012] or 40Gy in 15 fractions [ARTE 2018; Perry 2017; Roa 2015]), or supportive care (Keime-Guibert 2007). The experimental arms in these trials were hypofractionated radiotherapy treatment alone (40Gy in 15 fractions [Roa 2004] or 25Gy in 5 fractions [Roa 2015]), radiotherapy (40Gy in 15 fractions) combined with a systematic anti-cancer treatment (TMZ [Perry 2017] or bevacizumab [ARTE 2018]), radiotherapy (50Gy in 28 fractions) with supportive care (Keime-Guibert 2007), or TMZ alone (Wick 2012).

In the six trials (Avaglio 2014; GLARIUS 2016; Green 1983; Malmstrom 2012; Stupp 2017a; Weller 2017) that included patients of all ages, with the elderly as a subgroup, the radiotherapy fractionation in the reference treatment was exclusively 60Gy in 30 fractions. In the reference arms of the trials, this was used alone (Malmstrom 2012), in combination with concomitant and adjuvant TMZ +/- placebo (Avaglio 2014; GLARIUS 2016; Stupp 2017a; Weller 2017), or in combination with intravenous carmustine (BCNU) (Green 1983). The experimental arms in these trials were mostly 60Gy of RT in 30 fractions in combination with additional or alternative SACTs (Avaglio 2014; GLARIUS 2016; Green 1983; Weller 2017). Malmstrom 2012 was the only trial that included an experimental treatment arm with TMZ alone and hypofractionated RT alone (34Gy in 6 fractions over two weeks). Stupp 2017a was the only trial to include a medical device (Tumour Treating Fields (TTF)) and they used this device in their experimental arm in combination with adjuvant TMZ following chemoradiotherapy (60Gy of radiotherapy plus TMZ).

Radiotherapy Fractionation and Delivery

All of the included RCTs, except one (Green 1983) used megavoltage (MV) photon radiotherapy to the tumour or tumour bed with a 2-3 cm margin. Green 1983 used whole brain radiotherapy (WBRT), which is likely a reflection of the more limited technological capabilities to deliver conformal radiotherapy in the 1970s when this trial was open to recruitment. A comparison of the BED and E2D2 of radiotherapy fractionation schedules used across all trials is outlined in Table 1.

Systemic anti-cancer treatment

TMZ was the most frequently used SACT. When combined with 60 Gy in 30 fractions, it was used as per the "Stupp" regimen (Stupp 2005). This comprises 75mg/m2 of TMZ given concomitantly with six weeks of radiotherapy, followed by adjuvant treatment delivered over five days each month at a dose of 150-200mg/m2. In the original Stupp regimen (Stupp 2005), adjuvant treatment was continued for a total of six cycles. Avaglio 2014; GLARIUS 2016; Stupp 2017a all followed this regimen. Weller 2017 specified that adjuvant TMZ could be continued for 6-12 cycles or longer and Perry 2017 specified that up to 12 adjuvant cycle of TMZ could be delivered. When TMZ was used alone (Wick 2012, Malmstrom 2012), this was given orally using a week-on/week-off schedule of 100mg/m2/day for up to six months of treatment (Wick 2012) or 200mg/m2 on days 1 to 5 of every 28 days for up to six cycles (Malmstrom 2012).

Bevacizumab was used in the experimental arm of three trials (ARTE 2018, Avaglio 2014, GLARIUS 2016) and was delivered intravenously at a dose of 10mg/kg every two weeks in all of these trials. Irinotecan was used in combination with bevacizumab and radiotherapy in the GLARIUS trial and delivered intravenously at a dose of 125mg/m2 every two weeks.

Green 1983 combined WBRT with intravenous BCNU (80mg/m2/day on three successive days every eight weeks) in their reference arm. The first experimental arm of this trial, BCNU was replaced by high dose oral methylprednisolone (400mg/m2/day in three divided doses for seven days) in four weekly cycles and their second experimental arm combined BCNU and high dose methylprednisolone. The last experimental arm in the trial by Green 1983, combined WBRT with procarbazine which was given orally at a total dose of 150mg/m2/day in three or four divided doses for 28 consecutive days every eight weeks.

Finally, Weller 2017 used rindopepimut (500ug) admixed with 150ug granulocyte-macrophage colony-stimulating factor (GM-CSF) given via monthly intradermal injection in their experimental arm and 100ug keyhole limpet haemocyanin in their control arm, both in combination with standard oral TMZ (150-200mg/m2 for 5 of 28 days) for 6-12 months or longer. In this trial, all patients had completed standard chemoradiation with 60Gy of radiotherapy and concomitant TMZ prior to commencing treatment in either the experimental or control treatment arm.

Other treatments

Carmustine wafers

Although not randomised between arms, Stupp 2017a was the only trial that specified that treatment with implanted carmustine wafers was permitted for patients on either arm of their trial. The proportion of patients receiving carmustine wafers in each arm was not reported.

Medical devices

Stupp 2017a was the only trial to use a medical device. Tumour treating fields (TTF) comprise an external medical device that is worn by the patient. It consists of four tranducer arrays which are connected to a portable device. These arrays are applied to the patients' shaved scalp via nine electrodes and emit low-intensity, intermediate frequency (200kHz) alternating electric fields to the brain. The patient carries the device in a backpack and is encouraged to wear the device for at least 18 hours per day. Determining the layouts of the transducer is performed using a TTF mapping software system. Patients and their families are trained on how to use the device and how to trouble shoot problems with the device by nursing staff and a device technician. The patients must replace the transducer arrays twice weekly and the treatment is delivered on an outpatient basis. Participants in the Stupp 2017a trial were randomised after the completion of chemoradiation and, therefore, the TTF treatment was given in the adjuvant setting only in combination with TMZ, and not given concomitantly with radiotherapy. TTF treatment was to be initiated at least 4 weeks but not more than 7 weeks from the last day of radiotherapy.

Supportive care

Keime-Guibert 2007 was the only trial to include supportive care as a management option. This was used alone in the reference arm and in combination with radiotherapy (50Gy in 28 fractions) in the experimental arm. Supportive care was defined as any mixture of treatment with corticosteroids and anti-epileptics, as well as physi-

cal and psychological support and management by a palliative care team. There was no information on the timing of when referral to the palliative care team was made.

Outcomes and follow-up

Table 3 outlines both the primary and secondary outcomes from each of the included trials that were of interest for the purposes of this review, along with the evaluation tools used to assess each outcome. All of the included trials, except Green 1983, reported overall survival outcomes using time-to-event analysis and provided median overall survival for either all participants (Malmstrom 2012, ARTE 2018 , Perry 2017, Roa 2004, Wick 2012, Keime-Guibert 2007), or for a subgroup of patients if the trial was not restricted to recruiting elderly patients (Roa 2015, Avaglio 2014, GLARIUS 2016, Stupp 2017a, Weller 2017). Although reporting median survival, several trials did not provide a hazard ratio to show the difference between survival for elderly patients in different treatment arms (Roa 2015, GLARIUS 2016, ARTE 2018). Median survival data, where reported, are tabulated in Table 4.

The proportion of patients alive at six months (Roa 2004, Wick 2012), 12 months (Perry 2017, Malmstrom 2012, ARTE 2018, Wick 2012), 18 months (Perry 2017) and 24 months (Perry 2017) was also used to report survival outcomes. Stupp 2017a and Green 1983 reported the proportion of patients who had died by the end of the study period.

The second main outcome of interest was health-related quality of life (HRQoL). The most common tools used to collect HRQoL data were patient-completed questionnaires, specifically the European Organisation for the Research and Treatment of Cancer (EORTC) QLQ-C30 and QLQ-BN20 questionnaires. The results of HRQoL outcomes for elderly patients using these questionnaires were reported for five trials (Perry 2017, Malmstrom 2012, ARTE 2018, Wick 2012, Keime-Guibert 2007). Roa 2004 was the only trial to use the Functional Assessment of Cancer Therapy-Brain (FACT-Br) questionnaire but the results of using this tool were not reported due to a low completion rate. Several of the studies that included both younger and elderly patients did record HRQoL, but did not report results of these assessments for elderly subgroups separately (Avaglio 2014, GLARIUS 2016, Green 1983, Stupp 2017a, Weller 2017).

Follow up times were varied and were often not documented in the trial publications. For those trials that did specify their follow up time, Avaglio 2014 had follow up for at least 17 months (with the end of study at 64 months after opening) and Stupp 2017a specified a median follow up of 40 months (interquartile range, 34-66 months) with a minimum follow up of 24 months. Only two patients in the over-65 age group were alive at 60 months of follow up. Wick 2012 had a minimum follow up of 12 months (median 25.2 months (range 20.0 to not reached)). Roa 2015 specified that all patients were followed up until death.

Excluded studies

In selecting studies for evaluation of treatment effectiveness, excluded studies numbered 145 records. Studies were excluded mainly for the following reasons:

Ineligible study design, e.g. non-randomised trial; editorial: Bent 2009; Blumenthal 2018; Boisen 2018; Boxerman 2013; Catterall 1980; Chamberlain 2005; Chong 2018; Cohen 2005; Corn 1994; Das 2017; Dherijha 2018; Espana 1978; Halperin 1993; Jeremic 1999; Koc 2008; Lamers 2008; Lorimer 2016; McCarthy 2017; Napolitano 1999; Pinzi 2017; Reyes-Botero 2018; Soffietti 2017; Solth 2018; Stupp 2002; Vellayappan 2017 (25 studies)

Ineligible study population, e.g. not elderly participants; not newly diagnosed glioblastoma: Ali 2018; Armstrong 2013; Athanassiou 2005; Balana 2016; Bampoe 2000; Batchelor 2013; Beije 2015; Bhandari 2013; Bhandari 2017; Bleehen 1981; Bleehen 1991; Blumenthal 2015; Bogdahn 2011; Boiardi 1992; Bower 1997; Brandes 2016; Brisman 1976; Brown 2016; Buckner 2001; Buckner 2006; Carpentier 2017; Castro 1997; Chang 1983; Chauffer 2014; Cianfriglia 1980; Clarke 2009; Combs 2008; Curran 1992; Deutsch 1989; Dinapoli 1993; Du 2018; Duncan 1986; Elinzano 2018; Eljamel 2008; Elliott 1997; Eyre 1983; Farkkila 1994; Field 2015; Field 2017; Fischer 1985; Fulton 1984; Gaber 2013; Gilbert 2013; Glinski 1993; Grossman 2003; Halperin 1996; Harada 1996; Hatlevoll 1985; Henriksson 2006; Hiesiger 1995; Hildebrand 1994; Hitchon 1999; Hofland 2014; Imbesi 2006; Iwadate 1993; Karacetin 2011; Kim 2011; Knerich 1990; Kocher 2008; Kochii 2000; Kong 2017; Lanzetta 2003; Lee 2015; Lenartz 2000; Levin 1979; Levin 2000; Levin 2006; Lissoni 1993; Ludgate 1988; Mallick 2018; Mao 2015; Marshall 2006; Montemor 2008; MRC 1983; Nabors 2015; Nelson 1988; Payne 1982; Peszynski 1988; Phillips 2003; Prados 2001; Reagan 1976; Shapiro 1976; Shapiro 1989; Shapiro 1992; Sharma 2003; Simpson 1976; Sneed 1998; Socha 2016; Solero 1979; Solomon 2013; Souhami 2004; Stadler 1984; Stupp 2005; Stupp 2009; Stupp 2014; Stupp 2015; Szczepanek 2013; Takakura 1986; Taphoorn 2005; Urtasun 1982; Ushio 1985; Wakabayashi 2018; Wang 2008; Weller 2003; Werner-Wasik 1996; Westphal 2003; Westphal 2006; Westphal 2015; Wick 2009; Wick 2016; Yang 2018; Zhu 2017 (112 studies)

Other reasons were insufficient information (3 studies: Felzmann 2013; Felzmann 2014; Muragaki 2017) and a different study objective (5 studies:Stragliotto 2013; Stummer 2006; Stummer 2011; Stummer 2017; Westphal 2013).

Risk of bias in included studies

All included studies were RCTs and the trial quality was generally high, with most studies assessed as having a low risk of bias overall Figure 3. For the individual study risk of bias explanations, please refer to the Characteristics of included studies tables.

Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

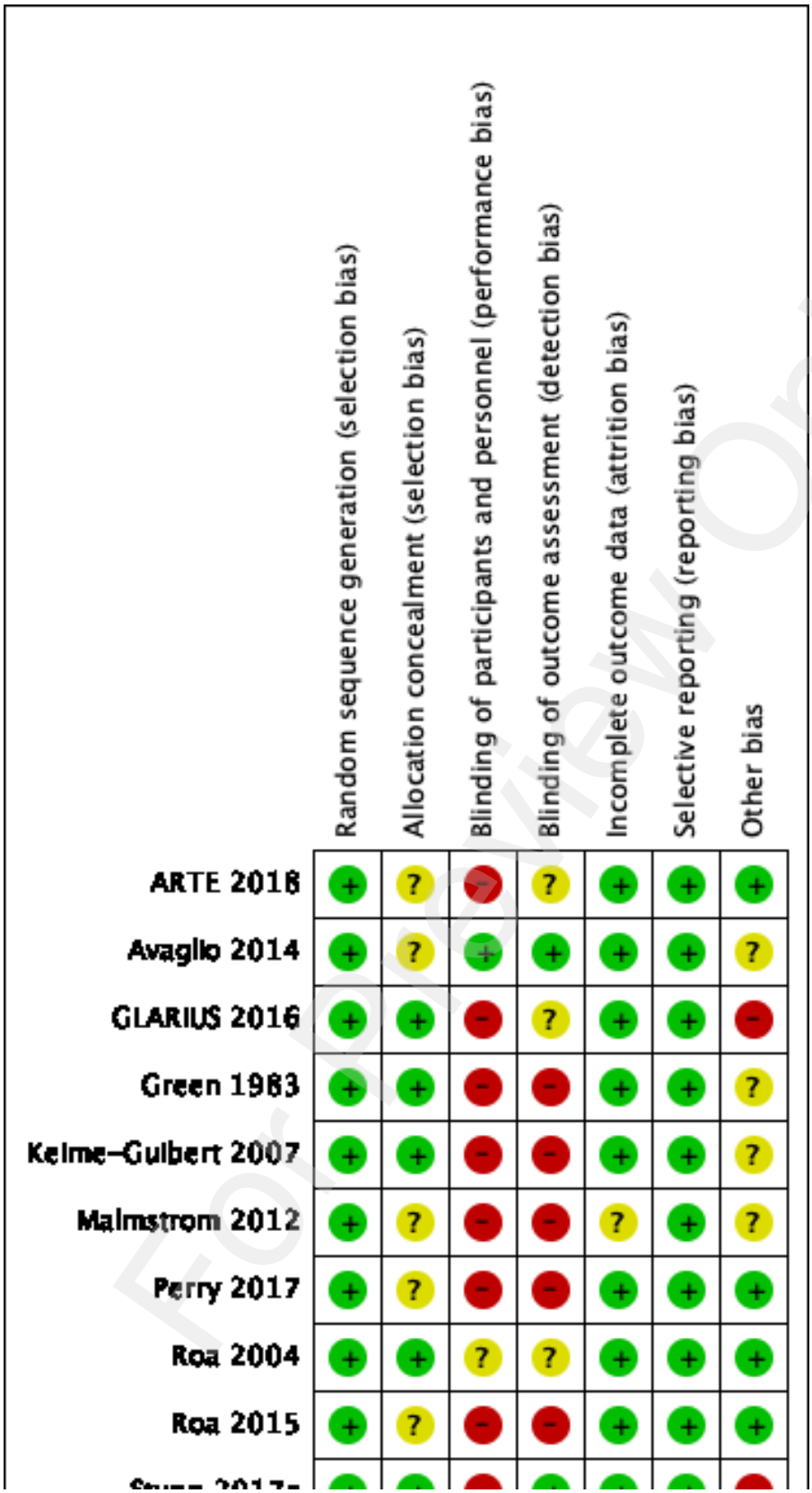
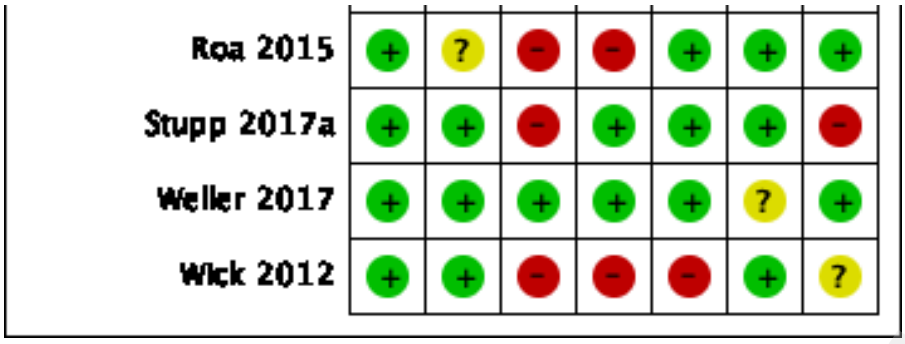


Figure 3. (Continued)



Allocation

The method of randomization was described for all but one of the studies (Green 1983); therefore, most studies were at low risk of bias for the sequence generation criterion. Regarding concealment allocation at the participant selection stage, four studies were assessed as being at low risk of bias for this criterion (Keime-Guibert 2007; Roa 2004; Stupp 2017a; Wick 2012). However, allocation concealment was not clearly described in the other studies, which were assessed as having unclear risk of bias for this criterion.

Blinding

Most studies were open label studies, therefore, were potentially at a high risk of bias for blinding, and most did not describe assessor blinding. However, one study was double-blind (Avaglio 2014) and, therefore, was assessed as having a low risk of bias for this criterion.

Incomplete outcome data

For the primary outcome, most included studies had good follow-up with low drop-out rates. One study (Wick 2012) that compared radiotherapy with temozolomide had relatively higher drop-out rates in the RT arm (14% vs 5%), which might have influenced the findings. This study was assessed as having an unclear risk of bias for this domain.

For studies that measured quality of life in an elderly population (Perry 2017; Roa 2004; Roa 2015), attrition was a problem that had a major impact on the quality of these findings. We therefore considered these studies to be at high risk of attrition bias for quality of life findings.

Selective reporting

All studies reported pre-specified outcomes and were considered to be at a low risk of bias for this criterion.

Other potential sources of bias

In the context of the review evidence, Stupp 2017a represented a high risk of bias due to the timing of randomisation in this trial. Randomisation was performed for a select group of patients who had completed concomitant CRT without progressive disease asthose who died during CRT or who had severe early toxicities would have dropped out by the time of randomisation. Consequently, we decided not to included this trial in the quantitative synthesis due to concern over networks transitivity. .

Similarly, Weller 2017 randomised participants after concomitant CRT and its findings would have downgraded for indirectness; however, this trial contributed no data to meta-analyses. All patients in the GLARIUS 2016 trial had MGMT unmethylated GBM, which is associated with shorter survival time that MGMT-methylated tumours. Whilst this could bias the findings of review meta-analyses, this trial contributed no data to pooled analyses. Reviewers had no other serious risk of bias concerns, although in some studies the risk of bias due to protocol deviations was assessed as unclear.

Quality of Economic Studies

The quality of the trial on which Ghosh 2018 is based has been discussed in the previous section (Roa 2015). The study was found to have a low risk of bias (with the exception of the blinding, which is open label). The CHEERs checklist (Husereau 2013) and the CHEC checklist (Evers 2005) were applied to the study to assess the quality of economic evaluation as recommended but the current guidelines (Shemilt 2018). The results can be found in Table 5 and Table 6. The results of the CHEERS reporting checklist show that a number of parameters are not reported (e.g sources of costs, time horizon, perspective). The results of the CHEC checklist show that there a number of issues with the methodological quality of the study, including inappropriate costing and analysis methods.

Effects of interventions

See: **Summary of findings for the main comparison** Summary of findings on overall survival comparing treatments to supportive care only; **Summary of findings 2** Summary of findings on overall survival comparing treatments to hypofractionated radiotherapy; **Summary of findings 3** Summary of findings on overall survival comparing treatments to standard radiotherapy; **Summary of findings 4** Summary of findings on quality of life; **Summary of findings 5** Summary of findings on progression free survival; **Summary of findings 6** Summary of findings on severe adverse events

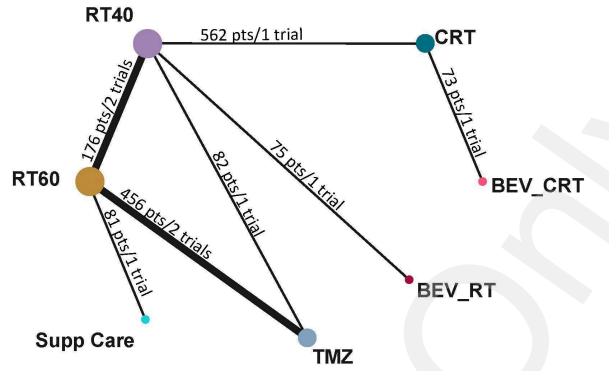
Results of network meta-analysis

Network meta-analysis could only be performed for the primary outcome of overall survival.

Overall Survival

Seven trials contributed data to this time-to-event outcome and, across all studies included in the network meta-analysis, the following treatments were used either as the experimental or the comparison treatment (Figure 4):

Figure 4.



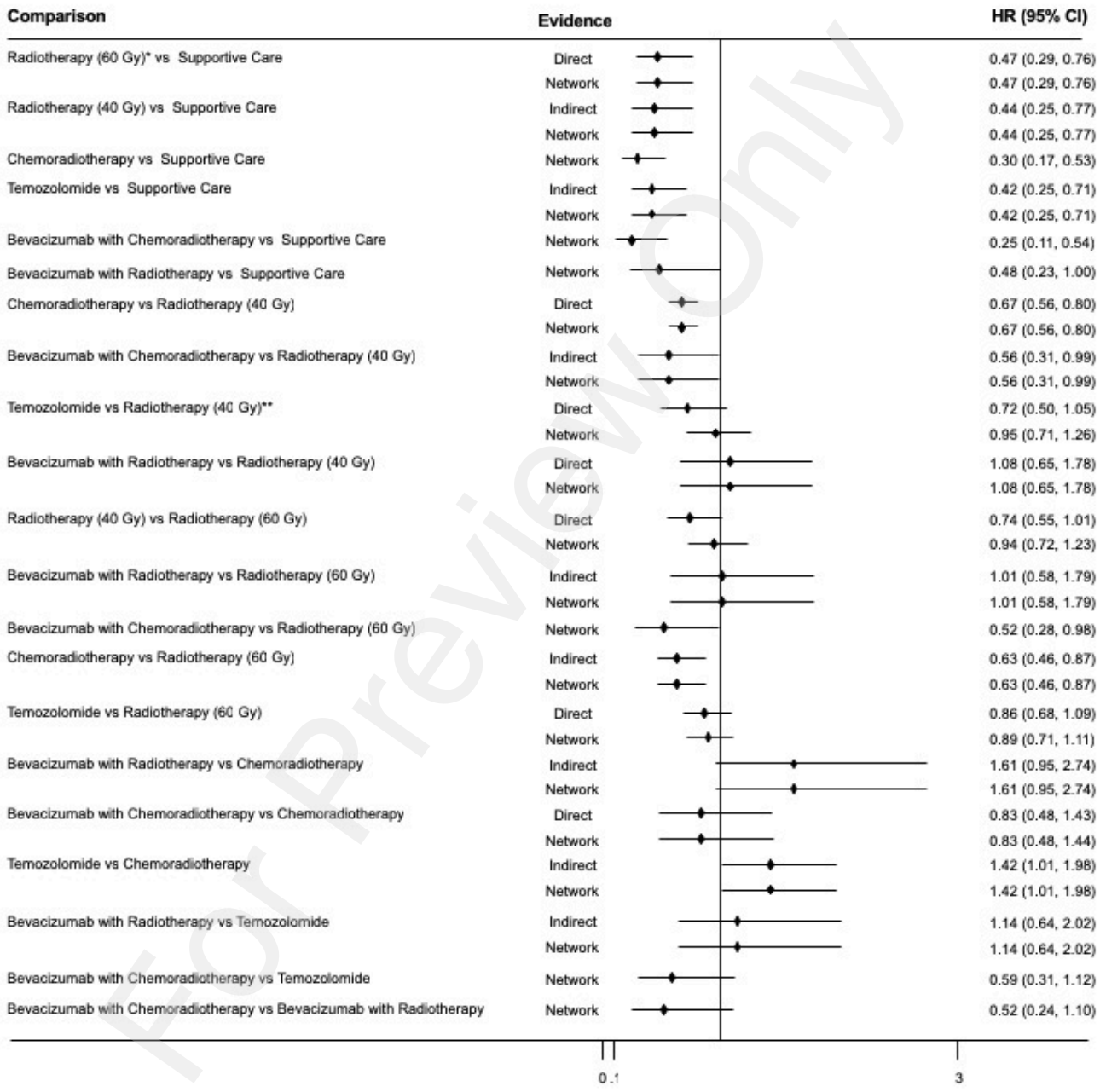
Main network of treatment interventions for glioblastoma in the elderly

Outcome: Overall Survival (time-to-event data)

- Four trial arms of hypofractionated radiotherapy (40Gy/15 fractions) (RT 40)
- Five trial arms of standard radiotherapy (60Gy/30 fractions), including one trial utilising a 50Gy/28 fractions (RT 60)
- One trial arm of supportive care only (SuppCare)
- Three trial arms of temozolomide (TMZ)
- Two trial arms of chemoradiotherapy, including one trial utilising 40Gy in 15 fractions and one utilising 60Gy in 30 fractions (CRT)
- One trial arm of bevacizumab plus chemoradiotherapy (BEV CRT)
- One trial arm of bevacizumab plus radiotherapy (BEV RT)

The forest plot is presented in Figure 5 and effect estimates and certainty ratings for the overall survival network can be found in Table 7. Evidence derived from the network only (i.e. where there were no common comparators) was not graded. Pooled network estimates suggested that, compared with supportive care only, any of the treatments except for bevacizumab plus radiotherapy lead to better overall survival. However, only three treatments (RT40, RT60 and TMZ) could be compared either directly or indirectly with supportive care through a common comparator. The graded evidence related to the three comparisons with direct and/or indirect evidence can be interpreted as follows:

Figure 5. Forest plot of all treatment comparisons for overall survival



- RT60 probably improves overall survival time compared with supportive care only (HR 0.47, 95% CI 0.47 to 0.76; moderate-certainty evidence)
- RT40 may improve overall survival time compared with supportive care only (HR 0.44, 95% CI 0.25 to 0.77; low-certainty evidence)
- TMZ may improve overall survival time compared with supportive care only (HR 0.42, 95% CI 0.25 to 0.71; low-certainty evidence)
- Effect estimates of other treatment options compared with supportive care were not graded for the reasons given in the Summary of findings for the main comparison.

Similarly, pooled network estimates for four treatments (CRT, BEV_CRT, TMZ, and BEV-RT) could be compared with hypofractionated radiotherapy (RT40) through a common comparator, and graded evidence can be interpreted as follows:

- CRT improves overall survival time compared with RT40 (HR 0.67, 95%CI 0.56 to 0.80; high-certainty evidence). On average, this equates to a 33% lower risk of death over the course of the disease and a 49% increase in survival time.
- BEV_CRT probably improves overall survival time compared with RT40 (HR 0.56, 95% CI 0.31 to 0.99; moderate-certainty evidence)
- There may be little or no difference in overall survival time between TMZ and RT40 (HR 0.95, 95% CI 0.71 to 1.26; low-certainty evidence)
- There may be little or no difference in overall survival time between BEV_RT and RT40 (HR 1.08, 95% CI 0.66 to 1.78; low-certainty evidence)

Based on these findings, the average absolute effects on risk of death and median survival time of treatments relative to supportive care have been illustrated in Summary of findings 2.

Pooled network estimates for four treatments (RT40, BEV_RT, TMZ and CRT) could be compared with 'standard' radiotherapy (60 Gy in 30 fractions) through a common comparator. The graded evidence related to these comparisons can be interpreted as follows:

- There may be little or no difference in overall survival time between RT40 and RT60 (HR 0.94, 95% CI 0.72 to 1.23; low-certainty evidence)
- CRT may improve survival time compared with RT60 (HR 0.63, 95% CI 0.46 to 0.87; low-certainty evidence)
- The evidence on effects of TMZ and BEV_RT compared with RT60 was graded very low-certainty.

Based on these findings, the average absolute effects on risk of death and median survival time of treatments relative to RT40 have been illustrated in Summary of findings 3.

Interpretation of other graded network estimates are as follows:

- BEV_RT may be associated with shorter overall survival time compared with CRT, however, the effect estimate includes the possibility of little or no difference (HR 1.61, 95% CI 0.95 to 2.74; low-certainty evidence)
- There may be little or no difference in overall survival time between BEV_CRT and CRT (HR 0.83, 95% CI 0.48 to 1.44; low-certainty evidence)
- TMZ may be associated with shorter overall survival time compared with CRT (HR 1.42, 95% CI 1.01 to 1.98; low-certainty evidence)
- The evidence on effects of BEV_RT compared with TMZ was graded very low-certainty.

Ranking the treatments according to effectiveness

Table 8 gives an overview of mean SUCRA ranking of treatments according to relative effects on overall survival. BEV with CRT was ranked as the best treatment and supportive care only as the worst treatment. The second best treatment was CRT and the third best treatment was TMZ. These rankings should be interpreted with caution as they do not take into account the certainty of the evidence.

Sensitivity Analysis

Four sensitivity analyses were conducted and ranking of treatments relative to each other remained consistent with the main network findings (Table 8).

Overall survival data from included studies not contributing data to the NMA

There were five trials (GLARIUS 2016, Green 1983, Roa 2015, Weller 2017 and Stupp 2017a) that did not contribute overall survival data to the NMA. .

For the elderly subgroup of patients aged 65 and over, Green 1983 reported the number of deaths (103/107) and the death rate (number of deaths per 10 patient months). The death rate in the elderly subgroup was significantly higher (p<0.00001) than in other age groups, however there was no evaluation of how death rates compared between the treatment groups.

For the Roa 2015 trial, a separate publication reported survival data per protocol and by intention-to-treat (ITT) for the 61 elderly patients (65 and over) who participated (Guedes de Castro 2017). The median overall survival difference was not statistically different in patients receiving 25Gy in 5 fractions of RT compared to those receiving 40Gy in 15 fractions of RT (6.8 months; 95% CI, 4.5-9.1 months compared to 6.2 months; 95% CI, 4.7-7.7 months respectively, p=0.936, no hazard ratio provided). The ITT analysis was conducted separately for 'elderly and not frail' patients and 'elderly and frail' patients and there was no significant difference in overall survival detected between treatment arms for either comparison.

For the GLARIUS 2016 trial, a separate abstract reported overall survival data for the modified ITT population for patients aged 65 and over (n=34) compared with younger patients. In the RT + BEV/IRI arm, younger patients survived significantly longer compared with those aged 65+ (median overall survival of 17.5 months for patients aged under 65 versus 13.4 months for patients aged 65+, p<0.001). For patients treated with CRT, no significant difference was found between age groups (median overall survival for younger patients was 20.0 months compared to 17.3 months for patients aged 65+, p=0.567). Whilst the median overall survival for patients aged 65+ years was reported as 13.4 months and 17.3 months in the BEV/IRI and TMZ arms respectively, there was no direct comparison stat-

ing the level of significance for overall survival between treatment arms performed for this age group.

For the, Weller 2017 reported the number of deaths for patients with maximally resected disease (MRD) receiving rindopepimut and TMZ (31/46) versus TMZ only (36/50), with a corresponding HR of 1.21 (95% CI, 0.71 to 2.06, p=0.48). This was also reported for the group of patients with significant residual disease (SRD) (HR 0.68, 95% CI, 0.39-1.19, p=0.18). Thus there were no clear differences in overall survival between treatment arms for either participant population.

Lastly, in Stupp 2017a, tumour treating fields plus adjuvant temozolomide (TTF_AC) was compared with adjuvant temozolomide only among patients receiving CRT. In the subgroup of patients 65 years and older, the estimated HR was 0.51 (95% CI, 0.33 to 0.77) in favour of TTF_AC, with 11% of participants in the TTF_AC (10/89) and 4% (2/45) in the CRT only group alive by the end of the study. This trial was not incorporated into NMA because participants were randomised after they had received radiotherapy and concomittant chemotherapy (i.e. participants received treatment prior to the study interventions), while other studies in the NMA randomised participants before they had received radiotherapy or chemotherapy (i.e. were participants were treatment naive).

Other Outcomes

Evidence from pairwise comparisons of trial data pertaining to elderly participants is reported by treatment comparison below.

Radiotherapy versus supportive care

One study (Keime-Guibert 2007) with 81 participants contributed data to this comparison.

Health-related quality of life

Evidence related to HRQoL at 30, 60, 90 and 135 day time-points after diagnosis. The data suggested slightly better HRQoL scores among people receiving supportive care at the first three time-points, and slightly better HRQoL scores for the radiotherapy arm at the 135 day time-point (Analysis 1.1). This study also reported cognition (Analysis 1.2) and fatigue scores (Analysis 1.3) for these time-points. At the furthest time-point (135 days), cognition scores favoured the supportive care arm, whereas there was no clear difference in fatigue scores between the study arms at any time-point. As evidence was derived from a single small study with high, unequal attrition (low response rate to questionnaires and more deaths occurring in the supportive care group), we assessed the HRQoL findings as low-certainty.

Progression free survival

Evidence suggested that radiotherapy probably improves progression free survival compared with supportive care only (HR 0.28, 95% CI 0.17 to 0.46; *moderate certainty evidence,* with downgrading as evidence was derived from a small single study).

Severe adverse events

Not reported.

Hypofractionated radiotherapy versus standard radiotherapy (60Gy)

One included study compared 40 Gy/15 fraction schedule with a 60 Gy/30 fraction schedule (Roa 2004) and another compared a 25 Gy/5 fraction schedule with a 40 Gy/15 fraction schedule (Roa 2015), therefore data were not pooled.

Health-related quality of life

Data were reported at four weeks' and eight weeks' after treatment in Roa 2015 and these suggested that there may be little or no difference in HRQoL between 25Gy/5 fraction and 40 Gy/15 fraction schedules at either time-point after the one week and three week treatment schedules, respectively (Analysis 2.1; Analysis 2.2). In Roa 2004, HRQoL data were measured using the KPS at three and six weeks after treatment as medians with interquartile ranges (IQR) and, similarly suggested little or no difference in effect on HRQoL. Subsequent follow-up of participants in Roa 2004 also suggested little difference in average HRQoL scores, however, attrition increased with time. We downgraded the certainty of this narrative evidence of little or no difference in HRQoL to low (sparse data [-1] and attrition bias [-1]).

Severe adverse events

There were no instances of grade 3 or higher treatment-related toxicity in Roa 2004 (Analysis 2.3), and this outcome was not reported in Roa 2015.

Progression free survival

This was not reported in Roa 2004. Roa 2015 provided a KM curve but not a hazard ratio for progression free survival. Alongside the KPM curve it was reported that median progression free survival showed no statistically significant difference between arms (4.2 v 4.2 months in arms 1 and 2, respectively; P = 0.716). We did not grade this evidence.

Chemotherapy (TMZ) versus radiotherapy

Two studies contributed overall survival data for this comparison (Malmstrom 2012; Wick 2012) but only one of them (Wick 2012) reported additional outcomes separately for the elderly population of interest.

Health-related quality of life

Wick 2012 reported no clinically meaningful or significant differences in overall QoL scores at 3, 6, or 12 month measurements or other individual QoL items (emotional function, social function, nausea and vomiting, fatigue, loss of appetite, future uncertainty), except for discomfort from communication deficits, which were greatest for patients in the radiotherapy group who died at between 6 and 12 months (P=0.002). There were presented graphically over time in a supplementary appendix without raw data.

Progression free survival

Evidence from Wick 2012 suggested that there may be little or no difference in event free survival (where events were progression or death) between TMZ and standard radiotherapy (373 participants; HR 1.15, 95% CI 0.92 to 1.44; Analysis 3.1; *low certainty evidence,* downgraded for study design limitations and imprecision).

Severe adverse events

Evidence derived from Wick 2012 (373 participants) suggested that, compared with standard radiotherapy:

- TMZ increases the risk of thrombo-embolic events (Analysis 3.2) and increases the risk of severe (grade 3+) neutropenia, lymphopenia, and thrombocytopenia (Analysis 3.3; Analysis 3.4;

Analysis 3.5; *moderate-certainty evidence*, downgraded -1 for imprecision); however the confidence intervals are imprecise and the actual effect may differ from the point estimate in these analyses.

- There may be little or no difference in the risk of serious infection, fatigue, nausea and vomiting, weight loss, neurological symptoms, seizures, elevated liver enzymes, and cutaneous adverse events (Analysis 3.6; Analysis 3.7; Analysis 3.8; Analysis 3.9; Analysis 3.10; Analysis 3.11; Analysis 3.12; Analysis 3.13; all low certainty evidence, downgraded -2 for serious imprecision).

Chemoradiotherapy (TMZ plus radiotherapy) versus radiotherapy

Evidence from one study (Perry 2017) contributed data to outcomes other than overall survival for an elderly population. The radiotherapy schedule used in this study was 40Gy in 15 fractions.

Health-related quality of life

This was briefly reported in Perry 2017 and investigators noted that attrition impacted the quantity of data. They conducted analyses using time to deterioration (with deterioration defined as a 10-point decrease in the score on the function domain or a 10-point increase in the score on the symptom domain) and plotted QoL scores over time. They reported that "only
nausea and vomiting and constipation were associated with significant differences in time to deterioration, which was shorter in the CRT group than in the radiotherapy alone group. They reported that "There were no other clinically important differences between trial groups, which supports our observation that quality of life was similar in the two treatment groups." We did not grade this evidence.

Progression free survival

The evidence suggested that chemoradiotherapy delays disease progression compared with radiotherapy only (562 participants; HR 0.50, 95% CI 0.41 to 0.61; Analysis 4.1; *high certainty evidence*).

Severe adverse events

Evidence suggested that chemoradiotherapy probably increases the risk of grade 3+ neutropenia, thrombocytopenia, and leucopenia, however the confidence intervals are imprecise and the actual effect may differ from the point estimate in these analyses. (Analysis 4.2; Analysis 4.3; Analysis 4.4; Analysis 4.5; *moderate-certainty evidence,* downgraded for imprecision).

Other evidence suggested that there is probably little or no difference in grade 3+ anaemia (Analysis 4.6) and other grade 3+ treatment-related toxicity (Analysis 4.7) (both *moderate-certainty evidence*, downgraded due to imprecision).

Bevacizumab plus CRT (TMZ plus radiotherapy) versus CRT

One study with 73 participants (Avaglio 2014) contributed data to this pairwise comparison.

Health-related quality of life

This was reported for overall trial but not for elderly subgroup specifically (for overall findings, see below).

Progression free survival

Evidence suggested that adding bevacizumab to chemoradiotherapy may make little or no difference to disease progression (HR 0.78, 95% CI 0.46 to 1.32; *low-certainty evidence*, downgraded due to imprecision and study design limitations; Analysis 5.1).

Severe adverse events

Evidence suggested that adding bevacizumab to chemoradiotherapy probably increases the risk of grade 3+ thrombo-embolic events compared with CRT alone (RR 16.63, 95% CI 1.00 to 275.42; *moderate-certainty evidence*, downgraded due to imprecision; Analysis 5.2). No other adverse events were reported for the elderly only. Serious adverse events reported for the overall sample including younger participants can be found below.

Bevacizumab plus radiotherapy versus radiotherapy

One study with 75 participants (ARTE 2018) contributed data to this pairwise comparison.

Health-related quality of life

In the publication, global health was reported in a forest plot along with individual HRQoL items, such as cognitive functioning, emotional functioning and pain, measured with EORTC QLQ-C30/BN20 scales. Investigators reported that "before progression, no differences were detected for individual scales in a generalized linear mixed model, except for less favorable values in arm A for global health (P=0.048) and pain (P=0.027)". No other data were provided or obtained and we did not grade this evidence.

Progression free survival

Evidence suggested that adding bevacizumab to radiotherapy probably delays disease progression (HR 0.46, 95% CI 0.27 to 0.78; *moderate-certainty evidence*, downgraded due to study design limitations; Analysis 6.1).

Severe adverse events

Low certainty evidence suggested that there may be little or no difference in various grade 3+ adverse events reported in this study, including thrombo-embolic events (Analysis 6.3); haematological events (Analysis 6.2); infections (Analysis 6.4); fatigue (Analysis 6.5); seizures (Analysis 6.6); headache (Analysis 6.7); neuropsychiatric events (Analysis 6.8); neurological events (Analysis 6.9); hypertension (Analysis 6.10); cutaneous adverse events (Analysis 6.11); and gastrointestinal events (Analysis 6.12).

Other comparisons did not report PFS for the elderly subgroups of participants.

HRQoL and adverse event data not specific to elderly patients

Several of the included studies (Avaglio 2014; GLARIUS 2016; Green 1983; Malmstrom 2012; Roa 2004; Stupp 2017a; Weller 2017) reported HRQoL or adverse event data for the overall trial population but not separately for the elderly subgroup of patients. Although they are not specific to the elderly population, these overall findings may give some indication of the degree of toxicity of the treatments and any detriment to patients' quality of life for the elderly subgroup too. We have therefore presented the main results below with corresponding P values when available. This evidence is not rated for certainty.

Health-related quality of life

- Malmstrom 2012 measured HRQoL at baseline, 6 weeks and 3 months using EORTC QLQ-C30 and BN-20 questionnaires. Pa-

tients in the TMZ arm generally reported better quality of life than in either of the radiotherapy arms (60Gy and 34Gy) but ratings for global health status were similar.

- Avaglio 2014 reported HRQoL outcomes in a separate publication (Taphoorn 2015). The addition of BEV to CRT delayed deterioration (reported as deterioration free survival [DFS]) across five pre-selected HRQoL scale measures (global health, physical functioning, social functioning, motor dysfunction and communication deficit). Deterioration was defined as a clinically significant deterioration in HRQoL (worsening of 10 or more points on the respective HRQoL scale), progressive disease, or death. It was suggested that the delayed disease progression in the BEV_CRT arm (reported in the main publication) may have influenced the DFS result. When progressive disease was excluded as an event, participants treated with BEV_CRT had a statistically significantly delayed deterioration in HRQoL domains of communication, social functioning and global health but not for motor dysfunction or physical functioning.
- GLARIUS 2016, which compared treatment with CRT to treatment with RT60 in combination with concomitant and adjuvant bevacizumab and adjuvant irinotecan, reported HRQoL using QLQ C30 and BN20 questionnaires measured at baseline and every 3 months until death or end of study. There was no significant difference between the treatment arms.
- Weller 2017 compared adding rindopepimut or control to adjuvant TMZ after CRT and reported no significant differences between patients in their trial arms in any of the HRQoL measures.
- Stupp 2017a reported HRQoL in a separate publication (Taphoorn 2018). There was no significant difference in HRQoL reported between the trial arms, except for itchy skin which was more prominent in the TTF arm at 3, 6 and 9 months (p=0.005, p=0008, p=0.04). There was no significant difference at 12 months.

Severe adverse events (CTCAE grade 3+)

- Green 1983 reported the percentage of patients in each of the four trial groups that experienced specific toxicities. The proportion of patients in the procarbazine arm who suffered a grade 3+ dermatologic or allergic reaction (25%) and nausea and/or vomiting (12.5%) were both significantly higher than for the other three arms of the trial. Infection rates were highest for the BCNU and methylprednisolone arm (34.3%) and rates of uncontrolled diabetes and skeletomuscular complications were highest for the methylprednisolone arm (3.5% and 7.8% respectively).
- Malmstrom 2012 reported toxicity using WHO grading for adverse events, except for nausea and vomiting for which they used the CTCAE version 2.0. In the overall population, episodes of grade 3+ haematological toxicities (neutropenia, pancytopenia and thrombocytopenia) were only seen in the TMZ arm. The incidence of grade 3+ seizures and fatigue was more common in the radiotherapy arms compared to the TMZ arm. Infection rates were similar across all arms. There were two patients who had fatal infections, one in the TMZ group and one in the 60Gy RT group. There was one death in the TMZ group attributed to bleeding due to grade 2 thrombocytopenia.
- Avaglio 2014 used CTCAE v3.0 to measure severe adverse events. Grade 3+ cerebral bleeding events (2.0% versus 0.9%) and wound healing events (3.3% vs 1.6%) were higher in the BEV plus CRT arm versus CRT alone. There were also higher rates of G3+ thromboyctopenia (15% vs 9.8%) and infection rates (12.8% versus 7.8%) in the BEV arm.
- GLARIUS 2016 used CTCAE v3.0 to measure severe adverse events. Rates of severe adverse events were 72% for the bevacizumab (BEV)-irinotecan (IRI) plus RT60 arm, and 84% in the CRT arm. For the BEV/IRI/RT60 arm, severe vascular events were most common (11.8%) and two cerebral haemorrhages occurred (one fatal). For patients in the CRT arm, severe haematological toxicity was most common (18.2%).
- In Weller 2017, the most common severe adverse events for the experimental (rindopepimut) versus placebo arm of the trial were: thrombocytopenia (9% vs 6%), fatigue (2% vs 5%), brain oedema (2% vs 3%), seizure (2% vs 2%) and headache (2% vs 3%). There was one death, secondary to pulmonary embolism, that was assessed as potentially related to the treatment in the experimental arm.
- Stupp 2017a reported that there was no significant increase in rates of severe adverse events when TTF were added to adjuvant chemotherapy (48% vs 44%, p=0.58). There was a numerically higher incidence of some adverse events in the TTF group but the authors report that this was a reflection of the longer duration of TMZ treatment in this group due to delayed occurrence of progression and that the difference disappeared when adverse event incidence was normalised to duration of treatment. There was a higher incidence of skin toxicity (grade 3 in 2%) for the TTF arm compared to the control arm.

Economic Evidence

The economic evaluation that was identified (Ghosh 2018) was a cost-effectiveness analysis (CEA) and cost-utility analysis (CUA). The associated study compared the use of a short course of radiotherapy in elderly patients based on the trial by Roa 2015. The trial reports clinical outcomes were expressed as overall survival (OS) and progression free survival (PFS) for the CEA and as quality adjusted life years (QALYs) for the CUA.

Direct unit medical costs (i.e. costs which result from the utilisation of the medical intervention) were collected from the associated trial (Roa 2015). The costs were broken down for each country participating in the trial. These costs were shown in an additional table. No indirect costs (i.e. costs associated with losses as a consequence of illness, such as production or leisure time lost to patients and their families) were included. The direct costs included the costs of the dexamethasone, MRI scans, CT scans and RT. The authors presented costs as USD 2015, but did not describe the methods for converting the costs from the various participating countries. The mean total cost of the 25 Gy arm was $2,475 and the mean total cost for the 40 Gy arm was $2,868. The authors report that confidence intervals were undefined for the difference in cost due to the negative cost difference, although the scientific rationale for this statement is unclear, as there is no reason why a CI could not be estimated when the point estimate for the difference in cost between the short-course and commonly used RTs is negative.

The results of the cost-effectiveness were expressed as Incremental Cost Effectiveness Ratios (ICERs). The reported ICERs in USD were -$3,062 for the restricted mean OS per life-year gained and -$17,693 USD for the restricted mean PFS. The presentation of negative ICERs is not advised, as negative data points have no meaningful ordering (O'Brien 2002). For overall survival, the study reports a net benefit with 25 Gy of -$46,907 at a societal willingness to pay lev-

el $50,000, a net benefit of -$93,438 at the $100,000 threshold, and a net benefit of -$159,970 at the $200,000 threshold. For progression free survival, net benefit is reported as -$1,933 at the $50,000 threshold, -$4,241 at the $100,000, and -$8,680 at the $200,000 threshold. Given the clinical outcome data presented in the paper, it is unclear how these numbers are calculated as they do not make intuitive sense.

The utility values for the CUA were derived from three different mapping algorithms from the EORTC QLQ-C30 questionnaire (Kontodimopoulos 2009, Kim 2012 and McKenzie 2009). Two reviews have identified limitations in using the EORTC QLQ-C30 mapping algorithms and the three algorithms used in this study performed poorly in validation tests, so their outputs should be used cautiously (Doble 2016; Woodcock 2018). The authors held the assumption that the participants would survive for four months with either treatment. The QALY valued for the 40 Gy treatment was therefore: QALY overall = 0:333 times the utility obtained at baseline. However, the QALY calculated using the mapping algorithm was calculated as: QALY = Utility at month 1 times 0:083 + Utility at month 4 times 0:333. This would result in a 25 Gy-treated QALY being calculated for 5 months, whereas the 40 Gy treated individual was being calculated for 4 months, which was against the authors stated assumption. This means that the gains calculated for the QALY ICERs may be due to this potential calculation error rather than the effect of the intervention itself.

Stochastic sensitivity analysis was carried out in the form of bootstrapping to assess sampling uncertainty. The authors did not carry out a deterministic sensitivity analysis, as variation in cost and survival effect size were analysed using the bootstrap procedure and cost-effectiveness acceptability curves. This is not in line with current UK guidelines (NICE 2012) who recommend the use of deterministic and probabilistic sensitivity analysis to assess parameter uncertainty. The International Society of Pharmacoeconomics and Outcomes Research (ISPOR) guidelines also recommend the examination of parameter uncertainty (Husereau 2013).

The authors conclude that since their ICER values are less than the threshold, they can conclude that the 25 Gy radiotherapy is cost effective. The reviewers cannot replicate the results of this economic evaluation from the data presented and the study results should be considered with extreme caution. As this was the only study identified and has potential quality issues, this demonstrates a paucity of economic evidence regarding the management of newly diagnosed glioblastoma in the elderly.

DISCUSSION

Summary of main results

The review included 12 studies involving approximately 1,818 elderly participants and several different treatment comparisons. Seven treatment options could be connected in a network meta-analysis for the outcome of overall survival. Other treatments and outcomes were evaluated in pairwise comparisons where data were available.

Overall survival

We found high certainty evidence that chemoradiotherapy results in a 33% lower risk of death on average over the course of the disease after diagnosis (20% to 44% lower), or about a 50% increase in survival time compared to treatment with hypofractionated RT (40 Gy) alone. Other evidence was assessed as moderate to very low certainty, with most evidence graded as low or very low certainty, meaning that the effect estimates may be substantially different from those estimated in our NMA. However, all treatments evaluated led to a clear increase in survival time relative to supportive care only, except for the bevacizumab plus RT option.

In terms of treatment rankings, BEV added to CRT ranked as the best treatment, CRT ranked second best, TMZ ranked third best, hypofractionated RT fourth, and supportive care only ranked last. These ranking should be interpreted with caution as they do not take into account the certainty of the evidence, notably that there may be little or no difference in overall survival when BEV is added to CRT. Therefore, the higher position of BEV_CRT in the ranking is not supported by evidence of a clear survival benefit over CRT. On sensitivity analysis, when CRT40 (with 40 Gy RT) and CRT60 (with 60 Gy RT) interventions were considered separately, CRT (with RT40) ranked first in the larger of the two networks thus created.

Summary of findings with illustrative effects can be found in the Summary of findings for the main comparison, Summary of findings 2 and Summary of findings 3. We were unable to conduct subgroup analyses by age threshold (65+ or 70+ year threshold) or MGMT methylation status; few included studies reported the latter and where these data were present, they were usually reported for the sample overall and not for the elderly subgroup.

Quality of life

Moderate-certainty narrative evidence suggests that overall, there may be little difference in quality of life between TMZ and RT, except for discomfort from communication deficits, which were more common with RT. Data on quality of life for other treatment comparisons were sparse and negatively impacted by attrition, with the limited available evidence derived from elderly participants suggesting little or no difference in quality of life with radiotherapy versus supportive care only, and short course versus longer/standard radiotherapy courses (Summary of findings 4). Narrative evidence from a single study of chemoradiotherapy versus RT only suggesting little difference in QOL was not graded.

Progression free survival

High-certainty evidence shows that chemoradiotherapy delays disease progression compared with hypofractionated RT only. Moderate-certainty evidence suggests that RT with 60 Gy probably delays disease progression compared with supportive care only and that bevacizumab with RT probably delays disease progression compared with hypofractionated RT alone. Evidence for other treatment comparisons is of low or very low certainty.

Severe adverse events

Moderate-certainty evidence suggests that severe haemtological toxicities and thromboembolism are more common with TMZ than with RT and the risk probably increases with the addition of BEV to CRT.

Overall completeness and applicability of evidence

The only outcome that could be assessed in a network was that of overall survival. Thus, it is not known how the treatment options compare with regard to the other important review outcomes, such as quality of life or severe adverse events. This is a serious limitation of the evidence gathered in this review as a treatment ranked

as best for overall survival, for example, could be worst for quality of life. More research on quality of life among patients receiving treatment for glioblastoma is necessary to elucidate these other relative effects. However, attrition is a notable problem for investigators gathering these sorts of data.

In general, the review evidence is applicable to elderly patients with a Karnofsky Performance Score of more than 70 percent, i.e. those patients capable of selfcare (see Table 2). We found little evidence to inform guidance on the most appropriate treatments for people with KPS less than 70 percent. Two studies that evaluated different hypofractionated radiotherapy regimen included patients at the frailer end of the spectrum, using a KPS of 50 percent (Roa 2004; Roa 2015). Evidence from Roa 2015 suggested little or no difference in the median survival between a 25 Gy/5 fraction regimen and the 40Gy/15 fraction regimen among elderly and frail patients; however, the effectiveness of the 25Gy/5 fraction regimen could not be evaluated against other possible treatment options in the network due to insufficient data. Malmstrom 2012 also permitted entry to their trial of patients (7/291 patients) with a WHO performance status of 3 if this was specifically due to neurological status. However, this was a minority of patients and the outcomes for these patients were not reported separately.

Data were also relatively scarce for certain treatments, particularly newer treatment options (e.g. those employing bevacizumab) and some treatment options lacked overall survival data in a comparable form (e.g. radiotherapy given as 25Gy in five fractions); therefore, such treatments could not be ranked at all against other treatments. Crucially, we were unable to compare chemoradiotherapy utilising 60 Gy in 30 fractions (standard) with hypofractionated regimens, either directly or indirectly, due to limitations of the network connections. Therefore, we could not ascertain a network effect estimate for standard versus a hypofractionated chemoradiotherapy regimen, nor rank these different regimen.

One study (Roa 2015) compared two hypofractionated chemoradiotherapy regimen (25 Gy in five fractions versus 40 Gy in 15 fractions). Unfortunately, we were unable to compare and rank the 25 Gy radiotherapy regimen because the overall survival data in this study were reported as median survival times with P-values, rather than as time-to-event data (HRs and 95% CIs). The difference in median survival was not statistically significant (P=0.936). We rated the resulting evidence as low-certainty. We were unable to obtain the relevant time-to-event data from the investigators for this review.

In addition to the limitations of the evidence with respect to performance status mentioned above, there were very few data on HRQOL and severe adverse effects reported specifically for elderly patients. In studies where the elderly were a subgroup of a sample with a broader age range, these outcomes were frequently reported by investigators for the overall sample. When we found no specific data on these outcomes for the elderly, we reported the main findings for the broader age group at the end of the results section. However the applicability of these findings to an elderly population is not known and the actual relative effects may be quite different.

Quality of the evidence

The network evidence that was rated as high quality/certainty was:

- Chemoradiotherapy increases time to death and delays disease progression compared with hypofractionated radiotherapy

Evidence of moderate quality/certainty, meaning that our actual effect may differ somewhat from our point estimate (or may change with further research), included the following:

- Chemoradiotherapy increases the risk of grade 3+ neutropenia, thrombocytopenia, and leucopenia compared with hypofractionated radiotherapy alone;
- Bevacizumab plus chemoradiotherapy increases time to death compared with hypofractionated radiotherapy alone;
- Standard radiotherapy increases time to death and delays disease progression compared with supportive care only;
- Bevacizumab plus radiotherapy delays disease progression compared with hypofractionated radiotherapy alone;
- Temozolomide increases the risk of grade 3+ thrombo-embolic events, neutropenia, lymphopenia, and thrombocytopenia compared with standard radiotherapy; and
- Bevacizumab plus chemoradiotherapy increases the risk of thrombo-embolic events compared with chemoradiotherapy alone.

Other evidence was low or very low quality/certainty and the effect estimates (if any) are likely to change with further research. Data on quality of life were sparse and the quality of the evidence tended to be of very low quality/certainty or unrateable.

SUCRA ranking does not take into account the certainty of the evidence and a high-ranked treatment may be based on low-quality evidence (Mbuagbaw 2017). In our main network meta-analysis, the evidence on bevacizumab added to chemoradiotherapy compared with chemotherapy alone was less robust than the evidence on chemoradiotherapy alone; however, it ranked higher than the latter. When compared with chemoradiotherapy, low-certainty evidence suggested that the addition of bevacizumab to chemoradiotherapy did not improve overall survival, highlighting that rankings should be interpreted with caution and that more research evidence may be needed to improve the certainty of the rankings.

Potential biases in the review process

There were some important differences between trial inclusion criteria, treatments and outcome reporting that could not be accounted for in this review process and could have contributed to potential bias.

Definitions of 'the elderly'

Eight trials defined the elderly subgroup as 65+ years old (ARTE 2018; GLARIUS 2016; Green 1983; Perry 2017; Roa 2015; Stupp 2017a; Weller 2017; Wick 2012) and only three studies contributed data for the elderly according to the review focus of 70+ years old (Avaglio 2014; Keime-Guibert 2007; Malmstrom 2012) (Table 9). People aged between 65 and 70 years were shown to have a longer median survival compared with those of 70+ years (6 months vs 3.2 months, respectively) in a large UK audit (Brodbelt 2015). Our decision to pool data for these studies was pragmatic and taken at the protocol stage, because we knew that data specifically for the 70+ age group would be sparse.

We also included one study (Roa 2004) that defined elderly patients as aged 60+ years because the review protocol dictated that the overall results from trials including younger patients could be included if the proportion of patients in the trial aged over 65 years exceeded 80%. In Roa 2004, the mean participant age was 72.4 years

for patients treated with 60 Gy and 71.0 years for patients treated with 40 Gy. The standard deviation for these groups was 5.4 and 5.5 years, respectively. Therefore the majority of participants in this trial were likely to be aged over 65 years; whether the proportion exceeded 80% as per our inclusion criteria is unclear. After attempting to contact the authors of Roa 2004, with no further information on the proportion of patients included aged over 65 years obtained, we decided to include this study based on this rationale. The median survival of 5.1 months in the RT60 arm of this trial was similar to the median survival reported by Malmstrom 2012 for patients aged 70+ who received 60 Gy (5.2 months) and less than the median survival reported for patients aged 70+ in Keime-Guibert 2007 (29.1 weeks), who received 50 Gy, and for patients aged 65+ in Wick 2012 (9.6 months) who received 60 Gy.

As younger participants survive longer than older participants, the effect of including studies with 65+ year old participants might have over-estimated the beneficial effects of treatments for the 70+ year old age group.

Radiotherapy treatment

Green 1983 was the oldest study included in the review and was published 21 years before the next included study (Roa 2004). As whole brain radiotherapy was used (WBRT) was used in Green 1983, the radiotherapy volume treated was much larger than the treatment volumes specified for the other trials that included radiotherapy. The larger treatment volume and likely sub-optimal planning and treatment delivery techniques would be considered unacceptable by modern standard and is likely to have affected the tolerability of the treatment and the rate of adverse events, especially for elderly patients. Whilst we included this trial, it did not contribute survival data to the NMA or data for pairwise comparisons of other review outcomes, therefore any potential bias introduced by including this study would be minimal.

Timing of randomisation

Most trials randomised patients in the period following surgical resection when they were radiotherapy and chemotherapy naive. Two trials (Stupp 2017a; Weller 2017) performed randomisation after patients had completed concomitant CRT and both specified that patients must have received at least 90% of the planned radiotherapy dose (60 Gy). This will have selected for a group of patients with a better prognosis than those in trials using the earlier timepoint of randomisation, by excluding those patients who were unable to tolerate treatment due to adverse events or who died or progressed prior to finishing radiotherapy. Whilst Stupp 2017a reported relevant time-to-event data for the elderly subgroup, we did not include these data in the NMA due to the risk of intransitivity.

Survival times

Most of the included studies (including Stupp 2017a and Weller 2017, which randomised participants after concomitant CRT) calculated overall survival from the time of randomisation, but for several studies the starting point for overall survival analysis was not described (ARTE 2018; Avaglio 2014; GLARIUS 2016) and for one trial (Wick 2012), overall survival was measured from the date of surgery.

Tumour response assessment

For those trials that reported a response rate or progression free survival, several (ARTE 2018; Avaglio 2014; Keime-Guibert 2007; Perry 2017; Stupp 2017a; Weller 2017; Wick 2012) used repeated magnetic resonance imaging (MRI) for the basis of their assessments. Roa 2015 did not specify the modality of imaging and in Keime-Guibert 2007, imaging was permitted with MRI or computed tomography (CT). ARTE 2018 and Weller 2017 used the response assessment in neuro-oncology (RANO) criteria (Wen 2010), GLARIUS 2016; Stupp 2017a; Wick 2012 specified the MacDonald criteria (MacDonald 1990), and Avaglio 2014; Keime-Guibert 2007; Perry 2017 described their response criteria, which were based on specific MRI appearances and/or steroid use and symptoms. Roa 2015 did not specify the criteria used. Although there are similarities between these response criterion, the differences may mean that the response rate or PFS results across these trials are not comparable.

Extent of surgical resection

Extent of surgical resection influences prognosis (Pessina 2018). Most trials permitted inclusion of patients who had undergone biopsy or partial or complete surgical resection. In the Keime-Guibert 2007 trial, which was one of the older included studies, at least half the participants had biopsy only. Including this trial in the NMA might, therefore, have led to the effect on overall survival estimated for other treatments to be slightly over-estimated.

In the trial by Weller 2017, the primary analysis was conducted on patients who had maximal surgical resection (MRD) only. Whilst in the context of NMA, this could have favourably biased the effect of the study intervention, Weller 2017 did not contribute data to the NMA, therefore did not bias the NMA findings. The extent of resection was not described in ARTE 2018, and we did not evaluate the extent of possible bias from including this trial; however, the direct evidence derived from this trial in the NMA was rated low-certainty.

Molecular sub-types

Two trials included patients with disease of particular molecular subtypes only, which may not have been comparable with patients included in other trials. Weller 2017 specified that only patients with GBM with confirmed epidermal growth factor receptor (EGFR) vIII expression were eligible for trial inclusion. The rationale was that rindopepimut was most likely to be active in disease expressing this mutation. This explains the relatively small number of patients enrolled (n=745) compared to the number assessed for eligibility (n=4652). In the GLARIUS 2016 trial, only patients with unmethylated MGMT were eligible for trial inclusion. As MGMT methylation has a known prognostic effect on survival of patients with GBM, it is important to consider the results of this trial and how they compare to results from other trials in this context.

Analysis and grading

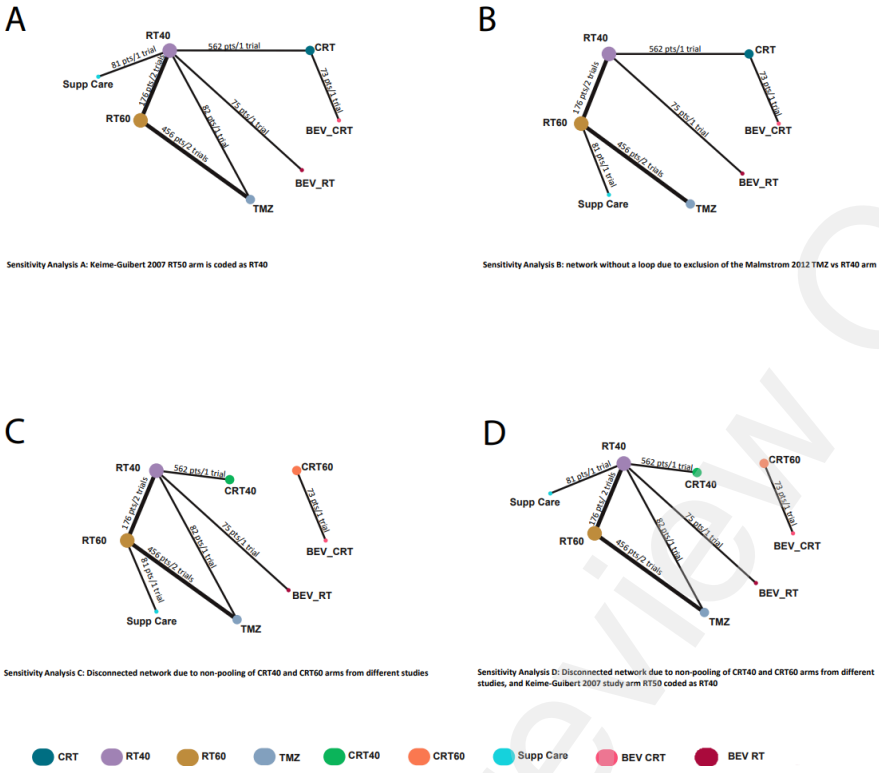
For the main network meta-analysis for overall survival, comparing all treatments with supportive care only, we made the following assumptions:

1. that it was reasonable to pool data on chemoradiotherapy (combined temozolomide and radiotherapy), irrespective of the radiotherapy dose schedule used (40Gy/15 fractions and 60Gy/30 fractions in Perry 2017 and Avaglio 2014, respectively);
2. that data on a 50Gy/28 fraction radiotherapy schedule from the one study (Keime-Guibert 2007) employing this unconventional dose schedule could be pooled with those of 60Gy/30 fraction.

The rationale for the first assumption was that 'standard' chemoradiotherapy might include either radiotherapy schedule combined

with temozolomide. In addition, pairwise analysis suggested that there was no clear difference in OS between 40Gy/15 and the 60Gy/30 schedules when employed without chemotherapy. However, the decision to pool these data was also influenced by the fact that pooling these data would facilitate a connected network. To evaluate the extent to which the first assumption impacted the findings of the review, we conducted a sensitivity analysis by not pooling these data, which resulted in a network with a disconnected (separate) comparison (Figure 6C). Findings of the relative effects of the interventions were similar to the main findings and made no difference to the treatment ranking of chemoradiotherapy. In grading this evidence, we therefore did not downgrade the evidence on chemoradiotherapy for intransitivity (differences in study characteristics that may modify treatment effect) because intransitivity did not appear to have a serious impact on the estimates of effect.

Figure 6. Network diagrams for four sensitivity analyses



With respect to the second assumption, we performed a sensitivity analysis by pooling the Keime-Guibert 2007 data (RT50Gy) with the 40Gy/15 fraction node (Figure 6A) and found that this also made no difference to the treatment rankings. Similarly, we did not downgrade the evidence for intransitivity.

The only loop in the network was derived from a single study with three arms (Malmstrom 2012), which led to duplication of data at the 40Gy/15 fraction node in the main analysis. To evaluate the impact of this on the findings, we performed a sensitivity analysis by removing one of the study arms (TMZ vs RT40) (Figure 6B). This made little difference to effect estimates and treatment rankings, therefore we did not downgrade for intransitivity (differences in study characteristics that may modify treatment effect).

Where studies evaluated the radiotherapy schedules only (i.e. without chemotherapy), we did not pool data for 40Gy/15 and 60Gy/30 schedules. However, we conducted an exploratory analysis by collapsing these nodes to evaluate the extent to which so doing would have impacted on the review findings.

Because most treatments were not part of a loop in the main network analysis, and the only loop came from a single study such that the results for the nodes in the loop correlated with one another, it was not possible to calculate indirect estimates of effect. This meant that we had to adopt a modified grading approach as it was not possible to assess incoherence (differences between the direct and indirect estimates of effect).

Calculation of absolute risk of death

As an assumed baseline risk for supportive care, we used survival data from Keime-Guibert 2007. Whilst this is an older study and had a lower proportion of patients having had maximal surgical resection, it was the only one to evaluate supportive care only. Noting that in the an epidemiological GBM study (Brodbelt 2015) the death rate for the 70+ age group was approximately 50% at three months from diagnosis (with a median survival of 3.2 months reported), we felt that the Keime-Guibert 2007 data were a reasonable baseline against which to illustrate the potential effects of the different treatments. Relative to the Keime-Guibert 2007 data, it could be argued then, for the relevant comparisons, that the estimates of more recent interventions relate to maximal surgical resection plus the experimental option (e.g. CRT) and not just the experimental option alone.

Agreements and disagreements with other studies or reviews

Our review evidence on hypofractionated (40Gy) versus standard radiotherapy, suggesting little or no difference in overall survival between these radiotherapy doses, contrasts with evidence from Bleehen 1991, a trial conducted among mostly younger patients, which implied that higher RT doses were more effective. Bleehen 1991 compared post-operative treatment with 60 Gy RT in 30 fractions with 45 Gy RT in 20 fractions for patients with grade 3 or grade 4 glioma aged 18+ years, reporting that the higher dose significantly improved overall survival in this study. Although 61% (n=272) of patients in Bleehen 1991 had a diagnosis of GBM and 32% (n=140) were aged over 60, no sub-group analysis for an elderly cohort were reported and therefore it is impossible to know if the same survival advantage would have been seen for the group of older (65+) patients in this trial.

Reyes-Botero 2018 was a single arm, non-randomised phase II trial (n=66) which treated patients aged 70+, and with a KPS of under 70 with TMZ 130-150mg/m2 per day for 5 days every 4 weeks concomitantly with BEV 10mg/kg every two weeks. Median overall survival of 23.9 weeks (95% CI, 19-27.6 weeks) was less than observed for patients of the same age treated with TMZ alone using the same schedule (9.0 months, 95% CI, 6.2-11.8 months) in a trial included in this NMA (Malmstrom 2012), however the patients in Malmstrom 2012 had better performance status. The adverse events which occurred from using TMZ and BEV were reported by the Reyes-Botero 2018 authors to be tolerable; however, there were three deaths from pulmonary embolism, intestinal perforation and cerebral haemorrhage, which were recorded as probably being attributed to treatment. These are in keeping with the characteristic adverse events accompanying treatment with bevacizumab described in trials included in this review (ARTE 2018; Avaglio 2014; GLARIUS 2016).

We know from service audits, surveys and guidelines (Brodbelt 2015; Palmer 2018; NCCN 2018; NICE 2018), that best supportive care is often the most popular treatment option for patients with poorer performance status. Although most studies in our review included relatively fit patients (KPS over 60-70), two trials (Roa 2004; Roa 2015) included unfit (KPS as low as 50) elderly patients. Findings from these two trials suggest that less intensive and less toxic treatment options, such as 40Gy in 15 fractions or 25Gy in 5 fractions, may be appropriate in selected cases. Interestingly, the median survival for unfit, elderly patients in Roa 2015 (reported in Guedes de Castro 2017) was superior in both treatment arms (40Gy in 15 fractions [6.2 months; 95% CI, 4.7-7.7 months], 25Gy in 5 fractions [6.8 months; 95%, 4.5-9.1 months]), compared with survival outcomes previously reported for fitter elderly patients receiving best supportive care alone (median OS 3.9 months, Keime-Guibert 2007).

Perez-Larraya 2011was a single arm phase II trial of TMZ (150-200mg/m2/day for 5 days every 4 weeks until progression) in elderly (age >70 years) and frail (KPS less than 70) patients. Median overall survival was six months and, in the small subgroup of patients known to have MGMT methylated disease, median survival was 31 weeks. Overall, quality of life and cognition improved on treatment and approximately one third of patients showed an improvement in KPS of at least 10 points. Although not a direct comparison, this survival time is also longer than reported for fitter elderly patients receiving supportive care alone (Keime-Guibert 2007). In line with conclusions from Roa 2004 and Roa 2015, this suggests that active treatment in carefully selected patients of poorer performance status can be well tolerated without significant deterioration in quality of life.

AUTHORS' CONCLUSIONS

Implications for practice

Evidence from recent service audits and surveys show a wide variation in treatment practice, with an often large proportion of elderly glioblastoma patients not treated with any active treatment after surgical intervention (Chong 2018; Palmer 2018; Solth 2018). The evidence in this review may, therefore, be useful to clinicians and patients considering active treatment by facilitating discussions around the likely magnitude of benefit from various active treatment options compared with supportive care alone.

Comparing seven interventions in a network with best supportive care, mainly among elderly people capable of self-care, the estimates for the relative effects of active treatment suggest a survival benefit in most scenarios. The exception was the treatment of bevacizumab with radiotherapy, where the 95% confidence interval included the possibility of no difference. Where illustrative median survival times were estimated, they suggest that all may offer some months of survival benefit (illustrative median overall survivals of 6.8 to 7.7 months for standard radiotherapy and chemotherapy options, respectively) compared with best supportive care only (median of 3.2 months for the 70+ age group in Brodbelt 2015).

CRT performs well in this analysis for elderly patients with good performance status. Although no direct comparison of CRT with 60Gy versus 40Gy was possible, CRT with 40 Gy was more effective and ranked higher than TMZ or RT alone. Also, the available evidence suggests that hypofractionated (40Gy) regimen may be as effective and well-tolerated as standard 60Gy regimen. Even shorter RT schedules (25Gy in 5 fractions and 34Gy over 2 weeks) have been tested in the elderly, but unfortunately it was not possible to comment on their effectiveness relative to 40 Gy or other treatment options because the 34 Gy regimen was included in the 40 Gy node for this NMA and the 25 Gy regimen did not contribute survival data to the NMA. It is therefore not possible to deduce if there are any important differences between the hypofractionated regimens, or whether shorter regimens should or could be used in practice.

We know from previous surveys and guidelines (NCCN 2018; NICE 2018), that best supportive care is often the most popular treatment option for patients with poorer performance status. We found little evidence to guide clinical practice in this regard, although findings from individual studies suggest that less intensive and less toxic treatment options may be appropriate.

BEV has a high treatment ranking, but it is not clear what added benefit, if any, is derived from the addition of BEV to CRT or RT alone. BEV_CRT improves survival compared with RT alone with moderate certainty; however, CRT alone is also superior to RT alone. When BEV_RT was compared with radiotherapy alone, the evidence was more uncertain. In light of the evidence found, there is currently no justification for adding bevacizumab to radiotherapy or CRT, outside of a clinical trial setting.

Implications for research

Hypofractionated radiotherapy

An important gap in knowledge highlighted by this review is the relative effectiveness and tolerability of CRT with hypofractionated regimen (40 Gy or other regimen) compared with standard CRT for elderly patients. In terms of giving short course radiotherapy alone, the most commonly used regimen tested being 40 Gy in 15 fractions. Alternative regimens such as 25 Gy in 5 fractions used in patients with poor performance status (Roa 2015) and 34 Gy in 3.4 Gy fractions over 2 weeks in fit patients (Malmstrom 2012) have shown encouraging outcomes for elderly patients when compared to 40 Gy in 15 fractions (Roa 2015) or 60 Gy in 30 fractions (Malmstrom 2012) respectively. Future research to compare shorter regimens, such as 25 Gy in 5 fractions, against 40 Gy in 15 fractions in fitter patients would be useful. Shorter, but equally effective treatments save days on treatment for patients and potentially have direct cost savings for health service providers. It would be important to measure toxicity in fitter patients receiving higher radiotherapy doses per fraction, as adverse side effects not seen in frailer patients may emerge in fitter patients if they live for longer.

Tumour treating fields

The trial of TTF combined with adjuvant chemotherapy reported the longest overall survival compared with the other interventions (Table 4), however, participants comprised a selected group with a more favourable prognosis. More research is required to understand if the survival benefit reported in this trial would still be demonstrated if elderly patients had been randomised prior to CRT. Also, HRQoL and adverse events were only reported for the overall trial cohort. Any impact on HRQoL and tolerability of wearing a portable device for at least 18 hours per day and managing technical issues relating to the device may differ for elderly patients compared to those in younger categories and it would be important to report these outcomes for elderly patients separately.

Bevacizumab

The limitations of the evidence for using bevacizumab to treat elderly patients with GBM have been outlined. More certain evidence of beneficial effects of bevacizumab use would be needed before using it in this population outside of clinical trials.

Other SACT

Apart from TMZ, no systemic anti-cancer agents have made an important contribution to improving survival for elderly patients with GBM. We await the results of a trial using hydroxychloroquine (NCT01602588) and a trial using a type of immunotherapy, which has offered such impressive benefits in other malignancies (NUTMEG 2018), although has yet to show promise for patients with GBM.

Definition of elderly and reporting of HRQoL for elderly patients

Any future trials for elderly patients with GBM would benefit from using a clear definition of the elderly. We have chosen aged 70+ for our definition and trials including younger patients often use 70 as an age cut-off (e.g. Bleehen 1991; Stupp 2017a). Despite the importance of understanding toxicity and tolerability of treatments for older patients, HRQoL and adverse event data for elderly patients with GBM are sparse and any future research which clearly articulates these outcomes for elderly patients would be welcomed.

Prediction of patients most likely to benefit from treatment

Two of the trials included in this analysis used molecular subtyping to choose the patients to include in their studies (GLARIUS 2016; Weller 2017). Future research that allows tailoring of treatments, with improved therapeutic index, based on molecular subtyping(Pinzi 2017) may mean that more specific, less toxic treatments could be offered to patients. This would be particularly useful for older patients who are less likely to tolerate combined, intensive treatment regimens.

Additional approaches to guide treatment decisions that require further investigation to guide treatment decisions for elderly patients with GBM include the the use of novel imaging techniques (Pinzi 2017) and geriatric and frailty assessment prior to treatment. It has been shown that specific cognitive and frailty evaluation is seldom performed prior to treatment but, when used, has been reported to alter treatment decisions by neuro-oncologists in up to 50% of cases. (Lorimer 2016). Further investigation into which assessments are both useful and pragmatic to perform in the clinic will help clinicians make better informed treatment decisions for their patients.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

ARTE 2018

Methods	Design: Phase II multi-centre, open-label RCT; randomisation in ratio 2 : 1 (Arm A: Arm B)
	Country: Switzerland
	Accrual dates: March 2013 to August 2015
	Trial reg: NCT01443676
	Funding: Roche Pharma (Basel, Switzerland)
Participants	No. enrolled: 75
	No. analysed: 75
	Inclusion criteria: age 65 years or older, newly diagnosed supratentorial glioblastoma, eligible for first infusion of bevacizumab between 28 and 49 days after surgery for glioblastoma, Karnofsky perfor-

ARTE 2018 *(Continued)*

	mance score of 60 or more, stable or decreasing corticosteroid dose within 5 days before enrolment, availability of paraffin-embedded tissue for central pathology review and determination of O6-methylguanine DNA methyltransferase (MGMT) promoter methylation status, and adequate hematological, renal and liver function. An amendment (November 2013) requested the absence of MGMT promoter methylation when it became clear that MGMT promoter methylation predicted larger benefit from TMZ alone than from RT alone in patients with GBM aged 65+. Age Approx. median 70 (range 65 - 79, 65 - 87 arm A and arm B) Gender: 36% Female, 64% Male Used diagnostic criteria: WHO classification (2007) Molecular type of GBM: MGMT methylated 21%, MGMT unmethylated 73%, missing (5%) (data for all participants). Note the amendment to alter inclusion criteria based on MGMT promoter methylation status in the first year of trial recruitment. Performance status: Karnofsky performance score (KPS) of 60 or more.
Interventions	Arm A: RT was administered to the gross tumour volume plus a 2 cm margin over 3 weeks, in 15 fractions of 2.66 Gy, to a total 40.0 Gy. Bevacizumab was administered intravenously at 10 mg/kg bodyweight every 2 weeks. Arm B: RT was administered to the gross tumour volume plus a 2 cm margin over 3 weeks, in 15 fractions of 2.66 Gy, to a total 40.0 Gy.
Outcomes	Primary endpoint: Overall survival (intention to treat population) Secondary endpoints: Survival rate at 12 months Adverse events Median PFS PFS rate at 6 months Median deterioration free survival (DFS) from baseline Cognitive functioning (serial MMSE measurements) Median time on steroids from study entry. Exploratory endpoints: Subgroup analysis for PFS and OS by cognitive function (MMSE), KPS, disease methylation characteristics.
Notes	The authors concluded that the ARTE trial did not confirm the hypothesis that the combination of bevacizumab with hypofractionated RT prolongs OS in elderly glioblastoma patients.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were allocated to treatment arms using a web-based randomisation system without stratification in a 2 : 1 distribution
Allocation concealment (selection bias)	Unclear risk	Not described in the study reports

ARTE 2018 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	open-label
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described in the study reports
Incomplete outcome data (attrition bias) All outcomes	Low risk	No patient was lost to follow up for OS
Selective reporting (reporting bias)	Low risk	All predefined outcomes were reported.
Other bias	Low risk	None noted

Avaglio 2014

Methods	Design: Phase III RCT Country: Multi-country Accrual dates: June 2009 through March 29, 2011 Trail reg: NCT00943826 Funding: F. Hoffmann–La Roche
Participants	No. enrolled: 921 (70+, N= 73) No. analysed: 921 (70+, N= 73) Inclusion/exclusion criteria: 18 years of age or older with newly diagnosed, histologically confirmed, supratentorial glioblastoma Add. Incl criteria: WHO performance status of 2 or lower; the use of stable or decreasing glucocorticoid doses within the 5 days before randomisation; adequate healing of craniotomy or cranial-biopsy site; adequate hematologic, hepatic, and renal function; and acceptable blood coagulation levels. Investigators submitted available tumor tissue blocks for pathological central review and analysis of status with respect to O-6-methylguanine–DNA MGMT. Treatment had to be initiated between 29 & 48 days after the most recent surgery. Exclusion criteria: Evidence of recent symptomatic intracranial haemorrhage on MRI, prior chemotherapy or immunotherapy for glioblastoma or low-grade astrocytoma, prior radiotherapy to the brain, a history of intracranial abscess within 6 months before randomisation, or a serious nonhealing wound Age Approx. 57 (all participants, in subgroup not given) Gender: 37% Female 63% Male Molecular type of GBM: MGMT methylated 26%, MGMT unmethylated 50%, missing (24%) (all participants) Performance status: WHO performance status of 2 or less0 (50%), 1 or 2 (50%)
Interventions	Arm 1: Patients received concomitant radiotherapy (60 Gy as 2-Gy fractions 5 days/wk) + oral temozolomide (75 mg per square meter of body-surface area per day for max. 49 days), in combination with in-

Avaglio 2014 *(Continued)*

	travenous bevacizumab (10 mg per kilogram of body weight) every 2 weeks. The last concomitant doses of TMZ and bevacizumab were administered on the day of the last dose of radiotherapy. Arm 2: patients received concomitant radiotherapy (60 Gy as 2-Gy fractions 5 days/wk) + oral temozolomide (75 mg per m2 of body-surface area per day for max. 49 days), in combination with intravenous placebo every 2 weeks. The last concomitant doses of TMZ and placebo were administered on the day of the last dose of radiotherapy. The concomitant-therapy phase in both arms was followed by a 28-day treatment break. In the maintenance phase, patients received TMZ (150 mg per m2 per day on days 1 to 5 during the first cycle and 200 mg per m2 per day during subsequent cycles if unacceptable toxic effects did not develop) + IV bevacizumab (10 mg per kilogram) or placebo every 2 weeks, for six 4-week cycles. In the monotherapy phase, IV bevacizumab (15 mg per kilogram) or placebo was continued every 3 weeks until the disease progressed or unacceptable toxic effects developed.
Outcomes	Co-primary endpoint: Investigator assessed PFS and OS at 1 and 2 years from date of randomisation. Survival estimates determined using Kaplan-Meier methods. Secondary endpoints: PFS assessed by independent review Safety HRQoL (QLQ-C30 and BN20)
Notes	All the data were collected by the sponsor and were analysed by an author employed by the sponsor, who vouched for the accuracy of the data. They summarised that their interpretation of the results is that this trial showed that the combination of bevacizumab with standard radiotherapy plus TMZ for the treatment of newly diagnosed glioblastoma did not improve overall survival but resulted in a 4.4-month improvement in median progression-free survival, with quality of life and functional status maintained; however, there was an increase in adverse events associated with bevacizumab therapy. The authors did not comment on the applicability of the evidence to elderly patients specifically.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Performed centrally with the use of an interactive voice-response system, with stratification according to study region and recursive partitioning analysis class
Allocation concealment (selection bias)	Unclear risk	Not described in the study reports
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The study sponsor, study investigators, and patients were unaware of the study-group assignments.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	In addition to investigator-assessed progression, radiologists at an independent review facility analysed all MRI scans. The independent reviewers were unaware of the study-group assignments, with read-only access to previous reviews until the final imaging data set was reviewed; at completion of the study, a review of the entire scan series verified the time of progression on MRI. In a final independent review, the determination of progression was calculated with the use of a prespecified algorithm that combined the assessment of the scans by the independent reviewer with the investigator's neurologic evaluation and assessment of glucocorticoid use.
Incomplete outcome data (attrition bias)	Low risk	ITT analysis

Avaglio 2014 *(Continued)*

All outcomes		
Selective reporting (reporting bias)	Low risk	Pre-specified outcomes are reported
Other bias	Unclear risk	Unblinding of the assignments was allowed at any time for safety reasons

GLARIUS 2016

Methods	Design: Phase II RCT Randomisation 2:1 Country: Germany Accrual dates: 2009-2011 Trial reg: NCT00967331 Funding: Roche
Participants	No enrolled: 566 No analysed: 182 Inclusion criteria: Chemotherapy and radiotherapy naive with newly diagnosed GBM; age older than 18 years, unmethylated MGMT (ratio <0.6)12; adequate healing of craniotomy; Karnofsky performance score (KPS) of 70% or greater; stable or decreasing corticosteroids within 5 days before random assignment; and adequate hematologic, hepatic, renal, and coagulation function. Exclusion: Stereotactic biopsy only; overt recent haemorrhage on brain magnetic resonance imaging (MRI); significant vascular disease; history of recurrent thromboembolism; evidence of bleeding diathesis or coagulopathy; gastrointestinal fistula or perforation; history of intra-abdominal or intracranial abscess within 6 months; serious nonhealing wound, ulcer, or bone fracture; and Gilbert-Meulengrachts disease. Age: Included patients aged over 18. Median age was 56 years. Thirty-four were aged 65+. Gender: 114 (67.1%) male. 56 (32.9%) female. Molecular type of GBM: Unmethylated MGMT GBM only. Patients were classified as nmMGMT if the ratio of MGMT to the b-actin reference gene (ACTB), calculated as (methylated MGMT/ACTB) 3 1,000, was less than 0.6. Performance status: Karnofsky performance score (KPS) of 70% or greater. KPS 90-100 (134 (78.8%)), KPS 70-80 (34 (20%)), NR (2 (1.2%))
Interventions	Arm 1: 60Gy RT + TMZ concomitant and adjuvant. Daily TMZ (75 mg/m2) during RT followed by six courses of TMZ. This arm included an optional predefined crossover at recurrence: patients could receive second-line BEV+IRI provided by the sponsor. Arm 2: 60Gy RT + BEV + IRI. BEV (Bevacizumab) (10mg/kg every 2 weeks) during radiotherapy (RT) followed by maintenance BEV (10mg/kg every 2 weeks) plus IRI (irinotecan) (125 mg/m2 every 2 weeks).
Outcomes	Primary endpoint: PFS at 6 months (modified intention to treat population). Estimated using binary proportions, a contingency table and Fisher's exact test for significance. Secondary endpoints:PFS in months (with HR), 1 year PFS rate, Median OS (with HR) calculated with a proportional Cox regression model 1 and 2 year OS rates, Change in HRQoL parameters over time, Change in KPS over time, Change in MMSE over time, Safety

GLARIUS 2016 *(Continued)*

Notes	Thirty-four patients were 65+years old and these findings were reported in a related conference abstract (Kebir 2016). The authors concluded: "BEV/IRI resulted in a superior PFS-6 rate and median PFS compared with TMZ. However, BEV+IRI did not improve OS, potentially because of the high crossover rate. BEV+IRI did not alter QOL compared with TMZ. BEV/IRI prolonged progression-free survival but OS was similar in both treatment arms. In the Cox model, age emerged as an independent prognostic factor in BEV/IRI treated patients only (Hazard Ratio, 2.72, p<0.001)."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were allocated to treatment arms using a web-based randomization system without stratification in a 2 : 1 distribution
Allocation concealment (selection bias)	Low risk	Randomization performed using a central web-based randomization system
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	No patient was lost to follow up for OS
Selective reporting (reporting bias)	Low risk	All predefined outcomes are reported
Other bias	High risk	All patients in this study had MGMT unmethylated GBM, which is associated with shorter survival time that MGMT-methylated tumours. Therefore, this may represent bias in the context of this review.

Green 1983

Methods	Design: 4-arm RCT Country: US Accrual dates: January 1976 toApril 1978 Trial reg: Not given Funding: National Cancer Institute, National Institute for Health, Department of Health and Human Services
Participants	No. randomised: 609 (overall) (65+, N=not specified) No. analysed: 527 (overall)(65+, N= 107) Inclusion criteria: histologically demonstrated supratentorial malignant glioma, patient age >=15yrs, and absence of major medical illness which could preclude treatment on any arm.

Green 1983 *(Continued)*

	Exclusion criteria: Any antineoplastic therapy prior randomisation, other than surgery (and conventional doses of corticosteroids within certain prescribed limits). Age Approx. 56 yrs overall Gender: 35% Female, 65% Male Molecular type of GBM: not reported (older study) Performance status: median Karnofsky performance status at baseline 70
Interventions	Arm 1: carmustine administered IV at a dose of 80 mg/m2/day on 3 successive days every 8 weeks. Dosage was decreased to 100 or subsequently to 80 mg/m2/day for the same indications of toxicity used for BCNU Arm 2: high dose (400mg/m2/day) oral methyl-prednisolone in three divided doses for 7 consecutive days without taper. After a 3-week interval, the treatment was repeated and continued in this 1 week on and 3weeks off cycle Arm 3: Procarbazine given orally at a total dose of 150mg/m2/day in three or four divided doses for 28 consecutive days every 8 weeks Arm 4: BCNU plus high dose methyl-prednisolone (as in mono arms) All participants received a total dose pf 6000 rads in 30-35 fractions of 172-200 rads, 5 days/week over 6-7 weeks, delivered to the whole brain by parallel opposed ports with megavoltage equipment.
Outcomes	Survival Reported using theMantel-Haenszel model for comparison of survivals; no HRs) Death rates Adverse events
Notes	The authors concluded: "This study indicates that BCNU and procarbazine are moderately useful agents in conjunction with radiotherapy for patients with malignant glioma. Both procarbazine and BCNU provide a significantly increased survival for patients with malignant glioma cmopared with methylprednisolone, even though the latter had been given in high doses to enhance possible oncoloytic effect. However, there was not a signfiicant difference in survival between the groups of patients receiving either procarbazine or BCNU alone.".

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Patients were randomised to one of the four treatment groups by means of a telephone call to the BTSG Operations Office."
Allocation concealment (selection bias)	Low risk	"Patients were randomised to one of the four treatment groups by means of a telephone call to the BTSG Operations Office."
Blinding of participants and personnel (performance bias) All outcomes	High risk	No specific details given in the primary journal publication but likely to be unblinded as some treatments IV and some oral treatments.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Primary endpoint based on survival so that will have a low risk of bias but it will not be blinded. High for adverse events.

Green 1983 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Primary outcomes as specified in the methods were reported for the total randomised population (Other analysis done on the "valid study group" which excluded 82 patients would be high risk).
Selective reporting (reporting bias)	Low risk	All predefined outcomes reported
Other bias	Unclear risk	Taken from the text in the paper: "The data in table 2 suggest heterogeneity with respect to dose of RT received. However, this could be produced by variations in the number of patients surviving long enough to receive a full course, and in fact, the heterogeneity in mean RT dose disappears if calculations are limited to those patients surviving over 2 months. The group randomised to procarbazine received fewer course of chemotherapy than the other groups, but the heterogeneity (in mean number of courses) among the four treatment groups was not statistically significant."

Keime-Guibert 2007

Methods	Design: Phase III RCT (a triangular sequential design for two-sided alternatives) Country: France Accrual dates: Feb 2001 to Jan 2005 Trial reg: NCT00430911 Funding: Research grant Programme Hospitalier de Recherche Clinique.
Participants	No. enrolled: 85 No. analysed: 85 Inclusion criteria: Patients 70 years of age or older; if they had histologically proven, newly diagnosed glioblastoma multiforme or anaplastic astrocytoma on the basis of the World Health Organization (WHO) classification and a Karnofsky performance score of 70 or more. Exclusion criteria: Not reported. Age Approx. 74 Gender: 37% Female, 63% Male Type of surgical procedure: Biopsy (n=44; 52%), partial resection (n=14; 16.5%) or complete resection (n=25; 29%). Used diagnostic criteria: World Health Organization (WHO) classification Molecular type of GBM: Not reported Performance status: Karnofsky performance score of 70 or more.
Interventions	Arm 1: supportive care plus radiotherapy (delivered by means of linear accelerators with a nominal energy of 6 mV or more, consisted of fractionated focal irradiation, at a dose of 1.8 Gy per fraction, given once daily 5 days per week, for a total dose of 50 Gy. The dose was defined according to the guidelines of the International Commission on Radiation Units and Measurements. Arm 2: supportive care only; Supportive care consisted of treatment with corticosteroids and anticonvulsant agents, physical and psychological support, and management by a palliative care team.

Keime-Guibert 2007 *(Continued)*

Outcomes	Primary endpoint: Survival as per intention to treat population. Median survival for both arms reported with a HR for death using a log-rank test. Secondary endpoints: PFS; change in performance status (KPS) over time; safety and tolerance of treatment but not clear which tool used to grade toxicity; HRQoL reported using EORTC QLQ-C30 and BN20. Few patients were alive after the first four follow up intervals (day 135) therefore HRQoL evaluated at days 1,30,60, 90 and 135 only. HRQoL reported as the change in mean HRQoL scores over time. Global assessment of deterioration over time also reported; cognitive functioning change over time reported using MMSE, Neuro-psychiatric Inventory (NPI) and the Mattis Dementia Rating Scale (MDRS).
Notes	Authors concluded that "RT increases the median survival of elderly patients with glioblastoma who have a good performance status at the start of treatment. As compared with supportive care, RT in such patients does not cause further deterioration in the Karnofsky performance status, health-related quality of life, or cognitive functions, but the survival benefit is modest." The trial was discontinued at the first interim analysis, which showed that with a preset boundary of efficacy, radiotherapy and supportive care were superior to supportive care alone.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization was performed at the data center of the Delegation for Clinical Research of the Assistance Publique – Hôpitaux de Paris, and patients were stratified according to the treatment center
Allocation concealment (selection bias)	Low risk	Randomization was performed at the data center of the Delegation for Clinical Research of the Assistance Publique – Hôpitaux de Paris, and patients were stratified according to the treatment center
Blinding of participants and personnel (performance bias) All outcomes	High risk	None (Open Label)
Blinding of outcome assessment (detection bias) All outcomes	High risk	None (Open Label)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comparisons between the two groups were made on an intention-to-treat basis; but low response rate on quality of life questionnaires. Therefore, HRQoL was at high risk for attrition.
Selective reporting (reporting bias)	Low risk	All relevant outcomes have been reported
Other bias	Unclear risk	Six patients received 90% or less of the planned radiation dose because of tumor progression (in five patients) and sudden death related to a pulmonary embolus (in one patient). One patient who was assigned to the RT group did not receive radiation because another tumor (duodenal cancer) developed before the start of RT; this patient received supportive care only

Malmstrom 2012

Methods	Design: Phase III RCT

Malmstrom 2012 *(Continued)*

	Country: Multicountry Accrual dates: Feb 2, 2000, and June 18, 2009 Trial reg: NCBTSG (the Nordic) Funding: Lion's Cancer Research Foundation, University of Umeå (Sweden); Cancer Fonden Sweden, and an unrestricted grant from Merck. Schering-Plough provided financial support for the study-group meetings. MDxHealth did the MGMT promoter methylation testing free of charge. In France, Merck provided temozolomide free of charge.
Participants	No. enrolled: 342, 291 randomised No. analysed: 291 altogether (123 in 70+ subgroup) Inclusion criteria: Patients with newly diagnosed, histologically confirmed glioblastoma (WHO grade IV astrocytoma) and aged 60 years or older were eligible. To resemble the characteristics of patients seen in clinics, patients with WHO performance scores 0–2 (even if neurological deficits gave them a performance score of 3) could be included. Patients were required to have adequate haematological (neutrophil count $1{\cdot}5\times10^9$/L or higher, platelets 100×10^9 /L or higher, and haemoglobin 100 g/L or higher), renal (creatinine concentrations in serum less than 1·5 times the upper limit of normal), and liver (bilirubin concentrations in serum less than 1·5 times the upper limit of normal and aspartate amino transferase and alanine aminotransferase no more than three times the upper limit of normal) functions, and were expected by the doctor to tolerate all treatment options. Exclusion criteria: Other primary cancers, except radically treated squamous-cell or basal cell carcinoma of the skin or other curatively treated malignancy without relapse at least 2 years after diagnosis, WHO performance score 3–4 (except a score of 3 owing to neurological defecits), any disorder that was likely to interfere with the study treatment, previous therapy for any brain tumour, except surgery or medical treatment within 3 years for other malignant diseases, and previous radiotherapy to the head that would prevent further irradiation. Age Approx. Median age for patients in three treatment groups was 70 years (70 years [range 60–88] in the TMZ, 70 years [60–83] in the hypofractionated RT, and 70 years [60–80] in the standard RT group); the median age for the additional 51 patients randomised only to two treatment groups was 3 years older (73 years, range 60–83). Gender: 40.7% Female, 59.3% Male Type of surgical procedure: Biopsy 26.7%, Resection (partial or complete) 73.3% Used diagnostic criteria: WHO 2007 criteria Molecular type of GBM: MGMT methylated 45%, MGMT unmethylated 55%, (data for 203 participants) Performance status (PS): WHO 0-2. (NB. In the results section, there were patients with WHO PS 3 included. The inclusion criteria allowed inclusion of patients with WHO PS 3 if their neurological status specifically gave them a PS of 3).
Interventions	Arm 1: Temozolomide (200 mg/m^2 on days 1–5 of every 28 days for up to six cycles), Arm 2: Hypofractionated radiotherapy (34 Gy administered in 3.4 Gy fractions over 2 weeks) Arm 3: Standard radiotherapy (60 Gy administered in 2 Gy fractions over 6 weeks)
Outcomes	Primary endpoint: Overall survival from date of randomisation estimated by the Kaplan-Meier method. Secondary endpoints: HRQoL (change in mean scores from baseline values for each treatment group at 6 weeks and 3 months); safety
Notes	After Oct 15, 2004, patients younger than 65 years who were deemed fit to receive combined treatment were excluded, owing to positive results of the European Organisation for Research and Treatment of

Malmstrom 2012 *(Continued)*

Cancer (EORTC) trial on concomitant and adjuvant temozolomide and radiotherapy for glioblastoma. The age cutoff of 65 years was based on subgroup analyses in that trial, which showed an increase in median survival for patients younger than 65 years who received combined treatment, whereas no such benefit was seen for older patients.

The authors of this trial concluded that "Our findings suggest that temozolomide chemotherapy or hypofractionated RT over 2 weeks might be valid alternative strategies, and that MGMT promoter methylation status might be a useful biomarker to help make treatment decisions."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation schedule
Allocation concealment (selection bias)	Unclear risk	The randomisation lists were generated by computer and were only available to the Oncology Centre staff. Each time a new patient was to be randomised, the participating institution sent a randomisation form to the Oncology Centre by fax, which was returned by fax to the investigator with the relevant treatment information.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Patients and study staff were aware of treatment assignment.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Patients and study staff were aware of treatment assignment.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Randomised 342, analysed 291 (85%); dropouts were balanced between TMZ and hypofractionated RT; no dropouts in standard RT arm
Selective reporting (reporting bias)	Low risk	All predefined clinical outcomes are reported
Other bias	Unclear risk	"At the time the study started, common practice included refraining from standard RT and offering a hypofractionated short course of RT or withholding antitumour therapy for patients older than 60 years who had a poor outlook. For these reasons, some centres were permitted to randomise patients to only two of the treatment groups (TMZ or hypofractionated RT) if this represented their standard of care."

Perry 2017

Methods	Design: Phase III RCT Country: Multicountry Accrual dates: November 2007 - September 2013 Trial reg: NCT00482677

Perry 2017 *(Continued)*

	Funding: Supported by grants (015469 and 021039) from the Canadian Cancer Society Research Institute, by an unrestricted grant from Schering-Plough (now Merck), and by the EORTC Cancer Research Fund from Belgium.
Participants	No. enrolled: 562 No. analysed: 562 Inclusion criteria: 65 years of age or older who had newly diagnosed glioblastoma (World Health Organization grade IV astrocytoma), which was histologically confirmed after surgery or biopsy performed less than 28 days before randomisation. Patients were deemed by their physicians not to be suitable to receive conventional radiotherapy (60 Gy in 30 fractions over a period of 6 weeks) in combination with TMZ. Eligible patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2 Age Approx. median age was 73 years (range, 65 to 90), with 29.5% of the patients older than 75 years of age Gender: 39% Female, 61% Male Type of surgical procedure: 68.3% of the participants underwent partial or complete surgical resection Used diagnostic criteria: WHO classification Molecular type of GBM: MGMT methylated 46.6%, MGMT unmethylated 53.4% (data for 354 participants) Performance status: ECOG 0-2
Interventions	Arm 1: Radiation was planned with the use of three-dimensional planning systems for a total dose of 40.05 Gy, administered in 15 daily fractions over a period of 3 weeks Arm 2: concomitant temozolomide was administered with radiotherapy at a dose of 75 mg per square meter of body-surface area per day for 21 consecutive days from day 1 until the final day of radiotherapy. Adjuvant temozolomide was administered at a dose of 150 to 200 mg per square meter per day for 5 consecutive days of a 28-day cycle for up to 12 cycles or until disease progression. Use of antiemetic and infection prophylaxis was at the discretion of the investigator.
Outcomes	Primary endpoint: Overall survival from date of randomisation Secondary endpoints: OS rate at 12, 18 and 24 months according to treatment group and MGMT status; PFS; safety HRQoL(using QLQ-C30 and QLQ-B20) reported as time to deterioration
Notes	Authors concluded that "In elderly patients with glioblastoma, the addition of temozolomide to short-course radiotherapy resulted in longer survival than short-course radiotherapy alone."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Treatment assignment was performed centrally with the randomization algorithm dynamically minimizing the chance of an imbalance between trial groups
Allocation concealment (selection bias)	Unclear risk	Treatment assignment was performed centrally

Perry 2017 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	None (Open Label)
Blinding of outcome assessment (detection bias) All outcomes	High risk	None (Open Label)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low risk overall because final analysis populations included the intention-to-treat population (all randomly assigned patients) for all efficacy end points and the as-treated population (all patients who received at least one dose of trial treatment) for safety and drug-exposure analyses. However, attrition was a major problem for quality of life data that impacted the quality of these findings.
Selective reporting (reporting bias)	Low risk	All predefined outcomes are reported
Other bias	Low risk	None noted

Roa 2004

Methods	Design: Phase III RCT Country: Canada Accrual dates: Between 1996 and 2001 Trial reg: N/A Funding: Alberta Cancer
Participants	No. randomised: 100 No. analysed: 95 Inclusion criteria: age >=60 years, histologically confirmed GBM, and KPS >=50 Exclusion criteria: previous cranial RT, concomitant or prior invasive cancer (except nonmelanomatous skin cancer and carcinoma-in-situ), failure to commence RT for GBM within 6 wks of surgical diagnosis, and inability to comply with follow-up requirements. Patients were also ineligible if pre- and postoperative imaging studies were unavailable for review Mean age [SD]. 72.4 years [5.4] in the 6 week arm and 71.0 years [5.5] Gender: 42% Female, 58% Male Type of surgical procedure: Biopsy 39% (37/95); Subtotal resection 52% (49/95); Total resection 9% (9/95) Used diagnostic criteria: Unclear (The diagnosis of GBM was confirmed centrally on all cases) Molecular type of GBM: NR Performance status: Karnofsky performance score of 50 or more
Interventions	Arm 1: Short-course RT (40Gy in 15 daily fractions over 3 weeks) Arm 2: 60Gy in 30 fractions over 6 weeks; Patients receiving standard RT were treated in two phases.

Roa 2004 *(Continued)*

	RT started within 6 weeks of surgery; The absorbed dose was to be within 10% of the prescribed dose. Chemotherapy was not prescribed before or during RT but could be given at the time of disease recurrence
Outcomes	Primary endpoint: Overall survival from date of randomisation. Survival curves generated using Kaplan-Meier method and relative risk calculated using a proportional hazards model. Secondary endpoints: OS from date of diagnosis; Proportion of patients alive at 6 months; HRQoL (KPS and FACT-Br v3); corticosteroid requirement
Notes	Authors also evaluated post-treatment corticosteroid requirements and found that fewer patients in the short course arm required an increase in their post-treatment daily dose of corticosteroids (23% vs 49%). Authors concluded that "There is no difference in survival between patients receiving standard RT or short-course RT. In view of the similar KPS scores, decreased increment in corticosteroid requirement, and reduced treatment time, the abbreviated course of RT seems to be a reasonable treatment option for older patients with GBM."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	An independent statistician at the coordinating centre (Cross Cancer Institute) produced computer-generated randomisation lists; Patients were stratified by extent of resection (biopsy v any degree of resection, as defined by the operative report) and KPS (<70 v >=70).
Allocation concealment (selection bias)	Low risk	An independent statistician at the coordinating centre (Cross Cancer Institute) produced computer-generated randomisation lists; Strata-specific, sequentially numbered, sealed opaque envelopes containing the treatment assignment were supplied by the statistician to the research nurse at the coordinating centre; Once patient eligibility had been determined and consent was obtained, participating centres contacted the coordinating nurse by fax to request randomisation. The next envelope in the appropriate strata was opened to determine treatment assignment.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No details given
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details given
Incomplete outcome data (attrition bias) All outcomes	Low risk	Out of 100 randomised (51 st RT & 49 shorter course RT) - overall drop out 5% (2 withdrawals & 2 deaths st adj RT vs 1 withdrawal in short RT); 12 vs 5 participants did not complete the treatment
Selective reporting (reporting bias)	Low risk	All predefined outcomes are reported
Other bias	Low risk	None noted

Roa 2015

Methods	Design: Phase III RCT non-inferiority Country: Multicountry Accrual dates: 2010 and 2013 (from Kepka 2014) Trial reg: NCT01450449 Funding: Supported by the International Atomic Energy Agency (IAEA) under the IAEA Coordinated Research Activities.
Participants	No. enrolled: 98 (65+, N=61) No. analysed: 96 (65+, N=59) Inclusion criteria: Frail patients were defined as 50 years old with a KPS of 50% to 70%; elderly and frail patients were defined as 65 yrs old with a KPS of 50% to 70%; and elderly patients were defined as 65 yrs old with a KPS of 80% to 100%. Incl: histopathologically confirmed newly diagnosed GBM (WHO grade 4); initial surgery/biopsy at diagnosis performed 6 weeks before random assignment; age 50 years at time of entry; KPS 50%; no previous chemotherapy or RT exposure Exclusion criteria: Patients fulfilling either of the following criteria were not eligible for the study: history of other malignancy or history of a serious infection or underlying medical condition Age Approx. No average; 50-65 yrs 37 (37.8%), >65 61 (62.2%) Gender: 53% Female, 47% Male Type of surgical procedure: Stereotactic biopsy (13.3%), partial resection (65.3%), total macroscopic resection (21.4%) Used diagnostic criteria: WHO classification Molecular type of GBM: NR Performance status: Karnofsky performance score of 50% or more
Interventions	Arm 1: short-course RT (25 Gy in five fractions delivered in 1 week) Arm 2: standard RT (40 Gy in 15 fractions delivered in 3 weeks)
Outcomes	OS from date of randomisation calculated using Kaplan-Meier estimates to obtain median survival time Secondary outcomes: PFS; HRQoL (assessed using QLQ-C30 and QLQ-BN20); Adverse events
Notes	We extracted data on the elderly subgroup from the substudy reported by Guedes de Castro 2017. Authors concluded that "short-course RT regimen of 25 Gy in 5 fractions is an acceptable treatment option for patients aged 65 years, mainly those with a poor performance status or contraindication to chemotherapy". Authors planned to report detailed HRQOL data in a separate paper.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random assignment was performed using Excel with the RAND option function (Microsoft, Redmond, WA).
Allocation concealment (selection bias)	Unclear risk	Not given

Roa 2015 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	None (Open Label)
Blinding of outcome assessment (detection bias) All outcomes	High risk	None (Open Label)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Randomised 98 elderly and/or frail, analysed 96
Selective reporting (reporting bias)	Low risk	All predefined outcomes were reported (hazard ratios were calculated from Kaplan Meier plots)
Other bias	Low risk	None noted

Stupp 2017a

Methods	Design: Phase III RCT Country: Multicountry Accrual dates: July 2009 and December 2014 Trial reg: NCT00916409 Funding: Novocure Ltd.
Participants	No. enrolled: 695 (65+, N = 134) No. analysed: 695 (65+, N = 134) maintenance temozolomide alone (150-200mg/m2/d for 5 days every 28 days for 6 cycles) Inclusion criteria: aged 18 years or older, had a Karnofsky performance score of 70 or higher (a score of ≥70 ensures independence in activities of daily living), and had newly diagnosed and histologically confirmed supratentorial glioblastoma (WHO grade IV astrocytoma). Exclusion criteria: Patients with evidence of progressive disease following radiochemotherapy, infratentorial tumour location, and severe co-morbidities were excluded Mean age not given for over 65+, only for the group as a whole (median 56 years, range 19 to 83 in arm 1 and median 57 years, range 19 to 80 in arm 2) Gender: for the total sample was 68% male and 32% female Used diagnostic criteria: WHO classification Molecular type of GBM: MGMT methylated 37%, MGMT unmethylated 53%, invalid sample (9%) (data for 571 participants) Performance status: Karnofsky performance score of 70 or higher
Interventions	Arm 1: tumour treating fields therapy plus maintenance temozolomide after standard chemoradiotherapy (up to 60Gy); delivered through 4 transducer arrays with 9 insulated electrodes each placed on the shaved scalp and connected to a portable device set to generate 200-kHz electric fields within the brain; All treatment was delivered on an outpatient basis and at home.

Stupp 2017a *(Continued)*

	Arm 2: maintenance temozolomide alone (150-200mg/m2/d for 5 days every 28 days for 6 cycles). If tumor progression occurred, second line therapy was offered per local practice.
Outcomes	Primary endpoint: PFS in intention to treat population Secondary endpoint: Overall survival Exploratory endpoints: Percentage of patients alive and progression free at 6 months Annualised survival rates HRQoL (QLQ-30 and QLQ-BN20) reported in a separate article (Taphoorn 2018). Mean change in HRQoL from baseline, deterioration free survival (DFS) and time to deterioration (TTD). MMSE KPS Adverse events and tolerability
Notes	Prior use of implanted carmustine wafers was allowed and randomisation was after patients had completed chemoradiation. Authors concluded for entire population that: "In the final analysis of this randomised clinical trial of patients with glioblastoma who had received standard radiochemotherapy, the addition of TTFields to maintenance TMZ chemotherapy vs maintenance temozolomide alone, resulted in statistically significant improvement in progression-free survival and overall survival."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were randomised at a ratio of 2:1; performed using a central web-based randomisation system and was stratified by extent of resection (biopsy, partial resection, gross total resection) and by the methylation status of the O6-methylguanine-DNA methyltransferase gene promoter (methylated, unmethylated, unknown)
Allocation concealment (selection bias)	Low risk	Randomisation performed using a central web-based randomisation system
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All MRIs were reviewed by 2 blinded central independent radiologists (BioClinica Inc) and were evaluated for tumour response and progression (Macdonald criteria); For cases in which the 2 reviewers were not in agreement, a third blinded radiologist adjudicated between them.
Incomplete outcome data (attrition bias) All outcomes	Low risk	For the main population: ITT for primary outcome, PP for secondary (OS); Overall 53 lost to followup (7.6%); 39/466 vs 14/229 (8.4% vs 6.1%) - 9 vs 1 disease progression
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes are reported

Stupp 2017a *(Continued)*

Other bias	High risk	In the context of the review, this trial may represent a high risk of bias due to the timing of randomisation, because patients that die during CRT or have severe early toxicities would have dropped out by the time of randomisation. Novocure Ltd had a role in the design and conduct of the study, collection, management, and analysis of the data. After the release of the interim results, 26 patients in the TMZ only arm with favourable prognostic factors and who had received more cycles of maintenance TMZ crossed over to receive TTF. These patients were analysed in the group to which they had been randomised (ITT analysis). The effect of this might have led to an underestimation the impact of the experimental intervention.

Weller 2017

Methods	Design: Phase III RCT Country: Multicountry Accrual dates: April 12, 2012, and Dec 15, 2014 Trial Reg: NCT01480479 Funding: Celldex Therapeutics, Inc
Participants	Inclusion criteria: 18 years or older with confirmed GBM histology and EGFRvIII expression analysis by real time (RT) PCR. Patients must have undergone maximal surgical resection and have completed standard radiotherapy (up to 60Gy) with concomitant TMZ (75mg/m2 per day). To be eligible, at least 90% of the planned RT dose had to be delivered. Patients had to have tumour tissue specimens (paraffin-embedded) from surgical resection available for central pathology review, MGMT status determination, and analysis of ECFRvIII status. Exclusion criteria: Disease progression during chemoradiation, any additional tumour-specific treatment for GBM, inability to taper corticosteroids to 2mg of dexamethasone or lower (or equivalent) per day for at least 3 days before randomisation, ECOG PS of 3 or higher in the week before randomisation, diffuse leptomeningeal disease, gliomatosis cerebri, infratentorial disease, active infection, metastatic disease, and immunosuppressive disease. No. enrolled: 745 (65+, N = 174) No. analysed: 745 (65+, N = 174) Molecular type of GBM: MGMT methylated 34%, MGMT unmethylated 59%, missing (7%) (data for all participants)
Interventions	Arm 1: Rindopepimut plus maintenance TMZ Arm 2: Control plus maintenance TMZ only All participants received standard chemoradiotherapy before randomisation and had to have received at least 90% of the planned radiotherapy dose to be eligible for trial inclusion.
Outcomes	Primary endpoint: OS from date of randomisation in patients with newly diagnosed, EGFRvIII positive GBM and minimal residual disease (MRD) (modified intention to treat analysis). OS analysis included HR and summarised using the Kaplan-Meier method. Secondary endpoints: OS in all patients (ITT), OS in patients with significant residual disease (SRD), PFS, Proportion of patients achieving an objective tumour response (using RANO criteria). Included requirement for corticosteroids.

Weller 2017 *(Continued)*

	HRQoL (MDASI-BT, QLQ-C30 and QLQ-BN20), Humoral responses to EGFR vIII, Post-treatment EGFRvIII expression status. Survival rates at 1,2 and 3 years. Adverse events
Notes	Standard RT dose was stated as "up to 60Gy" and standard TMZ dose was 75mg/m2 per day

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients "were randomly assigned (1:1) to the treatment groups with a pre-specified randomisations sequence with a block size of four."
Allocation concealment (selection bias)	Low risk	"Patients, investigators, and the trial funder were masked to treatment allocation".
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Study treatments were prepared in the pharmacy and given to study staff in blinded pre-loaded syringes.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"The retrospective imaging review committee assessment, masked to treatment assignment and investigator assessments, was used for the primary analyses of progression-free survival and objective tumour response.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low attrition for primary outcome
Selective reporting (reporting bias)	Unclear risk	Health related quality of life not yet reported. Will possibly come with a future publication.
Other bias	Low risk	None noted.

Wick 2012

Methods	Design: Phase III RCT | non-inferiority trial with a 25% margin Country: Germany Accrual dates: 15 May 2005 - 2 Nov 2010 (last randomisation on 2 Nov 2009) Trial reg: NCT01502241 Funding: Merck, Sharp & Dohme
Participants	No. enrolled: 412 No. analysed: 373 Inclusion criteria: de novo histologically confirmed AA or GB and > 65 years of age, Karnofsky performance score (KPS) > 60, no prior systemic chemotherapy or RT to the brain, and adequate bone marrow reserve, liver, and renal function. Exclusion criteria: Failure to confirm AA or GB would have resulted in exclusion from the intention-to-treat-population. Age Approx. 71.5 years Gender: 53% Female, 47% Male

Wick 2012 *(Continued)*

	Type of surgical procedure: Resection: complete 28% partial 30% biopsy 39% Used diagnostic criteria: Inclusion into the trial was based on local diagnosis. Histologic diagnoses were confirmed centrally according to the WHO classifications 2000 and 2007; there was no change in the diagnostic criteria for AA or GB between the two versions of the WHO classification Molecular type of GBM: MGMT methylated 20%, MGMT unmethylated 36%, inconclusive/missing (44%) (data for all analysed participants) Performance status: Unclear
Interventions	Arm 1: standard radiotherapy (60 Gy in 30 x 2 Gy fractions) Arm 2: temozolomide (TMZ)a one week on/one week off schedule
Outcomes	The primary endpoint was overall survival (OS), measured in days from surgery to death. Secondary efficacy end points included event-free survival (EFS), best response, HRQOL (QLQ-C30 and QLQ-BN20 and safety.
Notes	Author conclusions: NOA-08 broadens the spectrum of primary treatment of elderly patients with malignant gliomas by demonstrating the non-inferiority of primary treatment of elderly patients with malignant gliomas with TMZ alone. It implements MGMT promoter methylation as a relevant biomarker to decide, when patients may be under-treated with primary RT alone.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participant allocation was done according to an electronically generated randomisation list in blocks of variable length without stratification. The sequence was generated prior to study start at the independent Contract Research Organization (CRO), Alcedis (Gießen, Germany).
Allocation concealment (selection bias)	Low risk	Enrolment was done at the study site by an investigator. Assignment was initiated by FAX transmission from the study site to the CRO for single patients fulfilling the eligibility criteria. A responsible project manager at the CRO performed the randomisation process and reported the assignment to the trial group via FAX transmission to the study site.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding of investigators or participants was impossible.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Similarly the data had to be analysed with knowledge of the group assignment. Biases were prevented by strict adherence to an analysis plan.
Incomplete outcome data (attrition bias) All outcomes	High risk	Overall drop out rate less than 20% with moderate imbalance between TMZ and RT with higher drop out in the RT group (5% vs 14%)
Selective reporting (reporting bias)	Low risk	Pre-specified outcomes were reported.
Other bias	Unclear risk	None noted.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Ali 2018	Ineligible population - no data for the elderly subgroup. This is a recent report of an older trial (RTOG 9006) with negative findings, for which recruitment occurred from 1990 to 1994. Hyperfractionated RT (72 Gy in 60 twice-daily fractions) was compared with standard RT (60 Gy in 30 daily fractions) for GBM treatment and the authors reported that there was no indication of, or trend towards, benefit with hyperfractionated RT for GBM. Although the study included 235/694 people 60 years of age and older, findings for the older subgroup were not reported separately.
Armstrong 2013	Ineligible population - no data for the elderly subgroup. This is a report of a secondary analysis of RTOG 0525 trial (NCT00304031) comparing conventional adjuvant temozolomide (TMZ) with dose-intensive TMZ in patients with newly diagnosed glioblastoma on quality of life outcomes. The trial recruited patients age 21 to 84 years. The proportion of patients age 65 or more is unknown and analysis was stratified only by age threshold of 50 years.
Athanassiou 2005	Ineligible population - no data for the elderly subgroup. This is a report of a phase 2 trial of TMZ and radiotherapy in comparison to radiotherapy alone in patients with newly diagnosed glioblastoma multiforme. The trial recruited patients age 18 and more with unknown proportion of elderly patients (65 years or more). The age (>50 years) is evaluated as a predictor for time to progression and overall survival - HR 1.75 (p-value 0.067) and 1.86 (p-value 0.058) respectively.
Balana 2016	Ineligible population - no data for the elderly subgroup. This is a report of a phase 2 GENOM 009 trial of bevacizumab (BEV) and TMZ in comparison to TMZ alone as neoadjuvant treatment in patients with unresected glioblastoma. The trial recruited patients age 18 to maximum 75 years. The number of participants available for analysis for progression free survival, overall survival and toxicity was 93 (45 TMZ and 48 TMZ+BEV) with unknown proportion of participants age over 65 or 70.
Bampoe 2000	Ineligible population - no data for the elderly subgroup. This is a report of a trial of brachytherapy as a boost treatment (plus radiotheraphy versus radiotheraphy alone) on quality of life in patients with glioblastoma multiforme. The recruitment occured between 1986 and 1996. The inclusion age was 18 to maximum of 70 years, thus there was no relevant subgroup of patients in this trial.
Batchelor 2013	Ineligible population - recurrent glioblastoma. This is a report of a phase 3, placebo-controlled, REGAL trial (NCT00777153) in patients with recurrent glioblastoma.
Beije 2015	Ineligible population - recurrent glioblastoma. This is a report of a side study of BELOB trial (NTR1929) in patients with recurrent glioblastoma. The side study assessed the kinetics of the circulating endothelial calls and their prognostic value.
Bent 2009	Ineligible study design. This is a report of a side study of EORTC Brain Tumor Group Study 26951 in participants with anaplastic oligodendroglial tumors or anaplastic oligoastrocytoma. The side study assessed the correlation between MGMT methylation status and outcome and therapy given in EORTC cohort.
Bhandari 2013	Ineligible study population. This is a conference abstract of a study which full text was published in 2017 (Bhandari 2017). The study did not include an elderly subgroup.
Bhandari 2017	Ineligible study population - no data for the elderly subgroup. This is a report of a comparative study of adjuvant TMZ six cycles versus extended 12 cycles in newly diagnosed glioblastoma multiforme. The study recruited 40 postoperative participants between 2012 and 2013 (age range 18 to 65 years). The report does not present any relevant age-related data analysis.
Bleehen 1981	Ineligible study population - no data for the elderly subgroup. This is a report of a randomised trial of misonidazole and radiotheraphy (4 weeks with 43.52 GY and 56.56 over 5.5 weeks) for grade 3 and 4 cerebral astrocytoma. The accrual stopped at the end of 1978, and a total of 55 participants

Study	Reason for exclusion
	age 18 to 75 years was recruited across three arms. The proportion of those age 65 (or 70) or over is unclear. The report does not present any relevant age-related data analysis.
Bleehen 1991	Ineligible study population - no data for the elderly subgroup. This is a report of a randomised trial of two radiotherapy doses in the treatment of grades 3 and 4 astrocytoma. The study randomised 474 patients between 1983 and 1988 (age range 18 - 73 years). There were a total of 140 participants age 60-73. The proportion of participants age 65 (or 70) or over is unknown. The report does not present any relevant age-related data analysis.
Blumenthal 2015	Ineligible study population - no data for the elderly subgroup. This is a report of a phase 3 randomised trial of radiation therapy (RT) and O6-benzylguanine + BCNU compared with RT and BCNU alone in newly diagnosed glioblastoma and gliosarcoma (SWOG S0001). The study was terminated in 2015, at the time of the interim analysis, per recommendation of the Data and Safety Monitoring Committee. Up to that point, 183 participants were registered. The proportion of participants age 65 or over is unknown (startification only by below/above 50 years). The report does not present any relevant age-related data analysis.
Blumenthal 2018	Not a suitable study design. Not a RCT, an exploratory analysis of RTOG 0525 and RTOG 0825 data.
Bogdahn 2011	Wrong population - recurrent glioblastoma. This is a report of a phase 2 randomised trial of targeted therapy for high-grade (recurrent /refractory) glioblastoma multiforme or anaplasticastrocytoma with TGF-beta2 inhibitor trabedersen.
Boiardi 1992	Wrong population - recurrent glioblastoma. This is a report of a randomised trial of '8-drugs-in-one-day' combination in treatment of recurrent glioblastoma multiforme.
Boisen 2018	Not suitable study design. This is a report with a secondary analysis of plasma YKL-40 as a biomarker for BEV efficacy using data from AVAglio trial (Chinot et al. 2014)
Bower 1997	Wrong population - recurrent glioblastoma. This is a report of a phase 2 randomised trial of TMZ in recurrent or progressive for high-grade glioblastoma multiforme.
Boxerman 2013	Not suitable study design. This is a report of a secondary analysis using RTOG 0625 and ACRIN 6677 studies to investigate whether early post-treatment progression on FLAIR or post-contrast MRI predict overall survival.
Brandes 2016	Wrong population - recurrent glioblastoma. This is a report of a phase 2 randomised, noncomparative study of fotemustine or BEV for patients with recurrent glioblastoma (AVAREG).
Brisman 1976	Wrong population - no data for the elderly subgroup. This is a report of a study evaluating adjuvant nitrosourea chemotherapy with carmustine (BCNU), lomustine (CCNU), or semustine (methyl CCNU) in addition to surgery and radiotherapy.The study included 62 participants between 1970 and 1972. Overall, there were less than 20 participants age 65 years or more (18 patients).
Brown 2016	Wrong population - recurrent glioblastoma. This is a report of a phase 2 randomised trial comparing cediranib plus gefitinib with Cediranib plus placebo in subjects with recurrent / progressive glioblastoma.
Buckner 2001	Wrong population - no data for the elderly subgroup. This is a report of a phase 3 study of RT plus carmustine with or without recombinant interferon-alpha in the treatment of patients with newly diagnosed high-grade glioblastoma. The study enrolled 383 participants between 1990 and 1994 of which 41% (146) are over 60 years of age. The report does not present any relevant age-related data analysis.
Buckner 2006	Wrong population - no data for the elderly subgroup. This is a report of a phase 3 trial of carmustine and cisplatin compared with carmustine alone and standard RT or accelerated RT in patients with glioblastoma multiforme (NCCT 93-72-52 and SWOG 9503). The study included 451 partic-

Study	Reason for exclusion
	ipants between 1994 and 1999 of which 34% (137) are over 60 years of age. The report does not present any relevant age-related data analysis.
Carpentier 2017	Wrong population no data for the elderly subgroup. This is a report of a phase 2 randomised trial of an intracerebral injection of CpG oligonucleotide for newly diagnosed glioblastoma. The study recruited 81 participants. The median age is around 60 years (range 42 - 78), and the proportion of those age 65 (or 70) or over is unknown. The report does not present any relevant age-related data analysis.
Castro 1997	Wrong population - insufficient details regarding population's age. This is a report of randomised study of two doses of neon ion irradiation therapy for glioblastoma. The study recruited 15 participants of unknown age.
Catterall 1980	Not suitable study design. This is a report of a controlled, non-randomised, pilot study comparing fast neutrons with megavoltage X-rays in the treatment of glioblastoma.
Chamberlain 2005	Not suitable study design. This is a correspondence to the editor of a journal regarding "Abbreviated course of radiation therapy in older patients with glioblastoma multiforme" (Roa 2004).
Chang 1983	Wrong population - no data for the elderly subgroup. This is a report of a randomised trial of postoperative RT and combined postoperative RT with chemotherapy in the management of malignant gliomas. The study entrolled 626 participants between 1974 and 1976. The proportion of trial participants age 65 (or 70) or over is unknown (27% were 60 years or over). The report does not present any relevant age-related data analysis.
Chauffer 2014	Wrong population - no data for the elderly subgroup. This is a report of a phase 2 randomised trial of irinotecan and BEV as neo-adjuvant to TMZ-based chemoradiation compared with TMZ-chemoradiation for unresectable glioblastoma (TEMAVIR trial, ANOCEF group). The study included 120 participants (age 18-70) between 2009 and 2011. The proportion of those age 65 (or 70) or over is unknown. The report does not present any relevant age-related data analysis.
Chinnaiyan 2018	Wrong population - no data for the elderly subgroup. This is a report of a phase 2 randomised study of everolimus in combination with chemoradiation (EVE+RT+TMZ) in newly diagnosed glioblastoma (NRG Oncology RTOG 0913). The study randomised 171 participants (age 18 or over) between 2012 and 2013. The proportion of those age 70 or over is around 16% (28/171). In the study, the EVE +RT+TMZ combination was significantly more toxic than RT+TMZ on its own with no results reported for the elderly subgroup.
Chong 2018	Wrong study design - an audit of treatments for the elderly with glioblastoma in a clinical setting in the United Kingdom.
Cianfriglia 1980	Wrong population - no data for the elderly subgroup. This is a report of randomised trial of CCNU-chemotherapy in hemispheric supratentorial glioblastoma. The study recruited 103 participants (age 12 to 80) of which 24 were 60-69 years old and three 70-79 years old.
Clarke 2009	Wrong population - no data for the elderly subgroup. This is a report of a phase 2 randomised trial comparing chemotherapy followed by either dose-dense or metronomic TMZ in patients with newly diagnosed glioblastoma. The study involved 85 participants (age 18-70) between 2005 and 2007. The median age in the trial is 56.3 (range 21-71), and the proportion of those age 65 (or 70) or over is unknown.
Cohen 2005	Not suitable study design. This is a approval summary from the Food and Drug Administration organisation in the US for TMZ combined with RT for the treatment of newly diagnosed glioblastoma multiforme. The report summarises the findings of Stupp et al. trial (N Engl J Med 2005; 352:987-96) where the age cap was at 70 years, and the analysis was stratified by <50 or >=50.
Combs 2008	Wrong population - no data for the elderly subgroup. This is a report of a randomised trial evaluating toxicity and outcomes in patients with primary glioblastoma treated with postoperative ra-

Study	Reason for exclusion
	diochemotherapy comparing two TMZ regimens. The study involved 160 participants between 1999 and 2007. The median age in the study is 60 years and the proportion of those age 65 (or 70) or over is unknown. The report does not contain any relevant age-related data analysis.
Corn 1994	Not suitable study design. This is a report of an exploratory analysis of white matter changes in participants of a trial living more than 18 months. The trial is a phase 1/2 dose-seeking study that evaluated twice-daily RT for supratentorial high grade malignant gliomas.
Curran 1992	Wrong population - no data for the elderly subgroup. This is a report of a randomised trial comparing an accelerated hyperfractionated RT (1.6 Gy twice daily fractions) and bis-chlorethyl nitrosourea for malignant glioma. The trial recruited 304 participants (age 18-70) between 1987 and 1989. The proportion of participants age 65 (or 70) or over is unknown. The report does not contain any relevant age-related data analysis.
Das 2017	Not suitable study design. This is an opinion piece summarising the available evidence on the management of glioblastoma in the elderly patients.
Deutsch 1989	Wrong population - no data for the elderly subgroup. This is a report of a randomised trial comparing BCNU with RT, streptozotocin with RT, BCNU with hyperfractionated RT, and BCNU following misonidazole with RT in the postoperative treatment of malignant glioma (BTCG study 77-02). The trial recruited 557 participants (age 15 or over) between 1978 and 1980. The median age in the trial was 58 (range 15 to 82 years), and the proportion of those age 65 or over is 24.4%. The trial report presents the overall survival data by age for all trial participants without accounting for treatment allocation.
Dherijha 2018	Not suitable study design. Not a RCT, a retrospective study of survival in elderly patients in two UK hospitals.
Dinapoli 1993	Wrong population - no data for the elderly subgroup. This is a report of a phase 3 randomised trial comparing PCNU and carmustine combined with RT in high-grade glioma. The trial recruited 346 participants (age 18 or over) between 1985 and 1989. The median age in the trial was 59 (age range 21 to 84 years), and the proportion of those age 65 (or 70) or over is unknown. The trial reports the overall survival by age group for all trial participants without accounting for treatment allocation.
Du 2018	Wrong population - no data for the elderly subgroup. This is a report of a randomised trial of temozolamide combined with three-dimensional conformal RT on residual disease after surgery of glioblastoma. The trial recruited 58 participants between 2013 and 2015. The average age in the study was around 45 years (age range 28 - 78), and the proportion of those 65 (or 70) or over is unknown. The report does not contain any relevant age-related data analysis.
Duncan 1986	Wrong population - no data for the elderly subgroup. This is a report of a randomised trial of mixed-schedule (neutron/photon) irradiation in the treatment of supratentorial astrocytoma (grade 3 & 4). The study involved 61 participants between 1979 and 1982. The study population was stratified by age group "16-39", "40-59", and "60 and over" with 25 participants in the final group. The report does not contain any relevant age-related data analysis.
Elinzano 2018	Wrong population - no data for the elderly subgroup. This is a report of a randomised phase 2 trial comparing poliglumex and RT with combined TMZ and RT for glioblastoma without MGMT methylation. The study randomised 63 participants between 2011 and 2014. Participants' age ranged from 21 to 82 and the proportion of those age 65 (or 70) or over is unknown. The report does not contain any relevant age-related data analysis.
Eljamel 2008	Wrong population - no data for the elderly subgroup. This is a report of a randomised phase 3 trial comparing ALA and Photofrin® fluorescence-guided resection with repetitive photody-namic therapy in patients with glioblastoma. The study recruited 27 participants (dates not given) whose mean age was 59.8 years; the proportion of those age 65 (or 70) or over is unknown. The report does not contain any relevant age-related data analysis.

Study	Reason for exclusion
Elliott 1997	Wrong population - no data for the elderly subgroup. This is a report of a randomised trail comparing RT combined with dibromodulcitol with RT and BCNU in high grade (3 and 4) astrocytoma. The study included 238 participants between 1980 and 1985 with 52% (118/229) being 60 years of age or more. No relevant age-related subgroup analysis - one of stratification factors is age <55 or >=55.
Espana 1978	Not suitable study design. This is a report of a one-arm phase 2 trial evaluating dianhydrogalactiol in malignant glioma.
Eyre 1983	Wrong population - no data for the elderly subgroup. This is a report of a randomised trial comparing RT and CCNU with RT, CCNU and procarbazine in patients with glioblastoma following surgery. The study recruited 117 participants between 1974 and 1975. The median age is around 50 years of age, and the proportion of those age 65 (or 70) or over is unknown. The report does not contain any relevant age-related data analysis.
Farkkila 1994	Wrong population - no data for the elderly subgroup. This is a report of a randomised trial comparing intratumoral recombinant gamma-interferon as adjuvant to open cytoreduction and external irradiation of 60 Gy in adults with high-grade cerebral glioma. The study recruited 32 participants (years unknown). The age ranged from 18 to 71 years, and the proportion of those age 65 (or 70) or over is unknown. The report does not contain any relevant age-related data analysis.
Felzmann 2013	Abstract associated with the poster Felzmann 2014.
Felzmann 2014	Conference poster with limited information. This is a conference poster of a randomised trial evaluating safety and efficacy of individualised dendritic cell-based cancer immune therapy for glioblastoma. The study recruited 105 participants (years unknown). The age ranged from 18 to 70 years, and the proportion of those age 65 and over is unknown. The report does not contain any relevant age-related data analysis.
Field 2015	Wrong population - recurrent glioblastoma. This is a report of a randomised phase 2 trial of carboplatin and bevacizumabin recurrent glioblastoma.
Field 2017	Wrong population - recurrent glioblastoma. This is a secondary analysis of health-related quality of life outcomes from a randomised phase 2 trial of carboplatin and bevacizumabin recurrent glioblastoma (Field et al. 2015).
Fischer 1985	Wrong population - no data for the elderly subgroup. This is a report of a randomised trial of RT with or without Levamisole in glioblastoma. The study randomised 25 participants (years unknown) of which only ten were over 65 years of age.
Fulton 1984	Wrong population - no data for the elderly subgroup. This is a report of a randomised trial comparing misonidazole combined with hyperfractionation in malignant glioma. The randomisation to three arms (RT, fractionated RT and fractionated RT with misonidazole) took place between 1981 and 1982. Subsequently RT arm was dropped and a high dose fractionated RT added. Overall, 128 people with glioblastoma were evaluated (age range 18 to 70) of which 47 were over 60 years of age. The report does not contain any relevant age-related data analysis.
Gaber 2013	Wrong population - no data for the elderly subgroup. This is a report of a randomised trial comparing toxicity and efficacy of continuous daily radiosensitizer doses of TMZ concomitant with RT in glioblastoma. The study recruited 60 participants between 2009 and 2012. The mean age is around 48 years, and the proportion of those age 65 (or 70) or over is unknown (>50 years 26 participants). The report does not contain any relevant age-related data analysis.
Gilbert 2013	Wrong population - no data for the elderly subgroup. This is a report of a randomised phase 3 trial of dose dense TMZ for newly diagnosed glioblastoma. The study randomised 833 participants between 2006 and 2008. The inclusion age is between 18 and 70 years (no mean or median given), and the proportion of those age 65 (or 70) or over is unknown (>=50 years 610 participants). The report does not contain any relevant age-related data analysis.

Study	Reason for exclusion
Glinski 1993	Wrong population - no data for the elderly subgroup. This is a preliminary report of a randomised trial of a postoperative hypofractionated RT compared with conventionally fractionated RT in malignant gliomas. The study recruited 108 participants (44 with histologically proven glioblastoma and 64 with anaplastic astrocytoma) between 1984 and 1989. The median age is around 45 years, and the proportion of those age 65 (or 70) or over is unknown. The report does not contain any relevant age-related data analysis.
Grossman 2003	Wrong population - no data for the elderly subgroup. This is a report of a randomised phase 3 trial comparing three cycles of infusional carmustine and cisplatin followed by RT with RT and concurrent carmustine in newly diagnosed supratentorial glioblastoma (ECOG trial 2394). The study randomised 219 participants between 1996 and 1999. The median age is 55 years, and the proportion of those age 65 (or 70) or over is unknown. The report does not contain any relevant age-related data analysis.
Halperin 1993	Not suitable study design. This is a report with the findings of an analysis of RT data from the CNS Cancer Consortium's randomised trial (AZQ versus BCNU) in primary malignant brain tumors. The aim of this analysis was to evaluate the influence of boost field size.
Halperin 1996	Wrong population - no data for the elderly subgroup. This is a report of a randomised phase 3 trial (two-stage randomisation) of external beam RT, mitomycin C, carmustine, and 6-mercaptopurine for anaplastic glioma of the brain. During the first randomisation, 327 participants were allocated to respective treatments and 164 at the second one (years not given). The mean age of participants at the time of first randomisation is 53 years, and the proportion of those age 65 (or 70) or over is unknown. The report does not contain any relevant age-related data analysis (stratification <45 years vs. >=45 years).
Harada 1996	Wrong population - insufficient details regarding population's age. This is a conference abstract of a randomised trial of two therapies (RT and MCNU and RT with MCNU with Interferon-beta) for a malignant glioma. The study recruited unspecified number of participants of unknown age.
Hatlevoll 1985	Wrong population - no data for the elderly subgroup. This is a report of a randomised trial of combined modality treatment of high grade (3 and 4) in operated astrocytoma. The study recruited 280 participants (years unknown) age between 20 and 69 years, thus there is no relevant subgroup of patients in this trial.
Henriksson 2006	Wrong population - no data for the elderly subgroup. This is a report of a randomised phase 3 trial comparing three cycles of infusional carmustine and cisplatin followed by RT with RT and concurrent carmustine in newly diagnosed supratentorial glioblastoma (ECOG trial 2394). The study randomised 219 participants between 1996 and 1999. The median age is 55 years, and the proportion of those age 65 (or 70) or over is unknown. The report does not contain any relevant age-related data analysis.
Hiesiger 1995	Wrong population - no data for the elderly subgroup. This is a report of a randomised trial of intra-arterial cisplatin compared with intravenous PCNU for primary brain tumors (Brain Tumor Cooperative Group trial 8420A).The study randomised 311 participants of a median age 45. The the proportion of those age 65 (or 70) or over is unknown. The report does not contain any relevant age-related data analysis.
Hildebrand 1994	Wrong population - no data for the elderly subgroup. This is a report of a randomised trial of adjuvant chemotherapy (dibromodulcitol and BCNU) given postoperatively in patients with newly diagnosed malignant gliomas.The study run between 1989 and 1991, and 269 participants were randomised to RT or RT with chemotherapy. The median age in the study is 54 years with range between 19 and 79. The proportion of those age 65 (or 70) or over is unknown. The report does not contain any relevant age-related data analysis.
Hitchon 1999	Wrong population - no data for the elderly subgroup. This is a report of a long-term follow-up of patients randomised trial to treatment with and without brachytherapy.The study randomised 26

Study	Reason for exclusion
	participants 15 years of age or older (mean age around 56 years). The proportion of those age 65 (or 70) or over is unknown. The report does not contain any relevant age-related data analysis.
Hofland 2014	Wrong population - no data for the elderly subgroup. This is a report of a randomised phase 2 trial of a neoadjuvant BEV and irinotecan comared with BEV and TMZ followed by concomitant chemoradiotherapy in patients with newly diagnosed glioblastoma. Overall, 65 participants were randomised between 2008 and 2010. The median age is around 60 years (age range 30 - 77 years) with unknown proportion of partcipants age 65 (or 70) or over. The report does not contain any relevant age-related data analysis.
Imbesi 2006	Wrong population - no data for the elderly subgroup. This is a report of a randomised phase 3 trial comparing intravenous and intraarterial ACNU in patients with a newly diagnosed glioblastoma.Overall, 43 participants were included in the study. The mean age is around 56 years (age range 32 - 69 years) and there there was no relevant subgroup of patients in this trial.
Iwadate 1993	Wrong population - no data for the elderly subgroup. This is a report of a randomised trial of intra-arterial mannitol infusion prior to ACNU and cisplatin for malignant brain tumors. The study randomised 98 participants (years unknown) age between 6 and 69 years, thus there was no relevant subgroup of patients in this trial.
Jeremic 1999	Wrong study design. This is a report of a phase 2 trial (single arm) of short course RT in elderly and frail patients with glioblastoma. The study involved 47 elderly and frail participants between 1987 and 1993. The age range of included participants was 60 to 76 with a median of 69 years.
Karacetin 2011	Wrong population - no data for the elderly subgroup. This is a report of a randomised trial comparing concomitant TMZ and RT with RT alone in newly diagnosed glioblastoma. The study included 40 participants between 2004 and 2006. The median age is 51 years (age range 19 - 73) with unknown proportion of partcipants age 65 (or 70) or over. The report does not contain any relevant age-related data analysis.
Kim 2011	Wrong population - no data for the elderly subgroup. This is a report of phase 3 randomised trial of RT followed by adjuvant TMZ with or without neoadjuvant ACNU-CDDP chemotherapy in newly diagnosed glioblastoma. The study included 82 participants (48.8% of the target sample) between 2005 and 2007; six participants were subsequently excluded due to ineligibility leaving data from 76 participant available for the analysis. The mean age is around 51 years in both arms with an unknown proportion of participants age 65 (or 70) or over. The trial was prematurely terminated due to unacceptable toxicity.
Knerich 1990	Wrong population - no data for the elderly subgroup. This is a report of a randomised trial comparing single versus multiple drug therapy in the combined treatment of malignant gliomas. The study included 173 participants between 1983 and 1989. The age of majority of the participants is between 51 and 77 years, and the proportion of partcipants age 65 (or 70) or over in unknown. The report does not contain any relevant age-related data analysis.
Koc 2008	Wrong study design. This is a report of a prospective evaluation of fluorescein sodium-guided surgery in glioblastoma.
Kocher 2008	Wrong population - no data for the elderly subgroup. This is a report of a randomised trial of postoperative radiotherapy and simultanous TMZ without adjuvant chemotherapy for glioblastoma. The study included 65 participants between 2002 and 2004. The median age is 58 and 59 in RT and RT+TMZ arms, respectively with range 34 and 69 years; there is no relevant subgroup of patients in this trial.
Kochii 2000	Wrong population - no data for the elderly subgroup. This is a report of a randomised trial of intra-arterial versus intravenous infusion of ACNU in newly diagnosed glioblastoma. The study included 84 participants between 1987 and 1995. The mean age is 54 and 59 in intra-arterial and intravenous arms, respectively with range from 16 to 78 years. The proportion of partci-

Study	Reason for exclusion
	pants age 65 (or 70) or over in unknown. The report does not contain any relevant age-related data analysis.
Kong 2017	Wrong population - no data for the elderly subgroup. This is a report of phase 3 randomised trial of autologus cytokine-induced killer cell immunotherapy in newly diagnosed glioblastoma. The study included 180 participants between 2008 and 2012. The mean age is 55 and 54 in CIK immunotherapy and control arms, respectively with range from 19 to 68 years. The proportion of partcipants age 65 (or 70) or over in unknown. The report does not contain any relevant age-related data analysis.
Lamers 2008	Ineligible population and design - no data for the elderly subgroup. This is a report of cost-effectiveness of concomitant and adjuvant TMZ for newly diagnosed glioblastoma in comparison to radiotherapy. The report does not contain any relevant age-related data.
Lanzetta 2003	Ineligible population - no data for the elderly subgroup. This is a report of phase 2 randomised trial of TMZ with radiochemotherapy for newly diagnosed glioblastoma. The study included 21 participants between 1999 and 2001. The median age of participants is 44 years with an unknown proportion of participants age 65 (or 70) or over.The report does not contain any relevant age-related data.
Lee 2015	Ineligible population - no data for the elderly subgroup. This is a report of a multicenter, phase 2, randomised trial of radiotherapy(RT) and TMZ for newly diagnosed glioblastoma. The study included 106 participants; the median age of participants is 55 in RT and 59 in TMZ arm. The proportion of participants age 65 (or 70) or over in unknown and the report does not contain any relevant age-related data.
Lenartz 2000	Ineligible population - no data for the elderly subgroup. This is a report of a randomised trial to evaluate the effect of adjuvant treatment of glioma with ML-1 standardised mistletoe extract. The study included 38 participants between 1994 and 1995. The mean age of participants is 57 years with an unknown proportion of participants age 65 (or 70) or over. The report does not contain any relevant age-related data.
Levin 1979	Ineligible population - no data for the elderly subgroup. This is a report of phase 3 randomised trial of BCNU, hydroxyurea, and radiationtherapy (RT) vs BCNU combined with RT for primary malignant gliomas. The study included 99 participants of unspecified age, and the report does not contain any relevant age-related data.
Levin 2000	Ineligible population - no data for the elderly subgroup. This is a report of phase 3 randomised trial of chemotherapy (postradiotherapy) an Alpha-Difluoromethylornithine-Procarbazine, N-(2-Chloroethyl)-N'-cyclohexyl-N-nitrosurea, Vincristine (DFMO-PCV) in comparison to PCV for glioblastoma. The study included 272 participants between 1998 and 1999. The median age of participants is 53 in DEMO-PCV and 50 in PCV arm with an unknown proportion of participants age 65 (or 70) or over. The report does not contain any relevant age-related data.
Levin 2006	Ineligible population - no data for the elderly subgroup. This is a report of a randomised, double-blind, placebo-controlled trial of marismastat after surgery and radiotherapy for glioblastoma. The study included 162 participants between 1996 and 19999. The median age of participants is around 57 years with an unknown proportion of participants age 65 (or 70) or over. The report does not contain any relevant age-related data.
Lissoni 1993	Ineligible population - no data for the elderly subgroup. This is a report of a randomised trial of radiotherapy (RT) compared to RT with the long-acting opioid antagonist naltrexone (NTX) for malignant glioma. The study included 21 participants between 1990 and 1992. The median age of participants is 52 in RT and 49 in RT+NTX arm; the proportion of participants age 65 (or 70) or over is less than 20.
Lorimer 2016	Not a RCT, a study examining prognostic factors.

Study	Reason for exclusion
Ludgate 1988	Ineligible population - no data for the elderly subgroup. This is a report of a randomised trial of superfractionated radiotherapy (RT) for malignant gliomas. The study included 76 participants of unspecified age between 1981 and 1983. The proportion of participants age 65 (or 70) or over in unknown. The report does not contain any relevant age-related data.
Mallick 2018	Wrong population - a small study with no elderly subgroup.
Mao 2015	Ineligible population - no data for the elderly subgroup. This is a report of phase 2 randomised, open-label, trial of early postsurgical TMZ with concomitant radiotherapy for newly diagnosed glioblastoma. The study included 99 participants between 2008 and 2012. The mean age of all participants is 50.2 (SD 11.8) years. The proportion of participants age 65 (or 70) or over is unknown, and the report does not contain any relevant age-related data.
Marshall 2006	Ineligible population - no data for the elderly subgroup. This is a secondary analysis of a randomised trial of cisplatin with concurrent radiotherapy in glioblastoma on hearing loss. The study included 451 participants, of which 230 randomised to arms C (standard RT with carmustine and cisplatin), and D (accelerated RT with carmustine and cisplatin). The mean age of participants at baseline is 55.8 years, and the proportion of participants age 65 (or 70) or over is unknown. The report does not contain any relevant age-related data.
McCarthy 2017	This is a commentary on the results of the Stupp 2005 trial.
Montemor 2008	Ineligible population - no data for the elderly subgroup. This is a report of a randomised trial of chemoradiotherapy with weekly paclitaxel (GR1) in comparison to RT alone (GR2) for anaplastic astrocytoma (AA) and glioblastoma (GB). The study included 61 participants between 1998 and 2002. The median age of participants range from 35.29 in GR1/AA group to 54.33 in GR2/GB; the proportion of participants age 65 (or 70) or over is unknown. The report does not contain any relevant age-related data.
MRC 1983	Ineligible population - no elderly patients. A RCT of radiotherapy (45 Gy in 20 fractions)plus misonidazole versus radiotherapy with placebo. No therapeutic benefit was reported with misonidazole.
Muragaki 2017	Insufficient information - this is a conference abstract of a randomised trial of autologus formalin-fixed tumor vaccine in newly diagnosed glioblastoma.
Nabors 2015	Ineligible population - no data for the elderly subgroup. This is a report of phase 2, open-label randomised trial (CORE study) of two cilengitide regimens in combination with standard of care in newly diagnosed glioblastoma and unmethylated MGMT. The study included 265 participants between 2009 and 2013. The median age of participants in the arms range from 55.6 (standard cilengitide) to 57.7 (control) years; the proportion of participants age 65 (or 70) or over is unknown. The report does not contain any relevant age-related data.
Napolitano 1999	Not a suitable study design. This is a report of phase 2 clinical, sequential, study of radiotherapy and a combination of BCNU and tamoxifen.
Nelson 1988	Ineligible population - no data for the elderly subgroup. This trial with four treatment arms (60 Gy to the whole brain; 60 Gy plus 10-Gy boost; 60 Gy plus carmustine (BCNU); and 60 Gy plus semustine plus dacarbazine) included Grade 3 and 4 gliomas and stratified findings by under or over 50 years. Eight patients were over 70 years.
Payne 1982	Ineligible population - no data for the elderly subgroup. This is a report of a randomised trial of chemotherapy with hypofractionated or standard radiotherapy for malignant astrocytoma. The study included 157 participants between 1977 and 1980. The median age of participants at baseline is 56 years, and the proportion of participants age 70 and over less than 20 participants (n = 13).

Study	Reason for exclusion
Peszynski 1988	Ineligible population - no data for the elderly subgroup. This is a report of a randomised trial of radiotherapy alone in comparison to radiotherapy with CCNU. The study included 139 participants, of which none was over 65 years of age.
Phillips 2003	Ineligible population - no data for the elderly subgroup. This is a report of a randomised trial of two options of radiotherapy (35 Gy in 10 fractions vs 60 Gy in 30 fractions) for glioblastoma in elderly. The study included 69 participants between 1990 and 1996. The median age of participants is 58 and 59 years in 60Gy and 35Gy arm respectively. The proportion of participants age 65 (or 70) or over is unknown. The report does not contain any relevant age-related data.
Pinzi 2017	This is an editorial on postoperative chemoradiotherapy in elderly patients with glioblastoma.
Prados 2001	Ineligible population - no data for the elderly subgroup. This is a report of phase 3 randomised trial of accelerated hypofractionation with or without difluromethylornithine (DFMO) in comparison with standard radiotherapy with or without DFMO in newly diagnosed glioblastoma. The study included 231 participants, and their median age is 57 years. The proportion of participants age 65 (or 70) or over in unknown. The report does not contain any relevant age-related data.
Reagan 1976	Ineligible population - no data for the elderly subgroup. This is a report of a randomised trial of three treatment schedules: radiotherapy (RT) alone, CCNU, and combination of both. The study included 63 participants between 1970 and 1972. The mean age of participants is 52.3, 53 and 58 in RT, CCNU and the combined arm respectively. The proportion of participants age 65 (or 70) or over is unknown. The report does not contain any relevant age-related data.
Reyes-Botero 2018	Ineligible study design - a non-randomised phase II trial (n=66) that treated patients aged 70+, and with a KPS of under 70 with TMZ 130-150mg/m2 per day for 5 days every 4 weeks concomitantly with bevacizumab 10mg/kg every two weeks.
Shapiro 1976	Ineligible population - no data for the elderly subgroup. This is a report of a randomised trial of carmustine (group A) and vincristine (group B). The study included 33 participants; the median age of participants is 60 years in group A and 58 in group B. The proportion of participants age 65 (or 70) or over is unknown. The report does not contain any relevant age-related data.
Shapiro 1989	Ineligible population - no data for the elderly subgroup. This is a report of a randomised trial of three chemotherapy (BCNU alone, alternating course BCNU and procarbazine and BCNU with hydroxyurea alternating procarbazine and VM-26) and two radiotherapy regimens for malignant glioma. The study included 571 participants between 1980 and 1981. The median age of participants is 56 years (range 15 - 84), and the proportion of participants age 65 and or over is 21%, but the report does not contain any relevant age-related data.
Shapiro 1992	Ineligible population - no data for the elderly subgroup. This is a report of a randomised trial of intra-arterial versus intravenous BCNU, with or without 5-fluorouracil (intravenous) for newly diagnosed glioma. The study included 505 participants, and the median age is 56 years. The proportion of participants age 65 (or 70) or over is 21.4%, but the report does not contain any relevant age-related data.
Sharma 2003	Ineligible population - no data for the elderly subgroup. This is a report of a randomised trial of two different radiotherapy regiments. The study included 50 participants age less than 60 years of age between 1996 and 1998.
Simpson 1976	Ineligible population - no data for the elderly subgroup. This is a report of a randomised trial of two different radiotherapy regiments. The study included 134 participants of unspecified age between 1965 and 1968. The report does not contain any relevant age-related data.
Sneed 1998	Ineligible population - no data for the elderly subgroup. This is a report of phase 2/3 randomised trial of brachytherapy boost with or without hyperthermia for glioblastoma. The study included 112 participants between 1990 and 1995. The median age of participants is 54 years (range 21-78).

Study	Reason for exclusion
	The proportion of participants age 65 (or 70) or over is unknown, and the report does not contain any relevant age-related data.
Socha 2016	Ineligible population - recurrent glioblastoma.
Soffietti 2017	Not a RCT, a single arm study.
Solero 1979	Ineligible population - no data for the elderly subgroup. This is a report of a randomised trial of radiotherapy alone, in combination with BCNU or CCNU. The study included 105 participants of unspecified age between 1972 and 1976.
Solomon 2013	Ineligible population - no data for the elderly subgroup. This is a report of a randomised trial of radiotherapy (RT) with nimotuzumab or placebo for high-grade glioma (anaplastic astrocytoma and glioblastoma). The study included 70 participants between 2005 and 2010. The mean age of participants is 45.5 and 47.2 years in arm without and with nimotuzumab, respectively. The proportion of participants age 65 (or 70) or over in unknown and the report does not contain any relevant age-related data.
Solth 2018	Ineligible study design - an clinical audit of treatment of GBM in the elderly in a UK setting.
Souhami 2004	Ineligible population - no data for the elderly subgroup. This is a report of a randomised trial of stereotactic radiosurgery (SRS) with standard radiotherapy (RT) and carmustine versus**RT with** carmustine for glioblastoma (report of RTOG 93-05 protocol). The study included 203 participants between 1994 and 2000. The mean age of participants is 55.5 and 56.4 years in RT alone and RT +SRS, respectively. The proportion of participants age 65 (or 70) or over in 26.5%, but the report does not contain any relevant age-related data.
Stadler 1984	Ineligible population - no data for the elderly subgroup. This is a report of a 6 months follow-up data from a randomised trial of misonidazole and radiotherapy for high-grade astrocytoma (The Vienna study). There were 45 participants available for the analysis by 1983 (study start in 1977). The mean age of participants is 52 years in misonidazole with RT arm and 56 years in arm with RT alone. The proportion of participants age 65 (or 70) or over and the report does not contain any relevant age-related data.
Stragliotto 2013	Not relevant study objective. This is a report of a randomised trial of add-on therapy of valganciclovir in cytomegalovirus-positive glioblastoma.
Stummer 2006	Not relevant study objective. This is a report of a randomised trial of fluorescence-guided surgery with 5-aminolevulinic acid for resection of malignant glioma.
Stummer 2011	This is a secondary report from the randomised 5-aminolevulinic acid study (Stummer 2006).
Stummer 2017	Not relevant study objective. This is a report of a randomised trial comparing three different doses of 5-aminolevulinic acid for resection of malignant glioma.
Stupp 2002	Not a suitable study design. This is a report of a study investigating the safety, tolerability, and survival of radiotherapy with temozolomide (TMZ) followed by adjuvant TMZ for newly diagnosed glioblastoma.
Stupp 2005	Ineligible population - no data for the elderly subgroup. This is a report of a randomised trial of radiotherapy (RT) alone vs RT with temozolomide (TMZ) both followed by adjuvant TMZ. The study included 573 participants between 2000 and 2002. The median age of the participants is 56 years, and the proportion of participants age 65 (or 70) or over in unknown.
Stupp 2009	Ineligible population. This is a report with a five-year follow-up data of Stupp 2005 trial.
Stupp 2014	Ineligible population - no data for the elderly subgroup. This is a report of phase 3 randomised trial of cilengitide with the standard of care for newly diagnosed glioblastoma with methylated MGMT

Study	Reason for exclusion
	(CENTRIC EORTC 26071-22072). The study included 545 participants between 2008 and 2011.The median age of the participants is 58 years in both arms with an unknown proportion of participants age 65 (or 70) or over. The report does not contain any relevant age-related data.
Stupp 2015	Ineligible population - no data for the elderly subgroup. This is a report of an interim analysis of the randomised trial of Tumor-Treating Fields with temozolomide (TMZ) in comparison to TMZ alone for glioblastoma. The study included 315 participants between 2009 and 2014. The mean age of the participants in the sample is 55.8 years (median 57) in both arms with an unknown proportion of participants age 65 (or 70) or over. The report does not contain any relevant age-related data.
Szczepanek 2013	Ineligible population - no data for the elderly subgroup. This is a report of a randomised trial of radiotherapy (RT) alone in comparison to RT with temozolomide (TMZ) both followed by adjuvant TMZ. The study included 58 participants between 2003 and 2005. The mean age of the participants is 55 years, and the proportion of participants age 65 (or 70) or over is unknown.
Takakura 1986	Ineligible population - no data for the elderly subgroup. This is a report of a randomised trial of radiotherapy (RT) alone in comparison to RT with ACNU for malignant gliomas. The study included 105 participants between 1980 and 1981. Neither the median age of the participants nor the proportion of participants age 65 (or 70) or over is given.
Taphoorn 2005	Ineligible population. This is a secondary analysis of Stupp 2005 trial focusing on the quality of life data.
Urtasun 1982	Ineligible population - no data for the elderly subgroup. This is a report of a randomised trial of radiotherapy and misonidazole for high-grade glioma. The study included 59 participants between XXXX and XXXX. The mean age of participants is 55, 56 and 59 years in RT alone, RT with metronidazole and RT with misonidazole respectively. The proportion of participants age 65 (or 70) or over is unknown, and the report does not contain any relevant age-related data.
Ushio 1985	Ineligible population - no data for an elderly subgroup. 13/105 patients were over 60 in this Japanese trial.
Vellayappan 2017	This is an editorial on combined-modality hypofractionated radiotherapy for elderly with glioblastoma.
Wakabayashi 2018	Inelgible population - no elderly subgroup.
Wang 2008	no pdf
Weller 2003	Ineligible population - no data for the elderly subgroup. This is a report of a randomised trial of radiotherapy with ACNU and VM26 in comparison to RT with ACNU and Ara-C for glioma (glioblastoma or anaplastic gliomas). The study included 375 participants between 1994 and 2000. The median age of the participants is 50 and 51 years in ACNU + VM26 and ACNU+Ara-C arm. The proportion of participants age 65 (or 70) or over is unknown, and the report does not contain any relevant age-related data.
Werner-Wasik 1996	Ineligible population - no data for the elderly subgroup. This is a report of phase 1/2 randomised trial of two regiments of radiotherapy (hypofractionated vs accelerated hypofractionated) both with carmustine for malignant gliomas. The study included 747 participants between 1983 and 1989. The mean age of the participants is 52.3 years in the study, and the proportion of participants age 65 (or 70) or over is unknown. The report does not contain any relevant age-related data.
Westphal 2003	Ineligible population - no data for the elderly subgroup. This is a report of phase 3 randomised trial of chemotherapy with BCNU wafer for primary malignant glioma. The study included 240 participants between 1997 and 1999. The mean age of the participants is 52.6 in wafer arm and 53.6 years in the placebo arm. The proportion of participants age 65 (or 70) or over is unknown, and the report does not contain any relevant age-related data.

Study	Reason for exclusion
Westphal 2006	Ineligible population. This is a secondary analysis of long-term follow-up data of a Westphal 2003 trial.
Westphal 2013	Not relevant study objective. This is a report of phase 3 randomised trial of locally applied adenovirus-mediated gene therapy with a prodrug converting enzyme (herpes-simplex-virus thymidine kinase; sitimagene ceradenovec) followed by intravenous ganciclovir in patients with newly diagnosed resectable glioblastoma (ASPECT).
Westphal 2015	Ineligible population - no data for the elderly subgroup. This is a report of phase 3, open-label randomised trial of nimotuzumab for newly diagnosed glioblastoma. The study included 149 participants between 2007 and 2010. The mean age of participants in the experimental arm is 52.9 and 55.9 years in the control arm. The proportion of participants age 65 (or 70) or over in unknown. The report does not contain any relevant age-related data.
Wick 2009	Ineligible population - no data for the elderly subgroup. This is a report of phase 3 randomised trial of sequential radiochemotherapy with procarbazine, lomustine, and vincristine or temozolomide for anaplastic glioma. The study included 318 (analysed data from 274) participants between 1999 and 2005. The median age of the participants is 44 in RT arm and 42 years in PCV or TMZ arm. The proportion of participants age 65 (or 70) or over is unknown, and the report does not contain any relevant age-related data.
Wick 2016	Ineligible population - no data for the elderly subgroup. This is a report of phase 2 randomised trial of radiotherapy (RT) and temsirolimus (TEM) in comparison to radiochemotherapy with Temozolomide for newly diagnosed glioblastoma without MGMT (EORTC 26082). The study included 257 participants between 2009 and 2012. The median age of the participants is 55 and 58 years in TEM and standard of care arm, respectively. The proportion of participants age 65 (or 70) or over is unknown, and the report does not contain any relevant age-related data.
Yang 2018	Ineligible population - no data for the elderly subgroup. This is a report of a randomised trial of radiotherapy (RT) with concomitant and adjuvant temozolomide (TMZ) versus RT with concomitant and adjuvant local delivery of ACNU rendezvousing with oral TMZ. The study included only participants age 18 to 65.
Zhu 2017	Ineligible population. This is a secondary analysis of Stupp 2015 trial focusing on the quality of life data.

RTOG=Radiation Therapy Oncology Group

Characteristics of studies awaiting assessment *[ordered by study ID]*

Guzauskas 2019

Methods	USA cost-effectiveness evaluation of TTF
Participants	
Interventions	
Outcomes	
Notes	

Characteristics of ongoing studies *[ordered by study ID]*

NCT01602588

Trial name or title	A Randomised Trial Investigating the Additional Benefit of Hydroxychloroquine(HCQ)to Short Course Radiotherapy (SCRT) in Patients Aged 70 Years and Older With High Grade Gliomas (HGG) (HCQ) ClinicalTrials.gov Identifier: NCT01602588
Methods	Phase II, parallel two-arm, open label RCT with randomisation in 1:2 ratio
Participants	Target sample: 57 Actual enrolment: 54 Inclusion: Aged 70+. ECOG PS 0 or 1.
Interventions	Reference arm: Short course RT alone. Dose is 30Gy in 6 fractions given on alternate days over 2 weeks. Experimental arm: Short course RT plus hydroxychloroquine 200mg orally BD from 14 days after surgery until progression.
Outcomes	Analysis will be by intention to treat, whereby patients will be examined according to the assigned treatment. Primary outcome: Survival time at 1 year. Secondary outcomes: Toxicity/adverse events during and up to 30 days after treatment. One year cause specific survival and 6 month progression free survival. HR QoL – difference between HRQoL at 8 weeks post treatment compared to baseline will be assessed. HRQoL questionnaires used are QLQ-C30 and BN20. Corticosteroid dependence.
Starting date	Opened to recruitment on 21st May 2012. Study completion date: November 2017.
Contact information	Professor Susan Short, St James's University Hospital, Leeds UCL (sponsor) CRUK (funder)
Notes	

NUTMEG 2018

Trial name or title	A Randomised Phase II Study of NivolUmab and TeMozolomide vs Temozolomide alone in newly diagnosed Elderly patients with Glioblastoma (NUTMEG) to analyse overall survival. Study registration ID: ACTRN12617000267358
Methods	Phase II parallel two-arm, multi-centre, open label RCT with randomisation in 2:1 ratio
Participants	Target sample size: 102

NUTMEG 2018 *(Continued)*	
	Adults 65 years or above, with newly diagnosed histologically confirmed GBM (WHO grade IV glioma including gliosarcoma) following surgery.
Interventions	Intervention: Patients will receive radiotherapy (40Gy/15 fractions, weekdays over 21 days) concomitantly with temozolomide (TMZ) tablets 75mg/m2 daily for 21 days. After a 4 week break the experimental group will receive nivolumab intravenous infusions (240 mg days 1 and 15 every 28 days for cycles 1-4; then 480 mg day 1 every 28 days for cycles 5-6) with concomitant adjuvant temozolomide tablets days 1-5, every 28 days) for 6 cycles. TMZ will be dosed at 150mg/m2 for the first cycle. If well tolerated TMZ is then given at 200mg/m2 for cycles 2 - 6. Comparator: Patients will receive RT (40Gy/15 fractions) concomitantly with temozolomide (TMZ) 75mg/m2. Patients assigned to the control group will receive the standard treatment of adjuvant temozolomide (150-200mg/m2 days 1-5 every 28 days) for 6 cycles.
Outcomes	Overall survival, progression free survival, Adverse events, QoL, Neurologic Functioning Patients are assessed at baseline then every 8 weeks until study treatment finishes/disease progression.
Starting date	02/03/2018
Contact information	NUTMEG Trial Coordinator nutmeg@ctc.usyd.edu.au
Notes	The study aims to evaluate whether the combination of adjuvant nivolumab with temozolomide improves overall survival outcomes for this patient population.

MGMT: TMZ: temozolomide; WHO: World Health Organization

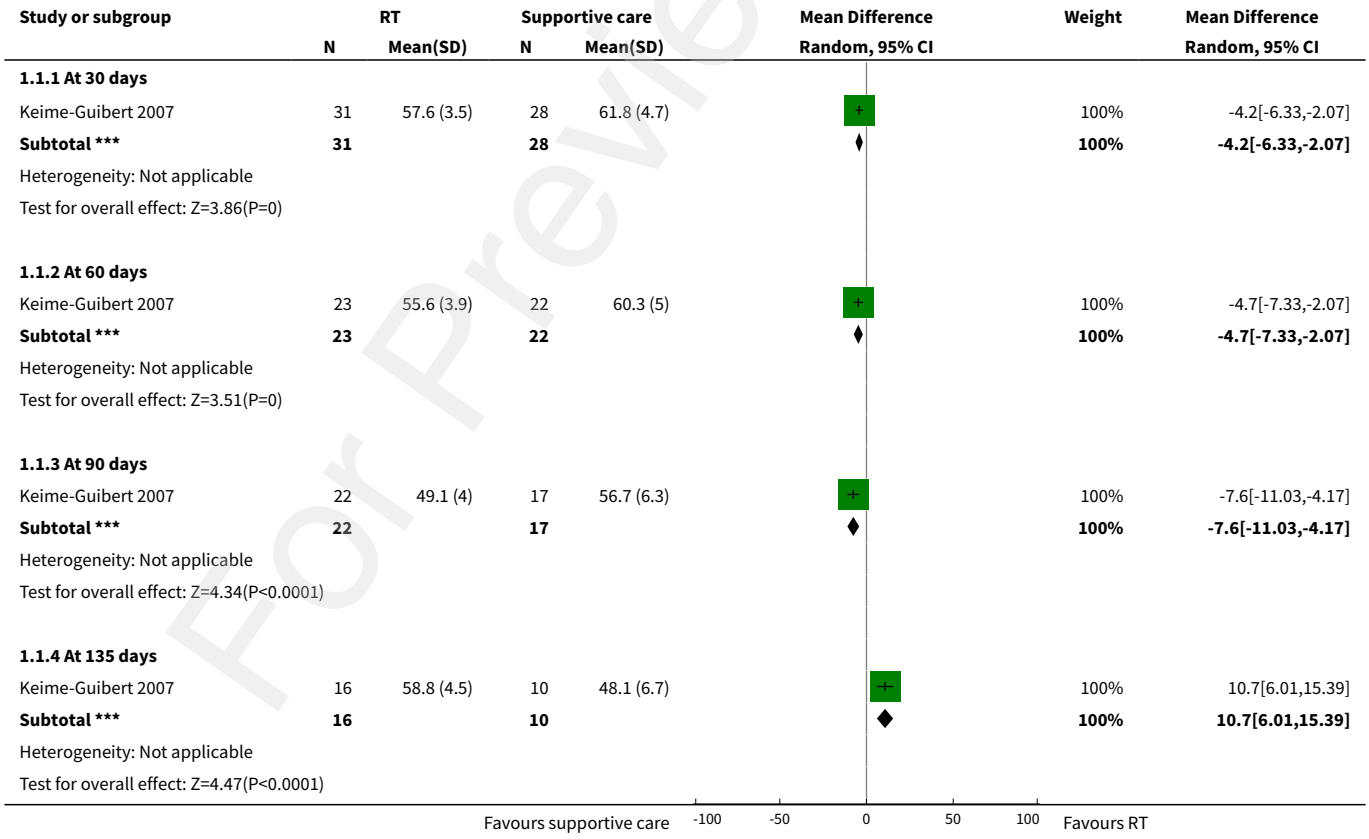
DATA AND ANALYSES

Comparison 1. RT (50 Gy) vs supportive care

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 HRQOL	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 At 30 days	1	59	Mean Difference (IV, Random, 95% CI)	-4.20 [-6.33, -2.07]
1.2 At 60 days	1	45	Mean Difference (IV, Random, 95% CI)	-4.70 [-7.33, -2.07]
1.3 At 90 days	1	39	Mean Difference (IV, Random, 95% CI)	-7.60 [-11.03, -4.17]
1.4 At 135 days	1	26	Mean Difference (IV, Random, 95% CI)	10.70 [6.01, 15.39]
2 Cognition	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.1 At 30 days	1	59	Mean Difference (IV, Random, 95% CI)	-0.40 [-3.24, 2.44]

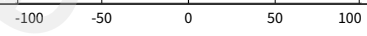
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.2 At 60 days	1	45	Mean Difference (IV, Random, 95% CI)	-5.60 [-9.20, 0.00]
2.3 at 90 days	1	39	Mean Difference (IV, Random, 95% CI)	-21.0 [-25.18, -16.82]
2.4 at 135 days	1	26	Mean Difference (IV, Random, 95% CI)	-13.0 [-18.84, -7.16]
3 Fatigue	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
3.1 At 30 days	1	59	Mean Difference (IV, Random, 95% CI)	2.10 [-0.49, 4.69]
3.2 At 60 days	1	45	Mean Difference (IV, Random, 95% CI)	8.60 [4.77, 12.43]
3.3 At 90 days	1	39	Mean Difference (IV, Random, 95% CI)	11.70 [8.24, 15.16]
3.4 At 135 days	1	26	Mean Difference (IV, Random, 95% CI)	0.5 [-6.68, 7.68]
4 Progression free survival	1	81	Hazard Ratio (Random, 95% CI)	0.28 [0.17, 0.46]

Analysis 1.1. Comparison 1 RT (50 Gy) vs supportive care, Outcome 1 HRQOL.



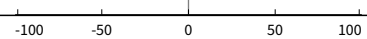
Analysis 1.2. Comparison 1 RT (50 Gy) vs supportive care, Outcome 2 Cognition.

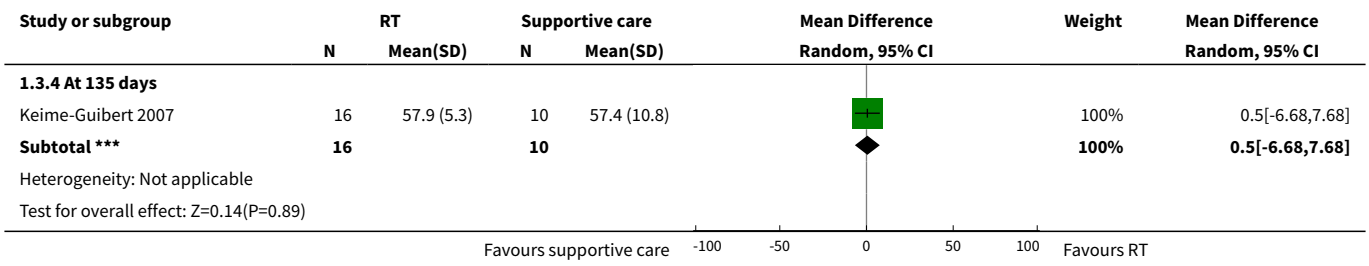
Study or subgroup	RT N	RT Mean(SD)	Supportive care N	Supportive care Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.2.1 At 30 days							
Keime-Guibert 2007	31	59.6 (4.9)	28	60 (6.1)		100%	-0.4[-3.24,2.44]
Subtotal ***	**31**		**28**			**100%**	**-0.4[-3.24,2.44]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.28(P=0.78)							
1.2.2 At 60 days							
Keime-Guibert 2007	23	57.4 (6.7)	22	63 (5.6)		100%	-5.6[-9.2,-2]
Subtotal ***	**23**		**22**			**100%**	**-5.6[-9.2,-2]**
Heterogeneity: Not applicable							
Test for overall effect: Z=3.05(P=0)							
1.2.3 at 90 days							
Keime-Guibert 2007	22	42.8 (7.1)	17	63.8 (6.2)		100%	-21[-25.18,-16.82]
Subtotal ***	**22**		**17**			**100%**	**-21[-25.18,-16.82]**
Heterogeneity: Not applicable							
Test for overall effect: Z=9.84(P<0.0001)							
1.2.4 at 135 days							
Keime-Guibert 2007	16	43.8 (6.7)	10	56.8 (7.8)		100%	-13[-18.84,-7.16]
Subtotal ***	**16**		**10**			**100%**	**-13[-18.84,-7.16]**
Heterogeneity: Not applicable							
Test for overall effect: Z=4.36(P<0.0001)							



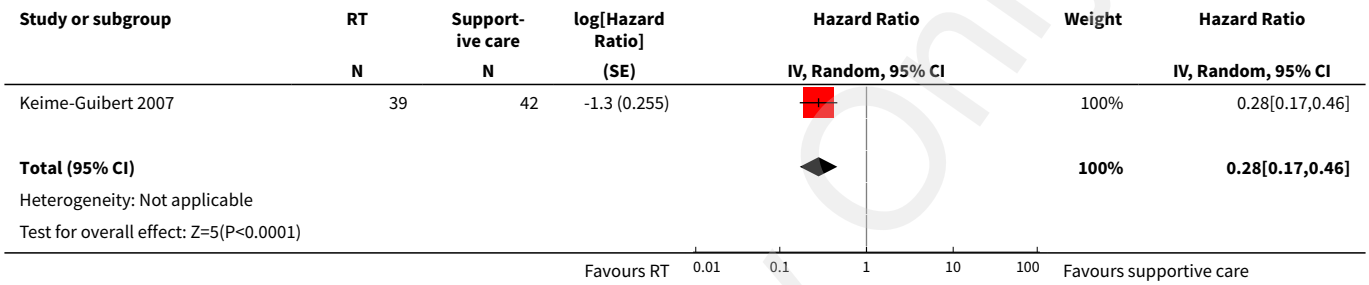
Analysis 1.3. Comparison 1 RT (50 Gy) vs supportive care, Outcome 3 Fatigue.

Study or subgroup	RT N	RT Mean(SD)	Supportive care N	Supportive care Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.3.1 At 30 days							
Keime-Guibert 2007	31	39.5 (4.9)	28	37.4 (5.2)		100%	2.1[-0.49,4.69]
Subtotal ***	**31**		**28**			**100%**	**2.1[-0.49,4.69]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.59(P=0.11)							
1.3.2 At 60 days							
Keime-Guibert 2007	23	48.9 (6.3)	22	40.3 (6.8)		100%	8.6[4.77,12.43]
Subtotal ***	**23**		**22**			**100%**	**8.6[4.77,12.43]**
Heterogeneity: Not applicable							
Test for overall effect: Z=4.4(P<0.0001)							
1.3.3 At 90 days							
Keime-Guibert 2007	22	52.8 (5)	17	41.1 (5.8)		100%	11.7[8.24,15.16]
Subtotal ***	**22**		**17**			**100%**	**11.7[8.24,15.16]**
Heterogeneity: Not applicable							
Test for overall effect: Z=6.63(P<0.0001)							





Analysis 1.4. Comparison 1 RT (50 Gy) vs supportive care, Outcome 4 Progression free survival.

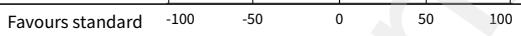


Comparison 2. Short course RT vs standard RT

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 HRQOL at 4 weeks	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.2 RT (40Gy) vs RT (60Gy)	1	85	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
1.3 RT (25Gy) vs RT (40Gy)	1	40	Mean Difference (IV, Random, 95% CI)	3.40 [-8.33, 15.13]
2 HRQOL at 8 weeks	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.1 RT (40Gy) vs RT (60Gy)	1	72	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 RT (25Gy) vs RT (40Gy)	1	24	Mean Difference (IV, Random, 95% CI)	0.0 [-13.58, 13.58]
3 Treatment toxicity G3+	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 RT (40 Gy) vs RT (60 Gy)	1	61	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

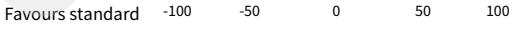
Analysis 2.1. Comparison 2 Short course RT vs standard RT, Outcome 1 HRQOL at 4 weeks.

Study or subgroup	Short course N	Short course Mean(SD)	Standard N	Standard Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
2.1.2 RT (40Gy) vs RT (60Gy)							
Roa 2004	43	0 (0)	42	0 (0)			Not estimable
Subtotal ***	**43**		**42**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
2.1.3 RT (25Gy) vs RT (40Gy)							
Roa 2015	20	51.7 (18)	20	48.3 (19.8)		100%	3.4[-8.33,15.13]
Subtotal ***	**20**		**20**			**100%**	**3.4[-8.33,15.13]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.57(P=0.57)							



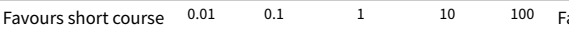
Analysis 2.2. Comparison 2 Short course RT vs standard RT, Outcome 2 HRQOL at 8 weeks.

Study or subgroup	Short course RT N	Short course RT Mean(SD)	Standard RT N	Standard RT Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
2.2.1 RT (40Gy) vs RT (60Gy)							
Roa 2004	38	0 (0)	34	0 (0)			Not estimable
Subtotal ***	**38**		**34**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
2.2.2 RT (25Gy) vs RT (40Gy)							
Roa 2015	12	48.6 (18.4)	12	48.6 (15.4)		100%	0[-13.58,13.58]
Subtotal ***	**12**		**12**			**100%**	**0[-13.58,13.58]**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							



Analysis 2.3. Comparison 2 Short course RT vs standard RT, Outcome 3 Treatment toxicity G3+.

Study or subgroup	Short course RT n/N	Standard RT n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.3.1 RT (40 Gy) vs RT (60 Gy)					
Roa 2015	0/35	0/26			Not estimable
Subtotal (95% CI)	**35**	**26**			**Not estimable**
Total events: 0 (Short course RT), 0 (Standard RT)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					

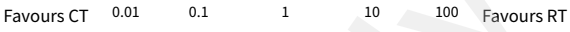


Comparison 3. CT vs RT

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Progression free survival	1		Hazard Ratio (Random, 95% CI)	Subtotals only
1.1 TMZ vs RT (60 Gy)	1	373	Hazard Ratio (Random, 95% CI)	1.15 [0.92, 1.44]
2 Thromboembolic event G3+	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 TMZ vs RT (60 Gy)	1	373	Risk Ratio (M-H, Random, 95% CI)	2.74 [1.26, 5.94]
3 Neutropenia G3+	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 TMZ vs RT (60 Gy)	1	373	Risk Ratio (M-H, Random, 95% CI)	7.30 [1.70, 31.31]
4 Lymphopenia G3+	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 TMZ vs RT (60 Gy)	1	373	Risk Ratio (M-H, Random, 95% CI)	41.99 [5.85, 301.31]
5 Thrombocytopenia G3+	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5.1 TMZ vs RT (60 Gy)	1	373	Risk Ratio (M-H, Random, 95% CI)	3.19 [1.07, 9.53]
6 Infection G3+	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6.1 TMZ vs RT (60 Gy)	1	373	Risk Ratio (M-H, Random, 95% CI)	1.39 [0.86, 2.26]
7 Fatigue/asthenia G3+	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
7.1 TMZ vs RT (60 Gy)	1	373	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.63, 1.91]
8 Nausea/vomiting G3+	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
8.1 TMZ vs RT (60 Gy)	1	373	Risk Ratio (M-H, Random, 95% CI)	5.48 [0.67, 45.05]
9 Weight loss G3+	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
9.1 TMZ vs RT (60 Gy)	1	373	Risk Ratio (M-H, Random, 95% CI)	4.57 [0.22, 94.47]
10 Neurological symptoms G3+	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
10.1 TMZ vs RT (60 Gy)	1	373	Risk Ratio (M-H, Random, 95% CI)	1.31 [0.82, 2.10]
11 Seizures G3+	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
11.1 TMZ vs RT (60 Gy)	1	373	Risk Ratio (M-H, Random, 95% CI)	1.19 [0.60, 2.39]
12 Elevated liver enzymes G3+	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
12.1 TMZ vs RT (60 Gy)	1	373	Risk Ratio (M-H, Random, 95% CI)	1.71 [0.97, 3.03]
13 Cutaneous adverse event G3+	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
13.1 TMZ vs RT (60 Gy)	1	373	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.06, 14.49]

Analysis 3.1. Comparison 3 CT vs RT, Outcome 1 Progression free survival.

Study or subgroup	CT N	RT N	log[Hazard Ratio] (SE)	Hazard Ratio IV, Random, 95% CI	Weight	Hazard Ratio IV, Random, 95% CI
3.1.1 TMZ vs RT (60 Gy)						
Wick 2012	195	178	0.1 (0.114)		100%	1.15[0.92,1.44]
Subtotal (95% CI)					**100%**	**1.15[0.92,1.44]**
Heterogeneity: Not applicable						
Test for overall effect: Z=1.23(P=0.22)						



Analysis 3.2. Comparison 3 CT vs RT, Outcome 2 Thromboembolic event G3+.

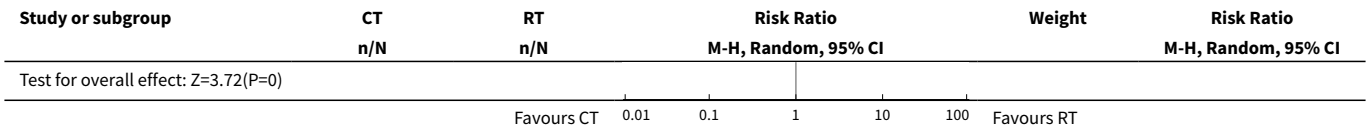
Study or subgroup	CT n/N	RT n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
3.2.1 TMZ vs RT (60 Gy)					
Wick 2012	24/195	8/178		100%	2.74[1.26,5.94]
Subtotal (95% CI)	**195**	**178**		**100%**	**2.74[1.26,5.94]**
Total events: 24 (CT), 8 (RT)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.55(P=0.01)					

Analysis 3.3. Comparison 3 CT vs RT, Outcome 3 Neutropenia G3+.

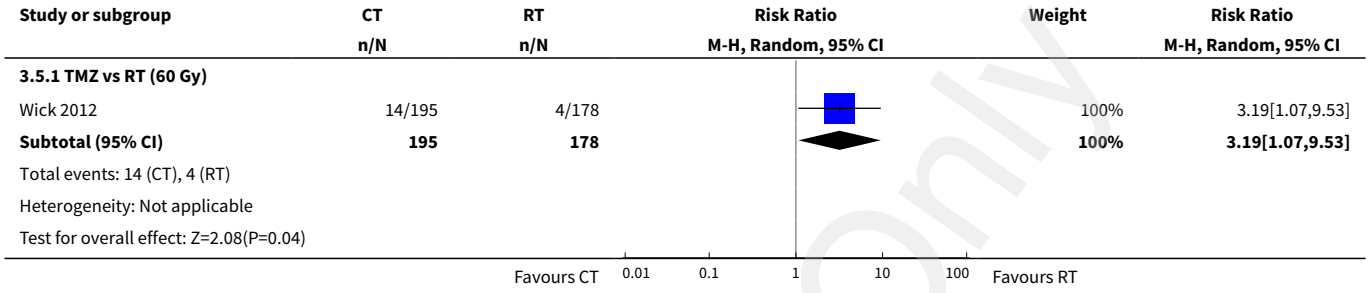
Study or subgroup	CT n/N	RT n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
3.3.1 TMZ vs RT (60 Gy)					
Wick 2012	16/195	2/178		100%	7.3[1.7,31.31]
Subtotal (95% CI)	**195**	**178**		**100%**	**7.3[1.7,31.31]**
Total events: 16 (CT), 2 (RT)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.68(P=0.01)					

Analysis 3.4. Comparison 3 CT vs RT, Outcome 4 Lymphopenia G3+.

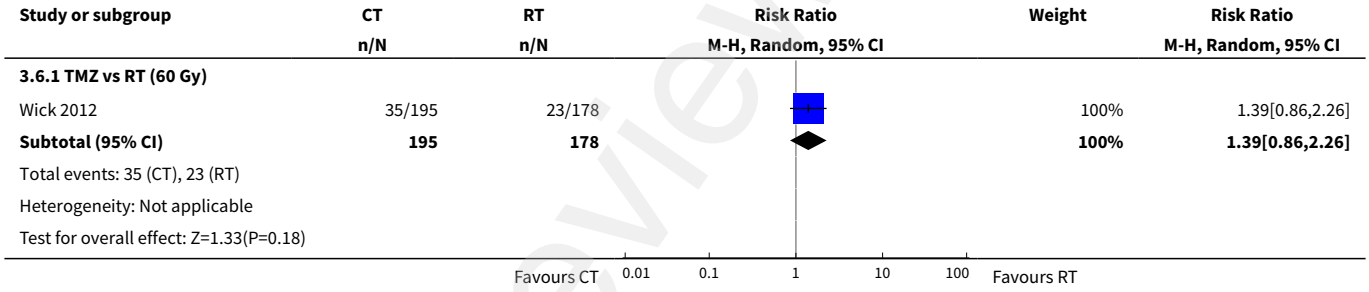
Study or subgroup	CT n/N	RT n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
3.4.1 TMZ vs RT (60 Gy)					
Wick 2012	46/195	1/178		100%	41.99[5.85,301.31]
Subtotal (95% CI)	**195**	**178**		**100%**	**41.99[5.85,301.31]**
Total events: 46 (CT), 1 (RT)					
Heterogeneity: Not applicable					



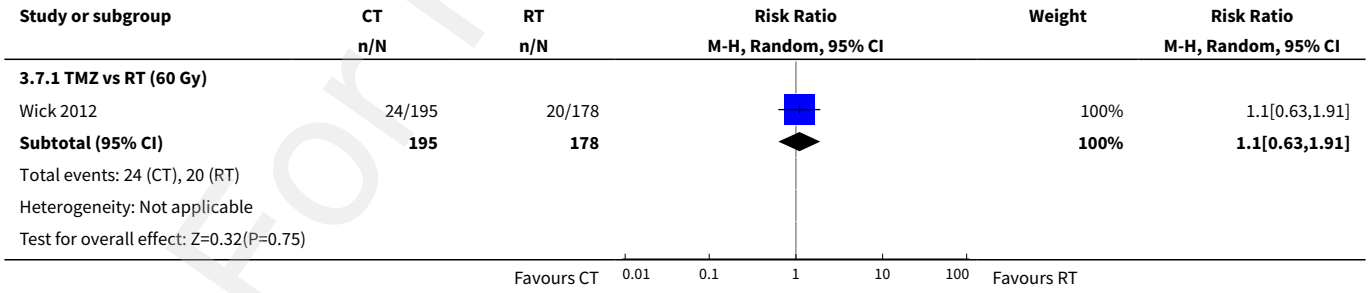
Analysis 3.5. Comparison 3 CT vs RT, Outcome 5 Thrombocytopenia G3+.



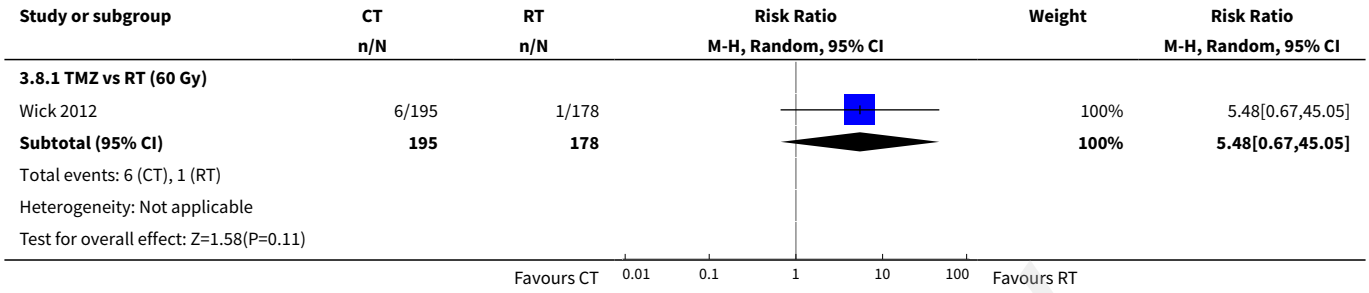
Analysis 3.6. Comparison 3 CT vs RT, Outcome 6 Infection G3+.



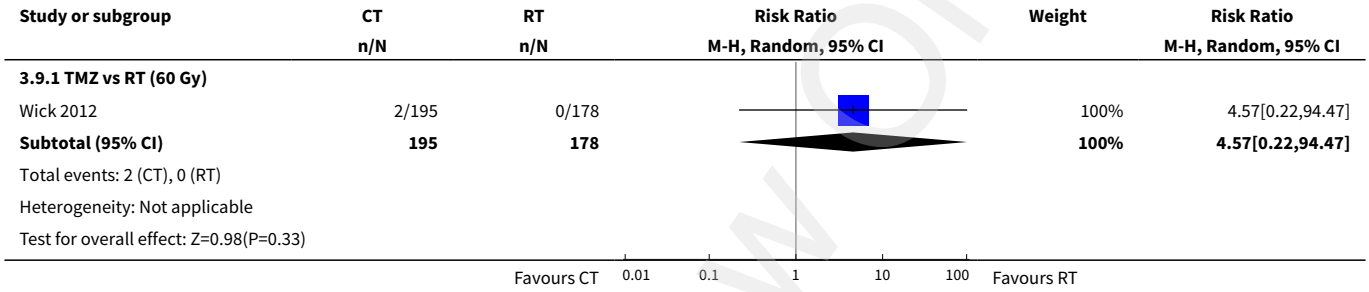
Analysis 3.7. Comparison 3 CT vs RT, Outcome 7 Fatigue/asthenia G3+.



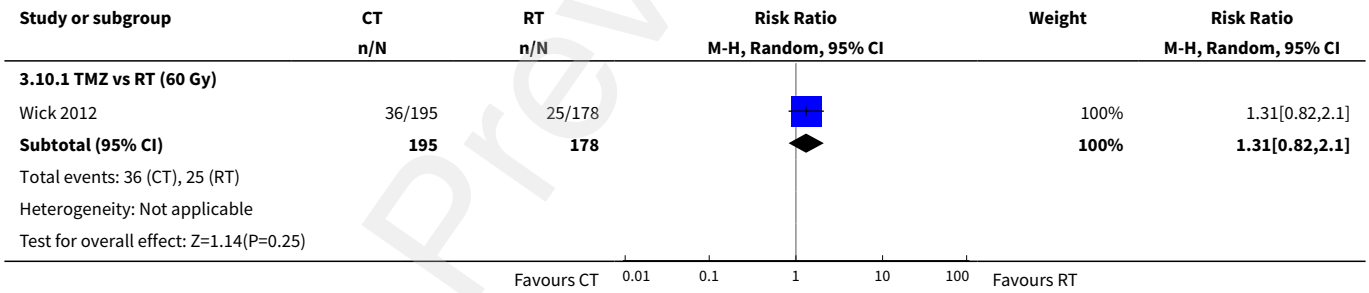
Analysis 3.8. Comparison 3 CT vs RT, Outcome 8 Nausea/vomiting G3+.



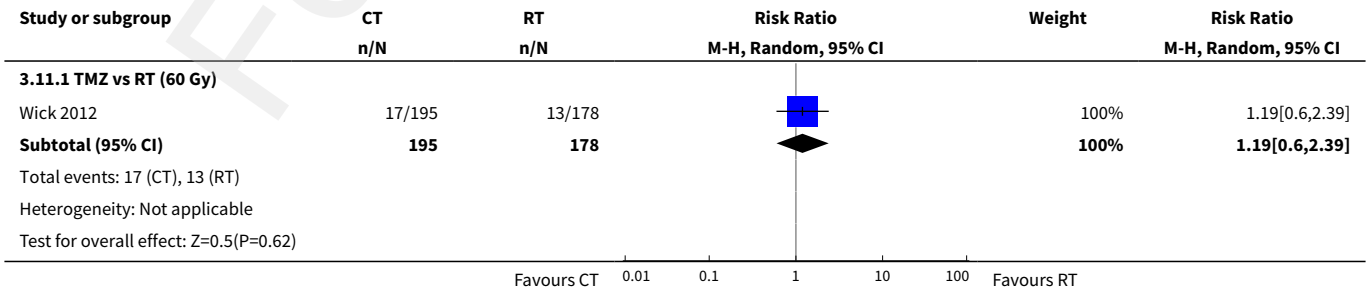
Analysis 3.9. Comparison 3 CT vs RT, Outcome 9 Weight loss G3+.



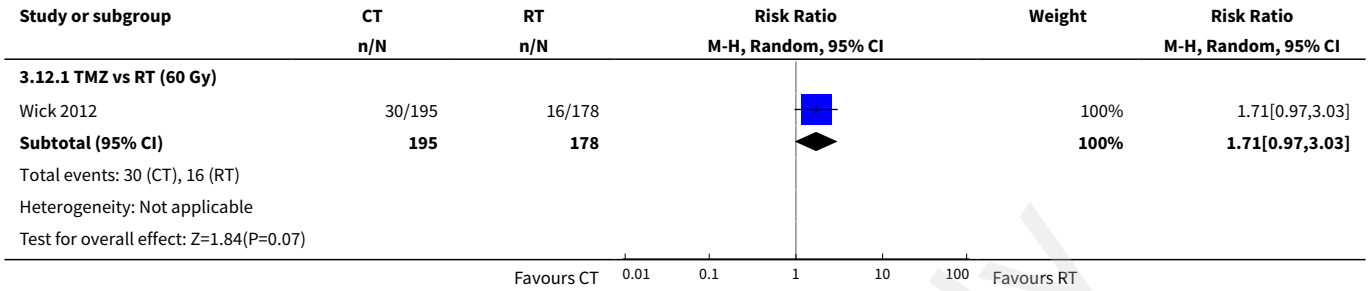
Analysis 3.10. Comparison 3 CT vs RT, Outcome 10 Neurological symptoms G3+.



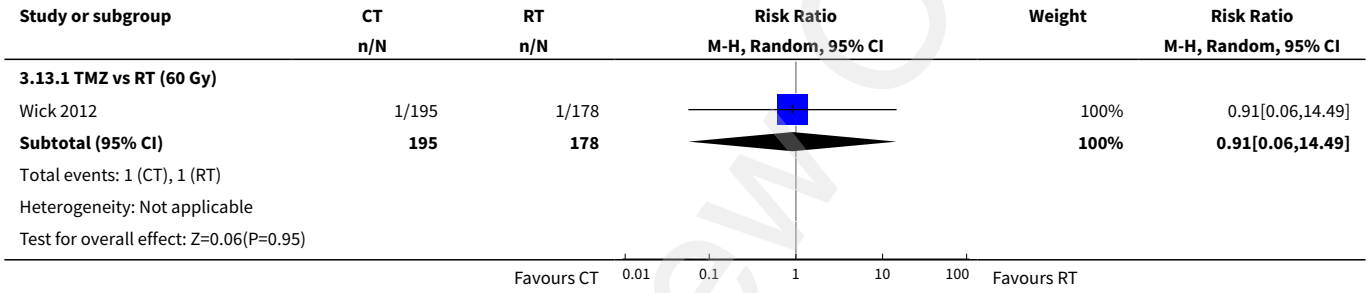
Analysis 3.11. Comparison 3 CT vs RT, Outcome 11 Seizures G3+.



Analysis 3.12. Comparison 3 CT vs RT, Outcome 12 Elevated liver enzymes G3+.



Analysis 3.13. Comparison 3 CT vs RT, Outcome 13 Cutaneous adverse event G3+.



Comparison 4. ChemoRT vs RT

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Progression free survival	1		Hazard Ratio (Random, 95% CI)	Subtotals only
1.1 TMZ+RT (40Gy) vs RT (40 Gy)	1	562	Hazard Ratio (Random, 95% CI)	0.50 [0.41, 0.61]
2 Neutropenia G3+	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 TMZ + RT (40Gy) vs RT (40Gy)	1	515	Risk Ratio (M-H, Random, 95% CI)	10.30 [2.45, 43.34]
3 Thrombocytopenia G3+	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 TMZ + RT (40Gy) vs RT (40Gy)	1	527	Risk Ratio (M-H, Random, 95% CI)	28.56 [3.92, 207.86]
4 Lymphopenia G3+	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

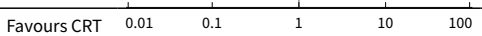
Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
4.1 TMZ + RT (40Gy) vs RT (40Gy)	1	521	Risk Ratio (M-H, Random, 95% CI)	2.65 [1.75, 4.01]
5 Leucopenia G3+	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5.1 TMZ + RT (40Gy) vs RT (40Gy)	1	528	Risk Ratio (M-H, Random, 95% CI)	18.16 [2.45, 134.64]
6 Anaemia G3+	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6.1 TMZ + RT (40Gy) vs RT (40Gy)	1	528	Risk Ratio (M-H, Random, 95% CI)	6.69 [0.35, 128.88]
7 Treatment toxicity G3+	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
7.1 TMZ + RT (40Gy) vs RT (40Gy)	1	528	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.68, 1.59]

Analysis 4.1. Comparison 4 ChemoRT vs RT, Outcome 1 Progression free survival.

Study or subgroup	ChemoRT N	RT N	log[Hazard Ratio] (SE)	Hazard Ratio IV, Random, 95% CI	Weight	Hazard Ratio IV, Random, 95% CI
4.1.1 TMZ+RT (40Gy) vs RT (40 Gy)						
Perry 2017	281	281	-0.7 (0.101)		100%	0.5[0.41,0.61]
Subtotal (95% CI)					**100%**	**0.5[0.41,0.61]**
Heterogeneity: Not applicable						
Test for overall effect: Z=6.84(P<0.0001)						

Analysis 4.2. Comparison 4 ChemoRT vs RT, Outcome 2 Neutropenia G3+.

Study or subgroup	ChemoRT n/N	RT n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
4.2.1 TMZ + RT (40Gy) vs RT (40Gy)					
Perry 2017	22/266	2/249		100%	10.3[2.45,43.34]
Subtotal (95% CI)	**266**	**249**		**100%**	**10.3[2.45,43.34]**
Total events: 22 (ChemoRT), 2 (RT)					
Heterogeneity: Not applicable					
Test for overall effect: Z=3.18(P=0)					



Analysis 4.3. Comparison 4 ChemoRT vs RT, Outcome 3 Thrombocytopenia G3+.

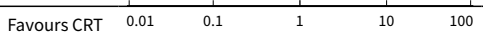
Study or subgroup	ChemoRT n/N	RT n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
4.3.1 TMZ + RT (40Gy) vs RT (40Gy)					
Perry 2017	30/270	1/257		100%	28.56[3.92,207.86]
Subtotal (95% CI)	**270**	**257**		**100%**	**28.56[3.92,207.86]**
Total events: 30 (ChemoRT), 1 (RT)					
Heterogeneity: Not applicable					
Test for overall effect: Z=3.31(P=0)					

Analysis 4.4. Comparison 4 ChemoRT vs RT, Outcome 4 Lymphopenia G3+.

Study or subgroup	ChemoRT n/N	RT n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
4.4.1 TMZ + RT (40Gy) vs RT (40Gy)					
Perry 2017	73/268	26/253		100%	2.65[1.75,4.01]
Subtotal (95% CI)	**268**	**253**		**100%**	**2.65[1.75,4.01]**
Total events: 73 (ChemoRT), 26 (RT)					
Heterogeneity: Not applicable					
Test for overall effect: Z=4.62(P<0.0001)					

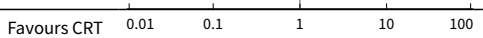
Analysis 4.5. Comparison 4 ChemoRT vs RT, Outcome 5 Leucopenia G3+.

Study or subgroup	ChemoRT n/N	RT n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
4.5.1 TMZ + RT (40Gy) vs RT (40Gy)					
Perry 2017	19/270	1/258		100%	18.16[2.45,134.64]
Subtotal (95% CI)	**270**	**258**		**100%**	**18.16[2.45,134.64]**
Total events: 19 (ChemoRT), 1 (RT)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.84(P=0)					

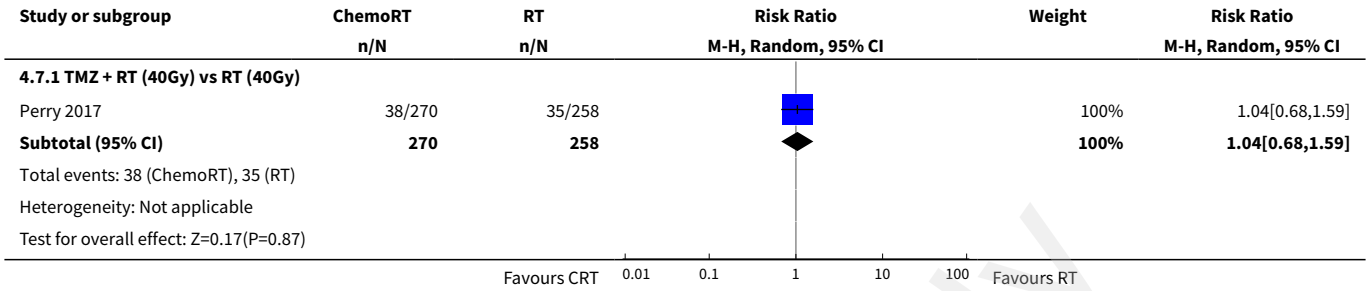


Analysis 4.6. Comparison 4 ChemoRT vs RT, Outcome 6 Anaemia G3+.

Study or subgroup	ChemoRT n/N	RT n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
4.6.1 TMZ + RT (40Gy) vs RT (40Gy)					
Perry 2017	3/270	0/258		100%	6.69[0.35,128.88]
Subtotal (95% CI)	**270**	**258**		**100%**	**6.69[0.35,128.88]**
Total events: 3 (ChemoRT), 0 (RT)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.26(P=0.21)					



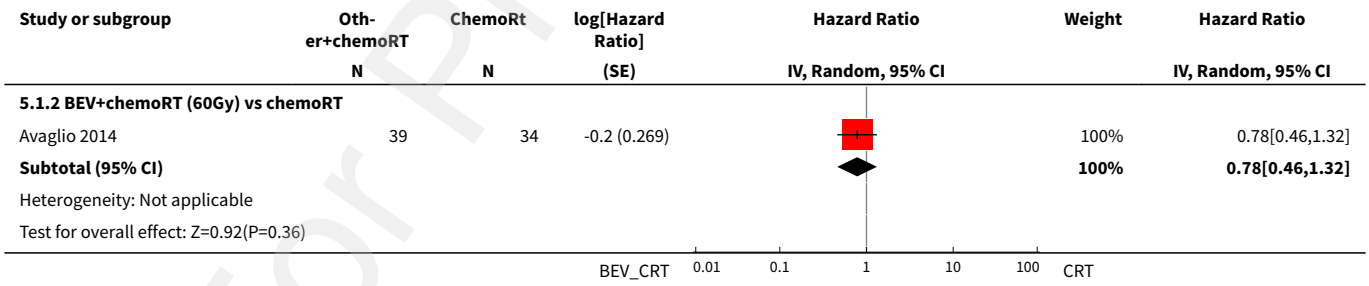
Analysis 4.7. Comparison 4 ChemoRT vs RT, Outcome 7 Treatment toxicity G3+.



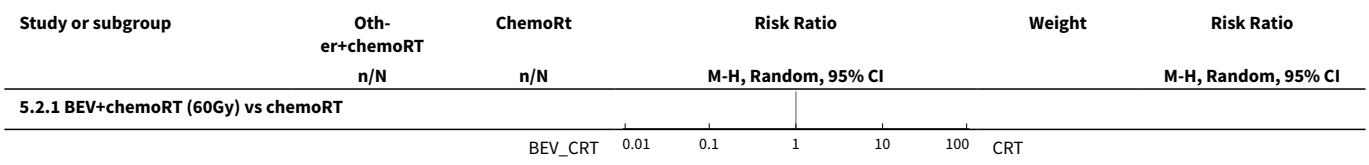
Comparison 5. Other+chemoRT vs chemoRT

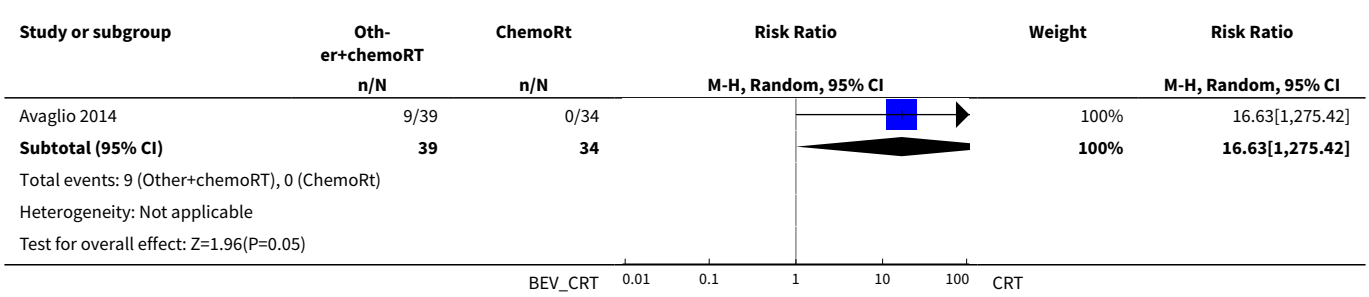
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Progression free survival	1		Hazard Ratio (Random, 95% CI)	Subtotals only
1.2 BEV+chemoRT (60Gy) vs chemoRT	1	73	Hazard Ratio (Random, 95% CI)	0.78 [0.46, 1.32]
2 Thromboembolic events G3+	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 BEV+chemoRT (60Gy) vs chemoRT	1	73	Risk Ratio (M-H, Random, 95% CI)	16.63 [1.00, 275.42]

Analysis 5.1. Comparison 5 Other+chemoRT vs chemoRT, Outcome 1 Progression free survival.



Analysis 5.2. Comparison 5 Other+chemoRT vs chemoRT, Outcome 2 Thromboembolic events G3+.

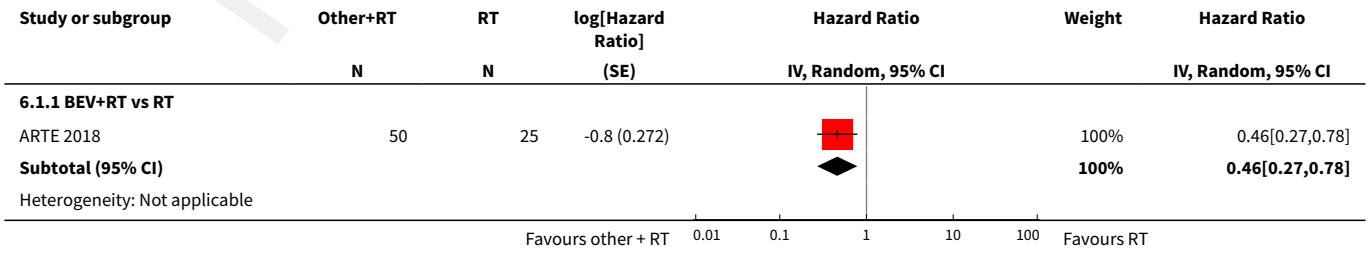


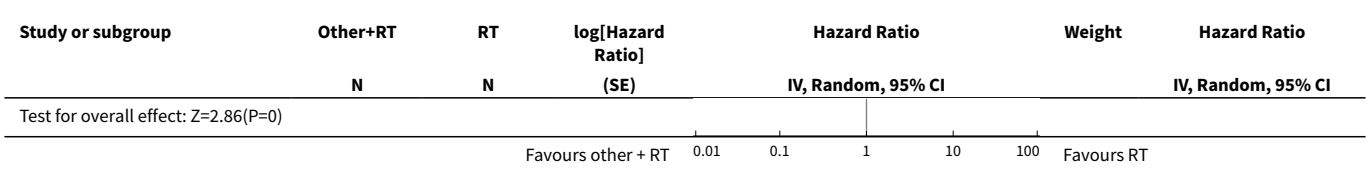


Comparison 6. Other+RT (40Gy) vs RT (40Gy)

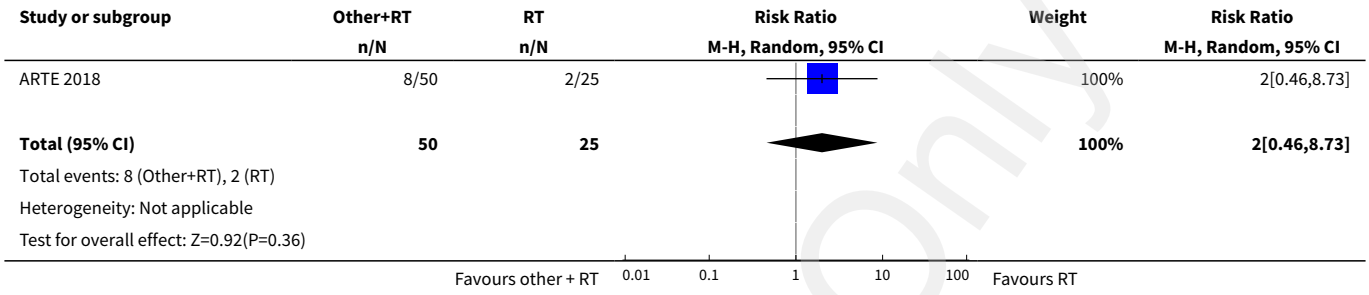
Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Progression free survival	1		Hazard Ratio (Random, 95% CI)	Subtotals only
1.1 BEV+RT vs RT	1	75	Hazard Ratio (Random, 95% CI)	0.46 [0.27, 0.78]
2 Thromboembolic events G3+	1	75	Risk Ratio (M-H, Random, 95% CI)	2.0 [0.46, 8.73]
3 Haematological events G3+	1	75	Risk Ratio (M-H, Random, 95% CI)	2.55 [0.13, 51.17]
4 Infections G3+	1	75	Risk Ratio (M-H, Random, 95% CI)	1.17 [0.33, 4.13]
5 Fatigue G3+	1	75	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.13, 4.20]
6 Seizures G3+	1	75	Risk Ratio (M-H, Random, 95% CI)	4.59 [0.26, 82.01]
7 Headaches G3+	1	75	Risk Ratio (M-H, Random, 95% CI)	0.17 [0.01, 4.03]
8 Neuropsychiatric events G3+	1	75	Risk Ratio (M-H, Random, 95% CI)	2.0 [0.24, 16.97]
9 Neurological events G3+	1	75	Risk Ratio (M-H, Random, 95% CI)	0.9 [0.34, 2.40]
10 Hypertension G3+	1	75	Risk Ratio (M-H, Random, 95% CI)	1.0 [0.20, 5.09]
11 Cutaneous adverse events G3+	1	75	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
12 Gastrointestinal events G3+	1	75	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.13, 4.20]

Analysis 6.1. Comparison 6 Other+RT (40Gy) vs RT (40Gy), Outcome 1 Progression free survival.

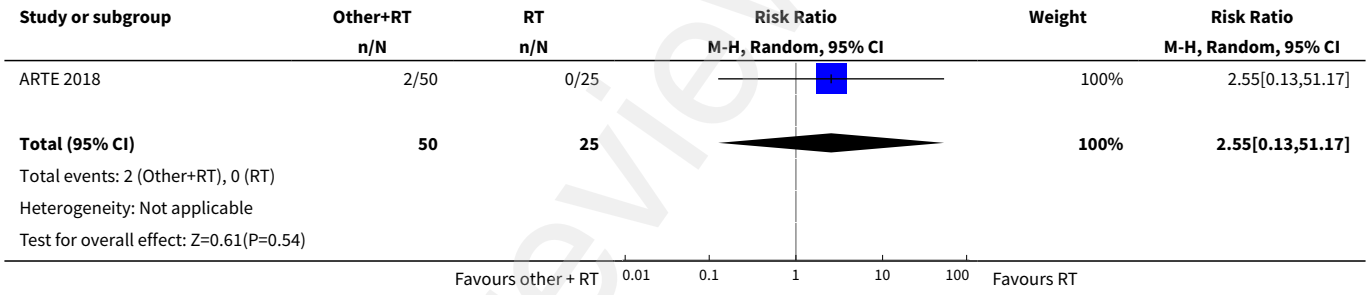




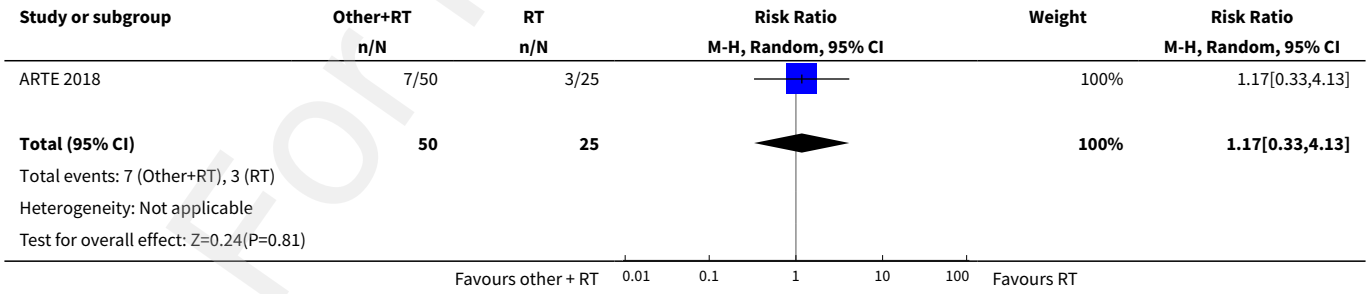
Analysis 6.2. Comparison 6 Other+RT (40Gy) vs RT (40Gy), Outcome 2 Thromboembolic events G3+.



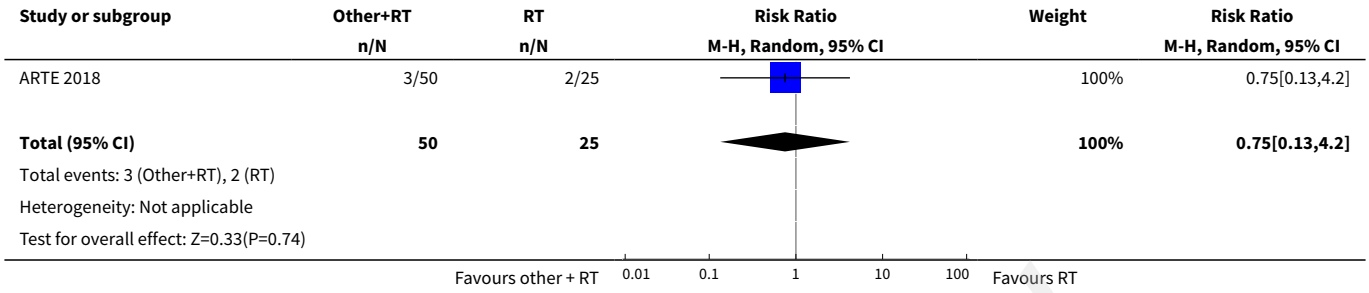
Analysis 6.3. Comparison 6 Other+RT (40Gy) vs RT (40Gy), Outcome 3 Haematological events G3+.



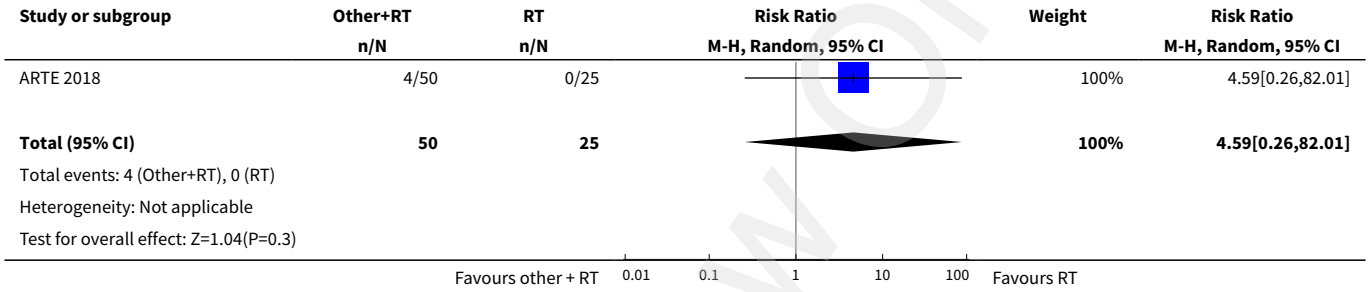
Analysis 6.4. Comparison 6 Other+RT (40Gy) vs RT (40Gy), Outcome 4 Infections G3+.



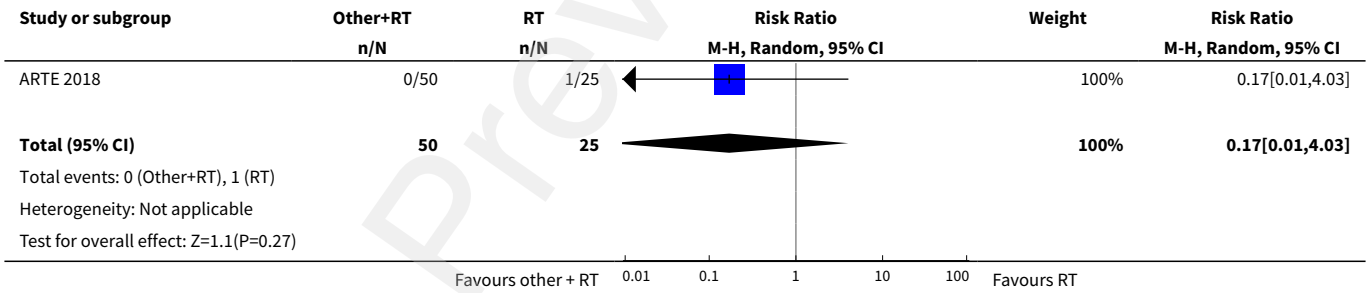
Analysis 6.5. Comparison 6 Other+RT (40Gy) vs RT (40Gy), Outcome 5 Fatigue G3+.



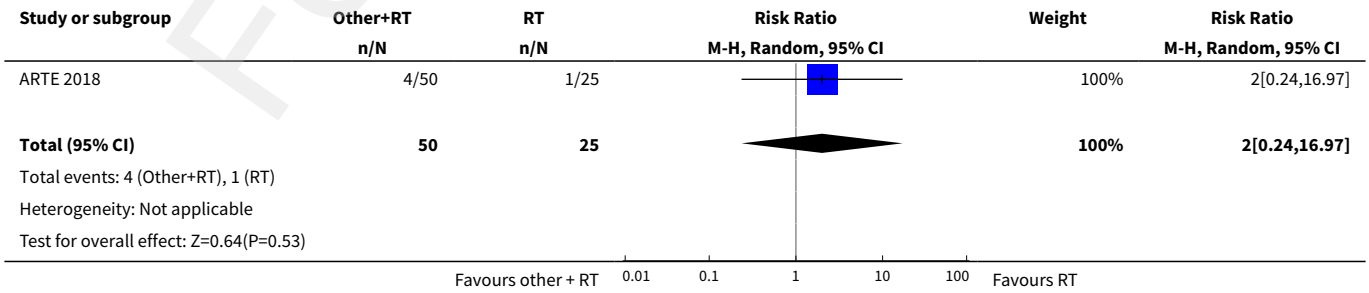
Analysis 6.6. Comparison 6 Other+RT (40Gy) vs RT (40Gy), Outcome 6 Seizures G3+.



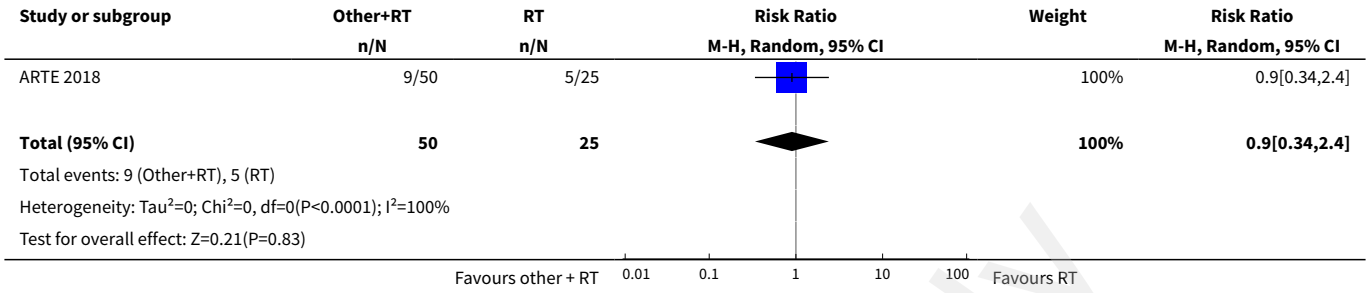
Analysis 6.7. Comparison 6 Other+RT (40Gy) vs RT (40Gy), Outcome 7 Headaches G3+.



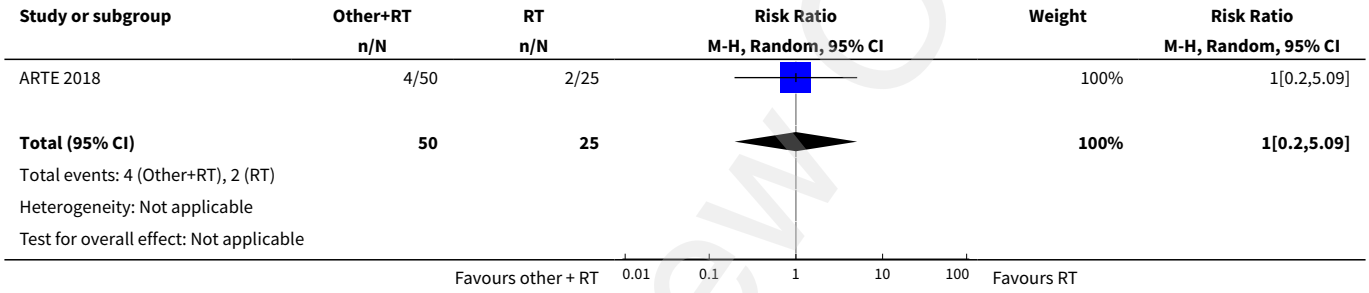
Analysis 6.8. Comparison 6 Other+RT (40Gy) vs RT (40Gy), Outcome 8 Neuropsychiatric events G3+.



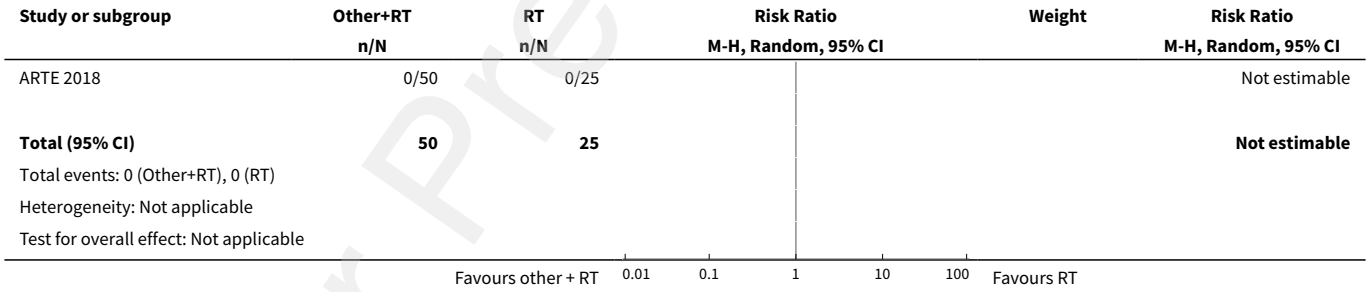
Analysis 6.9. Comparison 6 Other+RT (40Gy) vs RT (40Gy), Outcome 9 Neurological events G3+.



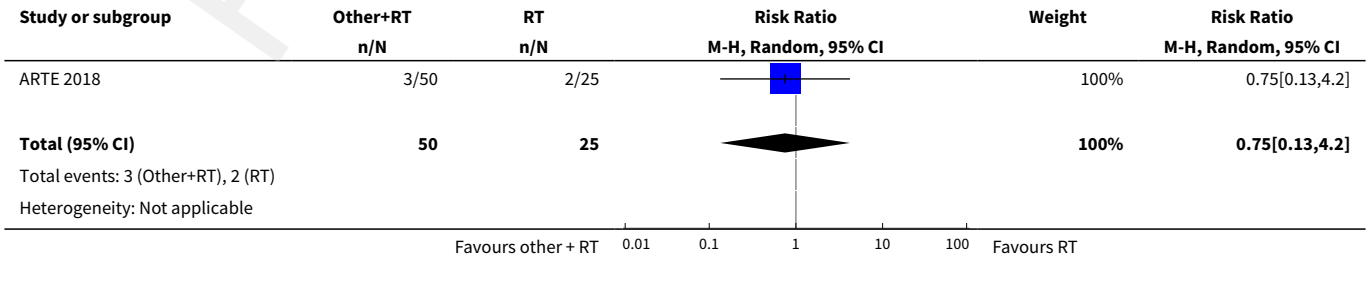
Analysis 6.10. Comparison 6 Other+RT (40Gy) vs RT (40Gy), Outcome 10 Hypertension G3+.

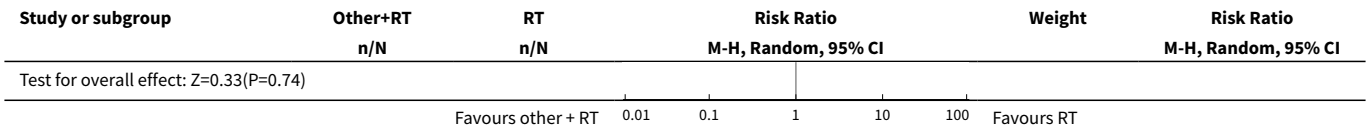


Analysis 6.11. Comparison 6 Other+RT (40Gy) vs RT (40Gy), Outcome 11 Cutaneous adverse events G3+.



Analysis 6.12. Comparison 6 Other+RT (40Gy) vs RT (40Gy), Outcome 12 Gastrointestinal events G3+.





ADDITIONAL TABLES

Table 1. Table of radiotherapy regimens used in included studies and biologically effective doses

Dose fractionation	EQD2 (Gy)	BED (Gy)
60Gy/30 fractions	60	75
50Gy/28 fractions	49	61
40Gy/15 fractions	42	53
34Gy/10 fractions	39	48
25Gy/5 fractions	33	41

EQD2 and BED calculated for an alpha/beta of 8
EQD2 = equivalent dose; BED = biologically effective dose
Gy = Gray

Table 2. Performance Scores

Karnofsky Status	Karnofsky Grade	ECOG Grade	ECOG Status
Normal, no complaints	100	0	Fully active, able to carry on all pre-disease performance without restriction
Able to carry on normal activities. Minor signs or symptoms of disease	90	1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
Normal activity with effort	80	1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
Care for self. Unable to carry on normal activity or to do active work	70	2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
Requires occasional assistance, but able to care for most of his needs	60	2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
Requires considerable assistance and frequent medical care	50	3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
Disabled. Requires special care and assistance	40	3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours

Table 2. Performance Scores *(Continued)*

Severly disabled. Hospitalisation indicated though death nonimminent	30	4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
Very sick. Hospitalisation necessary. Active supportive treatment necessary	20	4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
Moribund	10	4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
Dead	0	5	Dead

As published in Am J Clin. Oncol: Oken 1982

Table 3. Table of outcomes reported in included studies

	Trial	OS	QoL	PFS	Severe adverse events	Cognitive impairments	Functional impairment	Fatigue
1	Green 1983	For 65+ age subgroup, number of deaths (overall, no time-point specified) and death rate (number of deaths per 10 patient-months) reported.	Not for 65+ subgroup.	Not for 65+ subgroup.	Not for 65+ subgroup.	Not for 65+ subgroup.	Not for 65+ subgroup.	Not for 65+ subgroup.
2	Roa 2004 (Elderly patients only in this trial, defined as age 60 years or over; mean age was 72 years with SD 5 years)	Median OS reported (ITT analysis), including HR and a KM curve. Percentage of patients alive at 6 months also reported (Table 1 and Figure 1 of main manuscript).	Low rates of FACT-Br version 3 completion (45% overall) by patients precluded meaningful analysis. Protocol specified FACT-Br completion at baseline, 3 weeks after starting RT, at the end of RT, and at 3-month intervals thereafter. Table 2 of main manuscript.	Not done.	Not reported.	Not reported.	Difference in averaged KPS scores and change in KPS over time between the two groups (0-6 months from start of RT). KPS at baseline, 3 weeks, 6 weeks, first and second follow up. Table 1, Table 2 and Figure 2 of main manuscript.	Not reported.
3	Keime-Guibert 2007 (Elderly patients only - aged 70 years or over).	Median OS reported (ITT analysis), including HR and KM curve.	QLQ-C30 and QLQ-BN20 and completion rate. Changes in mean score at baseline, day 30, day 60, day 90 and day 135.	Median PFS.	Tolerance of treatment reported but not clear	QLQ-C30 includes cognitive. MDRS score at	KPS decline over time.	QLQ-C30 includes fatigue.

Table 3. Table of outcomes reported in included studies *(Continued)*

					which toxicity scoring used.	baseline, 60 days and 135 days. MMSE score. NPI (Neuropsych inventory).		
4	Malmstrom 2012 (Patients in this trial all aged over 60 years old but reported data for 70+ years subgroup)	Median OS and 1 year survival percentage. As this study had three arms, survival analyses were done using three pairwise comparisons. A KM curve was presented for the overall patient population and a subgroup of patients aged 60-70 years and aged over 70. HR reported for this outcome (Table 2). OS for patients with mMGMT and umMGMT disease also reported. The two radiotherapy arms combined for this analysis. In the supplementary appendix, OS and KM reported comparing the TMZ arm and the hypofractionated RT arm. These outcomes were reported for patients overall, a subgroup of patients aged 60-70 and a subgroup of patients aged over 70. HR reported for these outcomes.	EORTC QLQ-30v3 and QLQ-BN20 at baseline, 6 weeks, 3 months and 6 months. Mean change of score from baseline reported for each domain (Figure 4). No data reported for 6 month time-point due to low completion rate.	Not reported.	WHO grading for all except nausea and vomiting (CTCAE v2), but only reported for overall sample and not elderly subgroup.	Reported as a category of a QoL assessment but only for overall sample and not elderly subgroup.	Not reported.	WHO grading system. Reported fatigue G2-5, but only for overall sample and not elderly subgroup.

Table 3. Table of outcomes reported in included studies *(Continued)*

		1 year OS probabilities also reported.						
5	Wick 2012 (All elderly patients – aged over 65 years)	Median OS reported (ITT analysis) with HR and KM curve. OS differences between patients with mMGMT and uMGMT disease also reported (with HR and KM curve). OS survival (PP analysis) also reported but no HR or KM curve for these outcomes. Survival % at 6 months and 1 year. Also report proportions for death, or disease progression or death for each arm.	EORTC QLQ-30 and BN20 used for HRQoL assessment. Results available for 82% of the patients (in appendix).	Median event free survival (rather than PFS) and also mMGMT and uMGMT. %EFS at 6 months and 1 year.	CTCAEv3 used to collect adverse event data.	MMSE performed at baseline, monthly during treatment and then every 3 months. Median score (with 95% CI) reported overall, before treatment and after primary treatment.	KPS at baseline.	Fatigue/asthenia G3-4 reported as an adverse event.
6	Avaglio 2014 (comprises several reports) Chinot 2014 main report presents findings for whole sample, elderly subgroup reported in supplementary appendix. Saran 2016 provides information on safety outcomes. Taphoorn 2015 reported HR QoL outcomes for sample as a whole.	OS for 60-69 and 70+ subgroups (found in supplementary appendix 2). No KM curves for these subgroups.	Taphoorn 2015 reports the results for QLQ-C30 and QLQ-BN20 for the whole sample (age >18), not for the elderly subgroup.	PFS for 60-69 and 70+ subgroups (number and HR).	Mason 2014 is a separate publication about arterial adverse events and gives event rates for the over 65 subgroup.	Not for elderly subgroup.	Not for elderly subgroup.	Not for elderly subgroup.
7	Roa 2015 (comprises several reports) (Guedes de Castro 2017 reports on outcomes only for those patients aged over 65s and Fidarova 2015 presents	Median OS reported (ITT analysis). Outcomes for elderly and frail, and elderly and not frail subgroups. No HR reported for OS outcomes. KM curves	The mean scores from a combination of EORTC QLQC30 and QLQ-BN20 reported at baseline, 4 weeks and 8 weeks. Categorical scales were transformed to linear scalers from 0-100. Differ-	Median PFS reported (ITT). No KM or HR for elder-	Adverse events were recorded weekly during RT, 4 weeks after RT and every	MMSE at baseline.	KPS at baseline.	Fatigue mentioned in Fidarova 2015 abstract for overall tri-

Table 3. Table of outcomes reported in included studies *(Continued)*

	quality of life results as a conference abstract).	included in Guedes de Castro 2017 Figures 1-4.	ence between mean scores between treatment groups reported in Guedes de Castro 2017 Table 3.	ly only patients.	3 months until tumour progression using CTCAE v3. AEs only reported in the case of a grade 3 or greater toxicity.			al population.
8	GLARIUS 2016 (comprises several reports) Herrlinger 2016 reports the main findings for the whole sample, aged from 18+ years. Kebir 2016 is an abstract which reports specifically on the differences in OS between younger and older patients in the trial.	Median OS for 65+ subgroup in both arms reported (modified ITT analysis). No HR or KM curve available for the elderly cohort. yes	Not reported separately for elderly subgroup.	Not reported separately for elderly subgroup.	Not reported separately for elderly subgroup.	Not reported separately for elderly subgroup.	Not reported separately for elderly subgroup.	Not reported separately for elderly subgroup.
9	Perry 2017 (All elderly patients – aged 65 years old or over).	Median OS reported (ITT). KM curve and HR reported for this outcome. Median OS also reported for subgroups of patients aged 65-70 years old, 71-75 and 76+. Also reported OS rate at 12, 18 and 24 months for all patients and for patients with umMGMT and mMGMT disease.	QLQC30 and BN20. Up to 18 months post treatment. Baseline/1 week/3 week reported. Time to deterioration in QoL reported.	Median PFS.	CTCAE v3 used for adverse event reporting.	MMSE at baseline.	ECOG at baseline.	Not separately reported.
10	Weller 2017 (Trial not restricted to elderly patients only. Includes patients aged 18 years +).	Report OS (events per patient) for patients aged 65+ subgroup. The subgroup if further divided into those who have minimal residual	Not for 65+ subgroup.	Not for 65+ subgroup.	Not for 65+ subgroup.	Not for 65+ subgroup.	Not for 65+ subgroup.	Not for 65+ subgroup.

Table 3. Table of outcomes reported in included studies *(Continued)*

		disease (MRD) and significant residual disease (SRD). There is a HR given for patients aged 65+ in the MRD subgroup and in the SRD subgroup separately. There is no HR reported for the 65+ group overall. No KM curves for the elderly subgroup.						
11	Stupp 2017a (Trial not restricted to elderly patients only. Includes patients aged 18 years +). Taphoorn 2018 is separate publication which reports on HRQoL outcomes.	Median OS for 65+ subgroup. HR and KM curve reported for this outcome in the 65+ subgroup. The proportion of patients in each arm of the trial who were alive at the end of the study also reported.	HR QoL was measured using EORTC QLQ-C30 and BN20 questionnaires at baseline and every 3 months for up to 12 months. Mean QoL scores and mean change from baseline reported. Outcomes not reported separately for elderly subgroup.	Not reported separately for elderly subgroup.	Not reported separately for elderly subgroup.	Not reported separately for elderly subgroup.	Not reported separately for elderly subgroup.	Not reported separately for elderly subgroup.
12	ARTE 2018 (All elderly patients in the trial – aged 65 years or over)	Median OS (ITT and PP) and 1 year survival rate. Also reported OS depending on molecular panel subtype. No HR reported for median OS differences. KM curves are shown.	Reported median deterioration free survival from baseline. Individual functional and symptom scores from EORTC QLQ-C30/BN20 before tumour progression analysed in a generalised linear model that controlled for time treatment interactions.	Median PFS. ITT and PP. And %PFS at 6 months. Also had independent central review for some patients. (66 with MRI available). Also looked at PFS per molecular panel subtype.	Yes, reported in supplementary material. G3-5 fatigue, seizures, headaches, other neuro, neuropsych, haematological, arterial hypertension, thromboembolic, all infections, cutaneous, GI.	MMSE at baseline and serial measurements (0,7,19 weeks).	KPS at baseline.	Fatigue reported as a category of QoL and as an adverse events.

CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 or QLQ-BN20 (specific for brain cancer); FACT-Br: Functional Assessment of Cancer Therapy scale [specific for brain cancer]); HR: hazard ratio; HRQoL: Health-related quality of life; ITT: Intention to treat; mITT: modified ITT; KM curve: Kaplan Meier curve; KPS: Karnofsky performance status; MMSE: mini mental state examination; mMGMT: Methylated MGMT; umMGMT: unmethylated MGMT; PFS: progression free survival; PP: per protocol; OS: overall survival.

Table 4. Median survival associated with treatment options evaluated in included studies *(Continued)*

Study ID	Age (years) and performance status	Treatment arm	Overall Survival (OS)			Progression Free Survival (PFS)		
			Median OS (months)	lower 95% CI (months)	upper 95% CI (months)	Median PFS (months)	lower 95% CI (months)	upper 95% CI (months)
Green 1983	Age ≥ 65 KPS ≥ 70%	4 arms; see Table 1	-	-	-	-	-	-
Keime-Guibert 2007	Age ≥ 70 KPS ≥ 70%	Supportive care	3.9	3.1	5.0	1.3	1.0	1.8
		RT (50Gy/28 fractions/5-6 weeks) + supportive care	6.8	5.9	8.1	3.5	2.5	5.2
Roa 2004	Age ≥ 60 KPS ≥ 50%	RT (40Gy/15 fractions/3 weeks)	5.6	-	-	-	-	-
		RT (60Gy/30 fractions/6 weeks)	5.1	-	-	-	-	-
Roa 2015[a] (elderly and/or frail)	Age ≥ 65 KPS 50-70%	RT (25Gy/5 fractions/1 week)	6.8	4.5	9.1	4.3	2.6	5.9
		RT (40Gy/15 fractions)	6.2	4.7	7.7	3.2	0.1	6.3
Roa 2015 (elderly and frail)	Age ≥ 65 KPS ≥ 50%	RT (25Gy/5 fractions/1 week)	7.5	5.3	9.7	-	-	-
		RT (40Gy/15 fractions)	6.7	4.5	8.9	-	-	-
Roa 2015[a](elderly and non-frail)	Age ≥ 65 KPS ≥ 80%	RT (25Gy/5 fractions/1 week)	8.0	5.9	10.0	-	-	-
		RT (40Gy/15 fractions/3 weeks)	8.0	5.3	10.3	-	-	-
Malmstrom 2012	Age ≥ 70 WHO 0-2	RT (60Gy/30 fractions/6 weeks)	5.2	4.0	6.3	-	-	-
		RT (34Gy/10 fractions/2 weeks)	7.0	5.2	8.8	-	-	-
		TMZ	9.0	6.2	11.8			

Table 4. Median survival associated with treatment options evaluated in included studies *(Continued)*

Malmstrom 2012 (unmethylated)	Age ≥ 70	RT (any schedule)	7.0	5.8	8.3	-	-
	WHO 0-2	TMZ	6.8	5.9	7.7	-	-
Malmstrom 2012 (methylated)	Age ≥ 70	RT (any schedule)	8.2	6.6	9.9	-	-
	WHO 0-2	TMZ	9.7	8.0	11.4	-	-
Wick 2012[b]	Age ≥ 65	RT (60Gy/30 fractions/6 weeks)	9.6	8.2	10.8	4.7	4.2	5.2
	KPS ≥ 60%	TMZ	8.6	7.3	10.2	3.3	3.2	4.1
Wick 2012	Age ≥ 65	RT (60Gy/30 fractions/6 weeks)	10.4	8.0	11.6	4.6	3.7	6.3
(unmethylated)	KPS ≥ 60%	TMZ	7.0	5.7	8.7	3.3	3.0	3.5
Wick 2012	Age ≥ 65	RT (60Gy/30 fractions/6 weeks)	9.6	6.4	not reached	4.6	4.2	5.0
(methylated)	KPS ≥ 60%	TMZ	not reached	10.1	not reached	8.4	5.5	11.7
Perry 2017	Age ≥ 65	RT (40Gy/15 fractions/3 weeks)	7.6	7.0	8.4	3.9	3.5	4.3
	ECOG 0-2	RT (40Gy/15 fractions/3 weeks) + TMZ + maintenance TMZ	9.3	8.3	10.3	5.3	4.6	6.2
Perry 2017[c]	Age ≥ 65	RT (40Gy/15 fractions/3 weeks)	7.9	-	-	-	-	-
(unmethylated)	ECOG 0-2	RT (40Gy/15 fractions/ 3 weeks) + TMZ + maintenance TMZ	10	-	-	-	-	-
Perry 2017[c]	Age ≥ 65	RT (40Gy/15 fractions/3 weeks)	7.7	-	-	-	-	-
(methylated)	ECOG 0-2	RT (40Gy/15 fractions/3 weeks) + TMZ+ maintenance TMZ	13.5	-	-	-	-	-
Avaglio 2014	Age ≥ 70	RT (60Gy/30 fractions) + TMZ + maintenance TMZ	-	-	-	-	-	-
	WHO 0-2	RT (60Gy/30 fractions) + TMZ + BEV + maintenance	-	-	-	-	-	-

Table 4. Median survival associated with treatment options evaluated in included studies *(Continued)*

Stupp 2017a[d]	Age ≥ 65 KPS ≥ 70%	RT (±60Gy/30 fractions/6 weeks) + TMZ + maintenance TMZ	13.7	7.6	24.8	-	-	-
	Age ≥ 65 KPS ≥ 70%	RT (±60Gy/30 fractions/6 weeks) + TMZ + maintenance TMZ + TTFields	17.4	9.0	31.5	-	-	-
ARTE 2018	Age ≥ 65 KPS ≥ 60%	RT (40Gy/15 fractions/3 weeks)	12.2	9.2	15.2	4.8	3.0	6.6
		RT (40Gy/15 fractions/3 weeks) + BEV	12.1	10.2	14.0	7.6	6.2	9.0
GLARIUS 2016[e] (unmethylated)	Age ≥ 65 KPS ≥ 70%	RT (60Gy/30 fractions/6 weeks) + TMZ + maintenance	17.5	-	-	-	-	-
		RT (60Gy/30 fractions/6 weeks) + BEV + IRI + maintenance	13.4	-	-	-	-	-
Weller 2017	Age ≥ 65 KPS ≥ 60%	RT (60Gy/30 fractions/6 weeks) + TMZ + maintenance	-	-	-	-	-	-
		RT (60Gy/30 fractions/6 weeks) + TMZ + maintenance + RIN	-	-	-	-	-	-

BEV: bevacizumab; ECOG: Eastern Cooperative Oncology Group; Gy: Grays; IRI: irinotecan; KPS: Karnofsky performance score; OS: overall survival; PFS: progression free survival; RIN: rindopepimut; RT: radiotherapy; TTF: tumour treating fields; TMZ: temozolomide; WHO: World Health Organization

[a]Data from the Guedes de Castro et al 2017 substudy report on patients ≥ 65 years only

[b]This study reported event free survival (EFS), not PFS. Findings by MGMT methylation status were reported by authors in the later (2017) publication.

[c]From Perry 2012 abstract

[d]MGMT promotor methylation status was not reported separately for the elderly subgroup. Median survival data were reported as time from randomisation not diagnosis. Randomisation in this trial occurred after concomitant chemoradiotherapy.

[e]From substudy data reported in a conference proceeding abstract by Kebir et al, 2016.

Table 5. CHEC list* for included economic studies

CHEC ITEM	Ghosh et al (2018)
Is the study population clearly described?	Y
Are competing alternatives clearly described?	Y
Is a well-defined research question posed in answerable form?	Y
Is the economic study design appropriate to the stated objective?	Y
Is the chosen time horizon appropriate to include relevant costs and consequences?	N
Is the actual perspective chosen appropriate?	N
Are all important and relevant costs for each alternative identified	N
Are all costs measured appropriately in physical units?	Y
Are costs valued appropriately?	N
Are all important and relevant outcomes for each alternative identified?	N
Are all outcomes measured appropriately?	N
Are outcomes valued appropriately?	N
Is an incremental analysis of costs and outcomes of alternatives performed?	Y
Are all future costs and outcomes discounted appropriately?	N
Are all important variables, whose values are uncertain, appropriately subjected to sensitivity analysis?	N
Do the conclusions follow from the data reported?	N
Does the study discuss the generalizability of the results to other settings and patient/client groups?	N
Does the article indicate that there is no potential conflict of interest of study researcher(s) and funder(s)?	Y
Are ethical and distributional issues discussed appropriately?	N

*Evers 2005

Table 6. CHEERS checklist* of included studies

CHEERS Quality Checklist		
Section of paper	**Component**	**Reported on Page Number**

Table 6. CHEERS checklist* of included studies *(Continued)*

Ghosh et al (2018)		
Title and abstract	Identify the study as an economic evaluation or use more specific terms such as ''cost-effectiveness analysis'', and describe the interventions compared.	114
	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	114
Methods	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	Supplementary Material
	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	Not Reported
	Describe the perspective of the study and relate this to the costs being evaluated.	Not Reported
	Describe the interventions or strategies being compared and state why they were chosen.	114-115
	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	Partially, stated but not justified
	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	Not Reported
	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	115
	Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	115-116
	Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	Not Reported
	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	115
	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	N/A
	Describe all structural or other assumptions underpinning the decision-analytical model.	N/A
	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	Partial, uncertainty discussed.
Results	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	Not Reported
	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	116-118 & supplementary material

Table 6. CHEERS checklist* of included studies *(Continued)*

	Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective).	116
	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	N/A
Discussion	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	118-119
Other	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	119
	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	119

*Evers 2005

Table 7. Table of estimate effects and certainty ratings for overall survival *(Continued)*

Comparison	Direct Evidence		Indirect Evidence		Network Evidence	
	HR (95% CI)	Certainty	HR (95% CI)	Certainty	HR (95% CI)	Certainty
RT60* vs Supp Care	0.47 (0.29 to 0.76)	Moderate[1]	Not estimable[2]	–	0.47 (0.29 to 0.76)	Moderate
RT40 vs Supp Care	–	–	0.44 (0.25 to 0.77)	Low[3]	0.44 (0.25 to 0.77)	Low
CRT vs Supp Care	–	–	–	–	0.30 (0.17 to 0.53)	Not graded[4]
TMZ vs Supp Care	–	–	0.42 (0.25 to 0.71)	Low[3]	0.42 (0.25 to 0.71)	Low
BEV_CRT vs Supp Care	–	–	–	–	0.25 (0.11 to 0.54)	Not graded[4]
BEV_RT vs Supp Care	–	–	–	–	0.48 (0.23 to 1.00)	Not graded[4]
CRT vs RT40	0.67 (0.56 to 0.80)	High	–	–	0.67 (0.56 to 0.80)	High
BEV_CRT vs RT40	–	–	0.56 (0.31 to 0.99)	Moderate[5]	0.56 (0.31 to 0.99)	Moderate

Table 7. Table of estimate effects and certainty ratings for overall survival *(Continued)*

TMZ vs RT40**	0.72 (0.50 to 1.05)	Low[6]	–	–	0.95 (0.71 to 1.26)	Low
BEV_RT vs RT40	1.08 (0.65 to 1.78)	Low[6]	Not estimable[2]	–	1.08 (0.66 to 1.78)	Low
RT40 vs RT60	0.74 (0.55 to 1.01)	Low[6]	Not estimable[2]	–	0.94 (0.72 to 1.23)	Low
BEV_RT vs RT60	–	–	1.01 (0.58 to 1.79)	Very low[7]	1.01 (0.58 to 1.79)	Very low
BEV_CRT vs RT60	–	–	–	–	0.52 (0.28 to 0.98)	Not graded[4]
CRT vs RT60	–	–	0.63 (0.46 to 0.87)	Low[8]	0.63 (0.46 to 0.87)	Low
TMZ vs RT60	0.86 (0.68 to 1.09)	Very low[9]	–	–	0.89 (0.71 to 1.11)	Very low
BEV_RT vs CRT	–	–	1.61 (0.95 to 2.74)	Low[10]	1.61 (0.95 to 2.74)	Low
BEV_CRT vs CRT	0.83 (0.48 to 1.43)	Low[6]	Not estimable[2]	–	0.83 (0.48 to 1.44)	Low
TMZ vs CRT	–	–	1.42 (1.01 to 1.98)	Low[10]	1.42 (1.01 to 1.98)	Low
BEV_RT vs TMZ	–	–	1.14 (0.64 to 2.02)	Very low[10,11]	1.14 (0.64 to 2.02)	Very low
BEV_CRT vs TMZ	–	–	–	–	0.59 (0.31 to 1.12)	Not graded[4]
BEV_CRT vs BEV_RT	–	–	–	–	0.52 (0.24 to 1.10)	Not graded[4]

[1] Evidence derived from a single small study

[2] Could not be estimated because the intervention was not connected via a loop in the evidence network

[3] Contributing direct evidence was of moderate or low certainty

[4] There was no direct evidence for this comparison, which did not connect via a common comparator, therefore the certainty of evidence was not graded.

[5] Contributing direct evidence was of high or moderate certainty

[6] Downgraded for study design limitations and imprecision

[7] Contributing direct evidence was of low certainty; network estimate imprecise

Table 7. Table of estimate effects and certainty ratings for overall survival *(Continued)*

[8] Contributing direct evidence was of high or low certainty

[9] Downgraded for imprecision, study design limitations and inconsistency

[10] Contributing direct evidence was of high or low certainty

[11]Downgraded for imprecision

*RT50 (Keime-Guibert 2007) coded as RT60.
**RT34 (Malmstrom 2012) coded as RT40.
Abbreviations: BEV_CRT = bevacizumab plus chemoradiotherapy; CI = confidence interval; ; CRT = chemoradiotherapy; RT40 = radiotherapy (40Gy in 15 fractions); RT60 = radiotherapy (60Gy in 30 fractions); Supp Care = supportive care; TMZ = temozolomide; TTF_AC = tumour treating fields with adjuvant chemotherapy (after concomitant chemotherapy)

Table 8. Overview of SUCRA rankings

Treatment option	Main NMA model	Sensitivity Analysis A	Sensitivity Analysis B	Sensitivity Analysis C	Sensitivity Analysis D
BEV_CRT	1.4	1.4	1.4	–	–
CRT	1.8	1.8	1.9	1.1*	1.1*
TMZ	3.8	3.8	3.7	2.8	2.8
RT40	4.3	4.3	4.2	3.3	3.3
BEV_RT	4.7	4.7	4.8	3.8	3.8
RT60	5.0	5.1	5.0	4.0	4.0
Supp_Care	7.0	7.0	7.0	6.0	6.0

*CRT40
BEV_CRT = chemoradiotherapy plus bevacizumab; CRT = chemoradiotherapy; RT40 = radiotherapy (40Gy in 15 fractions); RT60 = radiotherapy (60Gy in 30 fractions); Supp_Care = supportive care; TMZ = temozolomide; TTF_AC = tumour treating fields with adjuvant chemotherapy (after concomitant chemotherapy)
Sensitivity analysis A: Keime-Guibert 2007 study's RT50 arm is coded as RT40; sensitivity analysis B: network without a loop due to exclusion of the Malmstrom 2012 TMZ vs RT40 arm to avoid duplication of data; sensitivity analysis C.1 and C.2: disconnected networks due to non-pooling of CRT40 and CRT60 arms from different studies; sensitivity analysis D: disconnected network due to non-pooling of CRT40 and CRT60 arms from different studies, and Keime-Guibert 2007 study arm RT50 coded as RT40.

Table 9. Characteristics of included studies *(Continued)*

Study ID	Elderly definition (years)	No. analysed	Male gender (%)	Performance status	MGMT methylated/ unmethylated/ unknown (%)	Treatment option			
						1	2	3	4
ARTE 2018	≥ 65	75	64	KPS ≥ 60	21%/73%/5%*	RT_{40}	RT_{40}+ BEV	-	-
Avaglio 2014	≥ 70	73	63	WHO 0-2	26%/59%/24%	RT_{60}+ TMZ + maintenance	RT_{60}+ TMZ + maintenance + BEV	-	-
GLARIUS 2016	≥ 65	34	67[c]	KPS ≥ 70	100% unmethylated	RT_{60}+TMZ	RT_{60}+BEV+IRI	-	-
Green 1983	≥ 65	107	65	KPS ≥ 70	-	RT_{60}+carmustine	RT_{60}+steroid	RT_{60}+p-rocar-bazine	RT_{60}+BC-NU+steroid
Keime-Guibert 2007	≥ 70	85	63	KPS ≥ 70	-	RT_{50}	Supportive care	-	-
Malmstrom 2012	≥ 70[a]	123	59	WHO 0-2	45%/55%/NR[e]	RT_{60}	RT_{30-34}	TMZ	-
Perry 2017	≥ 65	562	61	ECOG 0-2	47%/53%/NR[f]	RT_{40}	RT_{40} + TMZ + maintenance TMZ	-	-
Roa 2004	≥ 60[b]	95	47	KPS ≥ 50	-	RT_{60}	RT_{40}		
Roa 2015	≥ 65[c]	61	58	KPS ≥ 50	-	RT_{40}	RT_{25}	-	-
Stupp 2017a	≥ 65	134	68	KPS ≥ 70	37%/53%/9%	RT_{60}+TMZ + maintenance TMZ	RT_{60}+TMZ + maintenance TMZ + TTF	-	-
Weller 2017	≥ 65	96	63[d]	ECOG 0-2	34%/59%/7%	RT_{60}+TMZ	RT_{60}+ TMZ + maintenance TMZ + RIN	-	-
Wick 2012	≥ 65	373	47	KPS ≥ 60	20%/36%/44%	RT_{60}	TMZ	-	-

BEV: bevacizumab; ECOG: Eastern Cooperative Oncology Group; Gy: Grays; IRI: irinotecan; KPS: Karnofsky performance score; RIN: rindopepimut; RT: radiotherapy; TTF: tumour treating fields; TMZ: temozolomide; WHO: World Health Organization

[a] The whole sample (n=291) comprised participants ≥ 60 years. The median age was 70 years for all study groups, ranging between 60 and 88 years.

[b] Median age was approximately 72 with a standard deviation of 5 years

[c] Data for the ≥ 65 year age group were reported in the Guedes de Castro 2017 substudy report.

[d] Gender data specific to the elderly subgroup were not reported separately

[e] For approximately 70% of participants with MGMT data available

[f] For approximately 63% of total participants with MGMT data available

APPENDICES

Appendix 1. Search strategies

MEDLINE search strategy for effectiveness evidence

1. Glioblastoma/
2. (glioblastoma* or Glioblastoma* or GB* or astrocyt*).ti,ab.
3. 1 or 2
4. exp Aged/
5. (aged* or old* or ageing* or geriatric*).ti,ab.
6. (elder* or "over 60" or "over 65" or "over 70" or "over 80" or "over 85" or "60 year*" or "65 year*" or "70 year*" or "80 year" or "85 year*").ti,ab.
7. 4 or 5 or 6
8. 3 and 7
9. Neurosurgery/
10. surgery.fs.
11. (surg* or neurosurg* or craniotomy* or resect* or EOR* or intraoperative*).mp.
12. exp Radiotherapy/
13. radiotherapy.fs.
14. (radiotherap* or RT or radiat* or irradiat*).ti,ab.
15. exp Antineoplastic Agents/
16. Antineoplastic Combined Chemotherapy Protocols/
17. (temozolomide or TMZ or Temodal or Temodar or Temodal or Temcad* or chemotherap* or procarbazine or Lomustine or CCNU or vincristine or PCV or cisplatinum or carboplatinum).mp.
18. exp Chemoradiotherapy/
19. (radiochemo* or chemoradio*).mp.
20. exp immunotherapy/
21. immunotherap*.mp.
22. exp steroids/
23. (dexamethasone or prednisolone or methylprednisolone).mp.
24. 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23
25. 8 and 24
26. randomized controlled trial.pt.
27. controlled clinical trial.pt.
28. randomized.ab.
29. placebo.ab.
30. clinical trials as topic.sh.
31. randomly.ab.
32. trial.ti
33. 26 or 27 or 28 or 29 or 30 or 31 or 32
34. (animals not (humans and animals)).sh.
35. 33 not 34
36. 25 and 35

MEDLINE search strategy for economic evidence

1. Glioblastoma/
2. (glioblastoma* or Glioblastoma* or GB* or astrocyt*).ti,ab.
3. 1 or 2
4. exp Aged/
5. (aged* or old* or ageing* or geriatric*).ti,ab.
6. (elder* or "over 60" or "over 65" or "over 70" or "over 80" or "60 year*" or "65 year*" or "70 year*" or "85 year*").ti,ab.
7. 4 or 5 or 6
8. 3 and 7
9. Neurosurgery/
10. surgery.fs.
11. (surg* or neurosurg* or craniotomy* or resect* or EOR* or intraoperative*).mp.
12. exp Radiotherapy/
13. radiotherapy.fs.
14. (radiotherap* or RT or radiat* or irradiat*).ti,ab
15. exp Antineoplastic Agents/

16. Antineoplastic Combined Chemotherapy Protocols/
17. (temozolomide or TMZ or Temodal or Temodar or Temodal or Temcad* or chemotherap* or procarbazine or Lomustine or CCNU or vincristine or PCV or cisplatinum or carboplatinum).mp.
18. exp Chemoradiotherapy/
19. (radiochemo* or chemoradio*).mp.
20. exp IMMUNOTHERAPY/
21. immunotherap*.mp.
22. exp STEROIDS/
23. (dexamethasone or prednisolone or methylprednisolone).mp.
24. 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23
25. 8 and 24
26. Economics/
27. exp "costs and cost analysis"/
28. Economics, Dental/
29. exp economics, hospital/
30. Economics, Medical/
31. Economics, Nursing/
32. Economics, Pharmaceutical/
33. (economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab.
34. (expenditure$ not energy).ti,ab.
35. value for money.ti,ab.
36. budget$.ti,ab.
37. 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36
38. ((energy or oxygen) adj cost).ti,ab.
39. (metabolic adj cost).ti,ab.
40. ((energy or oxygen) adj expenditure).ti,ab.
41. 38 or 39 or 40
42. 37 not 41
43. letter.pt.
44. editorial.pt.
45. historical article.pt.
46. 43 or 44 or 45
47. 42 not 46
48. 25 and 47

key:

mp=title, original title, abstract, name of substance word, subject heading word
pt=publication type
ab=abstract
fs= floating subheading
sh=Medical Subject Heading

Similar strategies were devised for Embase.

Appendix 2. 'Risk of bias' assessment

We will assess the risk of bias according to the following criteria.

1. Random sequence generation

- Low risk of bias e.g. participants assigned to treatments on basis of a computer-generated random sequence or a table of random numbers
- High risk of bias e.g. participants assigned to treatments on basis of date of birth, clinic identification-number or surname, or no attempt to randomise participants
- Unclear risk of bias e.g. not reported, information not available

2. Allocation concealment

- Low risk of bias e.g. where the allocation sequence could not be foretold
- High risk of bias e.g. allocation sequence could be foretold by patients, investigators or treatment providers
- Unclear risk of bias e.g. not reported

3. Blinding of participants and personnel

- Low risk of bias if participants and personnel were adequately blinded
- High risk of bias if participants or personnel, or both, were not blinded to the intervention that the participant received
- Unclear risk of bias if this was not reported or unclear

4. Blinding of outcomes assessors

- Low risk of bias if outcome assessors were adequately blinded to the intervention that the participant received
- High risk of bias if outcome assessors were not blinded to the intervention that the participant received
- Unclear risk of bias if this was not reported or unclear

5. Incomplete outcome data

We will record the proportion of participants whose outcomes were not reported at the end of the study. We will code a satisfactory level of loss to follow-up for each outcome as follows.

- Low risk of bias, if fewer than 20% of patients were lost to follow-up and reasons for loss to follow-up were similar in both treatment arms
- High risk of bias, if more than 20% of patients were lost to follow-up or reasons for loss to follow-up differed between treatment arms
- Unclear risk of bias if loss to follow-up was not reported

6. Selective reporting of outcomes

- Low risk of bias e.g. review reports all outcomes specified in the protocol
- High risk of bias e.g. it is suspected that outcomes have been selectively reported
- Unclear risk of bias e.g. it is unclear whether outcomes had been selectively reported

7. Other bias

- Low risk of bias, i.e. no other source of bias suspected and the trial appears to be methodologically sound
- High risk of bias, if we suspect that the trial was prone to an additional bias
- Unclear risk of bias, if we are uncertain whether an additional bias may have been present

CONTRIBUTIONS OF AUTHORS

Theresa Lawrie and Catherine Hanna were involved in all stages of the review and wrote the first draft, with further revisions undertaken by both according to comments from the other authors and peer reviewers. Ewelina Rogozinska assisted with study selection, data extraction, analysis and grading of the evidence. Ashleigh Kernohan, Tomos Robinson and Luke Vale prepared the economic evaluation components. All authors approved the final version.

DECLARATIONS OF INTEREST

Theresa A Lawrie: none known

Catherine R Hanna: none known

Ewelina Rogozińska: none known

Ashleigh Kernohan: none known

Luke Vale: none known

Tomos Robinson: none known

Helen Bulbeck: none known

Usama M Ali: none known

Robin Grant: none known

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