# Comments on NICE health technology appraisal assessment report on "Carmustine implants and temozolomide for the treatment of newly diagnosed high grade glioma" from Brain service guidance GDG (via NCC for Cancer)

## Opening remark

The authors of this report have done a comprehensive job in obtaining access to relevant literature and have clearly taken some high level advice with respect to basic management of malignant glioma in the UK. They have then criticised the published literature and it is at that point that the report is less convincing. In many places the report has the feel of an ability to criticise the statistical aspects without a real understanding of the mechanics of patient assessment and treatment delivery. In many places their recommendations present a bind whereby their recommendations to improve the statistical quality would result in either an untenable clinical situation or one that is simply unethical. An example of this is the suggestion that blinding may be carried on to the end of the patients life, such that the choice of subsequent therapy might not be influenced by prior knowledge of treatment allocation within the trial. Clearly this would not be in the patient's interest since choice of second line therapy in real life is made on the basis of a knowledge of success or failure of first line therapy. Withholding that knowledge would be both therapeutically inappropriate and ethically questionable. My second major criticism is the emphasis this report places on median survival with an acknowledged intention to avoid emphasising tail effects late in the study. Since, for Temozolomide particularly, it is the later part of the curve that is clinically the most interesting, this could downplay the contribution this part of the curve makes to the clinical and economic assessment, which is inappropriate. Again this will be dealt with later.

A further criticism is the emphasis the report makes that these results may not be generalisable to the entire population of patients with glioblastoma. It is fully accepted that it is not just the diagnosis of glioblastoma that matters, but the clinical situation in which that diagnosis is made when treatment allocation is decided. Thus an elderly, infirm patient would not receive the same treatment as a young, fit patient. It is fully expected that the results from each of these studies would not be generalised to the entire population, rather the study should be judged within the context exactly of that population from which the data are derived. Indeed, one could go further and suggest that if sub-group analysis is reliable then one might try to select from within the study population, just those who are most likely to benefit where that choice is possible. Again, more of this later.

## Page specific points

### Page 1

On the opening page (p1) the authors say that 'existing approaches to chemotherapy have not convincingly demonstrated a survival benefit'. In fact, the evidence from three overviews, and particularly the Stewart overview, does demonstrate that there is a statistically significant benefit to chemotherapy in this situation and has convinced the majority of the establishment in this discipline. In raising doubt on this issue the authors say that 3 later trials did not show benefit. They might not know that these studies, and particularly the largest, MRC, trial have endured heavy methodological criticism. For most of the neuro-oncology community the question is not whether chemotherapy produces a statistically significant effect (it does), rather whether this is clinically worthwhile. It is true in the UK we have felt that the benefit was outweighed by other disadvantages.

In the objectives (p1), they suggest that they will investigate adjuvant and concomitant Temozolomide compared to surgery alone. I do not understand how they intend to do that since no comparative study has ever been done and virtually all the surgery alone data derives from a previous era when diagnostic criteria were considerably different. The comparison is of course conventional treatment with surgery + RT vs the same regime plus adjuvant/ concomitant TZ.

**Page 4**

The Temozolomide study is criticised for excluding patients with surgical complications and those who died soon after surgery. Since the decision to use Temozolomide and its cost occur after surgery, it is difficult to understand this criticism. The population defining this study and indeed the population who would be eligible for Temozolomide is that population which follows surgery.

The Temozolomide study is criticised for including in the analysis 7-8% of patients who were re-categorised at central review as having grade 3 tumours. Much is made of this throughout the document. The authors fail to realise that the diagnosis of malignant glioma is highly subjective. Entering into the study was based on a local diagnosis (as would happen in real life if this agent were licensed and supported). The fact that a central reviewer reclassifies a tumour, does not necessarily mean that this is a 'true' or 'absolute' classification, simply that there is a disagreement with the local pathologist. It gives a consistency to the analysis, since all tumours are reviewed by one panel. Indeed to emphasise this point, the EORTC have recently compared diagnoses on a given panel of tumours made by various senior pathologists who are regularly used in clinical trial central reviews. They found major disagreements amongst these pathologists. Hence it is clear that the output of central review depends on which pathologist is used. It follows that central pathology review does not give a 'true measure' of the presence of glioblastoma. It merely gives a measure of that pathologists opinion. It may or may not be more valid than the local pathologist. What, hopefully, it does do is give a uniformity to assessment. In real life, patients will be offered Temozolomide on the basis of the local pathologists diagnosis and hence analysis of this trial in these terms gives a more realistic interpretation of the outcome of such treatment and the comparison between treatments.

Furthermore, much is made of trial results being driven by 'chemo-sensitive tumours' on the assumption that they will influence the outcome favourably for a chemotherapy treated arm. It is equally possible that these chemo-sensitive tumours will influence results in the reverse direction. Whilst this may initially seem paradoxical, the example within this discipline of anaplastic oligodendroglioma is clear and illustrative. This highly chemo-sensitive tumour was thought almost certainly to require adjuvant chemotherapy. When the study was done, no improvement in survival was seen as a result of use of adjuvant chemotherapy in this group of tumours in spite of the chemo-sensitivity. The inclusion of such patients in an adjuvant trial, such as the two described here, may then act to dilute a population that would otherwise show a difference and adversely influence the results of the trial against the extra intervention. The point I make is that *no assumption* can be made that because a tumour is chemo-sensitive it will influence the outcome in a positive direction.

**Page 5**

The authors admit their model is particularly sensitive to median overall survival benefit. As argued elsewhere in this document, this is not the most appropriate parameter on which to judge the outcome, certainly of the Temozolomide trial where

the difference in median survival may be dominated by a resistant population, but a highly beneficial effect might be seen in a sensitive subpopulation which shows uyp in the later stages of the study, after the time point of medial survival.

In their discussion (1.61) the authors say the trials reviewed are variable in quality. This does not of course mean that they are necessarily poor quality, they may be variably good! Later they say that 'the impact of specific tumour type needs to be explored further'. They are indicating here separation according to MGMT status. Whilst I certainly agree with this, until it is possible reliably to separate out tumour types which benefit most (and currently it is not), it might be unreasonable to deny a mixed and currently inseparable population access to treatment from which a significant sub-population might benefit, simply because the other population may not.

**Page 6**
I find statements such as 'evidence for effectiveness of TMZ is *limited*' of little use. All evidence is limited!

**Page 10**
They say that grade I and II tumours are low-grade, slow growing and unlikely to spread. This is simply untrue. Low-grade tumours may infiltrate widely, that is they spread avidly and widely in the brain.

**Page 13**
They attach a degree of certainty to the MGMT story that may not be justified. Statements such as MGMT activity <u>will</u> be decreased or absent when the promoter is methylated, offers a degree of certainty that is not yet established from the research. More generally on this issue the authors here are remarkably accepting of the Hegi paper and the potential implications. This study was performed *retrospectively* on a *minority subset* of patients from a *few, selected institutions*, using an assay *which is not validated for clinical use* and which on her own admission is difficult to reproduce. The relationship to MGMT promoter methylation to outcome needs to be validated prospectively before any clinical reliance can be placed on it. (also see remarks under page 5 above).

**Page 13**
Again minor errors, high-grade glioma is not associated with tubero sclerosis. Neither are there excess high-grade gliomas in immuno-compromised patients or those with AIDS. Errors like this (which I am sure were not made by their expert advisors) show their naivity when straying from their own fields into clinical areas.

**Page 16**
Statements such as 'the brain and spinal cord are particularly sensitive to radiotherapy' show a rather facile knowledge of the area and are clearly lifted from an undergraduate textbook. They can actually be highly tolerant in the acute situation.

**Page 21**
Whilst the authors criticise heavily the trial work performed in patients with glioma, they are remarkably uncritical of the work of Elizabeth Davis et al with respect to patient views and relatives attitudes. There is no criticism of methods or statistics and no criticism of the environment in which these data were obtained. The conditions in which these patients were managed may not have reflected optimal management conditions nor indeed the generally accepted standard of today.

**Page 27**
Inclusion criteria for the Temozolomide study did not include grade 3 tumours intentionally. Hence the statement under the heading population is erroneous. If grade 3 tumours were entered these were done on the basis of a local pathology report of GBM subsequently altered or a protocol violation.

**Page 29**
**External validity**
Much is made of the generalisability of the data presented here. The presumption is that there is a desire to generalise these findings to all patients with glioblastoma and this may not necessarily be the case. I think no-one is suggesting that the results of concomitant adjuvant Temozolomide should be applied to patients whose characteristics lie way outside the recruitment characteristics for the trial. For example, a 75 year old man with an unresectable glioblastoma and dense hemiparesis would clearly not be a candidate for any treatment, let alone concomitant chemo radiotherapy. Neither would you seek to generalise the gliadel data to inoperable patients, this would be frankly silly! I feel the Peninsula group would have been better spending their time looking at those groups definable within the study who *might benefit*, rather than try to generalise to those groups outwith the study who might not.

**Page 60**
The group criticised the Temozolomide trial for its lack of blinding suggesting that this may lead to selective post-trial treatments, which could lead to bias. I would suggest that even if the trial had been blinded, insistent of maintenance of blinding after the trial so that treatment decisions could be made independent of this would be both inappropriate and unethical. Furthermore, the trial reflects what would be done in routine practice.

Also since more chemotherapy was given at relapse in the non-experimental arm, this should work to lessen any difference between the groups and gives more credibility to the study rather than less.

**Page 86, Paragraph 2**
The logic here is difficult to understand. Patients in the control group do receive **more chemotherapy** and it is **more expensive** and this is what happens in real life. Hence it could be said upfront that treatment with radiotherapy and Temozolomide obviates treatment with chemotherapy at a later stage and **reduces costs**. This is what really happens, it is difficult to understand how a reduction in chemotherapy later can be considered to underestimate the costs of radiotherapy-plus-Temozolomide.

Throughout the document, great emphasis is given to the value of QALY in estimating the worth or value of a treatment. Whilst this is a concept which might have great credibility amongst health economists, it may not reflect what either clinicians or patients consider as most important. We have then to accept this document from the point of view of health economists, which may not reflect the view of other groups in society.

**Page 87**
An assumption is made that the post progression costs between two arms in the Temozolomide study are equal. This is not reasonable. Since we see that clinicians left to their own devices use less chemotherapy in the Temozolomide arm and hence the post progression costs are reduced in this arm.

Furthermore the model takes no account of the fact that a patient living longer in a disease stabilised state, may be able to *contribute* to society, continue employment etc. This is not a fanciful notion. Glioblastomas tend to affect the higher social class patients, many of whom can continue to work in managerial or other capacities for a period following treatment, no account of this is taken in the model. If one took only health costs into account the longer a patient was kept alive the less value it would have in this model and cure would be disastrous!

On **page 92**, the group argue for a time independent risk of death model rather than a state dependent risk of death. Their argument is persuasive, but I wonder if it holds true for a dual population such as probably exists for patients with glioblastoma (viz MGMT +/-).

**Page 93**

It appears that the model is heavily dependent on median survival time since that is the match that underlies the model. Is this justified when the question being asked concerns two year survival rather than median survival? I note that the fit of the model is weakest in the tail, which is the most interesting part clinically.

In paragraph 4, (page 93) there is a statement that they have used data from a review of peri-operative deaths during craniotomy for glioma. Since a decision to use Temozolomide is made after surgery and hence that decision process excludes any patients who have died pre-surgery, what is the justification for this?