Dosimetric Study of Craniospinal Irradiation in Children: Intensity Modulated Radiation Therapy vs. Volumetric Modulated Arc Therapy

การศึกษาเปรียบเทียบปริมาณรังสีของการฉายรังสีบริเวณสมองและไขสันหลังในเด็ก ระหว่างการฉายรังสีปรับความเข้มและการฉายรังสีปรับความเข้มเชิงปริมาตร

Warissara Rongthong[1], Siwadol Pleanarom[1], Nan Suntornpong[1], Teeradon Treechairusame[1], Kullathorn Thephamongkhol[1]

[1]Division of Radiation Oncology, Department of Radiology, Faculty of Medicine Siriraj Hospital, Mahidol University

วริศรา รงค์ทอง[1], ศิวดล เปลี่ยนอารมย์[1], นันทน์ สุนทรพงศ์[1], ธีรดนย์ ตรีชัยรัศมี[1], กุลธร เทพมงคล[1]

[1]สาขาวิชารังสีรักษา ภาควิชารังสีวิทยา คณะแพทยศาสตร์ศิริราชพยาบาล มหาวิทยาลัยมหิดล

Corresponding author

Warissara Rongthong

Division of Radiation Oncology, Faculty of Medicine Siriraj Hospital

2 Wanglang Road, Bangkoknoi, Bangkok 10700, Thailand

Email: warissara.ron@mahidol.ac.th

ผู้นิพนธ์ประสานงาน

วริศรา รงค์ทอง

สาขาวิชารังสีรักษา ภาควิชารังสีวิทยา คณะแพทยศาสตร์ศิริราชพยาบาล

2 ถนน วังหลัง เขตบางกอกน้อย กรุงเทพฯ 10700

อีเมล: warissara.ron@mahidol.ac.th

Submitted: May 14, 2020

Revised: June 30, 2020

Accepted: July 7, 2020

Abstract

Background: Long-term craniospinal irradiation (CSI)-related toxicities are the major concerned in pediatric medulloblastoma. To reduce the risk to normal structures, the more conformal radiation therapy is preferred.

Objective: To evaluate and compare the dosimetric parameters of CSI between intensity modulated radiation therapy (IMRT) and volumetric modulated radiation therapy (VMAT) in terms of target coverage and normal tissue sparing in pediatric patients with standard risk medulloblastoma.

Materials and Methods: Ten children with medulloblastoma previously treated with three-dimensional conformal radiation therapy (3D-CRT) CSI were included in this study. All the planning computed tomography (CT) scans were performed in the supine position with a customized thermoplastic mask on a head rest set. CSI was performed with IMRT and VMAT for each child. Both plans were compared.

Results: IMRT achieved better target coverage. However, more than 95% of the volume of the planning target volume (PTV) was covered by 95% of the prescribed dose for both plans. VMAT achieved better dose homogeneity and conformity. Doses to the OARs complied with the institutional protocol except for the doses to the eyes, lens, and thyroid for both IMRT and VMAT. Due to the lack of an institutional protocol for plan optimization at the time of study, the doses to these organs did not get enough concern. No difference in mean dose to non-target tissues was found between IMRT and VMAT ($p = 0.101$). The mean monitor units (MU) value of VMAT was significantly lower than that of IMRT ($p < 0.05$).

Conclusions: With the same protocol compliance of target coverage and dose to OARs, VMAT is preferred due to its higher conformity, better dose homogeneity, and use of lower MU.

Keywords: Craniospinal Irradiation, Pediatrics, Radiation Therapy, Volumetric Modulated Arc Therapy, Intensity Modulated Radiation Therapy

บทคัดย่อ

หลักการและเหตุผล: นอกจากการเพิ่มผลตอบสนองต่อการรักษาแล้ว สิ่งที่ควรให้ความสำคัญอย่างยิ่งในการรักษาโรคเมดัลโลบลาสโตมาในเด็ก คือ การลดผลข้างเคียงระยะยาวจากการฉายรังสีที่สมองและไขสันหลัง (CSI)

วัตถุประสงค์: เพื่อประเมินและเปรียบเทียบค่าตัวแปรเชิงรังสีคณิตของ CSI ระหว่างการฉายรังสีปรับความเข้ม (IMRT) และการฉายรังสีปรับความเข้มเชิงปริมาตร (VMAT) ทั้งในแง่ของการครอบคลุมรอยโรคและการหลีกเลี่ยงอวัยวะปรกติข้างเคียงในผู้ป่วยเด็กที่ได้รับการวินิจฉัยเป็นเมดัลโลบาสโตมากลุ่มความเสี่ยงมาตรฐาน

วัสดุและวิธีการ: การศึกษานี้ใช้ข้อมูลผู้ป่วยเด็ก 10 รายที่ได้รับการวินิจฉัยว่าเป็นเมดัลโลบลาสโตมาและได้รับการรักษาด้วย CSI โดยนำภาพจำลองการรักษาด้วยเอกซเรย์คอมพิวเตอร์ของผู้ป่วยทุกรายอยู่ในท่านอนหงาย วางศีรษะบนชุดอุปกรณ์ยึดศีรษะร่วมกับใส่หน้ากากเทอร์โมพลาสติก ผู้ป่วยทุกรายจะได้รับการวางแผนการรักษา CSI ใหม่ ทั้ง IMRT และ VMAT แผนการรักษาทั้ง 2 แบบจะถูกนำมาเปรียบเทียบกัน

ผลการศึกษา: IMRT สามารถครอบคลุมรอยโรคได้ดีกว่า อย่างไรก็ตาม >95% ของปริมาตร planning target volume (PTV) ได้รับปริมาณรังสี >95% ของปริมาณรังสีที่กำหนดในทั้ง 2 แผนการรักษา และ VMAT มีค่า homogeneity index และ conformity index ที่ดีกว่า แผนการรักษาทั้ง 2 แบบมีปริมาณรังสีต่ออวัยวะปรกติข้างเคียงสอดคล้องกับเกณฑ์ของสถาบันยกเว้นปริมาณรังสีที่ลูกตา เลนส์ และต่อมไทรอยด์ เนื่องจากขณะที่ทำการศึกษาทางสถาบันยังไม่มีเกณฑ์สำหรับ plan optimization อวัยวะเหล่านี้จึงไม่ได้รับความใส่ใจเท่าที่ควร ปริมาณรังสีเฉลี่ย (mean dose) ต่อ non-target tissues ไม่แตกต่างกันระหว่างแผนการรักษาทั้ง 2 แบบ ($p = 0.101$) ค่าเฉลี่ยของ monitor units (MU) ของ VMAT ต่ำกว่า IMRT อย่างมีนัยสำคัญทางสถิติ ($p < 0.05$)

ข้อสรุป: แผนการรักษาทั้ง 2 แบบมีความสอดคล้องกับเกณฑ์ของสถาบันเหมือนกันทั้งในแง่ของการครอบคลุมรอยโรคและการหลีกเลี่ยงอวัยวะปรกติข้างเคียง แนะนำให้ใช้ VMAT สำหรับฉายรังสีที่สมองและไขสันหลังเนื่องจากรังสีครอบคลุมและกระชับกับรอยโรคมากกว่า มีความสม่ำเสมอของรังสีดีกว่า และใช้ MU ต่ำกว่า

คำสำคัญ: การฉายรังสีที่สมองและไขสันหลัง, มะเร็งในเด็ก, รังสีรักษา, การฉายรังสีปรับความเข้มเชิงปริมาตร, การฉายรังสีปรับความเข้ม

J Thai Assoc Radiat Oncol 2020; 26(2): R68-R76

Introduction

Medulloblastoma is an embryonal tumor that has a high propensity of spinal drop metastasis. The standard treatment of this tumor is combined modalities of surgery, radiation therapy, and chemotherapy. After surgery, craniospinal irradiation (CSI) is given to every child patient older than 3 years old.[1] The role of CSI can be either treatment or for prophylaxis neuraxis dissemination. In standard risk medulloblastoma, the aim of CSI is to prevent spinal drop metastasis. However, the side effects of CSI in children are a major concern, especially the long-term toxicities.[2] The common long-term CSI-related toxicities in children include neurocognitive impairment, hearing loss, a short stature, endocrine abnormalities, cerebrovascular disease, pulmonary dysfunction, and secondary cancer. These complications affect childhood cancer survivors' quality of life for the rest of their lives.[1, 3-5]

To reduce these CSI-related toxicities, proton therapy, a highly precise and more conformal radiation therapy with limited dose

to normal structures, is usually adopted to treat pediatric patients in high-income countries.[2, 6] In contrast, three-dimensional conformal radiation therapy (3D-CRT) CSI has been adopted to treat pediatric patients in middle-income countries, such as Thailand, for decades now. Nowadays intensity modulated radiation therapy (IMRT), volumetric modulated radiation therapy (VMAT), and TomoTherapy® are widely available in Thailand, and these techniques have also been adopted for CSI in pediatric patients. Theoretically, VMAT could reduce the risk to normal structures from using lower monitor units (MU) and a shorter treatment time compared to IMRT. In dosimetric studies, VMAT showed better target coverage and more homogeneity, while IMRT reduced the volume received a dose of 2 Gy (V2) and the volume received a dose of 5 Gy (V5) to the body.[7, 8] The organs at risk (OARs) were spared differently between techniques. Neither IMRT nor VMAT could meet the criteria of dose constraint for the eyes, lens, and cochleae.[7] Currently, there is no clinical data supporting that VMAT is better than IMRT or vice versa. In our institute, VMAT is routinely used for CSI in pediatric patients due to its convenience compared to IMRT. We previously explored and published the benefits of IMRT over 3D-CRT CSI in terms of providing a homogeneous dose in target coverage and a minimized radiation dose to the OARs.[9]

The aim of this study was to evaluate and compare the dosimetric parameters of CSI between IMRT and VMAT in terms of target coverage and normal tissue sparing in pediatric patients with standard risk medulloblastoma.

Materials and Methods

Patients

After the approval by the Institution's Ethics Committee (Si 661/2559), ten children with medulloblastoma previously treated with 3D-CRT CSI at Siriraj Hospital, Bangkok, Thailand, between 2006 and 2016 were included in this study. Following the CSI protocol at Siriraj Hospital, all the planning computed tomography (CT) simulations were performed in the supine position with a customized thermoplastic mask on the head rest set and CT axial images were obtained from the vertex to coccyx with a 3 mm contiguous slice thickness.

Delineation of the target and OARs

Both the target and OARs were delineated as follows: the clinical target volume (CTV) included the entire brain, meninges, and entire spinal canal down to the end of the thecal sac covering the cerebrospinal extension to the spinal ganglia. No CTV boost was created. The planning target volume (PTV) was generated with a 5 mm margin from the CTV in all directions. The OARs were contoured, including the eyes, lens, optic nerves, optic chiasm, cochleae, thyroid, lungs, heart, liver, and kidneys. Non-target tissue was created by subtracting the PTV and OARs from the whole-body volume.

Treatment planning

Two separate treatment plans (IMRT and

VMAT) were performed for each child by the second author and reviewed by the first author. The CSI dose was 23.4 Gy in 13 fractions (1.8 Gy per fraction), which represents the common dose for standard risk medulloblastoma. All the plans were optimized and calculated by Eclipse version 13.6. The dose calculation was performed with Anisotropic Analytical Algorithm (AAA). The CSI plan used 2–3 isocenters depending on the patient length. IMRT used 5 fixed coplanar beams (angle: 0, 45, 130, 230, and 315 degrees) for the brain and 3 fixed coplanar beams (angle: 130, 180, and 230 degrees) for the spine. VMAT used 2 coplanar full rotations (360 degrees) for the brain and one complete arc for the spine. Both IMRT and VMAT used 6 MV photons at a dose rate of 600 MU/min. The priority and optimization were individualized for each plan without the standard protocol. In the initial step, the PTV dose coverage was the first priority in the optimization process. More than 95% of the volume of the PTV was covered by 95% of the prescribed dose and the maximum dose did not exceed 107%.

Plan evaluation

Both VMAT and IMRT were compared in terms of target coverage, homogeneity, and OARs sparing. PTV coverage was assessed as the volume of the PTV receiving at least 95% (PTV95%) and 107% of prescribed dose (PTV107%). The dose homogeneity was determined by the homogeneity index (HI) and conformal index (CI) as follows.[10]

HI = Maximum isodose in the target/reference isodose.

CI = Volume of the reference isodose/target volume.

The OARs were evaluated by the max dose (Dmax) or mean dose (Dmean). Dmax was used for evaluating the dose to the lens, optic nerves, and optic chiasm. Dmean was used for evaluating the dose to the eyes, cochleae, thyroid, lungs, heart, liver, kidneys, and non-target tissue.

Statistical analysis

The paired t test was used to compare the means. A p-value of < 0.05 was considered statistically significant. SPSS (version 21, SPSS Inc., Chicago, IL, USA) was used for the statistical analysis.

Results

Ten patients' CT data sets were available for dose calculation and evaluation. All the dosimetric data are shown in **Table 1**. IMRT had a larger volume of target coverage by 95% of the prescribed dose without significant difference in the hot spot volume (PTV107%). VMAT achieved better CI and HI, close to 1. The eyes and thyroid received lower doses with VMAT compared to IMRT. The lungs, livers, and kidneys received lower doses with IMRT compared to VMAT. The other OARs, including the lens, optic nerves, optic chiasm, cochleae, and heart, received negligible differences in doses between both plans. The mean dose to non-target tissue also showed no difference between IMRT and VMAT. The dose limit for each

OAR was created as shown in **Table 1**, based on the published pediatric normal tissue effects in the clinical (PENTEC) and institutional protocol.[11] Doses to the OARs were complied with the protocol, except for the doses to the eyes, lens, and thyroid for both IMRT and VMAT. The mean MU of VMAT was significantly lower than for IMRT (1756.99±293.99 in IMRT vs. 723.98±170.23 in VMAT, $p < 0.05$).

Table 1 Dosimetric comparison between IMRT and VMAT

Parameters	IMRT (mean±SD, %*)	VMAT (mean±SD, %*)	*P*	Dose limit (Gy)	Endpoint
PTV95% (cc)	1982.96±189.95	1953.24±191.28	0.002	NA	
PTV107% (cc)	93.27±176.98	18.39±19.47	0.197	NA	
CI	0.85±0.06	0.88±0.04	0.086	NA	
HI	1.12±0.02	1.09±0.01	0.009	NA	
Right eye (Dmean, Gy)	19.70±1.68, 0	17.57±2.80, 0	0.014	<10†	Blindness, double vision, dry eyes
Left eye (Dmean, Gy)	19.86±2.06, 0	17.66±2.92, 0	0.018	<10†	Blindness, double vision, dry eyes
Right lens (Dmax, Gy)	18.51±2.29, 0	16.33±4.03, 0	0.132	<7†	Cataract
Left lens (Dmax, Gy)	18.46±2.85, 0	16.08±3.56, 0	0.117	<7†	Cataract
Right optic nerve (Dmax, Gy)	24.65±0.66, 100	24.35±0.24, 100	0.084	<54†	Blindness
Left optic nerve (Dmax, Gy)	24.54±0.75, 100	24.47±0.29, 100	0.799	<54†	Blindness
Optic chiasm (Dmax, Gy)	24.68±0.39, 100	24.44±0.33, 100	0.127	<54†	Blindness
Right cochlea (Dmean, Gy)	24.33±0.75, 100	23.79±0.73, 100	0.070	<35	Hearing loss
Left cochlea (Dmean, Gy)	24.27±0.66, 100	23.94±0.36, 100	0.099	<35	Hearing loss
Thyroid (Dmean, Gy)	15.84±2.58, 0	13.33±1.95, 0	0.001	<10	Hypothyroidism

Table 1 Continue

Parameters	IMRT (mean±SD, %*)	VMAT (mean±SD, %*)	*P*	Dose limit (Gy)	Endpoint
Right lung (Dmean, Gy)	5.75±1.00, 100	6.50±0.74, 100	0.045	<10	Radiation pneumonitis
Left lung (Dmean, Gy)	5.36±1.03, 100	6.22±0.64, 100	0.033	<10	Radiation pneumonitis
Heart (Dmean, Gy)	6.34±1.23, 100	6.23±1.35, 100	0.808	<10	Heart failure
Liver (Dmean, Gy)	4.70±0.69, 100	5.52±0.68, 100	0.005	<10	Veno-occlusive disease
Right kidney (Dmean, Gy)	5.41±1.25, 100	7.39±1.15, 100	0.009	< 17.8	Kidney injury
Left kidney (Dmean, Gy)	5.29±1.00, 100	6.86±1.37, 100	0.016	< 17.8	Kidney injury
Non-target tissue (Dmean, Gy)	5.38±0.60, 100	5.53±0.51, 100	0.101	NA	

NOTE. *p* values calculated by paired t-test.

* Percent of patient received dose per protocol for OARs dose limitation.

† Dose limitations were based on pediatric normal tissue effects in the clinical (PENTEC) except for the remark based on the institutional protocol.

Abbreviations: CI = conformity index; Dmax = maximum dose; Dmean = mean dose; HI = homogeneity index; IMRT = intensity-modulated radiotherapy; PTV = planning target volume; PTVx% = volume of PTV receiving ≥ x% of prescribed dose; VMAT = volumetric-modulated arc therapy; NA = not applicable

Discussion

In our study, IMRT achieved better target coverage. The non-significant larger volume of PTV107% in IMRT cannot be ignored as this larger high dose volume may transfer to a better target coverage. However, both plans were evaluated as achieving more than 95% of the volume of PTV covered by 95% of the prescribed dose. Interestingly, VMAT had better CI and HI values, and gave a lower dose to the OARs in the head and neck region, while IMRT could better limit the dose to those OARs in the body below the neck level.

Al-Wassia et al. compared IMRT and VMAT for CSI in pediatric medulloblastoma. They performed a dosimetric study in ten children and found that IMRT had superior target coverage, while VMAT had superior HI values,

which is the same result as ours. However, no difference of CI values was detected and the doses to the normal structures were not consistent. They found that IMRT had better dose reduction to the optic chiasm, liver, and lungs, whereas VMAT had better dose reduction to the eyes, lens, optic nerves, heart, cochleae, thyroid, and kidneys.[7] This may result from differences in the optimization criteria between their plans and ours.

Seravalli E et al. compared five different techniques for CSI, including 3D-CRT, IMRT, VMAT, TomoTherapy®, and proton pencil beam scanning (PRT), as utilized in 15 institutes across Europe for one example pediatric patient. They found that the modern photon techniques (IMRT, VMAT, and TomoTherapy®) decreased the mean dose to the thyroid, parotid glands, heart, esophagus, and pancreas compared to 3D-CRT. A further reduction of the mean dose to the OARs was found when comparing PRT to modern photon techniques. Focusing on modern photon techniques, they observed a wide range in the mean dose to the OARs among the institutes with each technique. They suspected that differences in the optimization criteria due to the lack of international guidelines for dosage constraints for OARs attributed to the difference in the OARs sparing, thus reflecting the inter-center variation in daily practice.[12]

From our study, both IMRT and VMAT were acceptable for CSI in pediatric patients with standard risk medulloblastoma. All PTV coverage was more than 95% of the volume by 95% of the prescribed dose. The dose to the OARs did not exceed the institutional dose limit, except for the dose to the eyes, lens, and thyroid for both techniques. Some normal structures were better spared with IMRT, whereas some were better spared with VMAT, as shown in Table 1. These may result from the plan optimization as there was no standardization between each plan and each patient. Institutional dose limits for OARs were created after the study was done. The dose to the OARs may be reduced by developing an institutional protocol for plan optimization to meet the institutional dose-constraints for OARs. Considering the risk of late complications and patient convenience, VMAT is preferred due to the indifference in the mean dose to the non-target tissue and as it uses lower MU. In addition, VMAT also had better dose conformity and dose homogeneity.

Conclusion

With the same protocol compliance of target coverage and dose to OARs, VMAT was preferred for CSI due to its higher conformity, better dose homogeneity, and use of lower MU. It is recommended that an institutional plan as an optimization protocol for the use of CSI should be developed and this needs to be consistent with the institutional guideline of dose-constraints for OARs.

Conflict of Interest

None

References

1. McGovern SL, Grosshans D, Mahajan A. Embryonal brain tumors. Cancer J. 2014;20:397-402.
2. Chhabra A, Mahajan A. Treatment of common pediatric CNS malignancies with proton therapy. Chin Clin Oncol. 2016;5:49.
3. Huang TT, Chen Y, Dietz AC, Yasui Y, Donaldson SS, Stokes DC, et al. Pulmo-nary outcomes in survivors of childhood central nervous system malignancies: a report from the Childhood Cancer Survivor Study. Pediatr Blood Cancer. 2014;61:319-25.
4. Christopherson KM, Rotondo RL, Bradley JA, Pincus DW, Wynn TT, Fort JA, et al. Late toxicity following craniospinal radiation for early-stage medulloblastoma. Acta Oncol. 2014;53:471-80.
5. Ribi K, Relly C, Landolt MA, Alber FD, Boltshauser E, Grotzer MA. Outcome of medulloblastoma in children: long-term complications and quality of life. Neuropediatrics. 2005;36:357-65.
6. Mahajan A. Proton Craniospinal Radiation Therapy: Rationale and Clinical Evidence. Int J Part Ther. 2014;1:399-407.
7. Al-Wassia RK, Ghassal NM, Naga A, Awad NA, Bahadur YA, Constantinescu C. Optimization of Craniospinal Irradiation for Pediatric Medulloblastoma Using VMAT and IMRT. J Pediatr Hematol Oncol. 2015;37:e405-11.
8. Lee YK, Brooks CJ, Bedford JL, Warrington AP, Saran FH. Development and evaluation of multiple isocentric volumetric modulated arc therapy technique for craniospinal axis radiotherapy planning. Int J Radiat Oncol Biol Phys. 2012;82: 1006-12.
9. Suntornpong N, Tuntipumiamorn L, Iampongpaiboon P, Liammookda P. Pilot Study: A Comparison of Dose Distribution between 3-Dimensional Conformal and Intensity Modulated Radiation Therapy for Craniospinal Irradiation in Medulloblastoma. ASEAN-JR. 2012;18:137-44.
10. Feuvret L, Noel G, Mazeron JJ, Bey P. Conformity index: a review. Int J Radiat Oncol Biol Phys. 2006;64:333-42.
11. Constine LS, Ronckers CM, Hua CH, Olch A, Kremer LCM, Jackson A, et al. Pediatric Normal Tissue Effects in the Clinic (PENTEC): An International Collaboration to Analyse Normal Tissue Radiation Dose-Volume Response Relationships for Paediatric Cancer Patients. Clin Oncol (R Coll Radiol). 2019;31: 199-207.
12. Seravalli E, Bosman M, Lassen-Ramshad Y, Vestergaard A, Oldenburger F, Visser J, et al. Dosimetric comparison of five different techniques for craniospinal irradiation across 15 European centers: analysis on behalf of the SIOP-E-BTG (radiotherapy working group). Acta Oncol. 2018;57:1240-9.