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Original Report

Estimating the excess lifetime risk of radiation induced secondary malignancy (SMN) in pediatric patients treated with craniospinal irradiation (CSI): Conventional radiation therapy versus helical intensity modulated radiation therapy

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Abstract

Purpose: To quantify the risk of radiation-induced second malignancies (SMN) in pediatric patients receiving craniospinal irradiation (CSI) either with 3-dimensional conformal radiation therapy (Conv CSI) or tomotherapy helical intensity modulated radiation therapy (Tomo CSI).

Methods and materials: A novel predictive model that accounts for short- and long-term carcinogenesis was incorporated into our institutional treatment planning system to quantify the lifetime risk of SMN in incidentally irradiated organs. Five pediatric patients previously treated with CSI were studied. For each case, Conv CSI and Tomo CSI plans were computed. The excess absolute number of SMN was computed for each plan for each patient. For female patients, age was varied to assess its impact.

Results: Tomo CSI has a much higher risk than Conv CSI for breast cancer. Tomo has a slightly increased risk for the lung, and conventional has a slightly higher risk for the thyroid. Both techniques have intermediate risks to the pancreas and stomach, and lesser risks to the bladder and rectum. For the breast, the magnitude of the absolute risks varied with age: 14.2% versus 7.4% (Tomo vs Conv) age 5; 16.9% versus 7.6% age 10, and 18.6% versus 8.0% age 15.

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Conclusions: Tomo has a higher risk for inducing breast and lung second cancers, and when using Tomo-based intensity modulated radiation therapy, care should be taken to avoid incidental radiation to the breast. When planning CSI, one needs to balance these cancer risks against other normal tissue effects.

Introduction

Craniospinal irradiation (CSI) remains an integral part of the treatment of pediatric central nervous system (CNS) malignancies including medulloblastoma and some ependymomas and germ cell tumors. These malignancies have a propensity to disseminate throughout the subarachnoid space, and the addition of CSI to surgery and chemotherapy is generally accepted to improve cancer control and survival.[1]

The target volume for CSI is the subarachnoid space, and thus the radiation fields encompass the contents of the calvarium and spinal canal, extending inferiorly to include the thecal sac (typically at or below the second sacral vertebrae). Delivering uniform dose throughout this large radiation treatment volume is one of the more technically challenging aspects of radiation oncology.[1] The standard, conventional approach uses several matching/abutting fields: opposed lateral fields to encompass the cranium and upper cervical spinal canal and a matching posterior spinal field (2 posterior spinal fields are needed for larger patients). The critical matching of these abutting fields is complex because daily reproducibility of patient setup and immobilization is difficult. The dose homogeneity across the radiation volume is less than optimal in the area of these matching fields. Furthermore, the "exit dose" from the posterior spinal fields results in incidental radiation of normal tissues and organs anterior to the spinal canal (eg, thyroid, heart, bowel), which may result in late toxicities such as the occurrence of radiation-induced second malignancies (SMN).

Intensity modulated radiation therapy is a technique advocated by some to be preferred over the conventional technique described above. Specifically, several published reports highlight the dosimetric benefits of helical-based IMRT (IMRT; Tomotherapy) to deliver CSI, yielding improved target dose conformality and dose homogeneity.[2,3] Furthermore, the treatment delivery is less complicated because there are no matching fields. However, these benefits may be offset by an increase in the volume of nontarget tissue and organs receiving low doses of radiation that may increase the risk of subsequent late SMNs (eg, at >10-20 years post-RT).

The incidence of SMN after conventional CSI with long-term follow-up has been reported to be 4.2% at 10 years in the Children's Oncology Group A9961 study.[4] Because of the lack of long-term follow-up, the risk/incidence is not known for pediatric patients treated with helical-based IMRT CSI. Being able to estimate the risk of SMNs may influence the selection of IMRT versus other approaches in patients needing CSI and/or the added information may influence the IMRT treatment planning process. Models have been created that appear to provide a reasonable estimate of the risk of SMNs based on parameters readily available at the time of radiation treatment planning.[5]

The purpose of this study was to use these models to quantify the risk of developing radiation induced SMNs in pediatric patients treated with conventional CSI versus helical IMRT CSI.

Table 1 Patient characteristics

Sex	Age	Diagnosis
F	10	High-risk medulloblastoma
M	14	Suprasellar germ cell tumor
F	5	Atypical teratoid rhabdoid tumor
M	16	Juvenile pilocytic astrocytoma
F	8	Medulloblastoma, average risk

All cases planned at 1.8 Gy/fraction, 36 Gy craniospinal irradiation followed by a tumor bed boost to 54 Gy.
F, female; M, male.

Methods and materials

Patient characteristics

The computed tomography (CT) planning images of 5 pediatric patients who were previously treated with CSI for brain tumors at our institution were studied. The patient age, diagnosis, and prescription doses are listed in Table 1.

Treatment simulation

All cases were simulated at the Department of Radiation Oncology, University of North Carolina at Chapel Hill, using a 16-slice, large-bore (80 cm), helical CT scanner and 0.23-T open magnetic resonance imaging scanner (Phillips, Eindhoven, Netherlands). Patients were simulated prone with the neck extended. Laser marks and scout CT scan were used for visual inspection and to correct alignment in all degrees of freedom. CT scans extended from the vertex to 5 cm below the S5 vertebrae with a 5-mm slice thickness.

Target and critical organ definition

Simulation images were imported into our in-house treatment planning system (TPS) PlanUNC (PLUNC). We delineated 2 clinical target volumes (CTVs): (1) CTV

craniospinal (CTV_CSI) and (2) CTV boost (CTV_boost). The entire subarachnoid space, brain, and spine (1 contiguous contour) was included in the CTV_CSI, and its contour was limited by the bony calvarium and spinal canal, but to carefully include the spinal ganglion and thecal sac. A T2-weighted magnetic resonance imaging scan was used to define the caudal extent of the thecal sac. For the CTV_boost the gross tumor volume and postoperative bed were included with a nonuniform 10- to 20-mm margin, depending on the tumor type and anatomic location. The planning target volume (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: cochleas, retinas, lens, optic nerves, chiasm, hypothalamus, pituitary, brainstem, thyroid, heart, breasts (female only), kidneys, bladder, rectum, pancreas, colon, and stomach.

Treatment planning

Two CSI plans were created for each patient: a conventional 3-dimensional (3D) conformal radiation therapy plan (Conv CSI) and a tomotherapy helical-based IMRT plan (Tomo CSI) (5 patients, 10 plans). Separate tumor bed boost plans were also created. The prescribed radiation dose was 36 Gy for the CSI plan and 18 Gy for the tumor bed boost plan, for a total dose of 54 Gy. For the modeling, 1.8 Gy/fraction given daily was used.

Tomo CSI

Helical IMRT plans were generated using TomoPlan (Accuray, Sunnyvale, CA) using a field width of 5.02 cm, 0.287 pitch, and a modulation factor of 2.0. The treatment plans were generated using an inverse planning optimizer. For tomotherapy planning, the PTV was separated into 2 structures: a PTV brain and PTV spine to allow separate plan optimization. Beams were directionally blocked through some of the OARs when possible such as the eyes, oral cavity, heart, and kidneys. The prescription dose was required to cover 95% of the volume of the PTV and OARs were added to the optimizer in a sequential fashion with priority placed on target conformality and coverage. Lung and breast tissue were included as OARs and plans were optimized to decrease integral dose to these organs. Plans were optimized until OAR doses could not be further reduced without reducing PTV coverage or increasing the hotspot. A maximum hot spot of 107% of prescription was deemed acceptable.[3] Dose distributions were fused to planning images and imported into our TPS (PLUNC) for calculations of dose-volume histograms (DVHs) to use in the analysis of SMN risk. A similar approach was separately taken for the tumor bed boost plan.

Conv CSI

The conventional 3D plans were produced using our in-house TPS (PLUNC). Lateral fields were used for the cranial fields with a table angle and collimator rotation to match divergence to the superior edge of the upper spinal field. For the spinal fields, the table and collimator were rotated 90° to allow for the use of the multileaf collimator, so the gantry could be rotated to match the divergence of the superior spinal field. The multileaf collimator was used for daily dynamic featherings (intrafraction feathering) using 3 predefined control points separated by 1 cm.[6,7] Field-in-field technique was used for all 3D plans to improve dose homogeneity and reduce hotspots. A separate 3D tumor bed boost plan was created using multiple static coplanar and noncoplanar conformal fields. All generated plans were considered clinically acceptable.

Modeling second malignancy risk

Biologically motivated mathematical modeling of carcinogenesis has a history spanning several decades.[8,9] Many biologically based models can be characterized as short-term, in that they focus on those processes occurring during and shortly (ie, about 1 month or less) after irradiation.[10-19] By contrast, another class of models can be characterized as long-term, in the sense that they track carcinogenesis mechanisms throughout the entire human or animal life span.[20-29]

The lack of detailed treatment of radiation-specific effects typically limits risk predictions from long-term models to exposure conditions where a known shape for the early dose-response relationship (eg, a linear shape) holds. Situations in which this dose-response relationship itself requires mechanistic analyses, such as at highly fractionated radiotherapeutic doses, are difficult to describe solely with long-term models. Conversely, the more detailed dose responses produced by short-term models can be converted into cancer risk at much later times only by considering the effects of factors such as age at exposure and time since exposure, which are not explicitly taken into account by the short-term formalisms. A unified approach of integrating short- and long-term formalisms is needed, where a detailed initial dose response for pre-malignant cell numbers is produced over a wide range of doses, and changes to the shape of this dose response over the latency period before the development of cancer are also analyzed.

As an example of a mechanistic model of spontaneous and radiation-induced carcinogenesis unifying short- and long-term processes, we used the novel approach previously described.[5,30] Briefly, the model integrates analyses of processes that operate during irradiation with those that operate on longer time scales before and after exposure. The model assumes that normal organ-specific stem cells, which reside in compartments generically called niches, can undergo initiation to a premalignant state, either spontaneously or by radiation, and can then undergo transformation into fully malignant cells that can eventually form tumors. Radiation is also assumed to have the potential to increase the mean number of premalignant cells per niche (ie, promotion). The model used here tracks the average

Table 2 The average absolute excess risks of SMNs by treatment type

Organ	Excess absolute risk of radiation-induced cancer (cases/100 irradiated patients)		Absolute difference (tomo-conv)	Relative risk ratio (tomo/conv)	*P* value
	Tomo CSI	Conv CSI			
Lung	5.6	4.3	**1.3**	1.3	**.0061**
Breast	15.7	7.5	**8.2**	2.1	**.011**
Rectum	0.04	0.02	0.02	2.0	.25
Bladder	0.16	0.19	-0.03	0.84	.47
Colon	0.3	0.2	0.1	1.5	**.039**
Stomach	1.0	0.8	0.2	1.3	.41
Pancreas	1.7	1.9	-0.2	0.89	.31
Thyroid	0.54	2.4	**-1.9**	0.23	**.016**

CSI, craniospinal irradiation; SMN, secondary malignancy. Bold values indicate statistically significant differences.

number of initiated niches filled with premalignant cells and the average number of premalignant cells per initiated niche using the so called initiation, inactivation and proliferation formalism. In earlier work,[5] we have shown that this model can reproduce the main dose-dependent features of radiation-induced second cancers after radiation therapy.

This unified model was incorporated into our treatment planning system (PLUNC) to quantify the lifetime risk of SMN in incidentally irradiated organs. Specifically, integral dose to organs at risk was calculated using DVHs and fed into the SMN predictive model in real time. A program that calculated the risk of SMN using this model was written in Fortran in a manner that it could be executed by the treatment planning software. The planning software would extract DVH data (integral dose) for OARs and feed these data into a local file that could be accessed by the second malignancy modeling code. This program was then executed by the TPS and the output was displayed in the TPS in a dedicated window. This process could be executed in real time every time a final dose was calculated for a plan.

The age-dependent mortality hazard for the general US population was taken from life tables[31] and combined with the additional mortality hazard in cancer patients, producing a patient-specific survival probability. The estimated risk of second malignancy was adjusted based on the patient-specific survival probability using a Markov model and was computed for each plan for each patient. The resulting lifetime SMN risk was therefore adjusted for mortality from competing risks. Because all radiation techniques should have a similar dose distribution in the CNS and therefore similar risk of secondary malignancies in the CNS, this risk was not calculated. Dose matrices from the Tomo CSI plans were imported into PLUNC for the SMN risk calculations.

Statistical analysis

A paired *t* test was used to compare SMN risks between Conv CSI and Tomo CSI with no adjustment for multiple comparisons. For female patients, age was varied to assess its impact. All statistics were performed using Stata 13 (StataCorp LP, College Station, TX)

Results

Risk estimates for each organ (average across the 5 cases planned) are shown in Table 2. The absolute excess risks of SMNs are generally low. The 1 exception to this finding is breast where Tomo CSI plans had a much higher risk than Conv CSI (excess absolute risk [EAR] of SMN 15.7 vs 7.5 cases/100 patients, $P = .011$). Tomo CSI also had a slightly increased risk for the lung (EAR 5.6 vs 4.3 cases/100 patients, $P = .0061$), whereas Conv CSI had a slightly higher risk for thyroid cancer (EAR 0.54 vs 2.4 cases/100 patients, $P = .016$). Tomo and conventional plans both had comparable moderate risks to the pancreas and stomach, and small risks to the bladder and rectum.

For each of the three female patients, the breast cancer risks were recomputed assuming an age of 5 years, 10 years, and 15 years. Receipt of CSI at age 5 was associated with an average SMN risk (Tomo vs Conv) of 14.2% versus 7.4%, at age 10 the risk was 16.9% versus 7.6%, and at age 15 the risk was 18.6% versus 8.0%.

Discussion

CSI still plays an integral role in the management of certain pediatric malignancies. Given that radiation is frequently unavoidable, there is interest in strategies to reduce the risk of CSI by limiting dose to critical organs. Helical tomotherapy has quickly risen to the forefront of these technologies because of the ease of delivery, the large number of treatment machines operating, and the exquisitely conformal plans that can be created. However, our current study highlights a potential increased SMN risk of IMRT-based CSI approaches.

Table 3 Previous studies of SMN risk following CSI with conventional or Tomotherapy techniques

	Relative risk tomotherapy vs conventional				
	Mirabel[40]	Myers[42]	Yoon[43]	Mu[41]	Current study
Metric used	Estimated absolute yearly rate	Excess relative risk	Excess incidence per 10,000 person-years	ICRP method: effective dose × tissue weighting factor	Excess absolute risk (cases/100 irradiated patients)
Lung	1	2	1.2	2.2	1.3
Breast	–	3	–	2.4	2.1
Rectum	–	–	–	–	2.0
Bladder	–	–	–	–	0.84
Colon	0.5	–	–	–	1.5
Stomach	0.7	–	1	1.8	1.3
Pancreas	–	–	1	–	0.89
Thyroid	0.33	–	1	1	0.23

Relative risk of tomotherapy vs conventional CSI.
CSI, craniospinal irradiation; ICRP, International Commission on Radiological Protection; SMN, secondary malignancy.

There have been multiple previous studies comparing 3D conformal plans with IMRT and Tomo. Sharma et al generated 3D, IMRT, and Tomo CSI plans for 4 patients and, although the target coverage was excellent ($V_{95\%}$ >98%) for all 3 plans, the dose homogeneity and dose to OARs was best with the Tomo CSI plans.[3] Hong et al similarly generated Tomo CSI plans for 3 patients previously treated with Conv CSI and again showed improved homogeneity, and reduced the dose to many OARs including the parotid glands (mean dose to each parotid decreased by 7.3 and 10 Gy, respectively).[2] In this study, they predictably found that the V_5 was significantly higher in the tomotherapy plans. Penagaricano et al prospectively followed 18 patients treated with Tomo CSI for a median of 16.5 months. The average V_{10} was 55% (median 57%), but despite the large volumes of lung receiving low-dose radiation, they had no patients develop acute radiation pneumonitis.[32] Thus with Tomo CSI, there are tradeoffs for the improved dose homogeneity and reduction of dose to normal critical structures; namely, an increase in low-dose spread.

The late risk of radiation-induced SMN has been studied in radiation techniques other than CSI, with the most significant increases in radiation sensitive tissues such as the breast and thyroid. In Hodgkin's lymphoma, for instance, rates of breast cancer in female patients treated with mantle field radiation have consistently been found to be markedly higher than population controls.[33-35] In a long-term follow-up study of the Late Effects Study Group of childhood cancer survivors, women who were 20 years from receiving mantle field radiation were 55 times more likely to develop breast cancer compared with the general age-matched population.[33] In patients treated with 3D conformal CSI, the largest risk of secondary malignancies has been in the CNS. In the long-term follow-up of the Children's Oncology Group A9961, a study that used a reduced CSI dose of 2400 cGy, the estimated cumulative incidence rate of secondary tumors at 5 and 10 years for the entire cohort was 1.1% and 4.2%, respectively, with the overwhelming majority (79%) of these malignancies appearing in the CNS.[4] Reports from other trials, single institutions, and Surveillance, Epidemiology, and End Results have shown a similar majority of SMNs in the CNS.[36-38] Unfortunately, no technological advance in radiation delivery can reduce the risk of SMNs in the target volume, but risks to other organs can potentially be reduced.

One of the potential downsides of Tomo CSI is that there is a larger spread of low dose to OARs; in particular, there is an increased dose to the lungs and breast tissue. Although the traditional pattern of second malignancy in patients treated with CSI using 3D conformal RT has been CNS cancers, with the increase in low-dose RT using Tomo CSI, there might be an increased risk of SMN outside the CNS. Several previous studies compared the risk of SMN after CSI using different treatment techniques and different risk models (Table 3).[39-43] Qualitatively, our results agree with these previous studies, showing an increase in risk of SMNs, specifically in the breast and lung tissue when using Tomo CSI. A relative strength of the current study is that we examined the risk of SMN in multiple organs in the neck, thorax, abdomen, and pelvis that are all exposed to incidental radiation during CSI. In addition to the breast and lung, we also found a modest but significant increase in risk of colorectal cancer using Tomo CSI vs Conv CSI.

A limitation of our study is that we did not include proton plans in our comparison. Protons have the dosimetric advantage of little to no anterior exit dose when patients are treated with a posterior beam; thus, the SMN rate for anterior organs at risk in patients treated with protons would be much smaller (essentially zero) than patients treated with any photon technique. With the proliferation of proton centers, proton CSI is rapidly

becoming the standard of care. However, proton treatment facilities currently remain sparse and, although most patients are willing to travel for treatment when there is a clear benefit for proton therapy, as is the case with CSI, financial, family, and patient variables make traveling for treatment less of an option for some families. Most patients treated with CSI continue to be treated with photons, and given that photon CSI still needs to be performed, minimizing risk for these patients is important. In addition, as mentioned previously, the majority of SMNs following CSI are found within the radiation target (craniospinal axis), and would be expected to be similar for protons, Conv CSI and Tomo CSI.

Compared with previous studies, our report represents the first use of a novel combined risk model for short- and long-term second malignancy modeling in pediatric patients. In addition, this report represents the first incorporation of a direct estimation of second malignancy risk into clinical treatment planning software to allow real-time comparison of plans based on risk of SMN. Our study is limited by a small number of patients, and a relatively homogeneous age distribution for which we conducted an age-varied sensitivity analysis. Overall, our study represents a novel direct implementation of excess risk estimation into a clinical planning system using a sophisticated risk estimation technique. The results of our study and the implementation of risk estimation into treatment planning could allow future direct comparison of treatment plans in real time.

In conclusion, our study presents a novel method for incorporating SMN estimation into a clinical radiation planning system, adds estimates of risk for several novel organs at risk in CSI, and reinforces previous increased risk estimates for breast and lung tissue when patients are treated with Tomo CSI. When using tomography-based IMRT, care should be taken to avoid incidental radiation to the breast. When making decisions about optimal technique for CSI, one needs to balance these cancer risks against other normal tissue effects.

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