HHS Public Access

Author manuscript

Pediatr Blood Cancer. Author manuscript; available in PMC 2017 September 01.

Published in final edited form as:

Pediatr Blood Cancer. 2016 September ; 63(9): 1608–1614. doi:10.1002/pbc.26061.

Late toxicities of intensity-modulated radiation therapy for head and neck rhabdomyosarcoma

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Abstract

Purpose/Objectives—To examine the late effects of intensity modulated radiation therapy (IMRT) in pediatric patients with rhabdomyosarcoma of the head and neck.

Materials/Methods—All one-year survivors of pediatric head and neck rhabdomyosarcoma treated with IMRT at a single institution from 1999-2014 were assessed for long term complications. Late toxicities were graded according to CTCAE version 4.03.

Results—Among 30 patients, median age at IMRT was 7.4 (1.5-20.8) years, median follow-up was 7.7 (1.2-14.4) years, and median IMRT dose was 50.4 (36-50.4) Gy. Tumor subsites included parameningeal (80%), orbit (13%), and other (7%). Common late toxicities were facial disfigurement (n=23, 77%), growth hormone deficiency (n=11, 37%), cataract (n=10, 34%), and dental problems (n=10, 33%). Twenty-two patients (73%) had ≥ 2 late toxicities and fourteen patients (47%) had ≥ 3 late toxicities. Seventeen patients (57%) experienced grade 2 toxicity and ten patients (33%) had grade 3 toxicity. Grade 3 toxicities included visual disturbance, cataract, facial disfigurement, chronic sinusitis/otitis, and hearing loss. Severe facial deformity was noted in nine patients (30%), and three patients underwent cosmetic surgery. Patients with severe facial deformity were treated at younger ages (median 6.0 years versus 8.1 years for patients with no/non-severe facial deformity) and more likely to have infratemporal fossa tumors. There were no secondary solid malignancies.

Conclusions—Late radiation toxicities are common in survivors of pediatric head and neck rhabdomyosarcoma treated with IMRT. While the majority of late effects are mild-moderate, they can significantly impact quality of life, particularly facial disfigurement.

Keywords

intensity modulated radiation therapy; pediatric rhabdomyosarcoma; late radiation effects

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Conflicts of interest

Leonard Wexler reports personal fees from Astra-Zeneca, outside the submitted work.

Introduction

Rhabdomyosarcoma is the most common soft-tissue sarcoma in pediatric patients. Approximately 350 children and adolescents younger than age 20 are diagnosed with rhabdomyosarcoma each year in the United States. [1] Thirty-five percent of rhabdomyosarcomas are located in the head and neck, with subsites including parameningeal (15%), orbit (10%), and other head and neck sites (10%). Treatment includes multimodality therapy with chemotherapy for all patients, surgery if possible, and radiation, depending on stage, Intergroup Rhabdomyosarcoma Study Group (IRSG) surgical-pathological grouping, and primary tumor site as defined by the IRSG. Survival rates for pediatric patients with rhabdomyosarcoma are approximately 70%. [2-3] Excellent local control can be achieved for patients with head and neck rhabdomyosarcoma treated with intensity modulated radiation therapy (IMRT). [4]

In an effort to reduce radiation doses to normal tissue, and thereby minimize the acute and long-term toxicity of radiotherapy, radiation techniques for patients with head and neck rhabdomyosarcoma have significantly evolved over the past 20 years from three-dimensional (3D) conformal planning to IMRT and also proton radiotherapy. [4-7] While Paulino *et al.* has published long-term radiation effects in children with head and neck rhabdomyosarcoma treated with 3D-conformal radiation techniques and several authors have reported late toxicities for children with rhabdomyosarcoma treated with proton radiotherapy, there are limited data detailing the late toxicities for head and neck rhabdomyosarcoma treated with IMRT, with most reports instead focusing on survival and local control rates. [4, 6, 8-12] The objective of the current report is to fill this gap by delineating the late effects of IMRT in a single-institutional cohort of pediatric patients with rhabdomyosarcoma of the head and neck.

Methods

Patients

We identified 30 eligible patients treated with IMRT for rhabdomyosarcoma of the head and neck between 1999 and 2014. Waiver approval was obtained from the Memorial Sloan Kettering (MSK) Institutional Review Board/Privacy Board. Eligible patients were ≤21 years of age, treated with IMRT at MSK, and had detailed follow-up data within our institution for at least one year after initiation of IMRT. Twenty-two patients (73%), in addition to the minimum follow-up of one year, also had at least one evaluation in our institutional pediatric or adult “long-term follow-up clinics”, which provide rigorous screening, monitoring, and treatment for potential late complications of cancer therapy in childhood cancer survivors. All patients who enter the pediatric long term follow-up clinic are given a referral for neurocognitive testing. Patients with locally recurrent disease to the head and neck were excluded from this cohort, which could confound reporting of late effects within the radiation field.

Radiation techniques and treatment

Patients received IMRT as previously described with plans designed using an inverse planning algorithm and delivered by a 6-mv linear accelerator with dynamic multileaf collimators. [4] All patients received once-daily fractions of 1.8 Gy with median dose of 50.4 Gy (range, 36 Gy to 50.4 Gy). Twenty-two patients (73%) received 50.4 Gy and one patient received an abbreviated course of 48.6 Gy due to the onset of severe mucositis prior to receipt of the final prescribed fraction. Three patients with orbital embryonal rhabdomyosarcoma received 45 Gy. One patient with alveolar rhabdomyosarcoma of the left neck received 5 Gy of intraoperative radiation therapy followed by 41.4 Gy of IMRT. One patient with nasopharyngeal botryoid rhabdomyosarcoma had a gross total resection and received 36 Gy; another patient with paranasal sinus alveolar rhabdomyosarcoma had a complete response to neoadjuvant chemotherapy and thus also received 36 Gy.

Late toxicities

Late toxicities were defined as occurring more than 90 days after radiation treatment. All toxicities were graded according to Common Terminology Criteria for Adverse Events (CTCAE), version 4.03, except for facial disfigurement and dental problems. Facial deformity was not graded according to CTCAE criteria, which grades any scarring or disfigurement of the head or neck region as grade 3. Rather, in an effort to better describe the range of facial disfigurement in this cohort, facial disfigurement was categorized as either “mild,” “moderate,” or “severe” by treating physicians. “Severe” was defined as visible from a distance or resulting in cosmetic surgery. Dental problems were also not graded according to CTCAE but rather grouped descriptively, as CTCAE only includes dental caries and not other dental abnormalities. The interval time from IMRT start to the development of the first grade 2, grade 3, and grade 4 toxicities was recorded for each patient, and a cumulative incidence curve for the development of late toxicities was made by the Kaplan-Meier method.

Results

Among 30 patients, the median age at initiation of IMRT was 7.4 years (range, 1.5 to 20.8 years), and 70% patients were ≤10 years of age at the initiation of IMRT. The median follow-up was 7.7 years from initiation of IMRT (range, 1.2 to 14.4 years). At least five years of follow-up was available for 26 patients (87%), and at least ten years of follow-up was available for thirteen patients (43%). The most common tumor subsite was parameningeal (80%), followed by orbit (13%) and non-parameningeal head and neck (7%). Embryonal and botryoid histologies were the most common (73%) compared to alveolar or undifferentiated. The median dose of IMRT was 50.4 Gy (range, 36 Gy to 50.4 Gy). All patients received chemotherapy (100%). Six patients had a surgical resection (20%), while the majority of patients underwent biopsy only. Patient characteristics are summarized in **TABLE I**.

Late toxicities and CTCAE grades are shown in **TABLE II**. The number of evaluable patients indicates the patients were screened for a specific late effect. For example, if a patient did not have a thyroid stimulating hormone (TSH) and T4 documented, that patient

was excluded from the number of evaluable patients for hypothyroidism. Common late toxicities were facial disfigurement (n=23, 77%), growth hormone deficiency (n=11, 37%), cataract (n=10, 34%), and dental problems (n=10, 33%). There were 22 patients (73%) with ≥ 2 late toxicities and fourteen patients (47%) with ≥ 3 late toxicities. Seventeen patients (57%) had ≥ 1 grade 2 toxicity and ten patients (33%) had ≥ 1 grade 3 toxicity. Grade 3 late toxicities included visual disturbance, cataract, chronic sinusitis/otitis, and hearing loss. A cumulative incidence curve for the first development of grade 2, grade 3, and grade 4 toxicities is shown in **Figure 1**. At ten years post-radiation, the incidence of grade 2, grade 3, and grade 4 toxicities approached approximately 60%, 43%, and 6% respectively.

Facial disfigurement

Some degree of facial disfigurement was the most common late toxicity in our study, and was noted in 23 patients (77%). Facial disfigurement was categorized as “mild” in nine patients (30%), “moderate” in six patients (20%), and “severe” in nine patients (30%). Patients with severe facial deformity are further described in **TABLE III**. Three of the patients with “severe” facial disfigurement underwent subsequent cosmetic surgery – one received definitive radiation to the orbit and two received definitive radiation to the infratemporal fossa. Patients with severe facial deformity had a trend toward younger age at treatment; the median age at initiation of IMRT was 6.0 years for patients with severe facial deformity versus 8.1 years for patients with no or non-severe facial deformity. The most common tumor site was the infratemporal fossa for patients with severe facial deformity.

Endocrinopathies

Thirteen patients (43%) experienced endocrine dysfunction after the completion of therapy. The most common endocrine dysfunction was growth hormone deficiency (n=11, 37%), followed by central hypothyroidism (n=7, 24%), primary hypothyroidism (n=3, 10%), adrenocorticotropic hormone (ACTH) deficiency (n=4, 13%), and luteinizing and follicle stimulating hormone (LH/FSH) deficiency (n=4, 13%). Nine of these thirteen patients had endocrine dysfunction in ≥ 2 categories.

Eye problems

Fourteen patients (47%) developed a late toxicity of the eye, including cataracts, visual disturbance, glaucoma, amblyopia, or ptosis, as detailed by patient in **TABLE IV**. Ten patients developed cataracts (34%), the majority of which were grade 1 (80%). Two patients underwent removal of their cataracts (grade 3) – one patient had a history of left orbital rhabdomyosarcoma and the other had left ethmoid sinus rhabdomyosarcoma. Six patients developed visual disturbances (20%). The majority of visual disturbances were decreased visual acuity, except for one patient who developed diplopia requiring prism glasses. The two patients who developed grade 3 visual disturbance were all treated for rhabdomyosarcoma of the orbit. One patient with a left ethmoid sinus tumor developed grade 1 glaucoma (3%), and one patient with an infratemporal fossa tumor developed grade 1 amblyopia (3%). Two patients (7%) with orbital rhabdomyosarcoma developed ptosis requiring surgical correction.

Ear disorders

Ten patients (33%) developed a late toxicity of the ear, including hearing loss or chronic otitis. Hearing loss was reported in six patients (20%), primarily in those with tumors located in the skull base as shown in **TABLE V**. Three patients experienced unilateral hearing loss ipsilateral to the tumor. Chronic otitis was reported in six patients (20%), and three were characterized as grade 3 requiring myringotomy tubes.

Nose

Late toxicities included chronic sinusitis (n= 7, 23%), epistaxis (n=4, 13%), and chronic nasal congestion (n=3, 10%). Grade 3 chronic sinusitis occurred in one patient with rhabdomyosarcoma of the right skull base requiring sinoplasty. All cases of epistaxis and chronic nasal congestion were grade 1.

Oral Cavity/Throat

Ten patients (33%) experienced dental problems. Dental problems included atrophic maxilla and failing dentition in the maxilla, requiring dental implants, in two patients; dental caries in two patients; shortened roots in two patients; pyogenic granuloma in one patient; delayed dental eruption in one patient; and poor oral hygiene with plaque accumulation and gingivitis in one patient. Trismus occurred in four patients (13%), all of whom experienced grade 1 trismus that did not interfere with eating. Two patients developed grade 1 voice changes (7%).

Neurocognition

A total of 28 patients (93%) in our cohort received >10 Gy to the temporal lobe. Of the 30 patients in our cohort, 28 patients had documented neurocognitive testing available post-radiation. Four patients (13%) had grade 1 neurocognitive dysfunction documented post-radiation, which was defined as mild cognitive disability not inferring with work, school, or life performance. These patients were < 8 years of age at time of treatment (range, 3.0 to 7.3 years). Two patients with rhabdomyosarcoma of the infratemporal fossa exhibited decreased processing speed with no special education requirements. One patient with nasopharyngeal rhabdomyosarcoma exhibited slowed processing speed and weakness in memory retrieval with recommendation of Section 504 Plan and is currently an honors student in the high school. Of note, this patient's medical history was complicated by a fall causing an epidural hematoma requiring craniotomy. One patient with rhabdomyosarcoma of the infratemporal fossa also had a Section 504 Plan in place and is currently enrolled in college. Of the 30 patients in our cohort, 14 patients were >18 years old at the time of last follow-up, and all are currently enrolled in college or have graduated college. Two of these patients completed masters degrees and are considering doctorate programs, and one patient is currently in law school.

Psychological/behavioral problems

Nine patients (30%) were noted to have psychological or behavioral problems, which were likely multifactorial in nature. The median age of patients with psychological or behavioral issues at initiation of IMRT was 11.3 years (range, 3.0 – 16.0 years). Six cases were grade 1,

and three cases were grade 2 requiring medication. Two of the patients had a history of developmental delay pre-dating treatment, and their psychological disorders included attention deficit hyperactivity disorder and behavioral outburst in one patient (grade 1) and depression (grade 2) in one patient. The other grade 2 psychological disorders included bipolar disorder (grade 2) and depression (grade 2). Grade 1 other psychological disorders included anxiety (3 patients), labile mood (1 patient), and depression (1 patient).

Secondary malignancy

There were no secondary solid malignancies but two patients (7%) developed secondary acute myeloid leukemia and myelodysplastic syndrome. Both patients received alkylating agents and anthracyclines. There were no other grade 4 toxicities. One patient, whose primary tumor site was the nasopharynx, developed a radiation-induced WHO grade 1 schwannoma of the right C2-C3 neural foramen nine years following IMRT. One patient developed a benign thyroid nodule.

Discussion

In this review of 30 patients treated with IMRT for rhabdomyosarcoma of the head and neck, we found that these patients commonly experience late toxicities from IMRT. As the radiation techniques for rhabdomyosarcoma of the head and neck have evolved from 3D-conformal planning to IMRT, it is increasingly important to examine how the late toxicities of treatment have changed. [4-5] In seventeen children treated with 3D-conformal radiation techniques for head and neck rhabdomyosarcoma, Paulino *et al.* observed a wide range of severe late toxicities occurring greater than 10 years after radiation, including midbrain hemorrhage, chondronecrosis, pontine hemorrhage, or esophageal stenosis. [8] While these toxicities were not observed in our cohort, it is possible that such issues will become apparent with longer follow-up since 10-year follow-up was only available for 12 patients in our study. Additionally, the patient who developed chondronecrosis and esophageal necrosis in their report received a higher dose per fraction of 250 cGy. Our study otherwise reported similar late effects, such as neuroendocrine dysfunction, hearing loss, visual problems, facial asymmetry, hypothyroidism, and impaired dentition.

There are limited data detailing the late toxicities for head and neck rhabdomyosarcoma treated with IMRT, with most reports focusing on survival and local control rates and with limited follow-up. [4, 11-12] Combs *et al.* reported late toxicities in nine patients with head and neck rhabdomyosarcoma treated with IMRT or fractionated stereotactic radiotherapy with a median follow-up of 17 months. [11] Late toxicities included reduced lacrimation, chronic eye swelling, visual disturbance, trismus, facial asymmetry, and growth hormone deficiency. Curtis *et al.* reported late toxicities in six children treated with IMRT for head and neck rhabdomyosarcoma with a median follow-up of 4.6 years. [12] Late toxicities included cataracts, hypothyroidism, growth hormone deficiency, facial asymmetry, and secondary malignancy. These studies are limited by relatively short median follow-up, thus preventing comparison to our findings.

In addition to comparing late toxicities associated with IMRT to those observed with 3D conformal techniques, it would also be useful to compare these results to proton therapy

data. Dosimetric comparison of IMRT to proton therapy treatment plans in a phase II trial of patients with pediatric rhabdomyosarcoma demonstrated the mean integral dose was 1.8 times higher for IMRT to the head and neck ($p<0.01$), and significant tissue sparing was seen in many critical structures such as chiasm, pituitary, hypothalamus, brainstem, cerebellum, maxilla, mandible, contralateral optic nerve, and temporal lobe with the use of protons. [7] Similarly, Kozak *et al.* in a dosimetric comparison of IMRT and proton therapy for parameningeal rhabdomyosarcomas reported a significant decrease in mean dose in all normal structures except for ipsilateral cochlea and mastoid with proton radiotherapy. [13] Childs *et al.* reported the late toxicities of proton radiation in 10 pediatric patients with parameningeal rhabdomyosarcoma including decreased height velocity, endocrinopathies, facial hypoplasia, chronic nasal congestion, and dental problems, with a median follow-up time of 5 years. [9] The late toxicities of 43 patients with any tumor site enrolled in this phase II trial have been reported by Ladra *et al.* and include: grade 3 late toxicities, including cataract, chronic otitis, and retinopathy with decreased visual acuity, in 7% of patients; grade 2 late toxicities, including dry eye, facial asymmetry, epistaxis, dry skin, chronic otitis, endocrine abnormalities, hearing loss, and cognitive disturbance, in 20% of patients. [6] For 39 pediatric patients with parameningeal rhabdomyosarcoma treated with pencil beam scanning proton radiotherapy, Weber *et al.* reported grade 1 late toxicities in 21% of patients, grade 2 late toxicities in 26% of patients, and grade 3 late toxicities in 8% of patients with no secondary malignancies at median follow-up of 3.4 months. Grade 3 toxicities included cataract and hearing loss. [10]

The most common late toxicity observed in our study was facial disfigurement in 77% of patients; three patients subsequently underwent facial reconstructive surgery. Paulino *et al.* similarly reported a high percentage of facial asymmetry in 73% of patients treated with 3D conformal radiation, including three patients who underwent facial reconstruction, and Childs *et al.* reported facial hypoplasia in 70% of patients for whom late toxicities were reported treated with proton radiation at a median follow-up of 5 years. [8-9] Combs *et al.* reported facial asymmetry in only one patient (5%) with a median follow-up of 17 months after IMRT, [11] suggesting that longer follow-up may be needed to observe this late effect. We noted that patients with “severe” facial disfigurement in our study had a trend toward younger age at treatment with median age of 6.0 years for those with severe facial disfigurement versus 8.1 years for those with no or non-severe facial deformity. Often facial deformities do not become apparent until after the adolescent growth spurt. The median age of our patients at last follow-up was 17.0 years (range, 5.4 to 32.0 years), and 24 patients (80%) were older than 12 years of age at last follow-up.

Soft tissue sarcoma survivors are known to be at risk of developing subsequent cancers, as reported by the Childhood Cancer Survivor Study. [14] As IMRT increases the volume of normal tissue exposed to low-dose radiation compared to 3D-conformal techniques, it is particularly import to monitor for the development of secondary solid malignancies within the radiation field. None of the patients in our cohort developed a secondary solid malignancy but two patients (7%) developed secondary acute myeloid leukemia and myelodysplastic syndrome (grade 4), presumably secondary to chemotherapy. While even wide-field radiation in pediatric patients with Hodgkin's disease has not been associated with development of leukemia, chemotherapy is known to be associated with subsequent

leukemia. [15] One patient developed a secondary radiation-induced neoplasm, a WHO grade 1 schwannoma, within the radiation field nine years following IMRT. Paulino *et al.* reported the development of only one secondary solid malignancy in their study of late effects of 3D-conformal radiation, which was a parotid mucoepidermoid carcinoma at the edge of the radiation field twenty years following radiation therapy. [8] In a report by Casey *et al.* on 242 pediatric patients treated with IMRT at our institution, six patients developed a secondary malignancy, four with secondary solid malignancies within the radiation field and two with myelodysplastic syndrome. [16] The median time from IMRT to a secondary solid malignancy was 7.2 years in that report, which is comparable to the median follow-up time in the current study. Curtis *et al.* reported the development of an osteosarcoma four years post-radiation therapy within the radiation field for a patient with a p53 mutation following IMRT. [12] Combs *et al.* reported no secondary malignancies in a study of 19 patients with head and neck rhabdomyosarcoma, but with median follow-up of only 17 months. [11] Ladra *et al.* reported no secondary malignancies in the phase II trial of proton radiotherapy for pediatric rhabdomyosarcoma with median follow-up of 3.9 years. [6] For all of these studies, including the present report, longer follow-up is needed to better assess the risk of secondary solid cancers after radiotherapy.

Our study has a number of limitations which must be considered. One important limitation is the lack of a validated grading system for facial disfigurement, as the CTCAE simply grades any scarring or disfigurement of the head or neck region as a grade 3. Our evaluation of facial disfigurement was subjective and based on the consensus of treating physicians. Additionally, we were unable to document the precise age at development of facial disfigurement which may be useful when comparing our results to other patient cohorts, as patients treated at younger ages may skew results for a higher incidence of facial disfigurement. Another limitation of our study was the inability to evaluate the patients' feelings about their facial appearance and the impact this may have on their quality of life. Facial asymmetry has considerable impact on quality of life, as three of our patients underwent subsequent facial reconstructive surgery and one of these patients developed depression in part related to facial disfigurement. The largest limitation of our study is the retrospective nature. A major strength of this study is the detailed screening for late toxicities provided by our institutional pediatric or adult "long term follow-up clinics", which included 73% of patients in this study. These patients are comprehensively examined and tested for known late effects of their cancer therapy in our "long term follow-up clinics." Routine screening and monitoring is critical for these patients to recognize and treat late toxicities of their cancer treatment. Additionally, lengthy follow-up is paramount, as studies have shown complications arising even >10 years following radiation therapy. [8] Though we required at least one year of follow-up post-IMRT, only three patients in our cohort had less than three years of follow up. With longer duration of follow-up, particularly for children treated in their first decade of life, more late sequelae are likely to emerge. Another limitation of our retrospective review was that the majority of patients did not have neurocognitive testing at baseline prior to radiation treatment, but rather neurocognitive testing was performed post-radiation. In the future, this would be helpful to assess in a prospective study.

It is imperative to closely observe the long-term effects of treatment for pediatric patients, who are at risk for adverse quality of life and even increased risk of death following cancer survival. [17-18] It should also be considered that even with evolving and more conformal radiation techniques, the delivery of radiation to normal structures directly abutting or involved by tumor cannot be spared in order to adequately treat the tumor according to current treatment standards. Unfortunately, we do not know which patients can safely have radiation eliminated or meaningfully dose-reduced. For parameningeal tumors where local recurrence is the dominant risk of treatment failure, some radiation late sequelae may be the unfortunate price of successful treatment of the tumor.

Conclusions

Late radiation toxicities are commonly seen in pediatric rhabdomyosarcoma survivors treated with IMRT to the head and neck. The majority of late effects are mild-moderate in severity. Facial disfigurement was the most common late effect of IMRT, especially in younger children with infratemporal fossa tumors. Future research efforts are needed to minimize the magnitude of radiation-related late effects. These data on late effects with IMRT for head and neck rhabdomyosarcoma will be useful for future comparison to other tissue sparing techniques such as proton therapy.

Acknowledgements

This work was funded in part by NIH/NCATS grant KL2 TR000458 of the Clinical and Translational Science Center at Weill Cornell and the NIH/NCI Cancer Support Grant P30 CA008748.

Abbreviations

ACTH	adrenocorticotropic hormone
CTCAE	Common Terminology Criteria for Adverse Events
FSH	follicle stimulating hormone
Gy	gray
IMRT	intensity modulated radiation therapy
LH	luteinizing hormone
MSK	Memorial Sloan Kettering
TSH	thyroid stimulating hormone
WHO	World Health Organization

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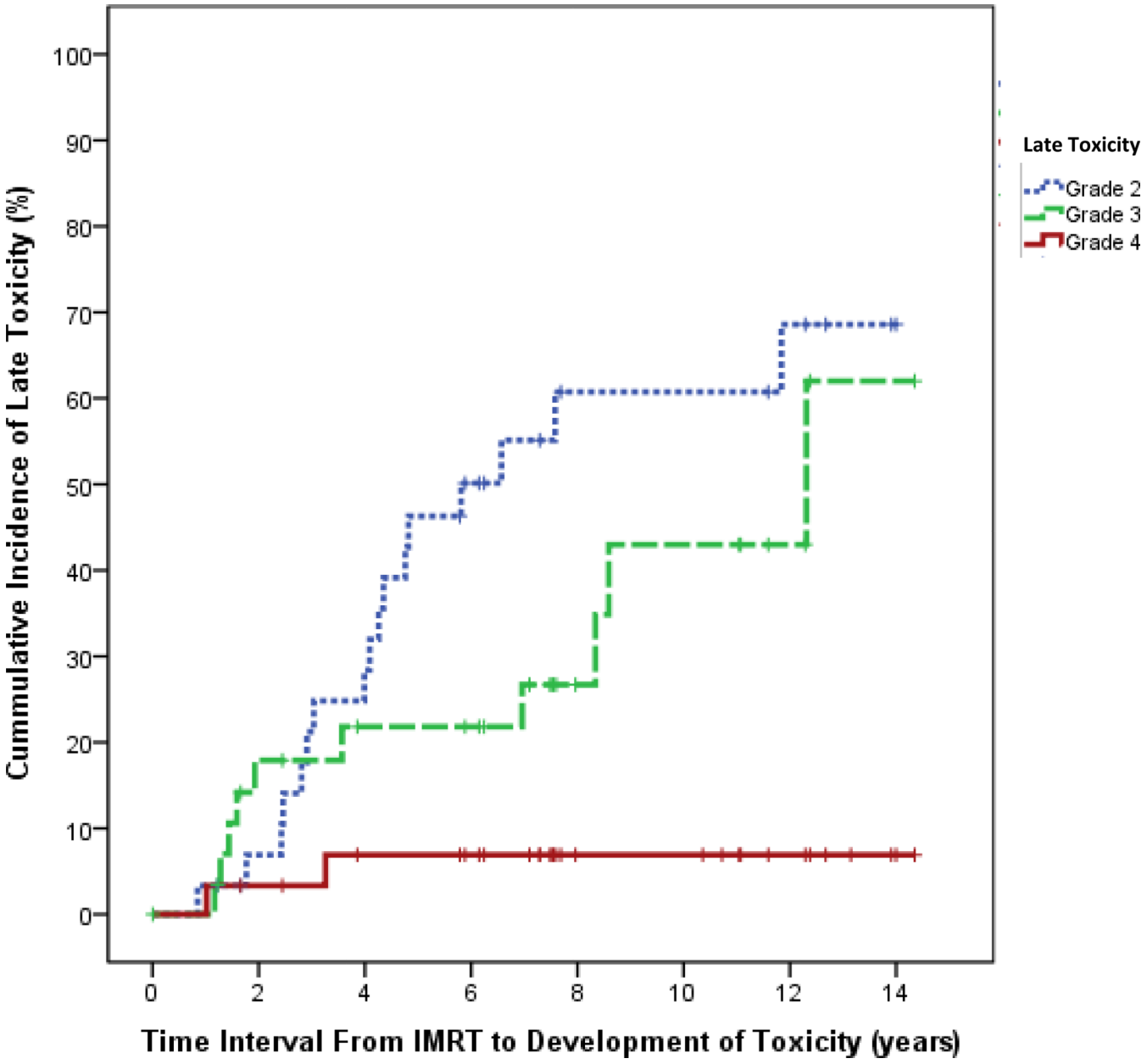

Figure 1.

Cumulative incidence curve for the development of late toxicities following intensity modulated radiation therapy (IMRT) for head and neck rhabdomyosarcoma in pediatric patients.

TABLE I

Patient Characteristics

Characteristic	No. (%)
Age at initiation of IMRT	
1-5 years	9 (30.0)
6-10 years	12 (40.0)
11-15 years	6 (20.0)
16-20 years	3 (10.0)
Gender	
Male	11 (36.7)
Female	19 (63.3)
Race	
Caucasian	26 (86.7)
African American	3 (10.0)
Asian	1 (3.3)
Tumor subsite	
Parameningeal	24 (80.0)
Infratemporal fossa	10
Nasopharynx	7
Paranasal sinus	3
Ethmoid sinus	2
Parapharyngeal region	2
Orbit	4 (13.3)
Neck	1 (3.3)
Buccal	1 (3.3)
Histology	
Embryonal/botryoid	22 (73.3)
Alveolar/undifferentiated	8 (26.7)
Surgery	
Biopsy only	24 (80.0)
Resection (subtotal or total)	6 (20.0)
Chemotherapy	
Any	30 (100)
Alkylators	29 (96.7)
Anthracyclines	21 (70.0)

TABLE II

Late Toxicities After Head and Neck Intensity Modulated Radiation Therapy for Pediatric Rhabdomyosarcoma

Late Toxicity	No. of Evaluable Patients	Any Grade No. (%)	Grade 1 No.	Grade 2 No.	Grade 3 No.	Grade 4 No.
Facial disfigurement	30	23 (76.7)	-	-	-	-
Growth hormone deficiency	30	11 (36.7)	1	9	0	0
Cataract	29	10 (34.5)	7	2	0	0
Dental problems	30	10 (33.3)	-	-	-	-
Psychological/behavioral problems	30	9 (33.0)	6	3	0	0
Central hypothyroidism	29	7 (24.1)	0	6	0	0
Chronic sinusitis	30	7 (23.3)	3	3	1	0
Chronic otitis	30	6 (20.0)	1	2	3	0
Hearing loss	30	6 (20.0)	0	3	2	0
Visual disturbance	30	6 (20.0)	3	1	2	0
Trismus	30	4 (13.3)	4	0	0	0
Epistaxis	30	4 (13.3)	4	0	0	0
Cognitive deficits	30	4 (13.3)	3	0	0	0
ACTH deficiency	30	4 (13.3)	0	3	0	0
LH/FSH deficiency	30	4 (13.3)	1	2	0	0
Primary hypothyroidism	29	3 (10.3)	0	3	0	0
Nasal congestion	30	3 (10.0)	3	0	0	0
Ptosis	30	2 (6.7)	0	0	2	0
Voice changes	30	2 (6.7)	2	0	0	0
Secondary malignancy	30	2 (6.7)	0	0	0	2
Thyroid nodule	28	1 (3.6)	1	0	0	0
Glaucoma	30	1 (3.3)	1	0	0	0
Amblyopia	30	1 (3.3)	1	0	0	0
Schwannoma	30	1 (3.3)	1	0	0	0

TABLE III

Severe Facial Disfigurement After Head and Neck Intensity Modulated Radiation Therapy for Pediatric Rhabdomyosarcoma

	Tumor site	Age at IMRT, years	Description
1	Left infratemporal fossa	9.8	Hypoplasia of left frontolateral facial bones
2	Right infratemporal fossa	6.0	Underwent facial reconstructive surgery; right orbital hypoplasia; also with related depression
3	Left orbit	8.4	Underwent facial reconstructive surgery left orbital hypoplasia
4	Nasopharynx, right>left	3.0	Mid-facial hypoplasia
5	Left ethmoid sinus	8.7	Left orbital and mid facial hypoplasia
6	Left orbit/infratemporal fossa	1.7	Left hypoplasia and mild facial asymmetry
7	Nasopharynx and ethmoid sinus, left >right	4.4	Facial hypoplasia and small jaw
8	Left infratemporal fossa	3.4	Facial hypoplasia and asymmetry
9	Left infratemporal fossa/orbit	7.3	Left facial and orbital hypoplasia; underwent facial reconstructive surgery

TABLE IV

Orbital Toxicities After Head and Neck Intensity Modulated Radiation Therapy for Pediatric Rhabdomyosarcoma

	Tumor site	Tumor laterality	Toxicity	Toxicity grade	Toxicity laterality	Comments
1	Orbit	Left	Cataract Ptosis	1 3	Left Left	Status post surgical correction
2	Orbit	Left	Cataract	1	Bilateral	
3	Nasopharynx	Right>left	Cataract	1	Right	
4	Infratemporal fossa	Left	Am blyopia	1	Right	Refractory amblyopia
5	Infratemporal fossa	Right	Visual disturbance	1	Unknown	Wears glasses
6	Orbit	Left	Cataract	1	Left	Blind in left eye pre-radiation
7	Nasopharynx/right orbit	Right>left	Visual disturbance Cataract	3 1	Right Left	Blind in right eye
8	Ethmoid sinus	Left	Visual disturbance Cataract Glaucoma	1 3 1	Left Left Unknown	Decreased visual acuity Status post cataract removal Diagnosed at outside institution
9	Orbit	Left	Visual disturbance Cataract Ptosis	1 3 3	Left Left Left	Decreased visual acuity Status post cataract removal Status post surgical correction
10	Ethmoid sinus/orbit	Left	Cataract	1	Unknown	
11	Infratemporal fossa/orbit	Left	Visual disturbance	3	Left	Left eye decreased visual acuity
12	Nas opharynx	Left>right	Cataract	1	Bilateral	Left greater than right
12	Skull base	Left	Visual disturbance	2	-	Diplopia requiring glasses
13	Infratemporal fossa/orbit	Left	Cataract	1	Left	Blind in left eye pre-radiation

TABLE V

Hearing Loss After Head and Neck Intensity Modulated Radiation Therapy for Pediatric Rhabdomyosarcoma

	Tumor Site	Tumor Laterality	Hearing Loss Grade	Hearing Loss Laterality	Comments
1	Neck	Left	2	Bilateral	Received vincristine; no cisplatin or carboplatin
2	Skull base	Left	2	Bilateral	Right mixed hearing loss, left conductive hearing loss; received carboplatin and vincristine
3	Skull base	Right	3	Unilateral	Right conductive hearing loss; received carboplatin and vincristine
4	Infratemporal fossa	Left	3	Unilateral	Left mixed hearing loss; received carboplatin and vincristine
5	Skull base	Left	3	Unilateral	Requires left hearing aid; received cisplatin and vincristine
6	Infratemporal fossa	Left	1	Bilateral	Bilateral conductive hearing loss