



# Long term outcomes of stereotactic conformal radiation therapy in the treatment of benign and low-grade brain tumors

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Health care assessments incorporating high end technology in cancer such as robotic surgery, intraoperative magnetic resonance imaging (MRI), particle beam therapy, high throughput molecular diagnostic etc. are challenging (1). In the field of radiation oncology, high-precision conformal techniques such as stereotactic radiosurgery/radiotherapy (RT), intensity modulated radiotherapy (IMRT) and particle therapy, etc., have been incorporated into routine clinical practice including for brain tumors based on dosimetric superiority and single arm studies without always being supported by randomized data.

Our trial in benign and low-grade brain tumors in young patient population, is in a sense unique that the evidence has been generated from prospective randomized trial in a controlled setting with an appropriately powered and relatively large number of subjects (2). More importantly however, we carefully chose the two most pertinent clinically meaningful endpoints of preservation of long-term neurocognition and endocrine function in this group of patients. We have shown that using high precision radiation delivery technology is indeed beneficial in these patients not only in maintaining long-term neurocognitive and endocrine functions but has obviated the slight fear of compromising efficacy in terms of high local control and survival, in view of relatively tight margins often associated with such techniques. It has taken us time to accrue and complete this trial but that was warranted to ensure meticulous median follow-up at a reasonable end point of more than 5 years. The study has not only fulfilled the primary endpoints for which it was designed but also has given us considerable information about the role of

patient related factors as well as the various structures in the brain influencing the development of RT induced sequelae. Relevant information related to the possible dose constraints to temporal lobes with respect to neurocognition has been already illustrated (3) and we are excitedly investigating the role of hippocampi (4) in a relatively large cohort with prospectively collected follow-up data. Similar constraints are being evaluated upon with respect to hypothalamic-pituitary axis for predicting neuroendocrine dysfunction in the same patient population.

Benign and low-grade brain tumors belong to a spectrum of tumors that occur in pediatric population with high and durable survival and therefore survivorship is an extremely important long-term endpoint. While there is little doubt that we must continue to explore alternative efficacious modalities to avoid cranial RT in any form in young patients, the present study does give a possible confidence to treating physicians about the value and safety of modern conformal RT techniques. While the trial chose the most advanced RT technique available at that time, it can still be used as a reasonable template for other high precision techniques such as proton and heavy ion therapy especially in the light of recent evidence from St Jude's hospital that showed better preservation of neurocognition (academic achievement) using high precision proton therapy when compared to a matched cohort treated previously with photon therapy in young adults diagnosed with craniopharyngiomas (5).

We are cognizant of the fact that the work is in no way accomplished and stringent follow-up of these patients are required to not only document their cognitive functions

and endocrine functions beyond 5 years but also to provide long-term risk estimates of other sequelae like vascular events such as stroke, microangiopathies or even second malignant neoplasms like radiation induced high grade gliomas, meningiomas or sarcomas which take at least 10 to 15 years to manifest and are considered to be frequent and important life-threatening adverse events associated with RT (6).

Although, we feel that randomized trials should be the done wherever feasible. We are not advocating that they are compulsory for evaluating health technology outcomes before implementing them in the clinics. A more pragmatic option could be a prospective collection of clinical data, meticulous measurement of dosimetric data, regular audits. Moreover, honest interpretation of the results of even smaller phase-II studies with clinically relevant end points can give us a wealth of information on their implementation feasibility. This trial exemplifies the evolving role of modern conformal RT techniques in the overall paradigm of brain tumor management not only in the contemporary era but also in the likely future which will witness the greater use of particle beam therapy in the radio therapeutic management of brain tumors. Therefore, suitable studies should be designed accordingly using not only patient centric long-term endpoints but also social endpoints of survivorship like integration of patients into the main stream society and educational issues.

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