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CLINICAL INVESTIGATION **Pediatric Tumors**

POTENTIAL REDUCTION OF THE INCIDENCE OF RADIATION-INDUCED SECOND CANCERS BY USING PROTON BEAMS IN THE TREATMENT OF PEDIATRIC TUMORS

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Purpose: To assess the potential influence of improved dose distribution with proton beams compared to conventional or intensity-modulated (IM) X-ray beams on the incidence of treatment-induced secondary cancers in pediatric oncology.
Methods and Materials: Two children, one with a parameningeal rhabdomyosarcoma (RMS) and a second with a medulloblastoma, were used as models for the purpose of this study. After defining the target and critical structures, treatment plans were calculated and optimized, four for the RMS case (conventional X-ray, IM X-rays, protons, and IM protons) and three for the irradiation of the spinal axis in medulloblastoma (conventional X-ray, IM X-rays, protons). Secondary cancer incidence was estimated using a model based on Publication No. 60 of the International Commission on Radiologic Protection. This model allowed estimation of absolute risks of secondary cancer for each treatment plan based on dose–volume distributions for the nontarget organs.
Results: Proton beams reduced the expected incidence of radiation-induced secondary cancers for the RMS patient by a factor of ≥2 and for the medulloblastoma case by a factor of 8 to 15 when compared with either IM or conventional X-ray plans.
Conclusions: The potential for a significant reduction in secondary cancers with pediatric cancers after using proton beams (forward planned or IM) in the treatment of RMS and MBD in children and adolescents represents an additional argument supporting the development of proton therapy for most radiotherapy indications in pediatric oncology. © 2002 Elsevier Science Inc.

Medulloblastoma, Protontherapy, Rhabdomyosarcoma, Secondary cancers.

INTRODUCTION

In the last 25 years, a continual improvement in cure rates has been reported for most pediatric cancers (1, 2). Along with more effective chemotherapy, better surgical and radiotherapy techniques have contributed, at least in part, to this improved outcome. Central nervous system tumors and soft-tissue sarcomas, frequently treated with postoperative radiotherapy, have shown a 10%–15% absolute increase in 5-year survival rates in the United States from 1975 to 1995 (1). Unfortunately, radiotherapy in children is frequently associated with severe side effects, such as growth and musculoskeletal abnormalities, endocrine and fertility dysfunctions, neuropsychologic and neurobehavioral deficits, and secondary malignancies (3).

The risk of developing secondary tumors is clearly increased in children surviving cancer. Factors predisposing patients to this serious complication are both genetic and treatment related (radiotherapy and chemotherapy). Children with retinoblastoma, leukemia, Hodgkin's disease, neuroblastoma, central nervous system tumors, and sarcomas are at highest risk for secondary cancer development after treatment (3). A Children's Cancer Study Group analysis of secondary tumors revealed a 23-fold excess risk of brain tumors in children with leukemia treated with cranial radiotherapy (4). In addition, children treated for Hodgkin's disease have a long-term actuarial risk of developing secondary cancers that is 22 times higher than that expected in the general population (5).

High-energy proton beams can provide a superior dose distribution and optimal target conformation compared to standard radiotherapy with photon beams, significantly reducing unnecessary irradiation of nontarget tissues. Treatment-related side effects, including radiation-induced secondary cancers, can potentially be substantially reduced. We have described previously the potential advantages of proton beams in treating the tumor bed in children with parameningeal-paraorbital rhabdomyosarcoma (RMS) as well as the spinal neuraxis in children with medulloblas-

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toma (6, 7). In both cases, a significant reduction of the nontarget integral dose was observed compared to any standard or optimized treatment technique with high-energy X-rays. In the present study, we have assessed the potential influence of dose reduction with proton beams on the incidence of secondary cancers in both tumor sites, compared with the expected incidence after standard or optimized X-ray beams (intensity-modulated [IM]).

METHODS AND MATERIALS

Description of the patients

The first patient (Case 1) is a 7-year-old boy with an embryonal RMS of the left paranasal sinuses infiltrating the left orbit (Stage III, Group III). The tumor was partially resected, and subsequent chemotherapy resulted in a complete response. The boy was then treated with high-energy proton beams to the tumor bed (tumor volume before surgical resection, plus safety margins), receiving a total dose of 50.4 Gy in 28 daily fractions of 1.8 Gy/fraction. The second patient (Case 2), treated to the spinal neuraxis for a medulloblastoma, was modeled on a spinal CT scan of a 3-year-old boy with an unrelated disease. A total dose of 36 Gy was to be delivered in 20 daily fractions of 1.8 Gy/fraction exclusively to the whole spinal theca and exit of the spinal nerve roots.

Volumes of interest were defined in each patient CT data set. Planning target volumes (PTVs) were defined in every CT slice for each tumor site. PTVs were drawn 5 mm around the clinical target volume. Additionally, a number of critical structures at high risk for secondary cancer development were outlined in every CT scan slice for the purpose of calculating the cancer incidence rate. For Patient 1, the bone and brain were defined. For Patient 2, the following volumes of interest were defined: stomach, esophagus, colon, breast, lung, thyroid gland, and bone. The volume of each critical structure, V, was calculated by integrating over the volume pixels corresponding to each critical structure.

Treatment planning

All treatment plans were produced on the basis of two sets of CT images and volumes of interest (one set for each patient). These data sets were transferred electronically from a commercial treatment planning system (TPS) in Geneva (CADPLAN V3.1, Varian) to the TPS at the Paul Scherrer Institut (PSI) in Villigen for proton plan and inverse planning calculations (8).

The following treatment plans were obtained for the purpose of secondary cancer assessment. For Patient 1 (RMS), the four plans were as follows: a conventional 6-MV X-ray plan, a spot-scanned proton plan, an IM X-ray plan, and an IM proton plan (7). A "conventional" X-ray plan was calculated using the CADPLAN V3.1 software and consisted of a set of three noncoplanar 6-MV X-ray beams (two lateral parallel and opposed beams, and an anterosuperior beam). The spot-scanned proton plan was calculated using two bilateral posterior oblique beams (left and right posterior obliques) with a beam energy of 160 MeV. Both IM X-ray and proton plans were calculated using software originally developed at PSI for the calculation of IM proton plans (9), but which has been modified to calculate also IM photon plans based on a superposition approach using dose kernels derived from the University of Wisconsin group (10). The algorithm is a gradient-based optimization dependent on both maximum dose and dose–volume constraints for critical structures (9). Both plans consist of nine equally spaced coplanar beams and have been calculated using exactly the same dose constraints as described in a previous paper (7)—that is, 50.4 Gy to the PTV and maximum dose constraints of 10 Gy, 30 Gy, 45 Gy, 55 Gy, and 35 Gy for the lenses, lacrimal glands, retinae, optic structures, and parotid glands, respectively. Figure 1 shows in a transverse plane (CT slice) through the central axis the comparative dose distribution for the four competitive treatment plans.

For Patient 2 (medulloblastoma), three treatment plans aiming to cover the whole spinal theca have been assessed: one single posterior field X-ray (6 MV) plan (conventional), an IM X-ray plan with nine beams (15-MV X-rays), and a single posterior field spot-scanned proton plan (138 MeV). Again, the proton plan was calculated using the TPS at PSI, whereas the forward planned X-ray plan was calculated using the VOXELPLAN software developed at the German Cancer Research Center in Heidelberg. The IM X-ray plan was calculated using the optimization software developed at PSI and mentioned above (9, 10). For this case, the IM X-ray plan was calculated with the single constraint of applying a uniform dose of 36 Gy to the whole spinal theca. No dose constraints were applied to any of the defined critical structures. Figure 2 shows the comparative dose distribution for the three competitive treatment plans on a sagittal plane (digital radiographic reconstruction of a CT set of the neuraxis) through the center of the spinal axis.

Calculation of secondary cancer incidence

The estimation of secondary cancer incidence was performed with a model based on the guidelines of the International Commission on Radiologic Protection (ICRP), Publication No. 60 (11). This model was described in greater detail by Schneider *et al.* in a paper that assessed the potential influence of dose reduction with proton beams on the incidence of secondary cancers in patients treated for Hodgkin's disease (12). The average dose, H_T in the outlined tissues, was assessed individually for each patient from the competitive treatment plans. The doses for bone surface and red bone marrow were extracted from the data for bone, scaled to the total body bone weight. For Patient 1, the fraction of red bone marrow in the skull was estimated to be 13%. For Patient 2, the fraction of red bone marrow (mostly vertebral bodies) was estimated to be 28.4% (13). Bone surfaces were estimated by assuming that the skull:whole skeleton and vertebral body:whole skeleton volume ratios were equal to the corresponding surface ratios. The dose prescription of the proton plans was given in ^{60}Co

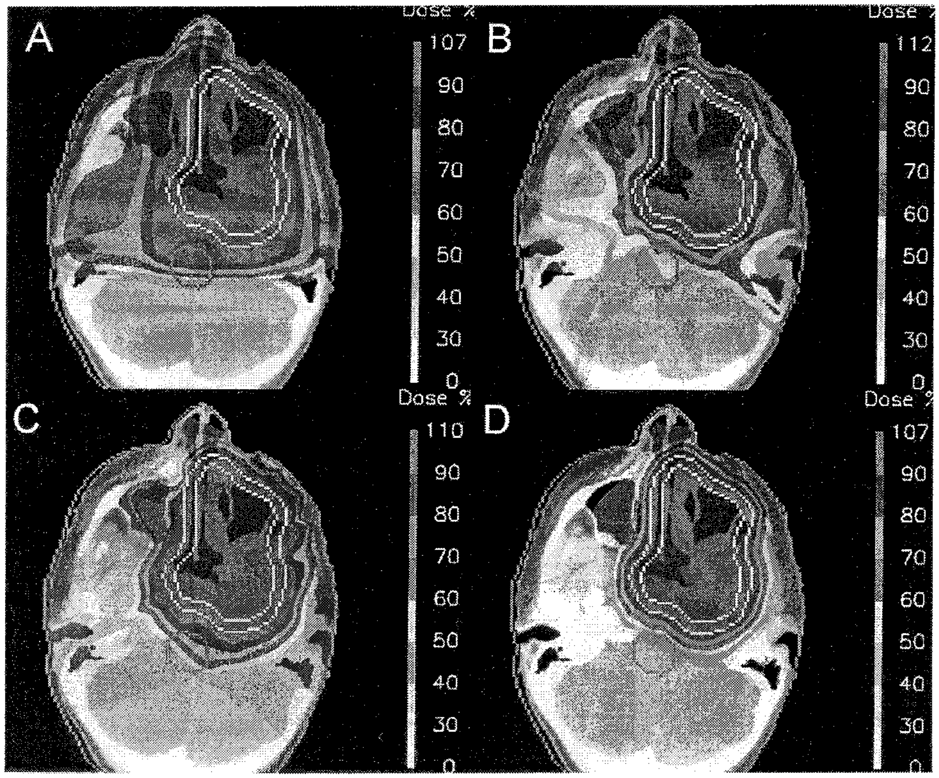

Fig. 1. Comparative dose distributions through the central axis for Patient 1. (A) Conventional photons, (B) IM photons, (C) Spot-scanned protons, and (D) IM protons.

γ-ray equivalents weighted with a relative biologic effectiveness of 1.1 (standard procedure for proton irradiation).

The absolute risk of secondary cancer was given in percent per lifetime per Sievert (*Sv*). Probability coefficients of death as a result of a fatal cancer (M_T) were obtained for each critical organ from Table B15 of the ICRP 60 (11). They were obtained by averaging death probability coefficients of two different models for a population of five countries. The product $M_T\ H_T/L_T$ gives the organ-specific cancer incidence (for an organ exposed to an average dose H_T), where L_T is the organ-specific lethality from Table B19 of the ICRP 60 (11). The lethality data are extracted from

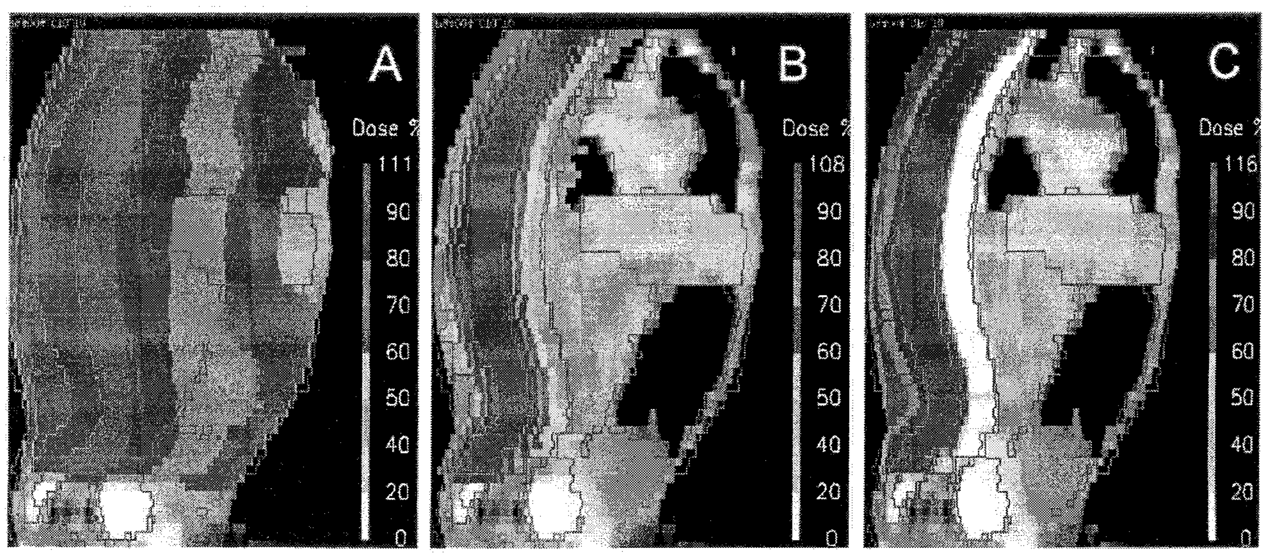

Fig. 2. Comparative dose distributions in a sagittal plane through the center of the spinal axis for Patient 2. (A) Conventional photons, (B) IM photons, and (C) Spot-scanned protons.

Table 1. Lethality data of ICRP 60 (11) for different cancer locations (14)

Tumor site	Lethality
Esophagus	0.95
Stomach	0.90
Colon	0.55
Breast	0.50
Lung	0.95
Bone	0.70
Leukemia	0.99

the U.S. Cancer Statistics Review 1973–1986 (14) and are listed in Table 1. The sum of all organ-specific cancer incidences gives the absolute incidence of secondary cancers.

In addition to the absolute secondary cancer incidence, we estimated an "avoidable" cancer incidence for each patient (12). The "avoidable" cancer incidence is defined as the true incidence of secondary cancer due exclusively to the irradiation of nontarget tissues. This excludes the potential cancer incidence arising in the PTV region ("nonavoidable"). The nonavoidable secondary cancer incidence was subtracted from the expected absolute cancer incidence.

RESULTS

Table 2 presents the estimated risk of secondary cancer incidence after radiotherapy (mostly sarcomas and leukemia) for the RMS case and the four competitive treatment plans. The expected risk with the IM proton plan was almost 2.4 times lower than with the conventional X-ray plan and was the lowest of the four treatment plans. The risk predicted for the IM proton plan was about half as great as that estimated for the IM X-ray plan.

Table 3 presents the estimated risk of secondary cancer incidence after treating the spinal axis in the medulloblastoma case. The absolute risk of yearly cancer incidence for each treatment plan is reported for the breast, gastrointestinal apparatus, lung, thyroid, mesenchyme, and bone marrow (leukemia). A yearly cancer incidence rate of 0.76%, 0.43%, and 0.05% was predicted for the 6-MV forward planned X-ray plan, for the 6-MV IM X-ray plan, and for the proton plan, respectively. A reduction in secondary cancer incidence of up to 15-fold was estimated with the use of proton beams compared to the standard 6-MV posterior X-ray beam treatment plan.

Table 3. Estimated absolute yearly rate (%) of secondary cancer incidence after treating a medulloblastoma case with either conventional X-ray, IM X-ray, or proton beams

Tumor site	X-rays (%)	IM X-rays (%)	Protons (%)
Stomach and esophagus	0.15	0.11	0.00
Colon	0.15	0.07	0.00
Breast	0.00	0.00	0.00
Lung	0.07	0.07	0.01
Thyroid	0.18	0.06	0.00
Bone and connective tissue	0.03	0.02	0.01
Leukemia	0.07	0.05	0.03
All secondary cancers	0.75	0.43	0.05
Relative risk compared to standard X-ray plan	1	0.6	0.07

Abbreviation: IM = intensity-modulated.

DISCUSSION

This study used a mathematical model purporting to predict the incidence of radiation-induced cancers to estimate the potential reduction in secondary neoplasms resulting from the improvement in dose distribution associated with proton beams or intensity-modulated radiotherapy in the treatment of two pediatric malignancies. The method was developed in a previous study regarding secondary cancer incidence after treatment of Hodgkin's disease with photon or proton beams (12). We compared our predictions for both tumors with data from the literature.

From the conventional X-ray plan (Table 1), our model predicts for Patient 1 (RMS) a yearly cancer incidence rate of 0.06%. Secondary cancers in pediatric RMS patients were studied by Heyn *et al.* (15), who observed an incidence of 0.19% per year. Assuming a constant hazard rate, the yearly risk was estimated by dividing the lifetime risk by the residual life expectancy of an RMS patient, i.e., life expectancy (76 years) minus average age at treatment (7 years). The estimated cancer incidence seems substantially lower (almost 3 times) than that observed by Heyn *et al.* (15). Several possible explanations for the above discrepancy may be considered. First, Heyn *et al.* (15) studied RMS from all sites, not just from the head-and-neck region, with a correspondingly large range of integral nontarget doses related to different tumor sites and to PTVs of variable size. Second, in our computations, we excluded those tumors potentially arising in the PTV region receiving the prescribed dose of 50.4 Gy (nonavoidable tumors). Third,

Table 2. Estimated absolute yearly rate (%) of secondary cancer incidence after treating a parameningeal rhabdomyosarcoma with either X-rays, IM X-rays, protons, or IM protons

	X-rays	IM X-rays	Protons	IM protons
Yearly rate (%)	0.06	0.05	0.04	0.02
Relative risk compared to standard X-ray plan	1	0.8	0.7	0.4

Abbreviation: IM = intensity-modulated.

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