Survival of patients with non-small cell lung cancer and brain metastases

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Survival of Patients with Non-small Cell Lung Cancer and Brain Metastases

Sir — The members of the Quality of Life after Treatment for Brain Metastases Trial Management Group (QUARTZ TMG) note the recent articles in *Clinical Oncology*, 2010, Volume 22 referring to the above. The first is a letter from colleagues in the UK describing their experience of survival for the above patient group [1]. The second is a retrospective audit from colleagues in India assessing the applicability of the Radiation Therapy Oncology Group (RTOG) recursive partitioning analysis prognostic classes for brain metastases in this context [2]. We applaud the continued interest in the optimal treatment of patients with non-small cell lung cancer and brain metastases, but must highlight a number of issues within these publications that cause us concern.

The letter from Bradley *et al*. [1] concerns a retrospective analysis of a small number of highly selected patients, with only the better performance status patients (World Health Organization 0 and 1; Karnofsky performance score [KPS] 100–70) receiving whole brain radiotherapy (WBRT). Although performance status is a well-known and important prognostic factor, it has never been shown to be a predictor for a response or lack of one to a specific treatment — in this case WBRT [3]. We thus question the use of this sole measure to determine treatment. Any measured difference in survival within this non-randomised highly selected group cannot solely be attributed to the decision to provide or not to provide WBRT, particularly in view of the heterogeneous list of other treatments this patient group received.

In the publication from Mumbai [2], the main conclusion was that 20 Gy in five fractions is as effective as longer fractionated courses. This fact has already been shown by the multiple RTOG dose-finding trials in the 1970s and 1980s [4,5], the Royal College of Radiologists' publication from 1996 [6] and the Cochrane review of 2006 [7]. However, as the Cochrane review points out, there has never been a full randomised controlled trial of supportive care plus or minus WBRT and this information is of utmost importance, particularly in the non-small cell lung cancer group. Within the Mumbai series, poor survival times were again seen: median overall survival was 4.0 months (range 0.5–30.0 months) and emphasised that the central question being addressed by QUARTZ remains as valid as ever.

Similarly, the addition of systemic therapy to WBRT, which occurred in both publications, cannot be claimed to improve survival as those patients receiving this treatment fall within a self-selecting population, with only the fittest patients (and thus those with the better prognoses) receiving treatment. Of the various prognostic factors explored in the publication from Mumbai, recursive partitioning analysis class (II versus III, P value = 0.023), KPS (<70 versus ≥ 70, P value = 0.039) and the use of systemic therapy emerged as significant on univariate analysis. The use of systemic therapy in these patients again reflects their performance status—it cannot be concluded that the use of systemic therapy improved survival from the data presented.

Systemic therapies may have a role to play, but that role must be explored and elucidated in randomised clinical trials. QUARTZ continues to play an important role in establishing the standard of care against which these new modalities should be tested.

A recent release of preliminary data from the first 151 QUARTZ patients (manuscript in preparation) suggests that not using WBRT does not result in obviously shortened survival or decreased quality of life. These data show a 6 month survival rate of $<10\%$, suggesting that no particular group of patients greatly benefits from WBRT. The wide range of baseline characteristics observed in the QUARTZ data (50% of patients entered were of KPS >70; 50% $<$ KPS 70) suggests that there remains widespread uncertainty over how to treat all patients, regardless of performance status. WBRT may be effective in some patients, but at present there is little evidence to allow the identification of those patients. This interim release has been helpful to reassure clinicians and patients partaking in QUARTZ that no harm is seen in either arm from the point of view of the length of survival. To fully answer the questions that pertain to potential benefits from WBRT re survival and patient-assessed quality adjusted life years (the primary end point of QUARTZ), we must await completion of this trial to attain the statistical power required.

The view of the QUARTZ TMG is that both publications [1,2] used cohorts of patients who had received WBRT to support the use of WBRT, but using such data can never produce the justification for this assumption. It may indeed be that all patients benefit from WBRT, but equally the data presented (because of the poor survival) could indicate that it is actually detrimental to all patients. The likelihood is that some subgroups of patients benefit and some do not, but only by performing large randomised trials, and comparing those who received WBRT with a comparable

group who did not, can we tease out these differences. Clinical practice must be evidence based, not anecdotal. All patients deserve the best available treatment, and the best way of determining that is within clinical trials. Early QUARTZ data suggest there is considerable uncertainty as to how these patients should be treated, and further investigation is essential. Patients with non-small cell lung cancer and brain metastases who may have received chemotherapy or targeted agents up front remain eligible for QUARTZ. As such, we believe all patients, regardless of performance status, should be considered for QUARTZ, and that the current standard of care for these patients should be inclusion in the trial.

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Magnetic Resonance Image-based Dose Volume Parameters and Clinical Outcome with High Dose Rate Brachytherapy in Cervical Cancers — A Validation of GYN GEC-ESTRO Brachytherapy Recommendations

Sir — The GYN GEC-ESTRO Brachytherapy Working Group has recommended contouring guidelines, concepts and terms in three-dimensional magnetic resonance image-based treatment planning in cervical cancer brachytherapy [1,2], with reports confirming the safety, feasibility, definite advantages, clinical outcome and late toxicities (limited series) [3,4]. We evaluated 24 patients treated with high dose rate brachytherapy who underwent at least one magnetic resonance scan for planning between May 2006 and December 2007 as a part of validation and implementation of the guidelines in a developing country setting. In our series, the mean High Risk Clinical Target Volume (HR-CTV) was 45.2 ± 15.8 cm^3, which is higher than the reported series, suggesting larger residual tumour volumes at brachytherapy and would require additional interstitial needles/tubes together with tandem ring/ovoids for better target coverage. The mean point A dose was 73.4 ± 4.5 Gy10 (median: 74.3), whereas the mean D_{90} doses were 70.9 ± 10.6 Gy10 (median 68). The mean ICRU rectal and bladder points were 63.5 ± 8.1 Gy3 and 80.4 ± 34.4 Gy3, respectively. The $D_{0.1\ cm^3}$ and $D_{2\ cm^3}$ for the rectum were 66.0 ± 9.9 Gy3 (median 64.5) and 57.8 ± 7.7 Gy3 (median 58.8), for the bladder were 139.1 ± 54.7 Gy3 (median 131.9) and 93.4 ± 24.6 Gy3 (median 91) and the sigmoid were 109.4 ± 45.2 Gy3 (median 91 Gy) and 74.6 ± 19.6 Gy3 (median 69.6).

With a median follow-up of 24 months (mean 26 months; range 16–42 months), three patients had local failures; one had positron emission tomography–computed tomography- and biopsy-proven right external iliac nodal failure and one patient had a cytology-proven left supraclavicular nodal failure. Of three local failures, two patients had persistent and progressive local disease and received the following doses at point A: 70 Gy10 and D_{90} 65 Gy10 (FIGO IIIB); 79 Gy10 and D_{90} 67 Gy10 (FIGO stage IIB), respectively, whereas the third patient with FIGO stage IIB developed local recurrence at the cervix 10 months after treatment. The mean survival was 30 months and actuarial disease-free survival was 71% at 2 years. So far, only one patient has grade 3 radiation proctosigmoiditis at 12 months after treatment with rectum 2 and 0.1 cm^3 doses of