Conventional Vs Conformal radiation therapy in the management of pediatric CNS tumours

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ABSTRACT

Pediatric patients with primary CNS tumors should be treated by 3D conformal radiation therapy techniques as it allows better sparing of risk organs Although the results of the current study were not statistically significant, but more number of patients and longer follow-up period may show statistical differences between both arms in favour of the 3D conformal arm. Base-line organ function should be obtained prior to surgery as many patients may have affection of one or more of these functions prior to beginning of radiation therapy and this may lead to overestimation of the late effects of radiotherapy. More sophisticated radiation therapy techniques, e.g: IMRT and proton radiotherapy are expected to lower radiation dose to risk organs in close proximity to the target volume and thus will lower treatment morbidity

Key words

(3D conformal radiotherapy- Pediatric malignancies- Pedatric CNS tumors- Late effects of radiation therapy)

List of abbreveations:

ALL: Acute lymphoblastic leukeamia

CCAS: Cerebellar cognitive affective syndrome

CRT: Conformal radiotherapy

CSI: Cranio-spinal irradiation

CTV: Clinical target volume

DRR: Digitally reconstructed radiograph

DVH: Dose-volume histogram

EPID: Electronic portal imaging device

GTV: Gross tumor volume

HRT: Hyperfractionnated radiotherapy

ICRU: International Committee on Radiation Units

IQ: Intelligence quotient

MLC: Multi-leaf collimator

PTV: Planning target volume

RT: Radiotherapy

3D: Three-dimensional

INTRODUCTION AND AIM OF WORK

Brain tumors are the most frequent among the solid malignant tumors listed for the pediatric age groups as they represent about 20% of all pediatric tumors (2nd most common after ALL) and are one of the leading causes of cancer-related death **(*Jemal A et al 2009*).** They occur in many locations within the brain, and are of various histological subtypes.

Surgical resection remains the mainstay of treatment. Radiation therapy also has a major role. It can be used either as adjuvant to surgery, or for definitive therapy when surgery has been incomplete or is impossible.

Chemotherapy has not appeared to contribute significantly to success until recently.

It has now been shown in randomized clinical trials, for example, that triple modality therapy gives better results than surgery plus radiation therapy alone in high-risk medulloblastoma patients **(*Bleyer et al 1990, Gurney et al 2009*).**

Radiotherapy (RT) continues to play an important role in the treatment of children with brain tumors, despite its known effects on cognitive function. The cognitive effects of RT are known to appear cumulatively after treatment and to persist, resulting in permanent deficits involving attention, memory, speed of mental processing, and visual– motor coordination . The acute effects of treatment, defined as those arising during treatment, have not been quantitatively studied, leaving open the possibility that the adverse cognitive effects observed after therapy completion begin much earlier than previously reported. Early identification of any adverse treatment effects, would improve our understanding of the effects of irradiation on the normal brain and its contribution to early and late post-RT cognitive sequelae. Understanding the time-course of treatment-related effects would also assist in the design of interventions meant to reduce the consequences of RT.

RT results in long-term disease control and alone is curative for many types of brain tumors **(*Pang et 2008, Ahern et al 2003, Conklin et al 1989, Ris et al 2001, Ogg et al 2008*).** The perceived and reported risks of RT, have motivated physicians to avoid RT as a first-line modality for certain children **(*Merchant et al 2000, Duffner et al 1993*).**

Conformal RT (CRT) has made it possible to reduce the volume of normal tissue that receives the highest doses of radiation and, in some cases, avoid altogether irradiation of functionally important regions of the brain such as the hypothalamic–pituitary unit, the cochlea, the optic pathway and the brain stem ***(Ellenberg et al 1987)***. This advancement has gained wide acceptability and should make the use of radiation more suitable for children.

The development of 3Dimensional Radiation Therapy Planning (DRTP) systems especially and the commercial availability of 3DRTP systems, led to widespread adoption of 3D planning. One of the keys to the acceptance of 3DRTP throughout the community was a series of research contracts funded by the National Cancer Institute (NCI) in the 1980s and early 1990s to evaluate the potential of 3DRTP and to make recommendations to the NCI for further research in this area ***(Smith et al 1991 and Zink et al 1995)***

Aim of Work:

The aim of the current study is to compare between 2 dimensional & 3 dimensional (Conformal) radiation therapy techniques in the management of pediatric brain tumors as regards:-

1- Physical outcome considering :-

a- Dose distribution inside the target volume.

b- Doses received by surrounding risk structures especially the optic pathway, the brain stem, the cochlea and the pituitary gland.

2- Clinical outcome considering:-

a- Response rate to RT, local tumor control & possible survival difference.

b- Toxicity of both techniques.

Review of literature

The most common fatal disease in children is cancer. After accidents, cancer is the leading cause of death in children aged 1–14 years ***(Jemal et al 2009, Bleyer et al 1990)***. A number of treatment options are available, including surgery, chemotherapy, and radiotherapy (RT). However, long-term negative potential consequences exist from treatment—using any modality—of childhood cancers. Survivors of childhood cancer are prone to social difficulties in later life, are more likely to require special education services, and to have a reduced likelihood of undertaking tertiary education, marrying as a young adult, and finding employment ***(Gurney et al 2009, Pang et al 2008).*** Also concerning is the potential for late health complications, in particular, those that arise as a result of the treatment of the primary disease. Such cases are of interest to clinicians because they are amenable to risk minimization by careful choices regarding the nature of the treatment.

Approximately 28% of children <15 years old who are diagnosed with cancer undergo RT ***(Ahern et al 2003).*** In RT, it is the cell-killing function of ionizing radiation that is the desired effect for the destruction of a targeted tumor. However unwanted doses to untargeted healthy tissues can have deleterious consequential effects, such as neurological, respiratory and cardiac complications or radiocarcinogenesis. This is not only of interest in the immediate regions around the targeted volume, but also in critical structures that are quite distant from the primary field, but that nonetheless receive a dose from scattered and leaked radiation. In the case of pediatric patients, the issue of doses to untargeted tissues is of particular concern. Normal tissues in children have the capacity not only to repair, but to grow, and are affected by radiation to a greater extent than adult tissues. Furthermore, the long potential lifetime of pediatric patients means that a longer time is available in which radiation-induced cancers can manifest

Postnatal Period and Childhood:

The postnatal period and childhood occurs from the time of birth to the beginning of the adult stage of life. This period is divided into 3 phases: infancy/early childhood, late childhood, and puberty. Different organs develop at different rates during these phases; hence the effects of irradiation are dependent on the time of exposure. Infancy/early childhood occurs from the time of birth to approximately 6 years of age. Normal tissues are newly formed and development occurs through cell replication or hypertrophy, depending on the organ. The late childhood years are between 6 years of age and just before the onset of puberty. Several organs now have their full complement of functional subunits, and growth is less robust during this time. Irradiation at this time will be less deleterious as the mitotic activity is diminished.

Puberty occurs during the time from onset of puberty into adolescence. The functional subunit complement is complete for most organs with the exception of the musculoskeletal system, breast tissue, and genitalia; for these latter organs or organ systems, radiation injury causes more late effects than during the early childhood phase.

Neural Growth Pattern

This is characterized by rapid postnatal growth, which slows in adolescence. The most active phases of synaptogenesis and myelinization are in the first 5 years, but continue for the subsequent 2 to 3 decades without significant volumetric changes. Other organs that develop according to this pattern are the liver, kidney, heart, and lung

Musculoskeletal Growth Pattern

Also called the general growth pattern, this is the classic example of this type with 2 growth peaks: 1 during the early postnatal period and the other at the onset of puberty. The gastrointestinal, head and neck, skin, and circulatory systems also follow this general growth pattern.

Neural (Brain)

Although the brain is most sensitive to the effects of ionizing radiation during the early fetal period, because of early postnatal growth it is extremely sensitive during the first few years of life. Several studies have shown that age at the time of irradiation has a significant effect on cognitive function in children with brain tumors. For example, a study from investigators at St. Jude Children's Hospital evaluated 87 children with ependymoma treated with conformal radiotherapy to doses ranging from 54 to 59.4 Gy. Although cognitive testing revealed that math and spelling scores remained stable at a median follow-up time of 59.6 months, the reading scores deteriorated, particularly in children irradiated at or less than 5 years of age ***(Conklin et al 1989***). Another study from the Children's Cancer Group showed that the intelligence quotient (IQ) decline was worse in children receiving craniospinal irradiation followed by posterior fossa boost for medulloblastoma when their age was 7 years at time of radiotherapy ***(Ris et al 2008).*** Investigators from the Children's Hospital of Philadelphia found that children less than 7 years of age at time of cranial irradiation had a mean full-scale IQ decline of 25 points 2 years after treatment ***(Ogg et al 2008).*** In older children with intracranial germinoma receiving cranial irradiation, ***Merchant et al 2000*** did not find a significant decline in IQs between pre- and post-irradiation scores. It is not surprising that many strategies have omitted or deferred radiotherapy in young children (less than 3 years of age) with brain tumors because of clinicians' fear of neurocognitive toxicity ***(Duffner et al 1993).*** The circle of Willis is also most affected when the radiotherapy insult occurs during the most rapid period of brain growth. A report has shown that radiation-induced Moyamoya syndrome is most common in children irradiated to the parasellar region to children less than 5 years of age ***(Desai et al 2006).***

As the number of long-term survivors of childhood cancer has grown, it has become increasingly clear that central nervous system therapy may have serious long-term effects on cognition and endocrine function. These complications have been studied most extensively in children with brain tumors and leukemia. Risk factors include perioperative morbidity, young age, large-volume, high-dose cranial irradiation, supratentorial location of tumor, moyamoya syndrome, and leukoencephalopathy. Cognitive decline is progressive over at least a decade. The most common radiation-induced endocrinopathies are hypothyroidism and growth hormone deficiency.

Treatment effects on growth are multifactorial and include growth hormone deficiency, spinal shortening, precocious puberty, undetected hypothyroidism, and poor nutrition. Fifty to eighty percent of children treated with craniospinal radiation for brain tumors will experience growth failure.

In hopes of reducing neurotoxicity, current treatments limit the dose and volume of radiation while adding chemotherapy. Results have not been uniformly positive, however, and may increase toxicity in some cases.

History:

In the late 1970s, a 2-year-old boy presented with signs and symptoms of a posterior fossa mass. CT scan revealed a tumor filling the fourth ventricle with obstructive hydrocephalus. Following surgery, he received craniospinal radiation (36 Gy CSI and boost to the tumor bed up to 55 Gy) plus a chemotherapy regimen which included vincristine, BCNU, methotrexate, and dexamethasone. Over the next several years, his cognitive abilities declined to the point he was considered to have mental retardation. His growth rate decelerated. He was also diagnosed with primary hypothyroidism. His CT scan began to show calcification in the basal ganglia and toward the end of his life, he developed respiratory failure requiring constant oxygen supplementation. By the time he died 8 years following diagnosis, he was severely demented, hypothyroid, growth hormone dependent, and had evidence of methotrexate leukoencephalopathy. The cause of death was BCNU-induced pulmonary fibrosis. **There was no tumor at autopsy.**

"***There are some remedies worse than the disease"***

Said Publius Syrus

1st century BC

This child's tragic outcome is unfortunately not unique. Similar cases have led investigators worldwide to begin to explore the long-term effects of

CNS therapy on children with brain tumors. The following paragraph will discuss cognitive and endocrine function of these children and the changes in treatment that have been instituted in an attempt to reduce neurotoxicity ***(Bloom et al 1969).***

The Role of Age

Young age at the time of radiation is indisputably one of the most important risk factors for neurotoxicity in children with brain tumors ***(Ellenberg et 1987, Radcliffe et al 1992).***

Retrospective studies on very young children with brain tumors are unfortunately often confounded by lack of baseline data. The larger the volume of radiation, the more vulnerable is the young brain. The rapid growth of the brain in the first 2 years of life makes babies particularly vulnerable to radiation toxicity. ***Mulhern et al*** compared normal-appearing white matter on quantitative MRI with age at time of radiation therapy, IQ, factual knowledge, and verbal and nonverbal abilities and found an inverse correlation, suggesting that either deficient development of white matter or loss following CRT might provide a neuroanatomical basis for the severe impact of RT on cognition in the very young.

The Role of Time Since Treatment

Radiation-induced dementia is a progressive disease. ***Hoppe-Hirsch et al***,***1995*** found that in her series of 120 children with medulloblastoma, 58% had IQ of 80% 5 years following diagnosis. That figure dropped to 15% by