Proton beam therapy for medulloblastoma

It is heartening to read a report1 of good functional outcomes following proton beam therapy in young patients with medulloblastoma, including the absence of many unpleasant side effects that can occur after conventional photon therapy.

The authors quote UK research,2,3 which criticises the current proton therapy treatment policy of dividing the x-ray (photon) equivalent dose by 1·1. This is done in order to compensate for the enhanced effectiveness of proton therapy caused by the greater proximity of ionisation effectiveness of proton therapy compared with photons.4 Radiobiological modelling studies, based on the high radiosensitivity of medulloblastoma cells, suggest a lower necessary dose reduction of 1·03–1·08 in order to maintain the same tumour control effect. A dose division by 1·1, compared with, for example, 1·05 (if correct), would incur a 4% overall change in effective dose, which could translate into a 4–8% reduction in tumour control. The number of patients required to detect such a change would be much larger than the 59 patients included in the study by Yock and colleagues, however: a minimum of several hundred and perhaps over a thousand patients might be necessary.5 This statistical power requirement indicates the need for national and international cooperation in the conduct and analysis of such rare treatments.4

The reported maintenance of cognitive function is important. With a predicted dose reduction for neural tissues of 1·2 or more, rather than the 1·1 used in practice, this outcome implies a sufficient reserve of cortical neural radiation tolerance compared with the dose required for tumour control.7 The brainstem necrosis in one child is likely to be caused by a combination of the lower radiation tolerance of brainstem than cortical brain, enhanced ionisation density effects, previous surgery, and the chemotherapy regimen used.4 Another important factor is that the meticulous treatments in Boston are given to children who may not only be fitter to travel, but are also from wealthier backgrounds, with better outcomes than those of less privileged children without such access to excellent care.

I declare no competing interests.

Bleddyn Jones
bleddyn.jones@oncology.ox.ac.uk
Gray Laboratory, CRUK/MRC Oxford Oncology Institute, University of Oxford, UK


We read the recent article by Yock and colleagues1 with great interest. We commend the authors for their study, which brings the very controversial issue of proton radiotherapy for medulloblastoma to the forefront. However, we feel caution should be exercised in adopting routine proton radiotherapy for medulloblastoma, particularly in the context of other recent studies.

Our main concern pertains to the primary outcome of the study, specifically the short follow-up. Another study2 showed that audiological toxic effects secondary to external beam irradiation are progressive, and a minimum 10 years follow-up is required to adequately assess ototoxicity.3 The 3 year follow-up in this study should be carefully assessed, as published reports suggest that proton and photon radiotherapy show similar ototoxicity.4 In fact, a study of intensity modulated photon radiotherapy5 showed a prevalence of grade 3 hearing loss of 6% with low doses to the cochlea. Median doses to the cochlea with proton radiation reported by Yock and colleagues were similar to doses with intensity-modulated radiation therapy.6 Treatment heterogeneity also confounds interpretation of this study, and carefully conducted clinical trials with uniform cisplatin dosing are required. We feel that the conclusions surrounding neurocognitive outcomes are also hampered by short follow-up times. Indeed, a recent study7 of proton radiotherapy versus photon radiotherapy using the same modality (craniospinal radiation with tumour bed boost) showed similar changes in intelligence quotas across both radiation modalities.

The study by Yock and colleagues provides a robust foundation, and we hope the authors consider reporting long-term outcomes in the coming decade. Considering the cost of proton therapy, and the state of the literature suggesting equipoise in both efficacy and side effects, we feel that a cautious approach in adopting widespread proton radiation technology for medulloblastoma is warranted. In light of the rising cost of health care in both North America and Europe, the feasibility of routine use of proton radiotherapy requires additional study. The time has now come for urgent properly controlled studies comparing proton and modern photon based radiation for medulloblastoma.

We declare no competing interests.

*Vijay Ramaswamy, Eric Bouffet
vijay.ramaswamy@sickkids.ca
Division of Haematology/Oncology, Hospital for Sick Children, Toronto ON, Canada

We must also be explicit that omission or reduction of chemotherapy after administration of proton beam radiotherapy is likely to substantially reduce the likelihood of cure in this group of patients, as there is no expectation that proton beam radiotherapy increases the chance of cure compared with conventional treatment with photons.

Ideally, a randomised clinical trial between conventional and proton beam radiotherapy would be done, but it has not, and it is now neither realistic nor appropriate for such a trial to take place. Therefore, case-control and historical comparison studies must be performed.

Key challenges in the care of children with medulloblastoma are: to avoid delayed diagnosis, to avoid morbidity from prolonged hydrocephalus and neurological damage developing before surgery; to minimise surgical morbidity and complications such as posterior fossa syndrome; to coordinate care so that radiotherapy treatment is started within 4 weeks of surgery, unless a neoadjuvant chemotherapy approach is used; to provide active neuro-rehabilitation from the time of diagnosis, specifically targeted to needs identified after neuropsychological evaluation; and to collect data and monitor late effects systematically.

In the UK, patients with medulloblastoma will be offered proton beam therapy when it is available in the NHS centres in Manchester and London. The UK is ideally positioned to extend the single centre work reported by Yock and colleagues to a national cohort of patients with medulloblastoma treated with proton beam radiotherapy 2018-9. Work should begin to collect morbidity and mortality data on all UK patients with medulloblastoma to optimise future management of the most common childhood malignant brain tumour.

We must also be explicit that omission or reduction of chemotherapy after administration of proton beam radiotherapy is likely to substantially reduce the likelihood of cure in this group of patients, as there is no expectation that proton beam radiotherapy increases the chance of cure compared with conventional treatment with photons.

Ideally, a randomised clinical trial between conventional and proton beam radiotherapy would be done, but it has not, and it is now neither realistic nor appropriate for such a trial to take place. Therefore, case-control and historical comparison studies must be performed.

Key challenges in the care of children with medulloblastoma are: to avoid delayed diagnosis, to avoid morbidity from prolonged hydrocephalus and neurological damage developing before surgery; to minimise surgical morbidity and complications such as posterior fossa syndrome; to coordinate care so that radiotherapy treatment is started within 4 weeks of surgery, unless a neoadjuvant chemotherapy approach is used; to provide active neuro-rehabilitation from the time of diagnosis, specifically targeted to needs identified after neuropsychological evaluation; and to collect data and monitor late effects systematically.

In the UK, patients with medulloblastoma will be offered proton beam therapy when it is available in the NHS centres in Manchester and London. The UK is ideally positioned to extend the single centre work reported by Yock and colleagues to a national cohort of patients with medulloblastoma treated with proton beam radiotherapy 2018-9. Work should begin to collect morbidity and mortality data on all UK patients with medulloblastoma to optimise future management of the most common childhood malignant brain tumour.

Looking to the future, we need to continue this quest for more effective and less damaging treatments, to improve survival and the quality of that survival.

We declare no competing interests.

Martin English, *Richard G Grundy, Andrew Peet, Stephen Lowis, David Walker richard.grundy@nottingham.ac.uk

Birmingham Children’s Hospital, Birmingham, UK (ME); University of Nottingham, Nottingham, UK (RGG, DW); University of Birmingham, Edgbaston, Birmingham, UK (AP); and Bristol Royal Hospital for Children, Bristol, UK (SL)


Author’s reply

We appreciate the comments in the letters from Vijay Ramaswamy and Eric Bouffet, Richard Grundy and colleagues, and Belddyn Jones, and would like to address some key points.

With regard to Ramaswamy and Bouffet’s letter, although we share their concerns about health-care costs, our priority is to determine which treatments produce the best disease control and highest quality of survival. While we agree that a randomised trial may be ideal, a randomised trial is now neither realistic nor appropriate. We do agree that it is important to report health outcomes in our cohort into the next decade.

Ramaswamy and Bouffet assert that we have short follow-up on our hearing data. However, our audiogram follow-up was actually 5-0 years. We agree that extended time is needed to more fully evaluate ototoxicity and the Article by Bass and colleagues demonstrates this nicely. The cited article by Polkinghorn reported 6% grade 3 hearing loss at a median audiogram