Concurrent chemoradiation therapy for improving survival in older patients with glioblastoma: a narrative review

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Despite the establishment of standard treatments for glioblastoma, the efficacy of concurrent chemoradiation therapy (CCRT) for older patients remains a matter of debate, even with the insights from recent randomized trials. This study offers an updated, evidence-based review of contemporary management using CCRT in older glioblastoma patients. Treating older glioblastoma patients necessitates a tailored approach, prioritizing individual patient needs. Additionally, this study emphasizes the efficacy of short-course CCRT, which has been confirmed through recent randomized trials.

Keywords: Glioblastoma; Concurrent chemoradiation therapy; Short-course concurrent chemoradiation therapy; Elderly patients

Introduction

Glioblastoma, the most common and aggressive form of primary brain cancer, poses a formidable challenge in neuro-oncology, characterized by a median overall survival (OS) of less than 15 months and a dismal 5-year survival rate of under 10% [1]. The disease predominantly affects individuals over 65 years of age, a group that unfortunately faces even poorer outcomes, with average survival times reduced to around 6 months [2]. This older patient population is particularly vulnerable, not only due to the aggressiveness of the disease but also because they are more likely to have additional health issues, take multiple medications, and experience social and support challenges. These factors, combined with a reduced capacity to withstand the physical demands of treatment, have historically led to a more cautious approach in their management [3]. These factors collectively exacerbate the impact of glioblastoma, reducing survival expectancy and complicating clinical management with a risk of treatment-related toxicities [4].

Historically, elderly patients have been underrepresented in clinical trials, which has resulted in a lack of specific treatment guidelines for this group. However, recent years have seen an effort to address this gap through trials aimed at evaluating treatments that could be feasible for elderly patients, including shorter courses of radiation therapy (RT) combined with temozolomide (TMZ) [5]. Despite these advances, there remains considerable uncertainty about the best approach to treating older patients with glioblastoma, particularly when it comes to balancing treatment efficacy with quality of life (QOL) considerations [6].

Given the significant proportion of glioblastoma patients who are elderly, it is imperative to critically assess the role and effectiveness of concurrent chemoradiation therapy (CCRT) in this demographic. Such an evaluation is crucial not only for enhancing survival and QOL but also for guiding clinical decisions and establishing evidence-based practices tailored to the unique needs of elderly glioblastoma patients. This review aims to provide a clear yet comprehensive overview of the current state of CCRT in the elderly.

Material and Method

In this narrative review, we provide a current overview of essential evidence to investigate the role of CCRT in elderly patients with glioblastoma, focusing on a patient-centered strategy for planning their care. Based on the existing landmark paper of CCRT, we have
included studies published subsequent to the paper [7]. Additionally, as the most recent systematic review in this theme covered articles up until 2019, we have incorporated studies published after that period [8]. Since the previous reviews included only randomized controlled trials (RCTs), our updated review has also exclusively included RCTs that involved elderly glioblastoma patients, were published in English, and found through Medline, Embase, and Cochrane search spanning from 2005 to 2022 (Fig. 1). An updated review was prepared, including relevant retrospective studies, grounded in key RCTs and meta-analysis (Table 1) [5,9–15].

Fig. 1. Search strategy results of updated systematic review.

Table 1. Randomized controlled trials and retrospective studies reviewed in this study

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Age cut-off (yr)</th>
<th>Intervention</th>
<th>Number</th>
<th>Median PFS (mo)a</th>
<th>Median OS (mo)b</th>
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<tr>
<td>Randomized controlled study</td>
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<tr>
<td>Perry et al. [5]</td>
<td>2017</td>
<td>65</td>
<td>HRT</td>
<td>281</td>
<td>3.3</td>
<td>7.6</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>HRT, TMZ</td>
<td>281</td>
<td>4.7</td>
<td>9.3</td>
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<tr>
<td>Gzell et al. [15]a</td>
<td>2014</td>
<td>70 (Subgroup)</td>
<td>SRT, TMZ</td>
<td>34</td>
<td>4.3</td>
<td>16.7</td>
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<tr>
<td></td>
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<td>SRT, TMZ, BEV</td>
<td>39</td>
<td>8.4</td>
<td>16.8</td>
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<tr>
<td>Stupp et al. [9]</td>
<td>2009</td>
<td>60 (Subgroup)</td>
<td>SRT</td>
<td>87</td>
<td>11.8</td>
<td>2 yr, 5.7%</td>
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<td>SRT, TMZ</td>
<td>83</td>
<td>10.9</td>
<td>2 yr, 21.8%</td>
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<td>Herrlinger et al. [11]</td>
<td>2016</td>
<td>65 (Subgroup)</td>
<td>SRT, TMZ</td>
<td>13</td>
<td>NR</td>
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<td></td>
<td>SRT, BEV</td>
<td>21</td>
<td>NR</td>
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<tr>
<td>Weller et al. [12]a</td>
<td>2017</td>
<td>65 (Subgroup)</td>
<td>SRT, TMZ</td>
<td>50</td>
<td>7.4</td>
<td>20.0</td>
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<td></td>
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<td>SRT, TMZ, RIN</td>
<td>46</td>
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<td>20.1</td>
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<td>Retrospective cohort studies</td>
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<td>HR, 3.1</td>
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<td>CT alone</td>
<td>123</td>
<td>NR</td>
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<td>Biau et al. [13]</td>
<td>2017</td>
<td>70</td>
<td>SRT, TMZ</td>
<td>33</td>
<td>NR</td>
<td>9.6</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>HRT, TMZ</td>
<td>37</td>
<td>NR</td>
<td>5.5</td>
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<tr>
<td>Ohno et al. [14]</td>
<td>2019</td>
<td>75</td>
<td>HRT</td>
<td>20</td>
<td>8.5</td>
<td>12.9</td>
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<td></td>
<td>HRT, TMZ, BEV</td>
<td>10</td>
<td>10.0</td>
<td>14.6</td>
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</table>

PFS, progression-free survival; OS, overall survival; HRT, hypofractionated radiation therapy (30–40 Gy in 10–15 Fr); SRT, standard radiation therapy (59.4–60 Gy in 30–33 Fr); TMZ, temozolomide; NR, not reported; RIN, rindopepimut; RT, radiation therapy; CT, chemotherapy; ref., reference; HR, hazard ratio.

aThe survival time was described when available, or presented as survival rates or HR; bAge-related PFS and OS were not reported separately.
Results

Concurrent chemoradiation therapy
Since 2005, concurrent chemotherapy and RT after maximal safe resection has been established as the standard treatment for younger patients newly diagnosed with glioblastoma. This followed the results of the Stupp trial, which showed a notable improvement in survival by incorporating TMZ with 60 Gy of RT in 30 fractions. A median OS increased from 12.1 to 14.6 months, and the 2-year survival rate improved from 10% to 26% [7]. However, a later analysis suggested that the benefit of TMZ combined with RT was less in patients aged 60 to 70 years compared to those aged 50 years and below, leading to concerns about the applicability of these benefits to elderly patients [9].

In light of evidence supporting shorter radiation schedules as equally effective and more tolerable for elderly patients, the NCIC CE.6/EORTC26062 trial aimed to clarify the advantages of concurrent chemoradiation in this age group. Conducted with patients over 65 years old (range, 65 to 90 years; median age, 73 years) and published in 2017, the study found that concurrent and adjuvant TMZ during short-course RT (40 Gy in 15 fractions) was more effective than radiation alone, showing a median OS of 9.3 versus 7.6 months and progression-free survival (PFS) of 5.3 versus 3.9 months, without significant differences in health-related QOL between the groups [5].

Analysis of patients with O6-methylguanine-DNA methyltransferase (MGMT) promoter hypermethylation in the CE.6 trial aligned with the findings from the NOA-08 and NORDIC trials, indicating longer OS (13.5 vs. 7.7 months) in patients with MGMT promoter hypermethylation (P < 0.001) [16]. A noticeable but not statistically significant benefit of TMZ was also observed in patients without MGMT promoter methylation (OS 10.0 vs. 7.9 months; P = 0.055). The advantage of combining radiation with chemotherapy in patients without MGMT promoter methylation was highlighted by Heiland et al. [10] in a recent retrospective review, showing longer OS (P = 0.009) for patients receiving concurrent chemoradiation compared to radiation alone.

Recent network meta-analysis showed that, in single treatment methods (RT or chemotherapy alone), no significant survival difference was observed between hypofractionated radiation therapy (HRT) and standard radiation therapy (SRT) (hazard ratio [HR], 0.94; 95% confidence interval [CI], 0.67–1.31), or between TMZ alone and other treatments (HR, 1.07; 95% CI, 0.73–1.58) [17]. However, when examining combined treatments, there appeared to be a tendency towards better survival outcomes with HRT plus TMZ compared to any single treatment approach, whether it was HRT alone (HR, 0.67; 95% CI, 0.44–1.01), SRT alone (HR, 0.63; 95% CI, 0.37–1.07), or TMZ alone (HR, 0.72; 95% CI, 0.41–1.72). A similar trend was observed with standard CCRT against HRT alone (HR, 0.74; 95% CI, 0.40–1.36), SRT alone (HR, 0.70; 95% CI, 0.42–1.15), or TMZ alone (HR, 0.81; 95% CI, 0.44–1.47). Ranking the effectiveness of these treatment strategies showed that HRT plus TMZ was most likely the best option, followed by SRT plus TMZ. Including retrospective studies, SRT plus TMZ was also significantly more effective in improving survival than HRT alone (HR, 0.36; 95% CI, 0.14–0.917), suggesting a strong and statistically significant advantage for combining SRT with TMZ over HRT alone.

In the GLARIUS 2016 trial, an abstract separately provided OS figures for the study’s modified intention-to-treat population, focusing on patients aged 65 and above (n = 34) in comparison to younger patients [11]. Within the RT plus bevacizumab/irinotecan (BEV/IRI) group, younger patients experienced a significantly longer survival than those aged 65 and older (with median OS being 17.5 months for those under 65 versus 13.4 months for those 65 and older, P < 0.001). Among those receiving CCRT, no notable difference in survival was observed between the 2 age groups (with median OS being 20.0 months for younger patients versus 17.3 months for those aged over 65, P = 0.567). Although median OS for patients aged over 65 was documented as 13.4 months in the BEV/IRI group and 17.3 months in the TMZ group, the reports did not explicitly compare the significance of OS between these 2 treatment groups for the older patients.

Weller 2017 disclosed the number of patient deaths among those with maximally resected disease receiving both rindopepimut and TMZ (31 out of 46) versus those receiving CCRT alone (36 out of 50), yielding a HR of 1.21 (95% CI, 0.71–2.06; P = 0.48) [12]. A similar outcome was reported for patients with significant residual tumor (HR, 0.68; 95% CI, 0.39–1.19; P = 0.18), indicating no distinct differences in OS across the treatment groups.

Hanna et al. [8] reviewed 12 studies involving 1,818 elderly patients and several treatment modalities in their network meta-analysis. They found that CCRT reduces the risk of death by an average of 33% throughout the disease course following diagnosis, equivalent to roughly a 50% extension in survival time compared to solely using HRT. Compared to supportive care alone, all adjuvant treatments demonstrated a definite prolongation of survival time, with the exception of the combination of BEV with RT. Regarding treatment efficacy rankings, the addition of BEV to CCRT emerged as the top option, followed by CCRT, TMZ alone in third, HRT in fourth, and supportive care alone in last place. The superior ranking of BEV with CCRT is not substantiated by definitive evidence of enhanced survival over CCRT alone.
Currently, it is still under review whether adding TMZ to RT truly benefits this specific group of patients. Therefore, for elderly patients known to have an unmethylated MGMT status and who are in borderline or poor health, radiation alone might be considered the preferred treatment option. However, therapeutic decision should be made in regard to preoperative functional status instead of biological age.

**Standard—versus abbreviated—course chemoradiation therapy**

Recent landmark study on the addition of TMZ to short-course radiotherapy for elderly glioblastoma patients found that the median OS was significantly longer with the combination therapy (9.3 months) compared to radiotherapy alone (7.6 months), with a HR for death of 0.67 (95% CI, 0.56–0.80; P < 0.001). PFS also improved, with a median of 5.3 months for the combination therapy versus 3.9 months for radiotherapy alone (HR for disease progression or death, 0.50; 95% CI, 0.41–0.60; P < 0.001) [5]. Biau et al. [13] provided a “real-life” analysis of elderly glioblastoma patients treated with various radiotherapy and TMZ regimens. The median OS for all patients was 5.2 months, with no statistical differences in survival between patients receiving the Stupp protocol or hypofractionated radiotherapy plus TMZ (P = 0.22). However, patients receiving hypofractionated radiotherapy alone had a significantly shorter survival time (3.9 months vs. 5.9 months, P = 0.018).

Ohno et al. [14] evaluated the survival benefits of hypofractionated radiotherapy combined with TMZ or TMZ plus BEV in patients aged 75 years or older. The median OS and PFS were 12.9 months and 9.9 months, respectively, indicating the potential benefits of these combined regimens in extending survival with acceptable toxicity levels.

The concurrent TMZ dose is lower in the HRT plus TMZ regimen than in the six-week SRT plus TMZ regimen. Some researchers question whether the reduced TMZ dose and total radiation dose in HRT can achieve comparable OS outcomes [18]. Recent meta-analysis study indicates that the median OS for SRT plus TMZ may be longer than for HRT plus TMZ, suggesting that expectations for survival improvement with HRT plus TMZ should be tempered compared to standard CCRT. However, the risk of blood-related side effects appears similar between the 2 regimens [19].

The role of MGMT methylation status in predicting TMZ’s effectiveness has led to increased consideration of TMZ for elderly patients with this biomarker. While some studies have shown a positive survival response with both standard and abbreviated regimens, this has not been universally observed, indicating that MGMT status alone should not dictate the addition of TMZ for elderly glioblastoma multiforme (GBM) treatment [15,20]. Moreover, meta-regression analysis did not find MGMT status to significantly affect OS differences, suggesting that while MGMT status may influence survival response to TMZ, it is not solely dependent on the choice of RT [13].

When considering abbreviated course of CCRT for elderly GBM patients, the impact on health-related QOL is crucial. Despite the potential for increased fatigue, global health, social, and cognitive functioning have been shown to improve with the HRT plus TMZ regimen [21]. These benefits must be weighed against the known side effects of TMZ, which vary by individual preference. Thus, a personalized approach balancing between the potential QOL and survival advantages against the side effects of TMZ is recommended when discussing the length of CCRT schedule.

Additionally, there are several ongoing trials subjected to elderly patients with glioblastoma. Arakawa et al. [22] conducted a phase III trial to evaluate hypofractionated radiotherapy combined with TMZ in elderly patients with newly diagnosed glioblastoma. While specific survival statistics were not provided in the initial summary, the study aimed to confirm the non-inferiority of the combined treatment over traditional approaches, focusing on OS and QOL as primary endpoints.

**Discussion**

Defining “elderly” based solely on chronological age fails to consider the specific factors of each patient, including physiological characteristics that impact their suitability for treatment. Functional status, performance status, and cognitive capacity are crucial in determining a patient’s true biological age, influencing their fitness for therapy. Despite this knowledge, a chronological age threshold of 65 years is commonly used for simplicity in treatment decisions and clinical trial criteria.

Elderly glioblastoma patients typically face a more aggressive disease progression and shorter OS compared to younger individuals. Additionally, treating glioblastoma in the elderly is challenging due to their increased susceptibility to treatment-related complications and cognitive impairments due to decreased cognitive reserve. A recent retrospective analysis of glioblastoma patients in the US National Cancer Database from 2005 to 2016 revealed that older age reduces the likelihood of receiving CCRT [23]. Factors contributing to this trend in older patients include lack of insurance, residing in lower income brackets, and the presence of other health conditions. There’s a growing body of evidence advocating for aggressive treatments, including maximal safe tumor removal, followed by CCRT for elderly glioblastoma patients with good functional health, although such approaches have yet to be studied.
prospectively [24]. Furthermore, identifying whether glioblastoma in elderly patients possesses distinct molecular traits linked to aggressive tumor behavior requires further research.

In 2008, Minniti et al. [25] conducted a prospective study with 32 GBM patients over 70 years old using SRT and chemotherapy, reporting a median OS of 10.6 months. Further, a long-term analysis of the EORTC 26981-NCIC CE.3 trial highlighted the survival benefits of combined chemoradiation over radiation alone, though these advantages decreased with age, particularly for patients over 60 years (10.9 months vs. 11.8 months OS). At a 2-year mark, CCRT showed a survival rate of 21.8% compared to 5.7%, but this benefit diminished significantly over 5 years (6.6% vs. 0%) [9]. Recent extensive retrospective review of 2670 patients with elderly glioblastoma demonstrated that CCRT led to longer OS than surgery with RT or surgery alone (8 months vs. 5 months vs. 3 months, respectively) [24]. As described in this study, meta-analysis by Hanna et al. [8] confirmed the effectiveness of CCRT in increasing OS compared to RT alone.

Conversely, some studies report no survival advantage with CCRT. Cao et al. [26], in a 10-year retrospective study from 2012, found reduced survival for elderly GBM patients receiving combined chemoradiation versus HRT followed by salvage TMZ (6.9 months vs. 13.3 months). Minniti et al. [21] compared HRT with SRT in combination therapies, finding similar median OS (6.7 months vs. 5.6 months) but noted higher neurotoxicity rates and worsened performance status in patients treated with SRT [26]. Other studies also indicate increased toxicity from CT, with a significant portion of elderly patients experiencing neurocognitive decline and severe toxicities [8]. However, recent landmark RCT in 2017 showed that abbreviated CCRT improves survival over HRT alone for elderly glioblastoma patients with good performance status, suggesting its viability as a treatment option. Though The CE.6/EORTC trial has set a new standard for patients with a KPS ≥ 70, many patients are diagnosed with borderline or poor performance status and are often underrepresented in clinical trials. Further research is essential for understanding the treatment outcomes for patients with compromised health and recurrent glioblastoma, potentially explaining the reluctance to administer aggressive treatments to the elderly (Fig. 2).

Regarding MGMT status, in key studies of the elderly (NOA-08, NORDIC, CE.6), MGMT promoter methylation has emerged as a critical factor for prognosis and treatment guidance, especially for patients with poor or marginal performance status [10,27,28]. Wick et al. [28]’s update on the NOA-08 trial, comparing RT with TMZ in patients over 65 with anaplastic astrocytoma or glioblastoma, reinforced MGMT promoter methylation’s role as a prognostic marker. Their analysis suggested that MGMT methylation, particularly the RTK II subtype, predicts better long-term outcomes, highlighting the need for further research into methylation profiling in the elderly.

**Conclusion**

The efficacy of CCRT in elderly patients with glioblastoma has not universally confirmed. Nonetheless, recent RCTs confirmed that elderly patients who maintain a good performance status could benefit from HRT combined with TMZ. For patients with marginal or compromised performance status, treatment decisions should be made with a focus on the patient, considering factors such as MGMT methylation status, QOL, cognitive function, and potential adverse effects.

**Conflicts of interest**

No potential conflict of interest relevant to this article was reported.

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