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EDITORIAL

Selecting patients for proton beam therapy

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A conservative estimate is that around 5% of all patients for radiation treatment (RT) may benefit preferentially from proton beam therapy (PBT) compared with conventional radiation therapy and as many as 15%. With nearly 67,800 patients in Australia receiving RT in 2017–2018, there is an urgent need to develop ways of selecting which patients will benefit most from PBT at the Australian Bragg Centre for Proton Therapy (ABC) as soon as it becomes operational. As the first particle therapy facility in Australia, the ABC is a valuable national resource and there is an imperative to deliver value for money invested by Commonwealth and State governments.

Different jurisdictions such as the United Kingdom, The Netherlands and Denmark have developed indications lists for patients who are thought to benefit most from PBT, principally children and those with rare tumours. These lists have been typically pragmatic or consensus-driven based on radiation treatment plan comparison studies (PBT compared to conventional radiation therapy), so-called in silico studies. So far, there have been very few prospective randomised trials and most prospective studies (PBT compared to conventional photon treatment) have been conducted in single centres.[1] With a considerable increase in the number of PBT facilities around the world in the last few years (https://www.ptcog.ch/index.php/facilities-in-operation), there now exists an opportunity to conduct clinical trials with robust outcome data including patient-reported measures and long-term consequences of treatment. Collaboration between particle therapy centres in Australia once more than one facility is operational, as well as international collaborations will allow prospective studies to be conducted for less common tumours. The establishment of consortia to pool and compare outcome data for patients for whom prospective studies are not feasible is already underway—for example, The European Particle Therapy Network.[2]

Limited outcome data from consortia already exist, although meaningful data will take many more years to accumulate. In the meantime, how to select patients for PBT now remains a priority. This is especially so for patients with more common tumours such as breast cancer where demand for PBT will quickly exceed ability to access the treatment unless transparent and robust selection criteria for PBT are established.

Two randomised clinical trials investigating PBT in women with breast cancer are currently recruiting. The 'RADCOMP' trial will evaluate cardiovascular morbidity and mortality, health-related quality of life and cancer control outcomes in women with locally advanced breast cancer with a study completion date of 2032 (ClinicalTrials.gov Identifier: NCT02603341). The Danish Breast Cancer Collaborative Group Proton Trial (ClinicalTrials.gov Identifier: NCT04291378) will evaluate 10-year risk of heart disease in women with early breast cancer, with radiation-associated secondary cancer as one of several secondary study outcomes. The study completion date is 2037.

The manuscript by Austin et al in this issue of the Journal of Medical Radiation Sciences demonstrates a method of selecting left-sided breast cancer patients for PBT based on cost-effectiveness of treatment rather than clinical trial outcomes.[3] The method uses Markov modelling, a way of synthesizing 'the available evidence for simulation studies, by describing disease and treatment progress, as well as associated factors such as a treatment's effects on a patient's life and the costs to society'.[4] Sixteen left-sided breast cancer patients had breast alone treatment plans generated for both intensity-modulated proton therapy (IMPT) and hybrid intensity-modulated photon treatment, both with a deep inspiration breath-hold technique. Dosimetric data were used to predict tumour control and toxicity (cardiac, pneumonitis and second primary cancer) probabilities. The probabilities were then used in a Markov model to

predict costs and number of quality-adjusted life years from the two treatments for each patient. IMPT was cost-effective for only one of 16 patients, a patient with a high lung dose which increased the second cancer risk. These data set could provide the basis for an expanded study including patients who will have nodal volumes irradiated or those who are unable to breath-hold for treatment (both scenarios increasing lung exposed to radiation and therefore increasing the risk of radiation pneumonitis) and those who receive systemic therapies such as trastuzumab that have cardiac effects. All these considerations are recognised as limitations in the current study which provides a valuable starting point for further investigation.

Different mathematical models exist for patient selection for PBT although a model is only as good as the data that informs it.[5] The Dutch have adopted a difference in Normal Tissue Complication Probability (ΔNTCP) approach to select patients for PBT who are not included on an indications list based on level 1 and 2 evidence. The Danish National Proton therapy Centre has also adopted this model for selection of patients who have a tumour which is not included on an indications list. The NTCP value reduction can be estimated for each patient by knowing the NTCP value for a particular side effect of treatment for a patient treated by photon therapy, producing a comparison proton dose plan and comparing the NCTP value for proton therapy. The first report of use of this NTCP model for selection of head and neck cancer patients for PBT was published recently.[6]

The Markov model approach reported by Austin et al takes the ΔNTCP model one step further by incorporating a quality of life utility value for each Markov state as well as costs of treatment including costs of managing side effects. Austin's publication in this issue adds to a body of work being undertaken by the Adelaide group demonstrating the potential for Markov modelling in patient selection for PBT at the ABC.

Both the NTCP model and the Adelaide group's Markov model for patient selection for PBT will become refined over time as more patients are added to the models and as real patient outcome data become available from collaborative consortia to test the models. Australia can contribute to international efforts to select patients for PBT by enrolling all patients treated at the ABC and other Australian particle therapy facilities when they open, on a national registry co-ordinated by the Trans- Tasman Radiation Oncology Group (TROG) Cancer Research. The aim is to collect an agreed set of minimum patient and tumour data elements available from electronic patient records in use in all Australian radiation oncology centres, linking to radiation treatment plans and patient outcomes using the Australian Computer Assisted Theragnostics (OzCAT) network distributed data platform. Grant applications for funding by the Australian Research data Commons have recently been submitted. If successful, data in the TROG registry will allow researchers to develop analytical models using machine learning that will allow for a prediction of likely outcomes of treatment for future patients. Until such analytical models can be developed, investing effort into creating Markov models for more common tumours that may be suitable for PBT at the ABC is a worthy endeavour.

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