Technology in Cancer Research & Treatment
Volume 18: 1-6

DOI: 10.1177/1533033819886899
journals.sagepub.com/home/tct
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The Risk of Radiogenic Second Cancer Based on Differential DVH: Central Nervous System Malignant Tumor in Children

Zheng Tang, MPhil[1], Xue Zou, MPhil[1], Qian Luo, MPhil[1], Ying Wang, MD[1,2], and Fu Jin, MD[1,2]

Abstract

Objectives: To quantify the risk of radiogenic second cancer in pediatric patients receiving hippocampal-sparing craniospinal irradiation either with intensity-modulated radiation therapy or tomotherapy due to the development of a solid second cancer after radiotherapy using the concept of excess absolute risk. **Methods:** Computed tomography images of 15 pediatric patients who received craniospinal irradiation treatment were selected for this study. For each case, intensity-modulated radiation therapy and tomotherapy plans were computed. Then, the dosimetry parameters were analyzed. Differential dose–volume histograms were generated, and the excess absolute risks were calculated for each plan of each patient. **Results:** The tomotherapy group was superior to the intensity-modulated radiation therapy group in target area homogeneity index ($P < .001$). Tomotherapy offered greater hippocampal sparing than intensity-modulated radiation therapy in terms of $D_{2\%}$ (15.66 vs 23.05 Gy, $P < .001$) and D_{mean} (9.79 vs 20.29 Gy, $P < .001$). Tomotherapy craniospinal irradiation induced a much higher risk than intensity-modulated radiation therapy craniospinal irradiation to the thyroid and lungs (excess absolute risk: thyroid 28.7 vs 26.9 per 10 000 PY, $P = .010$; lung 20.5 vs 18.9 per 10 000 PY, $P = .003$). Both techniques conferred a higher risk to the stomach, but there was little difference. In addition, the 2 plans induced less carcinogenic risk to the liver (excess absolute risk 4.2 vs 4.0 per 10 000 PY, $P = .020$). **Conclusions:** The tomotherapy plan has obvious advantages in the protection of the hippocampus for children undergoing craniospinal irradiation treatment. Tomotherapy increased the risk of radiogenic second cancer in organ at risk, and therefore, it is imperative to take the risk factor into consideration in the formulation of treatment protocols.

Keywords

tomotherapy, intensity-modulated radiotherapy, craniospinal irradiation, risk of radiogenic second cancer

Abbreviations

CSI, craniospinal irradiation; CT, computed tomography; CTV, clinical target volume; dDVH, differential dose–volume histograms; EAR, excess absolute risk; HI, homogeneity index; IMRT, intensity-modulated radiation therapy; OAR, organ at risk; PTV, planning target volume; RED, risk equivalent dose; RTOG, Radiation Therapy Oncology Group; TOMO, tomotherapy.

Received: July 25, 2018; Revised: October 28, 2018; Accepted: September 26, 2019.

Introduction

In recent years, growing attention has been paid to children's malignant tumors. According to an epidemiological analysis of children's malignant tumors in China, the incidence of malignant tumors is lower than the world average, but the mortality rate is higher than that of other foreign Countries.[1]

Central nervous system malignant tumors are the most common malignant solid tumors in children, and they have the

[1] Chongqing University Cancer Hospital, Chongqing, China
[2] Chongqing Key Laboratory of Translational Research for Cancer Metastasis and Individualized Treatment, Chongqing University Cancer Hospital & Chongqing Cancer Institute & Chongqing Cancer Hospital, Chongqing, China

Corresponding Author:
Xue Zou, Chongqing University Cancer Hospital, No. 181 Hanyu Road, Shapingba District, Chongqing 400030, China.
Email: 294266801@qq.com

Table 1. Study Population Characteristics.[a]

Age	Years
Mean, SD	8.3 ± 3.4
Median (min/max)	9 (3-14)
Gender	Number of patients (%)
M	10 (67)
F	5 (33)
Diagnosis	Number of patients (%)
Medulloblastoma	8 (54)
Germ cell tumor	5 (33)
Ependymoma	2 (13)
Dose	30 Gy/15 F

[a]N = 15.
Abbreviations: F, female; M, male; SD, standard deviation.

second highest incidence rate among children's malignant tumors, accounting for approximately 20%.[2] Currently, craniospinal irradiation (CSI) is still an effective treatment for multiple central nervous system tumors in children. Compared to traditional radiotherapy, tomotherapy (TOMO) can achieve up to 160-cm whole-body image-guided intensity-modulated therapy. It avoids the problem of field exposure and has great advantages, including accurate irradiation, uniform dose distribution, protection of endangered organs, and reduction in normal tissue adverse reactions.[3]

With the development of radiotherapy technology, the overall survival time of children with such tumors has been increased, and the 5-year survival rate is approximately 72%.[4] Second cancers account for approximately 16% of all cancers, and solid tumors are the leading cause of death among cancer survivors in the United States.[5] For pediatric tumors, the second cancer caused by treatment may lead to more deaths than the primary tumor.[6] Therefore, secondary carcinogenic risk (SCR) has become a major concern of long-term radiotherapy survivors.

Most studies[7-10] on the risk of second cancer pertain to lymphoma, breast cancer, and rectal cancer, while the studies of the central nervous system of children are relatively rare. In this study, differential dose–volume histograms (dDVHs) of various organs and EAR models are used to quantify the risk of second cancer in pediatric patients treated with intensity-modulated radiation therapy (IMRT) CSI versus TOMO CSI.

Materials and Methods

Patient Characteristics

The computed tomography images of 15 pediatric patients previously treated with CSI for central nervous system malignancies at our institution were studied. Sex, age, diagnosis, and prescribed doses of all selected cases are listed in Table 1.

Treatment Planning

Target delineation was performed using an Eclipse 11 (Varian Eclipse 11.0.31, Varian) treatment planning system. According to the 50 and 62 reports by the International Commission on Radiation Units and Measurement, we delineated the clinical target volume (CTV), including the entire subarachnoid space, brain, and spine (1 contiguous contour), excluding the hippocampal avoidance region. The hippocampus was delineated according to the guidelines of the Radiation Therapy Oncology Group (RTOG) 0933 Protocol. Contouring began at the most caudal extent of the crescentic-shaped floor of the temporal horn and continued posterocranially along the medial edge of the temporal horn. The hippocampal avoidance region was generated by expanding the hippocampal contour by 3-mm margin in 3 dimensions to account for the necessary dose falloff between the hippocampus and the whole-brain planning target volume (PTV). The PTV was defined as the CTV plus a uniform 5-mm margin in 3 dimensions.

The following organs at risk (OARs) were also defined on the planning image set: cochlea, lens, optic nerve, optic chiasm, pituitary gland, brain stem, thyroid, heart, liver, spleen, lungs, kidneys, and stomach. Dose constraints for OARs were adopted from the QUANTEC-recommended standard. The planning objective for OARs was defined as follows: the maximum dose (D_{max}) of the lens was limited to 8 Gy; the maximum dose (D_{max}) of thyroid gland was limited to 45 Gy; the D_{max} of the liver was limited to 25 Gy; the maximum dose (D_{max}) of the kidneys was limited to 20 Gy, and the mean dose (D_{mean}) was limited to 10 Gy. For the lungs: $V20 < 30\%$ and $V5 < 60\%$ and for the heart: $V30 < 40\%$ and $V40 < 30\%$.

Two CSI plans were created for each patient: an IMRT plan (IMRT CSI) and a tomotherapy plan (TOMO-CSI). The prescribed dose of PTV was 30 Gy in total administered in 15 fractions over 3 weeks. For all treatment plans, the prescribed 100% isodose covered at least 95% of the PTV, and the percentage volume of PTV receiving greater than 107% of the prescription was limited to 2%. Differential DVHs were generated for each plan to analyze the risk of radiogenic second cancer.

Model of Second Cancer Risk

Based on Schneider *et al*'s[11] study, the calculation of the second carcinogenic risk was carried out for radiosensitive organs and tissues using C++ language and dDVH by means of excess absolute risk (EAR), defined by Equation 1.

$$\mathrm{EAR}^{\mathrm{org}} = \frac{1}{V_T}\sum_i V(D_i)\,\beta_{\mathrm{EAR}}\mathrm{RED}(D_i)\mu(\mathrm{agex},\mathrm{agea}), \quad (1)$$

where risk equivalent dose (RED) is the dose–response relationship for radiation-induced cancer in units of dose defined by Equation 2. The modifying function μ contains the population-dependent variables defined by Equation 3. And agex and agea are the age of exposure and attainment, respectively. β_{EAR} is the initial slope, which is the slope of the dose–response curve at low dose. V_T is the total organ volume, and the sum is taken over all bins of the DVH V (D).

Table 2. PTV and Hippocampus Parameters.

	PTV		Hippocampus	
	HI	CI	$D_{2\%}$	D_{mean}
TOMO	1.067 ± 0.008	0.817 ± 0.047	15.66 ± 0.50	9.79 ± 0.14
IMRT	1.087 ± 0.006	0.855 ± 0.047	23.05 ± 0.46	20.29 ± 0.41
P value	<.001	.036	<.001	<.001

Abbreviations: CI, target coverage index; HI, homogeneity index; IMRT, intensity-modulated radiation therapy; PTV, planning target volume; TOMO, tomotherapy.

$$\mathrm{RED}(D_i) = \frac{e^{-\alpha' D_i}}{\alpha' R}\left(1 - 2R + R^2 e^{\alpha' D_i} - (1-R)^2 e^{-\frac{\alpha' R}{1-R} D_i}\right), \tag{2}$$

where D_T and d_T are the prescribed dose to the target volume with the corresponding fraction dose, respectively. The number of cells is reduced by cell killing, which is proportional to α' ($\alpha' = \alpha + \beta d = \alpha + \beta D_i / D_T d_T$), and is defined using the linear quadratic model. The repopulation/repair parameter R characterizes the repopulation/repairability of the tissue between 2 dose fractions. If no full repopulation/repair occurs, it is 0, but otherwise 1.

$$\mu(\mathrm{agex}, \mathrm{agea}) = e^{\left[\gamma_e(\mathrm{agex}-30) + \gamma_a \ln\left(\frac{\mathrm{agea}}{70}\right)\right]}. \tag{3}$$

In this form, the fit parameters are gender averaged and centered at an age at exposure of 30 years and an attained age of 70 years. The initial slope β_{EAR} and the age-modifying parameters γ_e and γ_a for a Japanese population and for different sites are taken from Preston *et al*.[12]

Statistical Analysis

SPSS 22.0 software was used for statistical analysis. A paired *t* test was used to compare EAR risks between IMRT CSI and TOMO CSI with no adjustment for multiple comparisons. Differences with $P < .05$ were statistically significant.

Results

Target Volume Coverage, Homogeneity, and Dose to Hippocampus

Table 2 lists the target coverage and homogeneity index (HI) for the craniospinal PTV and the dose received by the hippocampus ($D_{2\%}$, D_{mean}) for each patient using IMRT and TOMO. The TOMO group was superior to the IMRT group in target area HI ($P < .001$). However, on target coverage, the TOMO group had no advantage. On average, TOMO offered greater hippocampal sparing than IMRT in terms of $D_{2\%}$ and D_{mean} ($P < .001$).

Mean Dose and dDVH of OARs

Table 3 lists the average mean dose administered to all patients for selected organs (thyroid, lungs, liver, and stomach). The average mean dose of the thyroid gland in the TOMO group was significantly lower than that of the IMRT group ($P = .002$). However, the average mean dose of the lungs in the TOMO group was higher than that of the IMRT group ($P < .001$). Figure 1 shows the dDVH from the IMRT treatment plans and the TOMO treatment plans for various organs of a representative patient.

Table 3. Average of Mean Dose to All Patients for Selected Organs.

D_{mean}, Gy	Thyroid	Lung	Liver	Stomach
TOMO	14.75 ± 0.14	5.76 ± 0.69	5.51 ± 0.76	5.84 ± 1.46
IMRT	17.17 ± 0.18	5.12 ± 0.54	5.34 ± 0.74	6.28 ± 1.23
P value	.002	<.001	.479	.171

Abbreviations: IMRT, intensity-modulated radiation therapy; TOMO, tomotherapy.

Risk of Radiogenic Second Cancer Estimates

Table 4 shows the mean EAR values for those sites. The TOMO CSI plans induced a much higher risk to the thyroid than IMRT CSI plans (EAR 28.7 vs 26.9 per 10 000 PY, $P = .010$). The TOMO CSI also induced an increased risk to the lungs (EAR 20.5 vs 18.9 per 10 000 PY, $P = .003$). For the stomach, there was little difference between the TOMO and IMRT plans, as both of them had high risks. The 2 plans conferred less carcinogenic risk to the liver.

Discussion

Craniospinal irradiation can prolong the survival time and improve the quality of life of children with multiple central nervous system tumors.[13] Tomotherapy can complete CSI at a time, eliminating the high-dose and low-dose regions brought about by subsection treatment, and has better target area coverage and dose uniformity than IMRT.[3] In this study, both plans met the requirements of the prescribed dose. The HI index in the TOMO group was better than in the IMRT group; however, the CI index in the TOMO group was not superior to that in the IMRT group. This is related to the better protection of the hippocampus.

For children who are in the developmental stage of childhood with tumors, with improved overall survival after treatment, the protection of neurocognitive function becomes particularly important. The radiation damage induced in the hippocampus affects learning ability, memory formation, and cognitive dysfunction in children, and as a result, it can affect their quality of life.[14] It has been reported that the incidence of cognitive dysfunction has significantly decreased and that the incidence of hippocampal metastasis is less than 5% after hippocampal-sparing whole-brain radiotherapy.[15,16] Many studies support the general finding that the RTOG 09-33 phase II study showed that the rate of memory decline after 4 months of hippocampal-sparing whole-brain radiotherapy (extrahippocampal 5-mm expansion) was 7%, which was significantly lower than that of the control group (30%; $P = .0003$), while the rate of hippocampal metastasis was only 4.5%. The study of

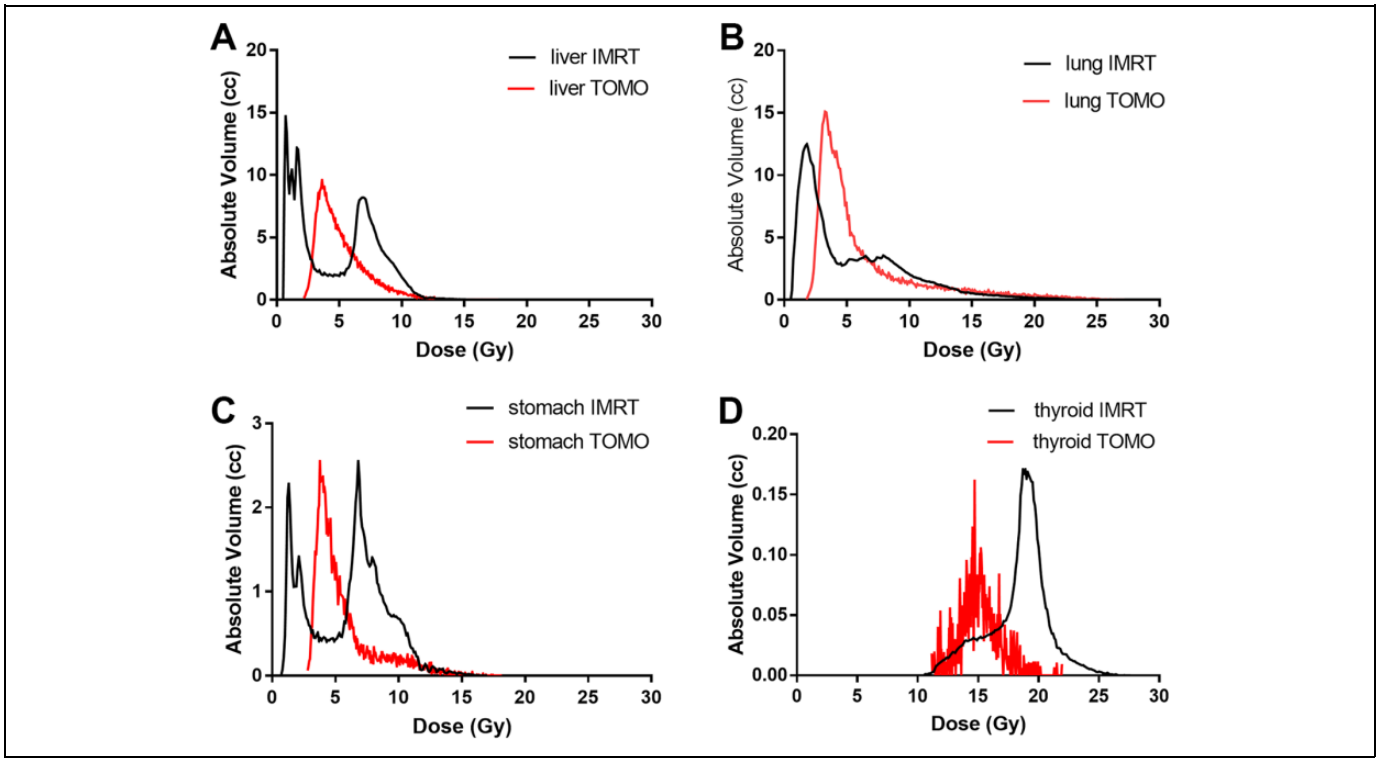

Figure 1. Differential DVHs for various organs of a representative patient. A, Differential DVH diagram of liver. B, Differential DVH diagram of lung. C, Differential DVH diagram of stomach. D, Differential DVH diagram of thyroid. The red line in each of the images represents the TOMO, and the black line represents IMRT. DVH indicates dose–volume histogram; IMRT, intensity-modulated radiation therapy; TOMO, tomotherapy.

Table 4. Summary of the Average EAR Estimated Risk for All the OARs by Treatment Type.[a]

Organ	Excess Absolute Risk of Radiation-Induced Cancer (per 10 000 PY)		Absolute Difference (TOMO-IMRT)	Relative Risk Ratio (TOMO/IMRT)	*P* Value
	TOMO-CSI	IMRT-CSI			
Thyroid	28.7	26.9	1.8	1.067	**.010**
Lung	20.5	18.9	1.6	1.085	**.003**
Stomach	23.4	22.8	0.6	1.026	.248
Liver	4.2	4.0	0.2	1.050	**.020**

Abbreviations: CSI, craniospinal irradiation; EAR, excess absolute risk; IMRT, intensity-modulated radiation therapy; OAR, organs at risk; TOMO, tomotherapy.
[a]Boldface values indicate statistically significant differences.

Gondi *et al*[17] and Ghia *et al*[18] showed that 5-mm expanded boundaries for hippocampus protection were safe and feasible. In this study, we used a 3-mm extended boundary to protect the hippocampus. The results showed that the hippocampus $D_{2\%}$ and D_{mean} were significantly lower in the TOMO group than in the IMRT group ($P < .0001$), while the target parameters met the clinical requirements. Therefore, TOMO is superior to IMRT in hippocampal-sparing CSI in children.

Although TOMO CSI treatment has remarkable advantages in dose uniformity and hippocampus protection, one problem that cannot be ignored is that the 360° rotation in TOMO treatment will increase the low-dose areas among the surrounding normal tissues. There have been numerous studies showing that the low-dose range of OAR can increase the risk of second cancer, and most radiogenic second cancers occur near the target volume.[7,19] The child cancer survivor study reported that the mortality rate of the recurrence or progression of primary cancer in children decreased, while the mortality of secondary tumors increased.[20] Some studies[21,22] showed that the different proportions of carcinogenic risks were observed in the lungs, breast, thyroid, stomach, liver, and other organs after different irradiation techniques or carcinogenic models for CSI radiotherapy.

Many studies have reported that the risk of radiogenic second cancer is more significantly increased in the thyroid gland, a radiation-sensitive organ, than in other organs. Stokkevåg *et al*[23] found that the thyroid gland had a higher risk of second cancer after CSI radiation therapy with photons and electrons through the lifetime attributed risk (LAR) index. Although our study used a different index, the study still showed that the risk of secondary thyroid cancer in the TOMO group was higher than that in the IMRT group, and the EAR reached 28.666 ± 2.075 ($P = .010$).

In fact, compared to adults, children's lungs are generally smaller in size, and thus, the volume of radiation in CSI treatment is broader, and the low-dose area is greater. In this study,

the EAR of the lungs in the TOMO group was 20.496 ± 2.285, which increased by an absolute difference of 1.6 ($P = .003$) compared to the IMRT group. This was consistent with the results of Holmes *et al*'s study,[24] where the TOMO group exhibited increased absolute risk of the lungs by 1.3 ($P = .0061$) compared to the three dimensional conformal radiation therapy (3D-CRT) group after CSI treatment. Therefore, more attention should be paid to protecting lung tissue and to minimizing the range of low-dose areas under the premise of meeting the requirements of the target for children.

The studies of Zhang *et al*,[22] Stokkevåg *et al*,[23] and Holmes *et al*[24] about SCRs in pediatric patients with cancer treated with CSI revealed that there was a general risk of second cancer in the stomach. Furthermore, in this study, both the TOMO and the IMRT groups had higher risk. This may be due to the gastric capacity of the receptive relaxation activity, which can increase the gastric cavity capacity from the 50 mL of an empty status to 1.5 L after eating. For the patients receiving radiotherapy, the volume of radiation exposure in the fasting state or the full state is different, which will affect the low-dose area, thus affecting the risk of radiogenic second cancer.

In this study, the TOMO and IMRT plans corresponded to lower risk of second cancer in the liver, which was consistent with the results of Zhang *et al*[22] and Stokkevåg *et al*.[23] This may be related to the regeneration, proliferation, and strong repair compensatory ability of liver cells.

Conclusions

In conclusion, TOMO CSI has obvious advantages in the protection of the hippocampus in children. But according to the EAR model, TOMO increased the risk of radiogenic second cancer in OARs, especially in the thyroid and lungs. Thus, attention should be paid to reducing the amount of radiation to the thyroid and lungs in TOMO CSI planning. Ultimately, it is imperative to consider the risk factor when formulating the treatment protocols.

Authors' Note

X.Z. drafted the manuscript, analyzed, and interpreted the data; Y.W. and F.J. made substantial contributions to conception and design of the study, acquisition of data and analysis, and was involved in revising the manuscript critically for important intellectual content; and Z.T. and Q.L. were involved in acquisition of data. All authors read and approved the final manuscript. The study was approved by the Ethics Committee of the Chongqing Cancer Institute (2015 ethical approval, [No. 002]), and all patients provided informed consent.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported generously by the National Natural Science Foundation of China under Grant (No. 11575038), the key project of Chongqing Health and Family Planning Commission (No. 2015ZDXM041).

ORCID iD

Xue Zou https://orcid.org/0000-0002-7905-2158

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