Proton Craniospinal Radiation Therapy: Rationale and Clinical Evidence

Anita Mahajan, MD

University of Texas MD Anderson Cancer Center, Houston, TX, USA

Abstract

Purpose: To review the existing evidence that supports the use of proton craniospinal irradiation (p-CSI) in pediatric patients.

Materials and Methods: A literature review was performed exploring the current evidence for the use of p-CSI. The theoretical advantages based on dosimetry and predictive toxicity models are described. The technical advances in p-CSI delivery are reviewed. The existing and emerging clinical data, including cost-benefit analyses are evaluated.

Results: The theoretical advantages based on dosimetry comparisons to x-ray–based CSI consistently support the potential benefit of p-CSI. Similarly, the predictive models suggest a reduction in the risks of organ toxicity and radiation-associated second malignancies. The early clinical data that are emerging confirm similar tumor control rates with some support of reduction in early measurable toxicities. Several studies support an overall cost-benefit advantage when the potential reduction in side effects with p-CSI is considered.

Conclusions: Based on the theoretical and early clinical outcomes, p-CSI appears to provide equal tumor control with potentially reduced risk of side effects when compared with data. Ongoing efforts will continue to evaluate these advantages.

Keywords: proton therapy; craniospinal radiation therapy; medulloblastoma; pediatric

Submitted 27 Apr 2014
Accepted 16 May 2014
Published 08 Sep 2014

Corresponding Author:
Anita Mahajan
Department of Radiation Oncology
MD Anderson Cancer Center
1515 Holcombe Boulevard, Unit 097
Houston, TX 77030, USA
Phone: +1 (713) 563-2350
Fax: +1 (713) 563-2331
amahajan@mdanderson.org

Review Article

DOI
10.14338/IJPT.14.00005.1

http://theijpt.org

Introduction

Craniospinal irradiation (CSI) is a radiation technique that is used in the treatment of central nervous system malignancies that have a substantial risk of subarachnoid spread. Medulloblastoma is the most common diagnosis in children for which CSI is part of the standard of care. Other diagnoses that may require CSI include other primitive neuroectodermal tumors, atypical teratoid rhabdoid tumors, central nervous system germ cell tumors, or any tumor that has evidence of cerebrospinal fluid spread diagnosed by a lumbar puncture or a magnetic resonance myelogram.

Three-dimensionally planned X-ray CSI (x-CSI)-based treatment has been used as the standard approach using multiple junctioning beams to cover the entire cerebrospinal fluid space extending from the cranium to the thecal sac, which lies at the level of the mid sacrum. Typically, low energy megavoltage photons are used with standard field arrangements of lateral/anterior oblique cranial and posterior spinal field(s).

Many toxicities are attributed to x-CSI, not only because of the effect on the normal structures that are encompassed in the treatment fields, but also because of the effect on organs treated by the exit dose from the spinal fields. Side effects during the radiation treatments include nausea, vomiting, anorexia, bone marrow suppression, skin erythema,

How to cite this article Mahajan A. Proton Craniospinal Radiation Therapy: Rationale and Clinical Evidence. Int J Part Ther. 2014;1(2):399–407.

alopecia, and fatigue. Late toxicities include spine growth retardation, endocrine insufficiencies from pituitary, hypothalamic, thyroid injury, hearing loss, and secondary malignant neoplasms (SMN). Efforts have been made to reduce these toxicities by reducing the CSI dose in low-risk patients, eliminating or delaying CSI in very young patients, incorporating electron therapy for the spinal component of the CSI, or by advanced radiation therapy (RT) planning techniques [1–4]. Proton radiation therapy (PRT) has been used therapeutically for over 50 years. As facilities have become hospital based and treatment planning systems have evolved, more complex, larger field, proton beam strategies have been evaluated. Because of the lack of an exit dose, PRT was evaluated for CSI in an effort to reduce normal tissue dose. In this article, the potential theoretical and clinical benefits of proton CSI (P-CSI) are explored.

Materials and Methods

A literature review was performed exploring the current evidence for the use of p-CSI. The theoretical advantages based on dosimetry and predictive toxicity models are described. The technical advances in p-CSI delivery are reviewed. The existing and emerging clinical data, including cost-benefit analyses are evaluated.

Results

Dosimetry Benefits

Multiple dosimetric analyses have been reported over the past 15 years. Lee et al and St Clair et al first described the potential dosimetric benefits of proton CSI (p-CSI) in patients with medulloblastoma [5, 6]. St Clair performed a dose-volume histogram (DVH) analysis of p-CSI to x-CSI and intensity-modulated X-ray therapy (IMXT) CSI plans in a 43-month-old boy. The p-CSI plan used a standard beam arrangement with 2 opposed cranial fields and a single posterior spine field that encompassed the entire vertebral body. The authors describe a significant dose reduction to the cochlea, transverse colon, stomach, kidney, heart, and lung with p-CSI. Of interest, intensity-modulated x-CSI DVHs revealed a reduction in high dose delivered to nontarget structures, but increased low dose volumes were noted in comparison to x-CSI [6].

Lee et al reported DVH analyses of 2 patients planned with p-CSI in comparison with both x-CSI and electron therapy x-CSI. There was a reduction in high and low dose normal tissue irradiation noted in the cochlea, mandible, thyroid gland, lung, kidney, heart, and lung with p-CSI in comparison with the other 2 modalities. Of note, doses to the several normal structures were also significantly reduced when using electron therapy for the spinal component of the CSI [5].

Both studies also noted a reduction of the cumulative dose delivered to nontarget intracranial structures, including the hypothalamus, pituitary gland, eyes, optic chiasm, and cochlea, with the PRT-based boost in comparison with the X-ray radiation therapy (XRT)-based boosts [5, 6].

Howell et al [7] evaluated dosimetric data on 18 patients between the ages of 2 and 18 years planned with p-CSI and x-CSI. Height and weight varied between 11.9 and 138.2 kg and 85 and 191 cm, respectively. In all cases, there was normal tissue–sparing of all structures with more homogeneous target coverage in the PRT plans. Yoon et al [8] described the dosimetric benefit of p-CSI in comparison with x-CSI and TomoTherapy-CSI (Accuray, Sunnyvale, CA, USA) in 10 patients with varying diagnoses that required CSI. Of

interest, TomoTherapy-CSI, similar to intensity-modulated x-CSI, showed an intermediate dose to normal structures in comparison with p-CSI and x-CSI but increased total body low dose compared with the other techniques. TomoTherapy did have a more favorable DVH comparison for the parotid glands, lenses, and thyroid gland in comparison with p-CSI and x-CSI.

Predictive Models

The predicted reduction of SMNs as a result of the lower normal tissue dose has been evaluated with several modeling studies. Miralbell et al calculated the risk of SMN reduction in a patient planned with a single beam XRT, 9-beam IMXT to single beam PRT for the spinal component of CSI [9]. The authors calculated a 15-fold reduction in SMN with PRT in comparison with the XRT plan and a 9-fold reduction in comparison with the IMXT plan. Other studies have supported these findings using different models and evaluating stray irradiation including the risk related to secondary neutron contamination in boys and girls [10, 11]. Zhang et al [12] examined the predicted risks of SMN in a 4-year-old patient treated with p-CSI and x-CSI in comparison with older patients. Brodin et al [13] compared plans of 10 different patients and predicted risks of SMN with varying doses (23.4 Gy relative biologic effectiveness [RBE] and 36 Gy RBE) and varying techniques: RapidArc, x-CSI, and intensity modulated proton therapy (IMPT)-CSI. In all of these studies, the risk of SMN is consistently predicted to be significantly lower with the PRT-based CSI approaches when considering variations in patient age, sex, XRT technique, and SMN predictive model and while adding the additional dose from secondary neutron irradiation with the associated high-radiation weighting factor.

Reduction of normal organ dysfunction with the use of p-CSI has also been extensively studied. Brodin et al [13] predicted lower rates of pneumonitis, cardiac failure, xerostomia, blindness, hypothyroidism, and ototoxicity based on 10 patients. Other authors have evaluated the predicted benefits in health of offspring and gynecologic toxicity [14, 15]. Lower rates of neurocognitive dysfunction has also been predicted when incorporating the boost dose for patients with medulloblastoma as a result of the lower dose delivered to the supratentorial brain and, in particular, the subventricular zones and hippocampus [16, 17].

Technique

Since the initial description of p-CSI, further improvements of the technique have been investigated. Cochran et al [18] described a posterior oblique modification to the original cranial fields described by St Clair to allow improved coverage of the cribriform plate and a statistically lower dose to the lenses. The posterior oblique fields are commonly used now for p-CSI treatment. Dinh and Jin independently evaluated the use of compensators for the cranial fields for CSI when using passive scatter PRT. The conclusions of this study suggested that compensator use increased heterogeneity within the brain and did not provide the ability to effectively reduce the dose to critical structures such as the cochlea [19, 20]. Dosimetry at the junction between spine fields was reviewed by Cheng et al [21], and comparisons were made between a moving gap approach with proton therapy and X-rays on the spine. The authors concluded that the dosimetric characteristics between the abutting spine fields were similar between x-CSI and p-CSI. In most centers the spine/spine and spine/cranial junctions are shifted once a week, similar to the approach used for traditional x-CSI. Giebeler [22] summarizes a standardized approach to supine p-CSI planning with passive scatter proton therapy.

This process is adaptable to a variety of patient sizes and incorporated planning parameters that allow optimization of the dose to the thyroid gland, esophagus, and lenses. Treatment setup and tabletop modification have been evaluated to enhance dosimetry and reliability of delivery for p-CSI [23]. Reproducibility of patient setup should be maximized to minimize dosimetric uncertainties. At this time at our institution, supine p-CSI is standard of care with daily kV-based image-guided radiation therapy.

In general, CSI requires careful evaluation of patient setup at simulation and daily treatments. Many institutions are using a supine setup that facilitates the use of sedation and patient comfort. In general, to ensure accurate treatment delivery, all supine CSI techniques require image-guided setup processes, which may require additional time, expertise, and equipment. In addition, p-CSI daily treatments often take longer than x-CSI because of the need for additional treatment isocenters for the spine owing to the field size limitation. Because many patients require sedation for daily treatments, the p-CSI delivery can take up to 45 to 60 minutes; the patient's medical condition and overall comfort requires significant attention.

A modified approach using spot-scanning proton therapy has been described by Timmermann et al [24]. Spot scanning p-CSI continues to be an area of active research. Pencil beam radiation therapy planning systems and equipment for p-CSI are being evaluated and used at a limited number of institutions.

Clinical Outcomes

Yuh et al [25] first described the outcomes of three 3-year-old girls who were treated with p-CSI between 2001 and 2003 at Loma Linda University Cancer Center. In this study, acute toxicities including odynophagia, hoarseness, dysphagia, leukopenia, nausea, and vomiting were eliminated. Grade 2 dermatitis was noted. Of interest, in these young patients, the plan did not encompass the whole vertebrae in an interest to spare the bone marrow. The authors report no vertebral growth asymmetry at the time of the report, but they caution that only a short follow-up was available at that time.

Acute toxicities during p-CSI have been reported by Suneja et al [26]. In this report, 12 of the 48 patients who were evaluated received p-CSI. These patients had a higher frequency of grade 2 and 3 anorexia. They also had a higher frequency of nausea, but not of vomiting, alopecia, or dermatitis in comparison with the patients receiving non-CSI PRT to the brain [26]. In our experience, 40% of our patients experience nausea requiring antiemetic for nausea prophylaxis. Most patients experience some degree of alopecia and dry skin depending on the final dose. Bone marrow suppression and recovery is being actively evaluated at our institution. Owusu-Agyemang [27] reviewed the anesthesia experience at our institution of 340 patients treated between 2006 and 2013. One hundred thirty (40%) patients were treated with p-CSI and anesthesia for all or part of the course of treatment. The treatments were tolerated well with a very low incidence of unexpected events.

Clinical efficacy has been reported by Ray et al [28] on 22 patients with leptomeningeal spinal metastasis who were treated with p-CSI. The authors concluded that, of these patients who were treated with definitive intent, 68% had a durable response at 1 year. Treatment toxicities included grade 1 erythema during treatment. Bian et al [29] reported favorable outcomes with good tumor control in 5 of 6 patients at 24 months post p-CSI for disseminated pilocytic astrocytoma. Jimenez et al [30] reported excellent tolerance of p-CSI in 11 young patients (median age, 41 months; range, 28 to 62 months), 9 with medulloblastoma and 2 with supratentorial primitive neuroectodermal tumors, after

maximal surgical debulking and pre-RT chemotherapy. At a median follow-up of 39 months post RT, none of the 11 patients who received p-CSI had experienced disease failure.

Jones et al [31] raised concerns regarding the possibility of differential RBE between tumor cells and normal tissue. In current practice, an RBE of 1.1 is used for planning purposes, but the authors suggest that it may actually vary between 0.8 and 1.2 depending on the type of tissue that is being irradiated. Additional concerns regarding a varying RBE within the Bragg peak have also been raised [32]. Failure patterns in 109 patients with medulloblastoma treated with PRT were reported by Sethi et al [33]. There has been no relationship noted between RT technique, proton end of range, linear energy transfer, or RBE in the 16 patients who exhibited a relapse during the median follow-up of 38.8 months. Further study is required to determine whether differential RBE or linear energy transfer planning approaches should be considered [32].

Additional reports have being describing the various aspects of p-CSI. Moeller et al [34] reported favorable 1-year auditory outcomes in patients who received p-CSI for medulloblastoma. The authors describe a reduced rate of high degree of hearing loss in patients who had been followed at least a year in comparison with previously X-ray-based CSI treatments. Jimenez [30] also described patient toxicity outcomes in a cohort of young patients with medulloblastoma and supratentorial primitive neuroectodermal tumors after chemotherapy followed by PRT. Six of the 9 patients who had measurable hearing loss at follow-up had a measurable loss before RT, and all 9 had received cisplatinum prior to RT. Three patients had grade 2 endocrinopathies requiring hormone replacement. Early neurocognitive evaluation has not revealed any significant decline in this cohort. Kuhlthau et al [35] reported health-related quality of life (HR-QoL) outcomes of 142 patients of whom 61 received p-CSI. Those patients who received p-CSI versus those who received partial brain PRT were noted to have worse core HR-QoL but similar tumor-related HR-QoL. In this study, both CSI and chemotherapy were associated with inferior HR-QoL scores. A comparison with patients treated with XRT was not available for this cohort.

Though CSI is less commonly used in adults, Barney et al [36] describe the acute toxicities of p-CSI in 50 patients aged 16 years and older. They note that the technique is feasible, that acute weight loss was 1.6% of the pre–p-CSI weight, and cytopenias were noticeable but appeared to be of limited duration. Overall survival and disease-free survivals were 84% and 68% at 5 years, respectively. When comparing adult patients with medulloblastoma treated with p-CSI and x-CSI, tumor control rates were similar with less weight loss and a shorter duration of bone marrow suppression in those receiving p-CSI [37].

Cost-Effectiveness

Efforts are now being made to assess the cost-effectiveness of p-CSI. In 2005, Lundkvist et al suggested that p-CSI for pediatric patients with medulloblastoma could be cost-effective and cost-saving in carefully selected patients with IQ loss and growth hormone replacement contributing to the greatest cost savings. Other contributing factors to cost-effectiveness included hearing loss, osteoporosis, cardiac disease, and SMNs [38]. Mailhot Vega et al [39] reported that p-CSI was associated with higher quality-adjusted life years and lower costs in comparison with x-CSI with a $32 579 difference in total lifetime cost. Hirano et al [40] reported that there was a 99% probability that p-CSI would be cost-effective at a societal willingness-to-pay value with respect to hearing loss and cochlear dose.

Ethics

Recent editorials have raised concerns regarding the ethical considerations of the increased expense and possible lack of access for children to proton therapy centers. Wolden [41] argues that at this time long-term outcomes are lacking to uniformly support PRT for all patients requiring CSI despite the theoretical advantages and early results. Johnstone et al [42] argue that the PRT centers are obliged to treat all curative patients who are referred to them because of the theoretical advantages and existing clinical data. They also state that parents should have a free and informed choice on their child's behalf.

Conclusions

Craniospinal irradiation is an important RT technique that contributes significantly to long-term survival in common pediatric central nervous system tumors; however, it is associated with a great number of acute and late toxicities. Efforts have been made to decrease or eliminate this large field irradiation, but continued modifications in CSI approaches, including the use of p-CSI, are warranted to further reduce the associated morbidities.

Proton-based CSI has been studied and increasingly used over the past 15 years. From the preliminary theoretical considerations, multiple dosimetric evaluations, predictive model applications, and clinical outcomes, there is mounting evidence that p-CSI provides equal tumor control and will be associated with fewer RT-related toxicities. Proton CSI is time consuming and technically challenging, and the utmost attention should be paid to every aspect of the treatment. Further refinements including the use of pencil beam PRT may allow further reduction in normal tissue doses and neutron contamination. Additional thought to RBE- or linear energy transfer-weighted planning is also warranted to refine the treatment planning and improve the therapeutic ratio.

ADDITIONAL INFORMATION AND DECLARATIONS

Conflict of Interest Disclosure: The author has no conflicts of interest to disclose.

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