

A Dosimetric Comparison Study of 3-Dimensional Conformal
Radiotherapy (3D-CRT), Intensity-Modulated Radiotherapy (IMRT), and
Volumetric-Modulated Arc Therapy (VMAT) in Complete-Resection
Pediatric Abdominal Neuroblastoma

การศึกษาเปรียบเทียบทางรังสีคณิตระหว่างวิธีการฉายรังสีสามมิติ,
การฉายรังสีปรับความเข้ม และการฉายรังสีปรับความเข้มเชิงปริมาตรในผู้ป่วยเด็ก
นิวโรบลาสโตมาในช่องท้องภายหลังได้รับการผ่าตัดได้หมด

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ABSTRACT

Background: Advanced radiotherapy techniques—intensity-modulated radiotherapy (IMRT) and volumetric-modulated arc therapy (VMAT)—deliver low peripheral radiation doses but full doses to desired target volumes and shortening treatment. However, potential late effects related to integral doses and secondary malignancy risks are concerned.

Objective: To compare the dosimetries of 3-Dimensional Conformal Radiotherapy (3D-CRT), IMRT and VMAT in terms of tumor coverage and organ-at-risk (OAR) sparing in neuroblastoma.

Materials and Methods: Patients aged 1 month–15 years, had completely resected high-risk abdominal neuroblastoma, and received radiotherapy. Treatment planning was reperformed for 3D-CRT, IMRT, and VMAT. Patients were divided into 2 subgroups; radical nephrectomy and non-radical nephrectomy groups then dosimetric data were analyzed.

Results: Among 3D-CRT, IMRT and VMAT, $V_{95\%}$ constraint, mean homogeneity indexes and integral doses were not significantly different. Conformity indexes were statistically lower for IMRT and VMAT than 3D-CRT. In the non-radical-nephrectomy group, IMRT and VMAT were superior to 3D-CRT in terms of V18Gy to ipsilateral kidneys and contralateral kidneys. In the radical-nephrectomy group, V18Gy of contralateral kidneys was within dose constraint for 3/4 patients with 3D-CRT but all patients with IMRT and VMAT. Mean V15Gy of liver volume were significantly different among 3 techniques, but V8Gy did not show significant difference. The means for $D_{80\%}$ of the spine were not significantly different. Overall passing rates were 12.55% (3D-CRT), 62.5% (IMRT) and 87.5% (VMAT).

Conclusions: IMRT and VMAT had superior OAR sparing (especially the kidneys), without compromising target coverage, than 3D-CRT in all cases.

Keywords: pediatric neuroblastoma, dosimetric study, 3D-CRT, IMRT, VMAT

บทคัดย่อ

หลักการและเหตุผล: การฉายรังสีปรับความเข้มและปรับความเข้มเชิงปริมาตรสามารถลดปริมาณรังสีบริเวณข้างเคียง และให้รังสีในบริเวณรอยโรคได้ตามต้องการ ทั้งสามารถลดเวลาการฉายรังสี แต่มีโอกาสเกิดผลข้างเคียงระยะยาวที่สัมพันธ์กับ integral dose และการเกิดมะเร็งทุติยภูมิ

วัตถุประสงค์: เพื่อเปรียบเทียบค่าทางรังสีคณิตของการฉายรังสีระหว่างการฉายรังสีสามมิติ, การฉายรังสีปรับความเข้มและการฉายรังสีปรับความเข้มเชิงปริมาตร ในแง่ของการครอบคลุมรอยโรคและหลีกเลี่ยงอวัยวะใกล้เคียงในผู้ป่วยเด็กนิวโรบลาสโตมา

วัตถุประสงค์และวิธีการ: ผู้ป่วยเด็กอายุ 1 เดือนถึง 15 ปีที่เป็นนิวโรบลาสโตมาบริเวณช่องท้อง ได้รับการผ่าตัดหมดและได้รับการฉายรังสี โดยผู้ป่วยจะได้รับการวางแผนการรักษาใหม่ด้วยเทคนิคการฉายรังสี 3 วิธี และแบ่งผู้ป่วยออกเป็น 2 กลุ่มคือกลุ่มที่ได้รับการผ่าตัดไตและกลุ่มที่ไม่ได้รับการผ่าตัดไต แล้วนำแผนการรักษาทั้ง 3 แบบมาเปรียบเทียบกัน

ผลการศึกษา: การฉายรังสีทั้ง 3 เทคนิค มีค่า $V_{95\%}$ ของรอยโรค ดัชนีความสม่ำเสมอของปริมาตรและ integral dose ไม่ต่างกัน แต่การฉายรังสีปรับความเข้มทั้ง 2 แบบมีค่าดัชนีความเข้ารูปของปริมาตรดีกว่าการฉายรังสีสามมิติ ในกลุ่มที่ไม่ได้รับการผ่าตัดไตการฉายรังสีปรับความเข้มทั้ง 2 แบบลด $V18Gy$ ของไตทั้ง 2 ข้างได้ดีกว่าในกลุ่มที่ได้รับการผ่าตัดไตการใช้การฉายรังสีสามมิติมีค่า $V18Gy$ ของไตด้านตรงข้ามผ่านเกณฑ์ได้ 3/4 ของผู้ป่วยที่เข้าร่วมการศึกษา ในขณะที่การฉายรังสีอีก 2 แบบผ่านเกณฑ์ได้ทั้งหมด ในแง่ของดัชนีการฉายรังสีปรับความเข้มทั้ง 2 แบบสามารถช่วยลด $V15Gy$ เฉลี่ยได้อย่างมีนัยสำคัญ ค่าเฉลี่ย $D_{80\%}$ ของกระดูกสันหลังไม่ต่างกัน เมื่อประเมินทุกข้อกำหนดพบว่าอัตราการผ่านเกณฑ์ของการฉายรังสีสามมิติ, การฉายรังสีปรับความเข้มและการฉายรังสีปรับความเข้มเชิงปริมาตรดังนี้ 12.55%, 62.5%, 87.5%

ข้อสรุป: การฉายรังสีปรับความเข้มทั้ง 2 แบบมีประโยชน์ต่อผู้ป่วยมากกว่าการฉายรังสีสามมิติในการหลีกเลี่ยงปริมาณรังสีบริเวณอวัยวะข้างเคียงโดยไม่กระทบต่อรอยโรคในทุกกรณี

คำสำคัญ: มะเร็งนิวโรบลาสโตมาในเด็ก, การศึกษาทางรังสีคณิต, การฉายรังสีสามมิติ, การฉายรังสีปรับความเข้ม, การฉายรังสีปรับความเข้มหมุนรอบตัวผู้ป่วย

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Introduction

Neuroblastoma is the most common solid tumor outside the brain in children. The prognosis of the disease is based on age, histopathology, molecular subtype, and the amplification of the MYCN gene. The International Neuroblastoma Risk Group staging system classifies patients into 3 risk groups^[1-2]: high, intermediate, and low. The high-risk group requires multimodality treatment: chemotherapy, surgery, radiotherapy (RT), stem cell transplantation, and immunotherapy. The traditional RT approach for pediatric neuroblastoma patients is delivery to the site of the primary

disease with an additional boost to the gross residual disease. Patients whose primary site has completely responded at the end of the induction therapy receive 21.6 Gy to the site of the primary locoregional disease, while the areas with gross residual disease is treated with an additional boost of 14.4Gy (making a total of 36Gy), in accordance with the COG 3891 trial. However, serious, long-term, side effects—such as abnormal body growth and bone development, as well as nephrotoxicity—could develop in long-term survivor.^[3]

Advanced RT techniques—intensity-modulated radiotherapy (IMRT) and volumetric-modulated

arc therapy (VMAT)—deliver much lower peripheral doses of radiation than the conventional, three-dimensional conformal radiotherapy (3D-CRT) while still delivering full doses to the desired target volume and shortened treatment times. However, pediatric practitioners should consider the higher integral doses and risks of secondary malignancy associated with the advanced techniques^[4-10].

The objective of this study was to compare the dosimetries of 3D-CRT, IMRT, and VMAT in neuroblastoma. The outcomes would facilitate the selection of RT techniques which are capable of providing high radiation doses to the area of a tumor while decreasing the doses to organs-at-risk (OARs), thereby reducing the incidences of long-term complications and secondary malignancies.

Materials and Methods

This retrospective cohort study drew upon data retrieved from the Siriraj Hospital registry data base. We reviewed 8 pediatric abdominal

neuroblastoma patients who had received postoperative RT at the Division of Radiation Oncology, Department of Radiology, Siriraj Hospital, January 2011–March 2018. The study was approved by the Ethics Committee of the Siriraj Institutional Review Board.

Participants

The study enrolled pediatric patients with abdominal neuroblastoma who had received a combination treatment (induction chemotherapy followed by a complete-resection and RT), in accordance with the Thai Pediatric Oncology Group's NB-13 protocol for neuroblastoma. The specific inclusion criteria for the patients were as follows: confirmed histologically or cytologically as having pediatric, high-risk, locoregional abdominal neuroblastoma; aged from 1 month to 15 years; and received pretreatment and/or posttreatment computed tomography (CT) imaging of the whole abdomen. High risk criteria for pediatric neuroblastoma is showed in a **Table1**.

Table 1 The criteria to define high risk patient from ThaiPOG guideline

INRG	Age	Tumor histology	Tumor differentiation	MYCN	Shimada histology
L1	Any	Any, except GN maturing or GNB intermixed	Any	Amp	Any
L2	Any	Any	Any	Amp	Any
M	<18	Any	Any	Amp	Any
M	≥18	Any	Any	Any	Any
MS	<18	Any	Any	Amp	Any

Abbreviation: INRG = International Neuroblastoma Risk Group; GN = Ganglioneuroma; GNB= Ganglioneuroblastoma; Amp= MYCN amplified

Treatment planning

All patients underwent CT simulations using an Eclipse network/treatment planning system and a 16-slice Brilliance Big Bore CT simulator (Philips Healthcare, Andover, MA, USA). The CT-simulation imaging series that were reviewed for each patient in accordance with the ANBL 0532 protocol^[6] were the target volumes and OAR delineations, which were contoured for the different planning techniques used by 3D-CRT, IMRT and VMAT as shown in **Figure 1**. The tumor bed was defined as the visible volume of a tumor on a CT and/or a magnetic resonance imaging (MRI) scan both prior to the attempted surgical resection and after the induction of chemotherapy. An additional 1.5 cm margin was added to generate the clinical target volume;

the margin was adjusted for anatomic barriers. The planning target volume (PTV) was expanded from the clinical target volume by a margin of about 0.5 cm. Finally, the prescription dose for delivery to the target was 21.6 Gy. The OARs comprised both kidneys, the liver, and the spine. The treatment planning was performed using a 3D-radiotherapy planning system by (Eclipse, version 13.6 (Varian Medical Systems Inc., Palo Alto, CA, USA). The 3 planning techniques for 3D-CRT, IMRT, and VMAT were based on the use of 6 MV photon beams. Calculations were made for each patient to enable comparisons of 5 aspects: tumor coverage, OAR sparing, conformity index (CI), homogeneity index (HI), and integral dose

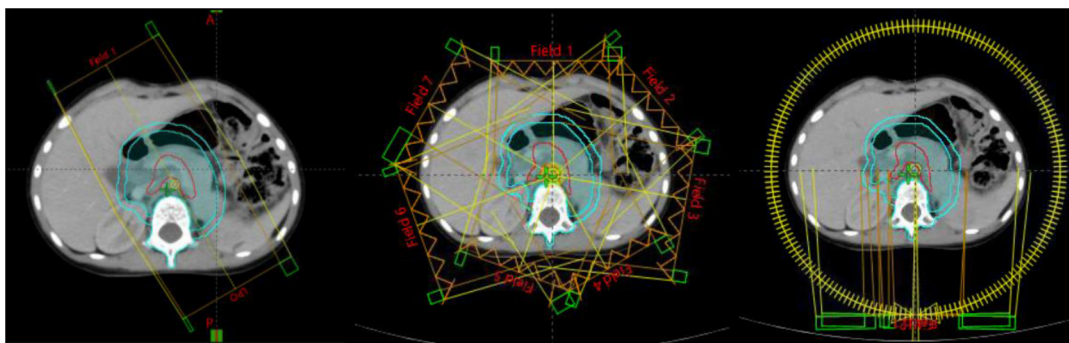


Figure 1 From left to right, the beam direction of 3-dimensional conformal radiotherapy (3D-CRT), intensity-modulated radiotherapy (IMRT), and volumetric-modulated arc therapy (VMAT).

In the case of 3D-CRT, the plan was created by using 2–4 angled photon fields with a multi-leaf collimator in order to preserve the OARs. For IMRT, the plan was developed by using the “sliding window” technique with seven coplanar beams (gantry angles 0°, 50°, 100°, 150°, 200°, 250°, and 300°). The plan was calculated

with a 0.25 x 0.25 cm beam resolution for all patients. As to VMAT, the plan was made by using one isocenter with two full rotations (gantry angles 181° to 179°, and 179° to 181°). The plan optimization used a 0.25 x 0.25 cm beam resolution for all patients.

For the dosimetric evaluations, comparisons were made of the tumor coverage, OAR sparing, CI, HI, and integral dose of each treatment plan. Tumor coverage was assessed by considering the maximal dose (D_{max}) as well as $V_{95\%}$ and $V_{107\%}$ (the proportion of the PTV which received 95% and 107% of the prescription dose, respectively).

$CI^{[8]}$ is an objective tool to evaluate the adaptation of the shape of a high-isodose envelop to the exact shape of the target volume. In this study, we used two CI formulas, Paddick conformity (PCI) and RTOG conformity (CI). VT, PI is the target volume within the volume of the prescription isodose line, VPI is the volume of the prescription isodose line, and TV is the target volume.

$$PCI = \frac{V_{T,PI}^2}{V_{PI} \times TV}$$

$$CI_{RTOG} = \frac{V_{PI}}{TV}$$

In general, a CI equal to 1 corresponds with the ideal conformation. CI values that are greater than 1 demonstrate that the irradiated area is appreciably larger than the target area; in other words, it signals over-treatment. On the other hand, CI values less than 1 indicate that only part of the target area is irradiated (that is, there is under-treatment). A Paddick CI is alternative CI which was built on the criticism of RTOG CI index due to the overlap of the volume receiving the prescription isodose. A maximal $CI_{Paddick}$ value equal to 1 corresponds

with ideal conformation. $CI_{Paddick}$ values are less than 1 demonstrate that only some parts of the target area is overlapping with target volume

The $HI^{[8]}$ provides an indication of the uniformity of the distribution of a dose in the target volume. The ideal value is zero; higher values signify progressively decreasing degrees of homogeneity. D5 and D95 are the minimum doses to 5% and 95% of the target volume, respectively, and D_p is the prescribed dose.

$$HI = \frac{(D_5 - D_{95})}{D_p} \times 100$$

Integral dose^[9-10] is a calculation of the total dose absorbed by a patient's body.

$$\text{Integral dose (Gy/L)} = \frac{\text{mean dose of (the total body - PTV)}}{\text{non-invaded body volume - volume of PTV}}$$

OAR sparing used 3 parameters: the mean dose (Dmean), Dmax, and dose constraint, in accordance with recommendations made by the Children's Oncology Group ANBL 1531 (NCT03126916) and the study by Beneyton et al.^[11] Optimisation priorities were defined before planning to achieve consistency between IMRT and VMAT. $V_{95\%} > 95\%$ of PTV was first priority in this study following by constraints for the OARs and parameters of PTV in **Table 2**

Statistical analysis

Statistical comparisons of the study plans were made using repeated measurement ANOVA. P-values less than 0.05 were considered to be statistically significant. The subgroup analyses were calculated using pairwise comparisons (Friedman test).

Table 2 Target volume constraints for PTV and OARs following priority in treatment planning

Volume	Constraint
PTV	V95% > 95% of PTV volume Dmax < 108% of prescribed dose
Ipsilateral kidney	V18Gy < 75% of volume of ipsilateral kidney V14Gy < 100% of volume of ipsilateral kidney
Contralateral kidney	V18Gy < 25% of volume of contralateral kidney
Liver	Mean dose < 15Gy V15Gy < 25% of volume of liver V8Gy < 50% of volume of liver
Vertebrae	80% of prescribed dose delivered to at least 80% of irradiated vertebral body D80% > 16.8 Gy
CI	CI = 1
HI	HI = 0

Abbreviation: PTV = planning target volume; Vx% = volume of PTV receiving ≥ x% of prescribed dose; Dmax = maximum dose; VxGy = percent of volume of organ receiving x Gy; Dx% = dose of organ receiving ≥ x% of total volume; CI = conformity index; HI = homogeneity index

Results

The patient characteristics are detailed in **Table 3**. At the time of starting RT, the mean age of the patients was 4.32 years. There were 5 males and 3 females. All were International Neuroblastoma Risk Group stage L2. The tumor beds were located in the midline of 4 of the patients but were lateralized in the other four. Four patients underwent radical nephrectomy, while the remainder received non-radical nephrectomy. The mean PTV was 466.66 ml (248.7–825.4 ml).

The targeted volume comparisons for the 3 techniques are presented in **Tables 4 and 5**. In 3D-CRT technique included 2 fields, 3 fields, 4

fields for 1, 4, and 3 patients, respectively. The mean values of D_{max} were 106.66%±0.99, 107.31%±1.17, and 107.23%±0.76 of prescription dose for 3D-CRT, IMRT, and VMAT, respectively. PTV-V95 were 99.14%, 98.24%, and 96.60% for 3D-CRT, IMRT, and VMAT, respectively. Both D_{max} and PTV-V95 were reached target criteria in all patients without significant difference among techniques. The mean values of the CIs were superior for IMRT and VMAT (1.28±0.17 and 1.21±0.2) than 3D-CRT (2.33±0.59). Although there were statistically significant differences in the distributions of the mean values for 3D-CRT and IMRT ($p < 0.05$) and for 3D-CRT and VMAT ($p < 0.05$), there was no statistical difference

Table 3 Patient characteristics

Patient	Age at diagnosis (years)	Gender	Localization	Nephrectomy	PTV volume (cm3)
1	$5\frac{10}{12}$	F	Left	No	589.91
2	$2\frac{9}{12}$	F	Right	Upper pole nephrectomy	248.7
3	$5\frac{9}{12}$	F	Midline	Yes	594.6
4	$2\frac{7}{12}$	M	Left	Yes	443.8
5	$3\frac{10}{12}$	M	Midline	Yes	351
6	5	M	Midline	No	386.6
7	$5\frac{9}{12}$	M	Left	No	825.4
8	$3\frac{1}{12}$	M	Midline	Yes	293.3
Mean	4.32±1.41				466.66±192.02

Abbreviations: PTV = planning target volume

between the values for IMRT and VMAT ($p=0.643$). The respective mean values of PCI were 0.45 ± 0.12 , 0.77 ± 0.09 , and 0.78 ± 0.10 for 3D-CRT, IMRT, and VMAT. The difference in the distribution of the mean values for 3D-CRT and IMRT was statistically significant ($p < 0.05$), as was that for 3D-CRT and VMAT ($p < 0.05$); however, the difference for IMRT and VMAT was not significant ($p= 1.00$). All 3 mean PCI values corresponded with CI. The mean values of HI were 0.08 ± 0.02 , 0.08 ± 0.02 , and 0.11 ± 0.02 for 3D-CRT, IMRT, and VMAT, respectively. The differences in the distributions of those mean values were not

statistically significant for 3D-CRT and IMRT ($p=1.00$), 3D-CRT and VMAT ($p= 0.06$), and IMRT and VMAT ($p=0.06$). Finally, the differences in the distributions of the mean integral doses were not statistically significant for 3D-CRT and IMRT ($p=0.69$), 3D-CRT and VMAT ($p=0.33$), and IMRT and VMAT ($p=0.18$).

The patients were divided into 2 groups: the first comprising the 4 patients without radical nephrectomy, and the second with the 4 cases with radical nephrectomy. Summaries of the related dosimetric parameters for PTV, integral dose and OARs are presented in **Tables 5, 6 and 7**.

Table 4 Summary of the dosimetric parameters for PTV (Dmax, V95%, V107%, CI, PCI, and HI) and integral dose

Parameters (mean)	3D-CRT	IMRT	VMAT	P-value		
				3DCRT vs.	3DCRT vs.	IMRT vs.
				IMRT	VMAT	VMAT
Target volume						
D _{max} (%)	106.66±0.99	107.31±1.17	107.23±0.76	< 0.05	0.51	1.00
V _{95%} (%)	99.14±1.11	98.29±1.40	96.60±1.07	0.76	< 0.05	0.08
V _{107%} (%)	0.00005±0.00014	0.50±1.41	0.005±0.01	1.00	0.72	1.00
CI	2.33±0.59	1.28±0.17	1.21±0.2	< 0.05	< 0.05	0.64
PCI	0.45±0.12	0.77±0.09	0.78±0.103	< 0.05	< 0.05	1.00
HI	0.08±0.02	0.08±0.02	0.11±0.02	1.00	0.06	0.06
Integral dose	1.06±0.81	0.96±0.62	0.89±0.56	0.69	0.33	0.18

Abbreviations: Dmax = percent of maximal dose per prescription dose; PTV= planning target volume; Vx% = volume of PTV receiving ≥ x% of prescribed dose; CI = conformity index; PCI = Paddick conformity index; HI = homogeneity index; 3D-CRT = 3-dimensional conformal radiotherapy; IMRT = intensity-modulated radiotherapy; VMAT = volumetric-modulated arc therapy

Table 5 Summary of the dosimetric parameters for PTV and integral dose of the 2 groups (non-radical nephrectomy and radical nephrectomy)

PARAMETERS (MEAN)	Non-radical nephrectomy			Radical nephrectomy		
	3D-CRT	IMRT	VMAT	3D-CRT	IMRT	VMAT
D _{max} (%)	106.45±1.37	107.03±1.68	107.02±0.97	106.88±0.54	107.6±0.41	107.45±0.54
V _{95%} (%)	99.79±0.20*	98.46±0.96	97.00±1.36*	98.49±1.31	98.15±1.89	96.21±0.61
V _{107%} (%)	0±0.00	1±2.00	0.0012±0.002	0.0001±0.0002	0.002±0.002	0.008±0.015
CI	2.53±0.13	1.38±0.14	1.32±0.23	2.12±0.82*	1.18±0.14	1.10±0.08*
PCI	0.39±0.02	0.71±0.07	0.73±0.11	0.50±0.16*	0.82±0.07	0.84±0.07*
HI	0.08±0.01*	0.09±0.01	0.11±0.02*	0.09±0.03	0.09±0.02	0.12±0.01
Integral dose	1.18±1.11	1.03±0.85	0.96±0.75	0.93±0.51*	0.89±0.43	0.81±0.41*

Note: * indicate p-value < 0.05 between 3D-CRT vs VMAT

Abbreviations: Dmax = percent of maximal dose per prescription dose; PTV= planning target volume; Vx% = volume of PTV receiving ≥ x% of prescribed dose; CI = conformity index; PCI = Paddick conformity index; HI = homogeneity index; 3D-CRT = 3-dimensional conformal radiotherapy; IMRT = intensity-modulated radiotherapy; VMAT = volumetric-modulated arc therapy

Table 6 Summary of the dosimetric parameters for OARs

Parameters (mean)	Goal	3D-CRT	IMRT	VMAT	P-value		
					3DCRT vs. IMRT	3DCRT vs. VMAT	IMRT vs. VMAT
Ipsilateral kidney							
V18Gy	< 75%	83.33±20.14	46.61±25.73	51.17±23.79	< 0.05	< 0.05	0.84
V14Gy	< 100%	87.53±15.80	73.88±15.97	85.41±3.80	0.67	1.00	0.84
D _{max} (Gy)		22.51±0.26	23.11±1.05	22.63±0.55	0.83	1.00	0.86
D _{mean} (Gy)		19.84±2.62	17.25±2.04	17.84±1.41	0.06	0.20	1.00
Contralateral kidney							
V18Gy	< 25%	24.62±13.22	11.28±8.91	12.20±9.53	< 0.05	< 0.05	1.00
D _{max} (%)		21.85±0.29	21.79±1.54	21.37±2.12	1.00	1.00	0.47
D _{mean} (Gy)		11.15±3.08	11.74±2.77	12.34±2.87	1.00	1.00	0.82
Liver							
V15Gy	< 25%	29.15±10.72	16.20±7.66	13.49±5.80	< 0.05	< 0.05	0.14
V8Gy	< 50%	48.29±14.75	45.93±6.57	44.82±5.28	1.00	1.00	1.00
D _{max} (Gy)		22.54±0.47	22.75±0.52	22.62±0.95	1.00	1.00	1.00
D _{mean} (Gy)	< 15Gy	9.50±2.53	9.14±1.08	8.81±0.79	1.00	1.00	0.62
Vertebrae							
D80%	> 16.8Gy	20.93±1.59	19.72±1.02	19.48±1.33	0.24	0.17	0.98
D _{max} (Gy)		22.67±0.41	22.89±0.34	22.93±0.13	0.34	0.40	1.00
D _{mean} (Gy)		21.55±0.63	20.66±0.57	20.61±0.8	0.05	0.09	1.00

Abbreviations: OARs = organs at risk; Dmax = maximal dose; Dmean = mean dose; Vx% = volume of organ receiving ≥ x% of prescribed dose; Dx% = dose of organ receiving ≥ x% of total volume; 3D-CRT = 3-dimensional conformal radiotherapy; IMRT = intensity-modulated radiotherapy; VMAT = volumetric-modulated arc therapy

Table 7 Summary of the mean values of dosimetric parameters for OARs of the 2 groups (non-radical nephrectomy and radical nephrectomy)

Parameters	Non-radical nephrectomy			Radical nephrectomy		
	3D-CRT	IMRT	VMAT	3D-CRT	IMRT	VMAT
Ipsilateral kidney						
V18Gy	83.34±20.14*	46.62±25.73*	51.18±23.79			
V14Gy	87.53±15.80	73.89±15.97	85.41±3.80			
Dmax	22.51±0.27	23.10±1.05	22.63±0.55			
Dmean	19.85±2.62*	17.25±2.04*	17.84±1.41			
Contralateral kidney						
V18Gy	24.90±19.56*	10.11±11.01*	10.66±11.65	24.35±5.02	12.45±7.77	13.75±8.36
Dmax	21.76±0.14	21.20±1.84	20.67±2.80	21.94±0.40	22.40±1.09	22.08±1.15
Dmean	10.40±2.88	10.11±11.01	10.66±11.65	11.90±3.52	12.65±1.40	12.89±2.27
Liver						
V15Gy	27.53±12.54**	13.29±10.50	10.98±7.28**	30.78±10.20*	19.11±1.11*	16.01±2.98
V8Gy	45.65±21.42	46.22±7.97	43.85±4.49	50.93±5.57	45.66±6.08	45.79±6.53
Dmax	22.29±0.41	22.65±0.78	22.24±1.31	22.79±0.44	22.85±0.14	23.00±0.13
Dmean	8.89±3.70	8.82±1.54	8.47±0.82	10.12±0.47*	9.45±0.26*	9.15±0.69
Vertebrae						
D80%	21.47±0.17	20.48±0.88	20.38±1.33	20.39±2.27	18.96±0.34	18.59±0.48
Dmax	22.61±0.54	22.90±0.50	22.85±0.12	22.73±0.32	22.88±0.16	23.02±0.09
Dmean	21.74±0.30	21.02±0.57	20.93±1.01	21.37±0.87	20.31±0.34	20.3±0.43

Note: * indicate p-value < 0.05 between 3D-CRT vs IMRT

** indicate p-value < 0.05 between 3D-CRT vs VMAT

Abbreviations: OARs = organs at risk; Dmax = maximal dose; Dmean = mean dose; Vx% = volume of organ receiving ≥ x% of prescribed dose; Dx% = dose of organ receiving ≥ x% of total volume; 3D-CRT = 3-dimensional conformal radiotherapy; IMRT = intensity-modulated radiotherapy; VMAT = volumetric-modulated arc therapy

In the case of the non-radical-nephrectomy group, the ipsilateral kidneys showed the following values. Constraints were reached in 2/4 and 3/4 in terms of V18Gy and V14Gy for 3D-CRT, whereas they were reached for all patients when using the advanced techniques. As to the contralateral kidneys of the non-radical-nephrectomy group, the following values were found. Constraint V18Gy was over the limit in 2/4 patients for 3D-CRT, whereas it was reached for all of the patients using the advanced techniques. The mean V18Gy was lower with the advanced techniques.

Turning to the contralateral kidneys of the radical-nephrectomy group, their values were as follows. The V18Gy constraint was reached for all patients with IMRT and VMAT but 3D-CRT group, 1/4 patient whose tumor was in midline cannot be reached a criteria.

Moving on to the dosimetric parameters for the OARs, the following results were demonstrated for the livers. The mean V15Gy values were different with statistical significance between 3D-CRT and IMRT ($p < 0.05$) and 3D-CRT and VMAT ($p < 0.05$), but no significance between IMRT and VMAT ($p = 0.135$). The V15Gy values were the highest with 3D-CRT in all cases. The V15Gy values were reached in 4/8, 7/8, and 8/8 patients with 3D-CRT, IMRT, and VMAT, respectively. The differences of the mean V8Gy values were not statistically significant for all 3 techniques. The V8Gy values were reached in 5/8, 5/8, and 7/8 patients with 3D-CRT, IMRT, and VMAT, respectively.

For 3D-CRT, IMRT, and VMAT, the D80% values of the vertebrae were reached in all patients (Figure 2).



Figure 2 The irradiated vertebrae dose should be uniform (80% of prescribed dose delivered to at least 80% of the irradiated vertebral body), with $D_{80\%} > 16.8$ Gy

Discussion

Advanced multimodality treatment (surgery, chemotherapy, and radiation) for pediatric neuroblastoma has been shown to result in improved survival rates, with 5-year overall survival rates ranging from 34% to 68% for children aged 1–14 years in the USA.^[12] The aims of RT should be to minimize the radiation dose to OARs without compromising the target coverage, and to decrease the secondary, radiation-induced, malignancy risks.

With abdominal neuroblastoma, most of the target volume is located in the midline and paraspinal region, and it is surrounded by critical organs, such as the bilateral kidneys, liver, and vertebrae. There has therefore been a gradually increasing trend to use advanced RT techniques such as IMRT and VMAT for the treatment of this disease. In this study, the mean $V_{95\%}$ of all patients could reach the constraint without statistically significant differences.

As to the dose distribution, the CI showed that the advanced techniques (IMRT and VMAT) show more adaptability in shaping a high isodose level to the target volume than 3D-CRT. The CI values for the advanced techniques were about half the level for 3D-CRT. This corresponded with the PCI values, which were comparable with the findings from other studies.^[4, 9, 10, 12] HI was not statistically different among the 3 techniques.

Due to the frequent occurrence of nephrectomy and the use of cisplatin prior to RT, a decrease in the RT dose to the kidney must be of concern, especially in cases of children with one remaining kidney. Among the patients who

had undergone radical nephrectomy in our study, there was one case for which 3D-CRT did not reach the dose constraint for the contralateral kidney, and the mean V18Gy values were twice as high for 3D-CRT as for the advanced techniques. On the other hand, the mean dose to the contralateral kidney with 3D-CRT was not different to the means for the advanced techniques.

As to the non-radical-nephrectomy patients, the value of the mean V18Gy was higher for 3D-CRT than for those of IMRT and VMAT, not only for the ipsilateral kidneys (83.34%, 46.62%, and 51.18%, respectively) but also for the contralateral kidneys (24.90%, 10.11%, and 10.66%). Therefore, the advanced techniques yielded more benefits than 3D-CRT for both the radical- and non-radical-nephrectomy groups in terms of the kidney dose constraint.

In a comparison of 3D-CRT (anterior-posterior and posterior-anterior opposing fields) and IMRT, Paulino et al.^[5] found that IMRT can be used for midline tumors with kidney sparing, but this benefit is at the cost of other organs that receive high mean doses. Their study determined that IMRT and VMAT showed more benefits than 3D-CRT in a number of ways. In this study, in terms of V18Gy of ipsilateral kidneys, the respective mean V18Gy values of 3D-CRT, IMRT, and VMAT for midline tumors were 59.32%, 17.48%, and 19.1%, whereas for lateralized tumors, they were 91.34%, 56.33%, and 61.87%. Similarly, Paulino et al.^[5] found that V18Gy was higher with 3D-CRT than IMRT and VMAT in terms of the mean doses both for ipsilateral kidneys

(midline tumors, 17.04Gy, 15.78Gy, and 15.89Gy; and lateralized tumors, 20.78Gy, 17.74Gy, and 18.59Gy, respectively) and for contralateral kidneys (midline tumors, 26.62%, 16.68%, and 18.48%; and lateralized tumors, 20.48%, 5.88%, and 5.93%, respectively). But in their study was established even in cases involving radical nephrectomies or lateralized tumors. The mean doses for contralateral kidneys were not different to those for lateralized tumors (11.14Gy, 9.91Gy, and 10.9Gy for 3D-CRT, IMRT, and VMAT, respectively). However, in cases of midline tumors, the mean doses were higher with the advanced techniques than with 3D-CRT (11.16Gy, 13.57Gy, and 13.78Gy for 3D-CRT, IMRT, and VMAT, respectively).

Radiation-induced liver disease is one of the important complications of RT. Generally in adult patients, when the mean dose of an irradiated whole liver reaches 30–35Gy, the risk of radiation-induced liver disease rises to about 5%–10%. In pediatric patients, there is no clear dose response for dose constraint, but the severity of liver toxicity is related to a higher mean liver dose. Research by Bölling et al.^[13] found that about 54% of patients who received a radiation dose of < 25 Gy developed radiation-induced liver disease. Nazmy et al.^[14] observed that V15Gy and V8Gy were related to the incidence of veno-occlusion disease, which is a common complication after bone-marrow transplantations. Our study showed that the mean V15Gy values could be reduced by using the advanced techniques, compared with using 3D-CRT, but the values showed no statistically significant

difference in terms of V8Gy. With the 3D-CRT and IMRT techniques, lower proportions of patients achieved the V8Gy and V15Gy dose constraints than with VMAT (5/8, 5/8, and 7/8 of patients for V8Gy, respectively; and 4/8, 7/8, and 8/8 for V15Gy). Consequently, VMAT seems to be of more benefit than the 2 other techniques. One explanation is that VMAT can provide a greater number of radiation beam angles, which means that VMAT can reach the dose constraint of V8Gy better than the other techniques.

RT is a well-known risk factor for spinal deformities in pediatric patients. Mayfield et al.^[15] found that an RT dose of more than 30Gy was associated with a high incidence of scoliosis. Paulino et al.^[16] found that doses > 17.5 Gy were associated with a 50%–60% incidence of scoliosis; on the other hand, radiation doses ≤ 17.5 Gy had a 10% scoliosis incidence. Hass-Kogan et al.^[12] reported that, for high-risk neuroblastoma patients, radiotherapy doses to the primary site of at least 20 Gy were required to achieve better locoregional control than 10Gy. Therefore, dose homogeneity and symmetric irradiation of the vertebral bodies should be ensured to minimize the risk of scoliosis. In a study by Paulino et al.^[5] that compared 3D-CRT and IMRT, the vertebral body was included in, and excluded from, the PTV. The research team found that both the PTV and the vertebral body plan showed a homogeneous dose distribution without the vertebral body. In this current study, we therefore included the vertebral body in the PTV as a second PTV to control the homogeneous dose distribution and

to limit the dose to the irradiated vertebrae. We defined that 80% of the delineated volume should receive at least 80% of the prescribed dose. All 3 RT techniques in our study were able to achieve these constraints. In addition, the HIs of the techniques showed no statistical difference (0.92 ± 0.02 , 0.92 ± 0.02 , and 0.89 ± 0.014 for 3D-CRT, IMRT, and VMAT, respectively).

The risk of developing secondary malignancy from RT is critical with pediatric patients. However, the relevant studies have mainly been retrospective. Chemotherapy regimens, genetic factors, lifestyle, and the environment are associated with secondary malignancies. Due to the variable patient populations, no precise predictive model of radiation-induced cancer risk is currently valid. Hall et al^[17] found that the use of IMRT can increase the risk of a secondary malignancy from the 1% associated with the use of conventional RT to 1.75% for patients who have survived 10 years after being irradiated. They hypothesized that children who were irradiated with IMRT received a much lower dose area and more leakage radiation to the whole-body area than with conventional RT. Several studies have reported a possible correlation between the integral dose and secondary malignancies.^[18-20] In our study, the integral dos-

es of the 3 techniques were not statistically different. However, it should be noted that secondary malignancy risk is not proportional to the average dose or the integral dose. A low-dose area can also be related to the development of malignancies. Therefore, in order to minimize the risk of developing malignancies in the future, radiation oncologists should still be concerned about both the integral doses and the low-dose areas.

Although our dosimetric study demonstrated benefits of advanced RT techniques over 3D-CRT, there are some limitations. Firstly, the sample size of our study was small. Secondly, although our study showed some advantages of advanced techniques, the dosimetric benefits may not translate to the clinical benefits. Further clinical studies with long term follow-up outcomes will be required.

Conclusions

The advanced techniques, IMRT and VMAT, showed more benefits than 3D-CRT in terms of critical organ sparing (especially the kidneys) for both the radical- and non-radical-nephrectomy patient groups, and without compromising the target coverage. Moreover, the integral doses of all 3 techniques were comparable.

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