

Peer Review File

Article information: <http://dx.doi.org/10.21037/apm-20-1206>

Reviewer #1

This is a very clearly written paper, which is very easy to follow. Succinct review of the evidence to date. Following comments would strengthen the argument:

Comment 1: Page 3 line 54: there is always the question when comparing biopsy to surgery whether it is the degree of resection that matters, or the fact that disease may be in an eloquent location (ie/ thalamus, etc) which would also portend to a poorer prognosis. This was a small study, in which there would be selection bias to those potentially resectable. May be relevant to discuss this point here.

Reply 1: Thank you for your comments. Please see expanded discussion of this point in revised manuscript.

Comment 2: Page 3 line 69: references to these techniques would be appropriate. Other PET modalities more commonly being studied than FDG (FMET, etc).

Reply 2: Please see additional references added.

Comment 3: Page 4 line 78: again, reference the trials you are discussing at this point (I realize they are referenced below, but best to do earlier for clarity).

Reply 3: Revision made to reference trials earlier.

Reviewer #2

This review article is very well written and highlights the up to date evidence on management of GBM in elderly and is certainly of interest to the readers. My recommendation is for publication with minor changes (see below).

Minor changes (page specific):

Page 3

Comment 1: Line 60 – 64 – This sentence is hard to read, suggest splitting into two sentences. Maximal safe surgical resection should be performed when feasible in appropriately selected elderly patients with newly diagnosed glioblastoma to obtain tissue for histology and molecular biomarkers, to achieve cytoreduction with reduction of mass effect, and to preserve cognitive and functional status and maximize OS.

Reply 1: Thank you for your comments. Please see revised sentence structure in resubmitted manuscript.

Page 5

Comment 2: Line 89 – 90 – “radiation therapy vs radiotherapy” for consistency throughout the paper

More recently, Roa et al (16) investigated short-course radiotherapy (40 Gy in 15 fractions) compared to ultra-hypofractionated radiotherapy (25 Gy in 5 fractions) in elderly/frail patients with glioblastoma.

Reply 2: Please see change to “radiation therapy” for consistency.

Comment 3: Line 92 – 93 – Author concluded in this paragraph that survival is extended but Roa et al 2015 found no differences in OS between 40/15 vs 25/5. Could author explain this sentence? This is an important finding for selected patients as treatment duration is only one week and survival is extended.

Reply 3: Please see revised manuscript with additional explanation and clarification.

Page 8

Comment 4: Line 160-162 – punctuation, consider using a semicolon or period before however.

A clinically significant benefit of TMZ was also found in the unmethylated patients (OS 10.0 vs. 7.9 months), however, this result did not reach statistical significance ($p=0.055$).

Reply 4: Corrected in revised manuscript with addition semicolon.

Comment 5: Line 166 – 168 – The word ‘determined’ appears twice in this text. Consider using a synonym in its place.

At present, it remains to be determined if the addition of TMZ to RT is in fact beneficial in this molecularly determined patient cohort.

Reply 5: Sentence re-worded in revised manuscript.

Comment 6: Line 167 – 169 – missing punctuation “ , radiation”

As a result, if the MGMT status was known to be unmethylated at the time of a treatment decision, for elderly patients with borderline or poor performance status radiation alone would be considered the standard of care.

Reply 6: Corrected in revised manuscript with addition of semicolon.

Page 9

Comment 8: Line 183 – delete “of”.

Patients with glioblastoma experience a wide of range of symptoms and can benefit from an integrative palliative care approach during the course of their illness and at end of life (EOL).

Reply 8: Corrected in revised manuscript with deletion.

Comment 9: Line 194 – suggest splitting into two sentences for clarity.

For this reason, engaging in discussions about Advanced Care Planning (ACP) with patients and their caregivers early in the course of disease or at the beginning of the EOL phase is recommended, and allows the patient and their caregivers the opportunity to be actively involved in decision-making related to EOL care.

Reply 9: Please see revised sentence structure in resubmitted manuscript.

Reply 9:

Page 10

Comment 10: Line 202 – remove coma “reserve,”

Functional and performance status alongside cognitive reserve, influence a patient’s true biological or physiological age (Figure 1).

Reply 10: Corrected in revised manuscript with removal of comma

Comment 11: Line 214- 216 – reads awkwardly, is author trying to explain that older age is associated with unfavourable molecular marker/ aggressive tumour biology?

More research is needed to better understand if in addition to these factors, older age itself imparts a worse prognosis due to unfavourable molecular markers and inherent aggressive tumour biology.

Reply 11: Please see revised manuscript with clarification.

Page 11

Comment 12: Line 238-248 – remove “) ” at the end of this sentence.

Wick et al. recently published the long term update of NOA-08, an RCT comparing radiation therapy to temozolomide in patients greater than 65 years with anaplastic astrocytoma or glioblastoma).

Reply 12: Corrected in revised manuscript with removal “)”).