Published in final edited form as:

Pediatr Hematol Oncol. 2016 September ; 33(6): 383–392. doi:10.1080/08880018.2016.1219797.

Long-term Effect of Chemo-Intensity-Modulated Radiation Therapy (chemo-IMRT) on Dentofacial Development in Head and Neck Rhabdomyosarcoma Patients

Adepitan A. Owosho, B.Ch.D¹, Paul Brady, BS², Suzanne L. Wolden, MD², Leonard H. Wexler, MD³, Cristina R. Antonescu, MD⁴, Joseph M. Huryn, DDS¹, and Cherry L. Estilo, DMD^{1,*}

¹Department of Surgery, Memorial Sloan Kettering Cancer Center

²Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center

³Department of Pediatrics, Memorial Sloan Kettering Cancer Center

⁴Department of Pathology, Memorial Sloan Kettering Cancer Center

Abstract

Dentofacial developmental abnormalities have been reported in head and neck rhabdomyosarcoma (HNRMS) patients treated with conventional radiotherapy technique and chemotherapy. This current study investigates dentofacial long-term effects among HNRMS survivors managed with intensity-modulated radiotherapy (IMRT) and chemotherapy. In general, IMRT is a more effective 3D-conformal radiotherapy technique, which delivers high doses of radiation to the tumor target while minimizing doses received by the surrounding normal tissues. The medical records and radiographs were reviewed to identify the following: 1. Facial asymmetry and jaw hypoplasia. 2. Effects on the dental tissue causing tooth agenesis/hypodontia, root agenesis/stunting/malformation, and/or enamel hypoplasia. 3. Trismus, hyposalivation/xerostomia. Thirteen patients reviewed were evaluated at the dental service. Seven patients presented with facial asymmetry and jaw hypoplasia, 9 patients presented with effects on the dental tissue [root agenesis/stunting/malformation (9), tooth agenesis/hypodontia (7) and enamel hypoplasia (3)] and 7 patients developed trismus and /or xerostomia. All patients with facial asymmetry and jaw hypoplasia also developed dental abnormalities. Patients with dentofacial developmental abnormalities were 7 years of age at treatment. Our study shows that dentofacial developmental abnormalities are still a burden in the era of IMRT and as prognosis of childhood malignancy improves and more patients become long-term survivors, these late dentofacial sequelae among childhood cancer survivors will be common. To minimize these complications, dental oncologists should be integrated into the care of children with head and neck cancers.

*To whom correspondence should be addressed. estiloc@mskcc.org, Telephone: 212-639-7644, Address: Dental Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY 10065.

Disclosure: All authors declare that there are no financial conflicts associated with this study and that the funding source has no role in conceiving and performing the study.

Keywords

IMRT; Chemotherapy; Dentofacial developmental abnormalities; Head and Neck Rhabdomyosarcoma

Introduction

Rhabdomyosarcomas are the most common soft tissue sarcomas in pediatrics, accounting for 5–8% of all childhood malignancies [1]. The head and neck is the commonest site for rhabdomyosarcoma [2, 3]. Head and neck rhabdomyosarcomas (HNRMS) are divided into 3 anatomic sub-sites: (i) parameningeal (PM) sites such as nasopharynx, nasal cavity, middle ear, paranasal sinuses, mastoid, parapharyngeal region, pterygopalatine and infratemporal fossa; (ii) orbital sites; and (iii) lesions that arise in non-PM/non-orbital sites [4]. Involvement of the PM sub-site is the most common sub-site [2, 3, 5].

The last three decades have seen significantly improved outcomes due to evolving multidisciplinary therapy paradigms, including improved surgical techniques, aggressive chemotherapy regimens and more effective conformal intensity-modulated radiotherapy (IMRT). The 5-year survival rate of RMS rose from 53% in 1980 to 62% in 2000, with greatest progress made with embryonal RMS [6]. However, survivors of childhood HNRMS remain at risk of dentofacial developmental abnormalities from radiotherapy and chemotherapy [7–11].

The following late sequelae of chemoradiation therapy-related toxicities to the dentofacial structures have been reported: facial asymmetry, jaw hypoplasia, tooth agenesis/hypodontia, root agenesis/shortening/malformation, enamel hypoplasia, trismus, and xerostomia [7–18]. It has been suggested that the use of modern conformal radiation therapy techniques such as IMRT might help minimize these late sequelae based on the claim of delivering high doses of radiation to the tumor target while minimizing doses received by the surrounding normal tissues [11], and further studies to characterize the long-term dental effects on survivors treated with IMRT have been recommended [19].

The use of chemotherapy-IMRT (chemo-IMRT) in the management of HNRMS, especially lesions arising in the parameningeal sub-sites (mid-face region), might suggest little to no long-term effect complication to the teeth and tooth-bearing regions of the lower jaw due to dose conformality and tissue-sparing capability of IMRT. The aim of this study is to investigate dentofacial long-term effects among HNRMS survivors managed with chemo-IMRT.

Patients and Methods

The study was approved by the Institutional Review Board of Memorial Sloan Kettering Cancer Center (MSKCC), New York. The medical records and radiographs of all HNRMS patients younger than 16 years of age at treatment with long-term survival of at least 5 years post-treatment with chemo-IMRT at MSKCC were reviewed for this retrospective study. The radiation dose to the affected region of the jaw was calculated from the pre-radiation

planning software. The method for dosimetric contouring of the jaw was described in our previous study [20]. Thirty-six patients met the inclusion criteria. However, only 13 patients were evaluated in the Dental Service of MSKCC. Table 1 summarizes patient characteristics, treatment modality and dentofacial abnormalities.

There were 8 females and 5 males, with a median age at treatment at 5 years (range 19 months to 13 years). The median survival time was 12 years (range 7 – 16 years). The median dental follow-up time was 9 years (range: 1 – 13). Tumor sites were orbit in 1 patient and parameningeal in 12 [infratemporal fossa (5), nasopharynx (5), parapharyngeal (1) and middle ear (1)] patients. Eight patients had tumor stage III and 5 patients had tumor stage IV. Ten patients had embryonal RMS, 2 patients spindle RMS, and 1 patient alveolar RMS. All patients were treated with multiagent chemotherapy and IMRT. The median radiation dose to the primary tumor was 50.4 Gy (range 45 to 50.4 Gy) and the chemotherapy agents were vincristine, doxorubicin, cyclophosphamide, ifosfamide, and etoposide.

All patients had no prior history of radiation or retreatment and completed a treatment course of chemotherapy and radiation. The effects of chemo-IMRT on the dental and facial tissue were divided into: 1. Effects causing facial asymmetry and jaw hypoplasia. 2. Effects on the dental tissue causing tooth agenesis/hypodontia, root agenesis/stunting/malformation, enamel hypoplasia. 3. Effects causing trismus, hyposalivation/xerostomia.

Results

Table 1 shows patient characteristics, clinical and radiographic findings. Nine of the 13 patients developed dentofacial abnormalities secondary to therapy. These patients were 1.6 to seven years of age at treatment. One patient was treated at age 7 and did not develop dentofacial abnormality. He was treated for orbital RMS and received a mean radiation dose less than 5 Gy to the mandible and 10 Gy to the maxilla. The remaining patients without dentofacial abnormality were 9 to 13 years of age at treatment and they developed xerostomia and/or trismus. The mean radiation dose to the affected regions in all patients were mandible (35.7 Gy, range: 5 – 53.6 Gy) and maxilla (42.2 Gy, range: 10 – 50.4 Gy). The maxillae of all patients were in the planning target volume (PTV) while, the mandibles of 5 patients (Patients 3, 5, 6, 8, 9) were in the PTV. The dosimetric information for a patient (Patient 7) was not available.

Facial asymmetry and jaw hypoplasia

Seven patients (Patients 1, 2, 4, 5, 6, 7, and 8) presented with facial asymmetry and jaw hypoplasia with ages at treatment ranging from 1.6 – 7 years old. The jaw hypoplasia was observed in the maxilla and mandible (Figure 1). The primary tumors in these patients were located in the mid-face region and received 25 – 50.4 Gy of radiation to the maxilla (Table 1).

Effects on the dental tissue

Nine patients (Patients 1 – 9) presented with effects on the dental tissue ranging from tooth agenesis, root agenesis/stunting and malformed enamel (hypoplastic or hypocalcified) with ages at treatment ranging from 1.6 – 7 years old. These patients received 45 – 50.4 Gy to the

mid-face (see Table 1). The most consistent feature in these patients was root agenesis/stunting involving all nine patients in both jaws and both anterior and posterior teeth. Tooth agenesis/hypodontia involving the posterior teeth was identified in seven patients (Patients 1 – 6, 9) (premolar and molars) (Figures 2). Enamel malformation (hypoplasia) was identified in three patients (patients 1, 2, 5).

Trismus and hyposalivation/xerostomia

Seven patients (Patients 7 – 13) presented with trismus and xerostomia with ages at treatment ranging 5 – 13 years old. The tumors in these patients resided in the mid-face region with the exception of one patient with orbital RMS. All patients in this group received 50.4 Gy of radiation to the primary tumor (see Table 1). Four patients (Patients 7, 8, 11 and 13) presented with trismus with ages at treatment ranging from 5 – 13 years old, while xerostomia was reported in 4 patients (Patients 9, 10, 11 and 12) with ages at treatment ranging from 7 – 13 years old.

Discussion

This study reports the long-term effects of chemo-IMRT on dentofacial development in 13 long-term survivors of head and neck RMS treated with a combination modality of chemotherapy and IMRT. The following dentofacial abnormalities were identified: facial asymmetry and jaw hypoplasia, tooth agenesis/hypodontia, root agenesis/stunting, enamel hypoplasia, trismus, and xerostomia. The severity of dentofacial developmental abnormalities in this study was related to the age at treatment and tumor/therapy site. In this study, patients < 7 years old presented with more significant dentofacial complications (facial asymmetry, jaw hypoplasia, tooth agenesis/hypodontia, root agenesis/stunting/malformation and enamel hypoplasia) compared to their older counterparts. Trismus and xerostomia were the most common long-term effects in the older (> 7 years at treatment) patient population. A similar finding was reported by Kaste et al., who observed that patients younger than 8 years old had a higher prevalence of dental abnormalities after radiotherapy [18]. The extent of dentofacial complications is believed to be related to the site of the primary tumor as well as the dose received to the jaws. For example, patients with lateral tumors developed jaw hypoplasia resulting in facial asymmetry at the site of the primary tumor. In addition, the patient treated for orbital RMS received mean radiation dose less than 5 Gy to the mandible and 10 Gy to the maxilla; subsequently, these patients did not develop significant dentofacial abnormalities. Kaste et al. further reported that radiation dose >20 Gy placed patients at a 4 – 10-fold higher risk of developing dental abnormalities [15]. Similarly, patients in this study who developed significant dentofacial abnormalities received at least 25 Gy to the maxilla and mid-face.

Ameloblasts have been shown to be damaged at 10 Gy and tooth development to be completely halted at 30 Gy [21]. However, dentofacial developmental abnormalities have been reported from far less radiation [22]. In this study we were able to show that patients who developed dentofacial abnormalities received greater than 10 Gy of radiation to the mandible. In our study, patients with posterior jaw involvement received greater than 30 Gy, which would account for the greater incidence of tooth agenesis in these regions.

It is postulated that the use of IMRT should help minimize late complications based on the claim of delivering high doses of radiation to the tumor target while minimizing doses received by the surrounding normal tissues [11]. It is well-known that chemotherapy alone can result in dental abnormalities such as tooth agenesis/hypodontia, root agenesis/stunting/malformation and enamel hypoplasia [23–29]. Studies have shown that the severity of dental abnormalities is related to type and intensity of chemotherapy agent and the age of the patients at first exposure and that patients younger than five years old are at a greater risk of dental developmental abnormalities [15, 30]. In animal models, the effects of vincristine, cyclophosphamide and doxorubicin have been suggested to be a result of inhibition of odontogenesis [31–34]. Vincristine inhibits the secretion of collagenous dentine matrix by odontoblasts and cyclophosphosamide induces apoptosis in primitive mesenchymal cells and pre-odontoblasts by binding to the DNA [31–33].

The prevalence of xerostomia in children who receive head and neck radiation is lower compared to the adult population [35]. In our study only four patients presented with xerostomia and it was in older patients (7 years old). In our study trismus was also reported in four patients. The prevalence of trismus in childhood nasopharyngeal carcinoma ranges from 7 – 27% [12, 36, 37]. Radiation dose to the salivary glands and temporomandibular joint and muscles of mastication are risk factors for xerostomia and trismus. Osteoradionecrosis (ORN) of the jaw is very rare in the pediatric population. None of our patients presented with ORN.

The use of proton RT is gradually gaining ground in the management of pediatric head and neck tumors because of its potentially greater normal-tissue-sparing capability [38, 39]; this would suggest that the use of proton RT might help minimize late complications. Future studies evaluating the long-term effect of proton RT on dentofacial development in head and neck RMS patients are encouraged.

Conclusion

Our study shows that dentofacial developmental abnormalities continue to be burden in the era of IMRT. The average age of diagnosis for children with head and neck rhabdomyosarcoma is 5 years and more than 50% of these patients are pre-pubertal when diagnosed. This is a uniquely vulnerable population in whom the use of radiation will produce long-term complications almost inevitably. As prognosis after diagnosis with childhood malignancy improves and more patients become long-term survivors, these late dentofacial sequelae among childhood cancer survivors will be more common. To minimize these complications a dental oncologist should be integrated into the care of children with head and neck cancers.

Acknowledgments

This study was supported in part through the NIH/NCI Cancer Center Support Grant P30 CA008748.

References

1. Gurney JG, Young JL, Roffers SD, Smith MA. Soft Tissue Sarcomas. National Cancer Institute. 1999;111–124.
2. Pappo AS, Shapiro DN, Crist WM, Maurer HM. Biology and therapy of pediatric rhabdomyosarcoma. *J Clin Oncol*. 1995; 13:2123–2139. [PubMed: 7636557]
3. Hicks J, Flaitz C. Rhabdomyosarcoma of the head and neck in children. *Oral Oncol*. 2002; 38:450–459. [PubMed: 12110339]
4. Wharam MD Jr. Rhabdomyosarcoma of Parameningeal Sites. *Semin Radiat Oncol*. 1997; 7:212–216. [PubMed: 10717216]
5. Turner JH, Richmon JD. Head and neck rhabdomyosarcoma: a critical analysis of population-based incidence and survival data. *Otolaryngol Head Neck Surgery*. 2011; 145:967–973.
6. Ognjanovic S, Linabery AM, Charbonneau B, Ross JA. Trends in childhood rhabdomyosarcoma incidence and survival in the United States, 1975–2005. *Cancer*. 2009; 115:4218–4226. [PubMed: 19536876]
7. Dury DC, Roberts MW, Miser JS, Folio J. Dental root agenesis secondary to irradiation therapy in a case of rhabdomyosarcoma of the middle ear. *Oral Surg Oral Med Oral Pathol*. 1984; 57:595–599. [PubMed: 6588339]
8. Kaste SC, Hopkins KP, Bowman LC. Dental abnormalities in long-term survivors of head and neck rhabdomyosarcoma. *Med Pediatr Oncol*. 1995; 25:96–101. [PubMed: 7603407]
9. Raney RB, Asmar L, Vassilopoulou-Sellin R, Klein MJ, Donaldson SS, Green J, et al. Late complications of therapy in 213 children with localized, nonorbital soft-tissue sarcoma of the head and neck: A descriptive report from the Intergroup Rhabdomyosarcoma Studies (IRS)-II and - III. IRS Group of the Children's Cancer Group and the Pediatric Oncology Group. *Med Pediatr Oncol*. 1999; 33:362–371. [PubMed: 10491544]
10. Paulino AC, Simon JH, Zhen W, Wen BC. Long-term effects in children treated with radiotherapy for head and neck rhabdomyosarcoma. *Int J Radiat Oncol Biol Phys*. 2000; 48:1489–1495. [PubMed: 11121653]
11. Estilo CL, Huryn JM, Kraus DH, Sklar CA, Wexler LH, Wolden SL, et al. Effects of therapy on dentofacial development in long-term survivors of head and neck rhabdomyosarcoma: the memorial sloan-kettering cancer center experience. *J Pediatr Hematol Oncol*. 2003; 25:215–222. [PubMed: 12621240]
12. Kupeli S, Varan A, Ozyar E, Atahan IL, Yalcin B, Kutluk T, et al. Treatment results of 84 patients with nasopharyngeal carcinoma in childhood. *Pediatr Blood Cancer*. 2006; 46:454–458. [PubMed: 16200569]
13. Welbury RR, Craft AW, Murray JJ, Kernahan J. Dental health of survivors of malignant disease. *Arch Dis Child*. 1984; 59:1186–1187. [PubMed: 6524952]
14. Maguire A, Craft AW, Evans RG, Amineddine H, Kernahan J, Macleod RI, et al. The long-term effects of treatment on the dental condition of children surviving malignant disease. *Cancer*. 1987; 60:2570–2575. [PubMed: 3664436]
15. Kaste SC, Goodman P, Leisenring W, Stovall M, Hayashi RJ, Yeazel M, et al. Impact of radiation and chemotherapy on risk of dental abnormalities: a report from the Childhood Cancer Survivor Study. *Cancer*. 2009; 115:5817–5827. [PubMed: 19834960]
16. Goho C. Chemoradiation therapy: effect on dental development. *Pediatr Dent*. 1993; 15:6–12. [PubMed: 8233995]
17. Jaffe N, Toth BB, Hoar RE, Ried HL, Sullivan MP, McNeese MD. Dental and maxillofacial abnormalities in long-term survivors of childhood cancer: effects of treatment with chemotherapy and radiation to the head and neck. *Pediatrics*. 1984; 73:816–823. [PubMed: 6728583]
18. Kaste SC, Hopkins KP, Jones D, Crom D, Greenwald CA, Santana VM. Dental abnormalities in children treated for acute lymphoblastic leukemia. *Leukemia*. 1997; 11:792–796. [PubMed: 9177429]
19. Gawade PL, Hudson MM, Kaste SC, Neglia JP, Constine LS, Robison LL, et al. A systematic review of dental late effects in survivors of childhood cancer. *Pediatr Blood Cancer*. 2014; 61:407–416. [PubMed: 24424790]

20. Hansen HJ, Maritim B, Bohle GC 3rd, Lee NY, Huryn JM, Estilo CL. Dosimetric distribution to the tooth-bearing regions of the mandible following intensity-modulated radiation therapy for base of tongue cancer. *Oral Surg Oral Med Oral Pathol Oral Radiol*. 2012; 114:e50–e54. [PubMed: 22769422]
21. Kaste SC, Hopkins KP, Jenkins JJ 3rd. Abnormal odontogenesis in children treated with radiation and chemotherapy: imaging findings. *AJR Am J Roentgenol*. 1994; 162:1407–1411. [PubMed: 8192008]
22. Fromm M, Littman P, Raney RB, Nelson L, Handler S, Diamond G, et al. Late effects after treatment of twenty children with soft tissue sarcomas of the head and neck. Experience at a single institution with a review of the literature. *Cancer*. 1986; 57:2070–2076. [PubMed: 3955515]
23. Avsar A, Elli M, Darka O, Pinarli G. Long-term effects of chemotherapy on caries formation, dental development, and salivary factors in childhood cancer survivors. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 2007; 104:781–789. [PubMed: 17618135]
24. Kaste SC, Hopkins KP, Bowman LC, Santana VM. Dental abnormalities in children treated for neuroblastoma. *Med Pediatr Oncol*. 1998; 30:22–27. [PubMed: 9371385]
25. Maciel JC, de Castro CG Jr, Brunetto AL, Di Leone LP, da Silveira HE. Oral health and dental anomalies in patients treated for leukemia in childhood and adolescence. *Pediatr Blood Cancer*. 2009; 53:361–365. [PubMed: 19484760]
26. Alpaslan G, Alpaslan C, Gogen H, Oguz A, Cetiner S, Karadeniz C. Disturbances in oral and dental structures in patients with pediatric lymphoma after chemotherapy: a preliminary report. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 1999; 87:317–321. [PubMed: 10102592]
27. Oguz A, Cetiner S, Karadeniz C, Alpaslan G, Alpaslan C, Pinarli G. Long-term effects of chemotherapy on orodental structures in children with non-Hodgkin's lymphoma. *Eur J Oral Sci*. 2004; 112:8–11. [PubMed: 14871187]
28. Pedersen LB, Clausen N, Schroder H, Schmidt M, Poulsen S. Microdontia and hypodontia of premolars and permanent molars in childhood cancer survivors after chemotherapy. *Int J Paediatr Dent*. 2012; 22:239–243. [PubMed: 22092748]
29. Marec-Berard P, Azzi D, Chaux-Bodard AG, Lagrange H, Gourmet R, Bergeron C. Long-term effects of chemotherapy on dental status in children treated for nephroblastoma. *Pediatr Hematol Oncol*. 2005; 22:581–588. [PubMed: 16166051]
30. Sonis AL, Tarbell N, Valachovic RW, Gelber R, Schwenn M, Sallan S. Dentofacial development in long-term survivors of acute lymphoblastic leukemia. A comparison of three treatment modalities. *Cancer*. 1990; 66:2645–2652. [PubMed: 2249205]
31. Stene T, Koppang HS. Autoradiographic investigation of dentin production in rat incisors after vincristine administration. *Scand J Dent Res*. 1980; 88:104–112. [PubMed: 6929558]
32. Orams HJ. Cyclophosphamide-induced changes in rodent odontogenesis. A light- and electron-microscopic study. *Cell Tissue Res*. 1983; 234:679–689. [PubMed: 6661756]
33. Vahlsing HL, Feringa ER, Britten AG, Kinning WK. Dental abnormalities in rats after a single large dose of cyclophosphamide. *Cancer Res*. 1975; 35:2199–2202. [PubMed: 1149033]
34. Dahl JE. Immediate and delayed effects of repeated doxorubicin injections on rat incisor mesenchymal cells. *Acta Odontol Scand*. 1985; 43:155–162. [PubMed: 3864334]
35. Effinger KE, Migliorati CA, Hudson MM, McMullen KP, Kaste SC, Ruble K, et al. Oral and dental late effects in survivors of childhood cancer: a Children's Oncology Group report. *Support Care Cancer*. 2014; 22:2009–2019. [PubMed: 24781353]
36. Daoud J, Toumi N, Bouaziz M, Ghorbel A, Jlidi R, Drira MM, et al. Nasopharyngeal carcinoma in childhood and adolescence: analysis of a series of 32 patients treated with combined chemotherapy and radiotherapy. *Eur J Cancer*. 2003; 39:2349–2354. [PubMed: 14556927]
37. Zubizarreta PA, D'Antonio G, Raslawski E, Gallo G, Preciado MV, Casak SJ, et al. Nasopharyngeal carcinoma in childhood and adolescence: a single-institution experience with combined therapy. *Cancer*. 2000; 89:690–695. [PubMed: 10931470]
38. Kozak KR, Adams J, Krejcarek SJ, Tarbell NJ, Yock TI. A dosimetric comparison of proton and intensity-modulated photon radiotherapy for pediatric parameningeal rhabdomyosarcomas. *Int J Radiat Oncol Biol Phys*. 2009; 74:179–186. [PubMed: 19019562]

39. Ladra MM, Edgington SK, Mahajan A, Grosshans D, Szymonifka J, Khan F, et al. A dosimetric comparison of proton and intensity modulated radiation therapy in pediatric rhabdomyosarcoma patients enrolled on a prospective phase II proton study. *Radiother Oncol.* 2014; 113:77–83. [PubMed: 25443861]

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Figure 1. Clinical picture of a 13-year-old patient (patient 2) treated for rhabdomyosarcoma of the nasopharynx at age 3; showing jaw hypoplasia of both the maxilla and mandible affecting the patients skeletal profile. (A) Lateral view of the face. (B) Anterior view of the face. (C) Patient's dentition.

Figure 2.
Panoramic radiograph of the same patient in figure 1 (patient 2). The radiograph shows teeth agenesis in # 1, 2, 4, 13, 15, 16, 17, 18, 20, 29, 31, and 32 as well as generalized root stunting, multiple over-retained primary teeth, and microdontia.

Table 1

Shows patient characteristics, clinical and radiographic findings

Patients #	Age at therapy (yr)	Radiation dose to tumor (Gy)	Tumor site	Dental visit follow-up (yr)	Facial asymmetry and jaw hypoplasia	Tooth agenesis / root stunting / enamel malformation / over-retained primary teeth	Trismus / xerostomia	Mean radiation dose to the affected region (Gy)
1	1.6	45	Left infratemporal region	13	Facial asymmetry, left maxillary and mandibular hypoplasia	Tooth agenesis: # 1, 2, 4, 13, 15, 16, 17, 18, 20, 29, 31, 32, generalized root stunting, enamel hypoplasia, multiple over-retained primary teeth and microdontia	NR	Maxilla (25), mandible (5)
2	3	50.4	Nasopharynx	13	Maxillary and mandibular hypoplasia	Tooth agenesis: # 1, 2, 4, 13, 15, 16, 17, 18, 20, 29, 31, 32, generalized root stunting, enamel hypoplasia, multiple over-retained primary teeth and microdontia	NR	Maxilla (35), mandible (35)
3	3	50.4	Left infratemporal region	6	Facial asymmetry, left maxillary and mandibular hypoplasia	Tooth agenesis: # 1, 2, 4, 13, 15, 16, 17, 18, 20, 29, 32, generalized root stunting, multiple over-retained primary teeth and microdontia	NR	Left maxilla (53.6), left mandible (53.6)
4	3	50.4	Nasopharynx	5	Maxillary hypoplasia	Tooth agenesis: # 1, 16, 17, 32, generalized root stunting and microdontia: # 2, 15, 18, 31	NR	Maxilla (35), mandible (35)
5	4	50.4	Nasopharynx	13	Maxillary hypoplasia	Tooth agenesis: # 1, 16, 17, 32, enamel hypoplasia and generalized root stunting	NR	Maxilla (50.4), mandible (42)
6	4	50.4	Left infratemporal region	7	Facial asymmetry, left maxillary and mandibular hypoplasia	Tooth agenesis: # 1, 15, 16, 17, 18, 31, 32, generalized root stunting, multiple over-retained primary teeth and microdontia	NR	Left maxilla (50.4), left mandible (50.4)
7	5	50.4	Right infratemporal region	9	Facial asymmetry, right maxillary hypoplasia	Generalized root stunting	Trismus	-
8	7	50.4	Left infratemporal region	8	Facial asymmetry, left maxillary hypoplasia	Root stunting: # 2, 15, 18, 31 and microdontia: # 1, 16, 17, 32	Trismus	Left maxilla (50.4), left mandible (50.4)
9	7	50.4	Right tonsillar region	5.5	NR	Tooth agenesis: # 1, 16, 17, 32, generalized root stunting and multiple over-retained primary teeth	Xerostomia	Maxilla (45), mandible (45)
10	7	50.4	Left Orbit	12	NR	NR	Xerostomia	Maxilla (10), mandible (5)

Patients #	Age at therapy (yr)	Radiation dose to tumor (Gy)	Tumor site	Dental visit follow-up (yr)	Facial asymmetry and jaw hypoplasia	Tooth agenesis / root stunting / enamel malformation / over-retained primary teeth	Trismus / xerostomia	Mean radiation dose to the affected region (Gy)
11	9	50.4	Nasopharynx	11	NR	NR	Trismus	Maxilla (50.4)
12	10	50.4	Right infratemporal region	12	NR	NR	Xerostomia	Maxilla (50.4)
13	13	50.4	Right infratemporal region	1	NR	NR	Mild trismus and xerostomia	Maxilla (50.4)

NR – none reported