Spinal deformity after intra-operative radiotherapy for paediatric patients

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ABSTRACT. The purpose of this study was to clarify the incidence and characteristics of late-onset complications of the spine in children who underwent intra-operative radiation therapy (IORT) for common paediatric malignant tumours. 12 children with more than 4 years of follow-up after IORT were included and, in 11 of these, thoracic and/or lumbar spines were irradiated. To compare doses of irradiation to the spine with the resulting deformities, dose simulations of IORT were carried out on two selected cases using a radiation treatment planning system with a pencil-beam algorithm. The mean follow-up period was 135 months (range, 53–234 months). Radiographic reviews found spinal deformity in six patients. Only one patient was symptomatic and the spinal deformity was severe (Grade 3), whereas spinal deformity was mild in the remaining five patients without clinical symptoms (Grade 1). In all of the six patients, anterior wedge-shaped deformity was dominant, and scoliosis was found in only two patients. In one particular case with nephrectomy, irradiation had penetrated much deeper than usual at the site of nephrectomy, and dose distribution was asymmetric, causing clinically significant spinal deformity with scoliosis. In conclusion, specific deformities of the spine observed after IORT can be explained on the basis of dose distribution of the electron beam to the spine.

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Identification of late morbidity of paediatric cancer therapy has become increasingly important, as recent therapeutic developments have improved the survival rate of affected children. Radiation-induced bone injury is one of the hazardous problems: a high dose of radiation therapy impairs bone growth and gives rise to physical disabilities in affected children. Late complications following skeletal irradiation for childhood tumours have been reported previously [1–6].

Intra-operative radiation therapy (IORT) is a technical refinement of radiation therapy that allows sparing of the dose-limiting tissues adjoining the target region. Following gross tumour removal, surgical displacement of critical organs or shielding of adjacent structures is carried out to minimise the radiation damage to the normal structure, and at the same time to deliver an effective irradiation dose to the therapeutic target in a single session. A high dose of electron beam irradiation with the proper acceleration energy can be delivered to residual tumours at the surgical site and neighbouring areas at high risk for microscopic disease. Combined with intensive chemotherapy, IORT has been applied successfully to paediatric malignant tumours [7–15]. In general, IORT has fewer and less severe adverse effects than conventional radiation therapy (external beam radiation therapy (EBRT)). However, the prevalence of

arterial and ureteral stenosis following IORT has attracted particular attention recently [16]. The reason that IORT and EBRT are associated with different patterns of complications may result from differences in dose fractionation and distribution between electron beams and high-energy X-ray beams. Moreover, electron beams have a shorter range in bony tissue than X-ray beams and therefore present very different dose distribution patterns to X-rays. This suggests that the biological effects of IORT may be particularly unpredictable in the paraspinal region of patients. The purpose of this study was to clarify the incidence and characteristics of late-onset complications of the spine in children who underwent IORT for common paediatric malignant tumours (mostly for neuroblastoma). We focused on serial radiological changes and reviewed the medical records of long-term survivors retrospectively.

Patients and methods

Patients

Subjects comprised 12 out of 24 children treated with IORT in our institution from November 1988 to December 2003, and for whom more than four years of follow-up data were available (Table 1). Among the 24 children, none was lost to follow-up within four years and 12 had died within the four years.

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Table 1. Patient characteristics

	All ^a	Survived >4 years
Total	25	12
Age at Tx (months)		
Median	37	25
Range	9–170	9–71
Gender		
Male	14	6
Female	11	6
Pathology		
NB	21	9
RMS	2	2
HB	1	0
YS	1	1

NB, neuroblastoma; RMS, rhabdomyosarcoma; YS, yolk sac tumour; HB, hepatoblastoma.

^aAll patients treated from November 1988 to December 2003.

Surgery and irradiation

At the time of the operation, IORT via electron beams was scheduled and was accomplished by transporting the patient from the operating room to the radiotherapy suite subsequent to tumour resection. Either single or multiple Lucite guide-cones of a rectangular or round shape were positioned in order to form a field for localised irradiation under sterile conditions. By placing the cones directly on the target volume after surgical exposure, a precise treatment volume was directed, and visual confirmation of the exclusion of adjacent organs was achieved. Normal tissue was physically excluded from the field of radiation or, when necessary, shielded with pliable lead. After placing the cone in the operation field, the IORT port was photographed in order to record the extent of the irradiation.

The irradiation fields were planned to include the tumour bed and the involved lymph nodes remaining after the intensive chemotherapy that preceded the tumour resection. At the time of resection, the surgeons and a radiation oncologist assessed the clinical target volume to include the range of the primary tumour and lymph node involvement.

Investigations

We reviewed medical records and interpreted radiographs and MRI of the spine. At review, the study group consisted of six males and six females, with a mean age of 34.8 months (range, 9–71 months) at the time of treatment and a mean follow-up period of 136.9 months (range, 53–237 months). At the time of final follow-up, their mean age was 170 months (range, 80–250 months). All of the patients had chemotherapy before and after resection of the tumour associated with IORT. Common Terminology Criteria for Adverse Events version 3.0 (CTCAE v3.0) was used to assess late complications.

Dose simulations of IORT were carried out for two selected cases with a commercial radiation treatment planning system (XiO version 4.3, CMS, St Louis, MO) using a pencil-beam algorithm in order to compare the irradiated dose to the spine with the resulting deformities. For this purpose, pre-operative CT data were retrieved and transferred to the treatment-planning

workstation. The intestines and other organs not in the field during IORT were virtually removed and replaced with air before simulation.

Results

Among the 12 subjects, 11 patients were irradiated on their thoracic and/or lumbar spines (Table 2). From the review of the radiographs, spinal deformity was observed in six patients. Only one patient (Case 3) was symptomatic and the spinal deformity was severe (CTCAE Grade 3), whereas the spinal deformity was mild in the remaining five patients without clinical symptoms (Figure 1) (CTCAE Grade 1). In all of the six patients, anterior wedge-shaped deformity was dominant, and apparent scoliosis was found in only two patients.

Cases

Case 9

Spinal deformities (Figure 1) were found in a 14-year-old boy treated at 6 years of age with 12 Gy of intra-operative radiation for left adrenal neuroblastoma. A 6 MeV electron beam was used to irradiate the para-aortic lymph node involvement. A lateral radiograph of the spine 9 years after IORT indicated anterior wedge-shaped deformity of the L1 to L3 vertebral bodies. The deformity caused radiographically minimal kyphosis without symptoms.

Case 12

An 8-year-old boy received 12 Gy of intra-operative radiotherapy for neuroblastoma of retroperitoneal origin at the age of 40 months. A 6 MeV beam was used for the para-aortic region, with the upper edge of the port being placed at the Th11 level. At the age of 5 years, an anterior radiograph indicated a compression-fracture-like deformity of the Th11 spinal body (Figure 2a). A coronal MRI (Figure 2b) indicated a butterfly-like deformity of Th11. In the simulated dose distributions, a 6 MeV electron beam reached a depth of approximately 2 cm into the spinal body (Figure 2c). The sagittal dose simulation (Figure 2d) indicated inhomogeneity of dose in the spinal column, depending on the density of the bones and the soft tissues.

Case 3

Case 3 was a 9-year-old girl (at the time of onset) with neuroblastoma that originated from the right adrenal gland. After several courses of chemotherapy, the tumour was resected (Figure 3a). At surgery, right nephrectomy was compulsory because of tumour invasion into the right renal artery. At the same time, intra-operative electron irradiation (6 MeV, 12 Gy) was carried out in the range of the para-aortic region and the resected cavity. The dose simulation to the target region after right nephrectomy indicates an asymmetric and deeper dose penetration to the right side of the lumbar spine (Figure 3b).

She developed back pain five years later, and her anteroposterior (Figure 3c) and lateral (Figure 3d) radiographs indicated severe kyphosis associated with mild

Table 2. 12 patients who survived for more than four years

Case no.	Sex	Age at IORT	Pathology	Primary site	Resection	Current state	Age at last follow-up	Duration of follow-up (months)	IORT site	Irradiate spine	Energy (MeV)	Dose (Gy)	Deformity
1	M	1 y 4 m	RMS	Retroperitoneum	GTR	Alive	20 y 10 m	237	LN	L4	6	10	(-)
2	F	1 y 3 m	NB	Post. mediastinum	GTR	Alive	20 y 3 m	231	Primary	Th9-10	6	10	Th9 anterior wedge
3	F	4 y 10 m	NB	Rt adrenal	GTR+ Rt kidney	Alive	18 y 10 m	170	Primary + LN	L1-5	6	12	L1-3 anterior wedge (Grade 3), Rt scoliosis
4	M	1 y 11 m	YS	Lt testis	GTR	Alive	18 y 4 m	200	Para-aorta	L3-4	6	12	L3,4 anterior wedge
5	M	2 y 3 m	NB	Rt adrenal	GTR	Dead	6 y 8 m	53	Primary + LN	L1-4	6	12	(-)
6	F	5 y 9 m	NB	Lt adrenal	STR	Dead	13 y 9 m	97	Primary + LN	Th10,11	9	15	Th10,11 anterior wedge, mild scoliosis
7	F	4 y 5 m	RMS	Lt pelvic	GTR	Alive	18 y 0 m	165	Primary + LN	(-)	6	15	(-)
8	F	9 m	NB	Retroperitoneum	GTR	Alive	10 y 3 m	115	Primary + LN	L1-4	6	10	(-)
9	M	5 y 11 m	NB	Lt adrenal	GTR	Alive	17 y 0 m	134	Primary + LN	L1-5	6	12	L1-3 anterior wedge
10	M	1 y 3 m	NB	Retroperitoneum	GTR	Alive	9 y 0 m	94	Primary + LN	L1-5	6	12	(-)
11	F	1 y 5 m	NB	Retroperitoneum	GTR	Alive	7 y 7 m	74	Primary + LN	Th12-L4	3	10	(-)
12	M	3 y 4 m	NB	Retroperitoneum	GTR	Alive	9 y 4 m	73	Primary + LN	Th11-L4	6	12	Th11 anterior wedge, mild scoliosis

IORT, intra-operative radiotherapy; F, female; M, male; RMS, rhabdomyosarcoma; NB, neuroblastoma; YS, yolk sac tumour; GTR, gross tumour resection; STR, subtotal tumour resection, LN, lymph node; y, years; m, months; Lt, left; Rt, right.

Figure 1. A 14-year-old boy who received 12 Gy of intra-operative radiotherapy for a neuroblastoma of left adrenal origin at the age of 6 years (Case 9). A 6 MeV electron beam was used to irradiate the para-aortic lymph node involvement. A lateral radiograph of the spine 9 years after IORT indicated anterior wedge-shaped deformities at the L1 to L3 vertebral bodies.

scoliosis. Anterior wedging of the L1 to L3 vertebrae was prominent. A CT image (Figure 3e) suggested rotational deformities of the spinal column. In this particular case, kyphosis was so striking that surgical intervention for the kyphosis was suggested (Grade 3) but was not carried out upon the patient's request.

Case 2

A gradual change occurred after IORT for posterior mediastinal neuroblastoma (Figure 4). After several courses of chemotherapy, her remaining tumour was removed at the age of 15 months. 10 Gy of IORT was performed with a round 6 MeV electron beam of 3 cm diameter for the Th9 and Th10 spines. 3 years after IORT, a deformity was found only in the anterosuperior part of the Th 11 vertebral body. Thereafter, the deformity gradually spread throughout the vertebral body and caused mild scoliosis.

Discussion

Radiation-induced musculoskeletal morbidity is common after EBRT for paediatric malignancies. Paulino [17]

reported that more than 50% of patients who underwent EBRT for paediatric extremity sarcomas required corrective surgical procedures for radiation-induced bone deformity within 20 years. EBRT-associated skeletal changes include scoliosis, kyphosis, chest and rib deformities, leg length discrepancy, hypoplasia of the bone and osteocartilaginous exostoses [5, 18].

In particular, spinal kyphoscoliosis might impose therapeutic burden on affected individuals. From the long history of experience with EBRT for paediatric tumours, it is well known that asymmetrical partial irradiation for a vertebra causes anterior and/or lateral wedging of the vertebral body, and ultimately leads to kyphosis and/or scoliosis. Fibrosis and contracture of the irradiated paravertebral soft tissues may accelerate progression of the deformity [6].

Significant morbidity of spinal deformities after EBRT was reported in the late 1970s and early 1980s. Riseborough et al [19] reported that EBRT produced scoliosis in 56 of 81 (76%) children with Wilms' tumour. Among them, 24% showed scoliosis of over 25° of the Cobb angle and 20% required orthotic or surgical treatment. Mayfield et al [20] reported spinal deformities after EBRT (mostly with orthovoltage X-ray, with a mean spinal dose of 2746 Rad) in children with neuroblastoma. Of 74 children, 56 (76%) had spinal deformity. Of these, 50% had scoliosis and 16% kyphosis. The scoliosis and/or kyphosis were progressive with age. In 20% of the patients who survived longer than 5 years, spinal deformity was severe enough to warrant medical intervention.

In 1990, Butler et al [5] reported on a series of 143 children who developed spinal deformities (scoliosis in 50 (35%) and kyphosis in 14 (9%)) following EBRT for paediatric malignant tumours. However, only one patient with kyphosis required treatment [5]. The authors' work indicates that clinically significant morbidity of spinal deformity is less prevalent than previously reported. The differences are probably attributable to recent advances in EBRT technique and dose reductions [5]. More recently, Makiperna et al [21] evaluated radiation-induced spinal deformity in a group of 44 children with Wilms' tumour, neuroblastoma or other solid tumours at a median follow-up time of 19 years. Scoliosis with or without kyphosis (found in 40/44 patients) was the most common spinal deformity. Local soft-tissue atrophy in the field of irradiation was clinically discerned in 35 patients. Clinical symptoms related to the back occurred in five patients, all of whom had severe scoliotic and kyphotic deformity. The authors concluded that spinal abnormalities were common in these survivors [21].

From all previous reports, it is thought that radiation-induced spinal deformity is discernable within 77 months after radiation therapy, with a frequency of 10–100% [6, 21, 22]. Recent reports have disputed the necessity of surgical measures for spinal deformities in general. Orthotic treatment is indicated if the deformity progresses. A corrective plaster cast may be effective in slowing the progression.

The efficacy of IORT for paediatric malignant tumours has now been established solidly. IORT is beneficial in the management of a variety of paediatric tumours, including brain tumour [23], neuroblastoma [7, 9–11, 24],

Figure 2. An 8-year-old boy who received 12 Gy of intra-operative radiotherapy for a retroperitoneal neuroblastoma at age 40 months (Case 12). A 6 MeV beam was used for treating the para-aortic region. At the age of 5 years, an (a) anteroposterior radiograph indicated a compression-fracture-like deformity of the Th11 vertebral body. (b) Coronal MRI indicated a butterfly-like deformity of the Th11 vertebral body. The upper edge of the irradiation field was placed at the Th11 level. (c) A 6 MeV electron beam penetrated ~2 cm into the bone. (d) Dose distributions can be modified depending on the bone and the soft-tissue densities.

Wilms' tumour [25, 26], soft-tissue tumour and other malignant tumours [14]. It is thought that late complications of IORT are satisfactorily low in affected children [11, 12, 14, 16, 24]. As such, it was surprising that IORT-induced spinal deformity was prevalent in our series; nevertheless, it was clinically insignificant in all but one case.

Little is known about IORT-associated spinal deformities. Kuroda et al [8] drew attention to two patients

with minor maldevelopment of the irradiated vertebra in their series that included 33 children with advanced stage neuroblastoma who were treated with IORT combined with intensive chemotherapy. Other than the minor spinal deformity, no major complication of IORT was found in their series. Oertel et al [27] reported that no patient had developed scoliosis or clinically significant local growth retardation in their series of IORT, which included 16 children who had survived paediatric

Figure 3. A girl who was 9 years old at the onset of right adrenal neuroblastoma (Case 3). (a) After several courses of chemotherapy, the tumour was resected. Because of extension of the tumour to the renal hilum, her right kidney was non-functional. After resection of the residual tumour, as well as the right kidney, intra-operative electron irradiation (6 MeV, 12 Gy) was delivered to the para-aortic region and the resected cavity. The upper limit of the field was above the root of the superior mesenteric artery; the lower limit was at the level of the iliac bifurcations. (b) Estimated dose distribution for the intra-operative radiotherapy performed after the resection suggested that the asymmetric shape of the irradiated structures owing to resection of the right kidney resulted in delivery of a stronger dose to the right side, as well as to the anterior part of the vertebral body. Five years later, the patient suffered back pain and (c) anteroposterior and (d) lateral radiographs indicated severe kyphosis and mild scoliosis. Anterior wedging of the vertebral bodies was prominent. (e) A CT image suggests rotational deformities of the spinal column.

Figure 4. Sequential changes after intra-operative radiotherapy for thoracic neuroblastoma (Case 2). At age 15 months and after several courses of chemotherapy, the patient was treated with intra-operative radiotherapy (10 Gy; 6 MeV; round electron beam of 3 cm in diameter delivered to Th9 and Th10 spinal vertebrae) to remove the residual tumour.

malignancies for longer than six months. Instead, they reported that six children showed late morbidity possibly related to IORT, which included a severe nerve lesion, an orthopaedic complication, a ureteral stenosis (not clinically significant), a renal atrophy (not clinically significant) and loss of a treated limb; however, it remains to be determined whether to positively assign the disappointing loss of the limb to radiotherapy alone or multifactorial vascular injuries owing to radiation, surgery or polychemotherapy, singly or in combination. The prevalence of morbidity in their series was higher than that in other reports, presumably because a higher IORT dose combined with external radiotherapy was employed.

Although it was not clinically significant in most cases, IORT-related spinal deformity was common in our series. IORT is often utilised in combination with EBRT [27]. In our series, however, all patients underwent only IORT to the locoregional area as the initial treatment. This raises the question of whether IORT using a single dose may be more hazardous than the combination technique. In our series, we usually utilised a single dose of IORT, ranging from 10 Gy to 20 Gy, equivalent approximately to 25–50 Gy in standard fractionation protocols [28]. Although this dose is lower than that commonly employed in adult IORT, it may be harmful for developing bones in children.

Based on a review of the dose distribution in our series, the anterior aspect of the vertebral body was disproportionately exposed to excessive radiation dose; thus, it was vulnerable to anterior wedge-shaped deformity of the spine (kyphosis) but not scoliosis. In a particular case with nephrectomy, irradiation dose reached much deeper than usual at the site of nephrectomy, and dose distribution was asymmetric, causing clinically significant spinal deformity with scoliosis.

Limitations of the study

Only a few patients in this study were followed to skeletal maturity. Statistical analysis was not carried out

because of the small number of cases. Simulations of the IORT dose distribution were carried out for pre-operative CT data with virtually modified anatomical structures.

Conclusions

In conclusion, we found six deformities in 12 children who were followed up more than four years. Dose distributions of the electron beams to the spine may account for the observed specific deformities of the spine after IORT. Particular attention should be paid to the dose distribution when paravertebral anatomical structures are modified, such as in the post-nephrectomy case.

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