Long Term Maxillofacial Effects of Radiotherapy in Young Nasopharyngeal Carcinoma Patients: Report of 3 Cases

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Nasopharyngeal carcinoma (NPC) is a rare and distinct malignancy that arises from the epithelium of the nasopharynx. It accounts almost 1 % of all pediatric malignancies. Oral complications of radiotherapy in the head and neck region are the result of the deleterious effects of radiation on salivary glands, oral mucosa, bone, dentition, masticatory musculature, and temporomandibular joints.
Here we present 3 male NPC patients 13, 14 and 15 years old. One of them had stage III and the others stage IV diseases. Administered dose of radiation was 66 Gy for case I, 70 Gy for case II and 68 Gy for case III. The follow-up period was more than 12 months except for case III and all of them were disease free in their last visit. All attended dental clinics for dental and TMJ problems. Dentitions were severely affected, trismus and severe xerostomia. Long term effects of radiotherapy which has a great impact on patients' quality of life and the role of supportive care and minimizing the late effects of ionizing radiation are discussed.
Keywords: *Nasopharyngeal carcinoma, children, radiotherapy, trismus, xerostomia, pediatric population*

INTRODUCTION

Nasopharyngeal carcinoma (NPC) is a rare and distinct malignancy that arises from the epithelium of the nasopharynx and differs from other head and neck cancers by its histological, epidemiological and biological characteristics.[1] World Health Organization (WHO) classifies the NPC by its histological types, such as type I is squamous cell carcinoma (SCC), type II is non-keratinizing carcinoma and type III is undifferentiated carcinoma, and pediatric NPC is almost always type II- III.[2] NPC shows direct expansion property and mostly spreads to parapharyngeal space (65-90%), bone destruction is not rare (25-35%). Since nasopharynx has a connection with lymphatic tissues, NPC metastasis easily to lymphatic nodes especially cervical nodes in early stages (70-80%).[3]

Incidence of head and neck cancers accounts only 2-5% in all childhood malignancies. The percentage of NPC in childhood head and neck cancers is 15%, whereas it accounts for only nearly 1% of all pediatric malignancies.[2-4] The mean age of disease is in between 5th-6th decade of life but in some populations it can make a second peak in 15-25 years age.[2-3-4] Not only for pediatric population but also for all age groups, NPC is a rare malignancy worldwide, if distinct increase in some geographic regions, as Southern China (including Hong Kong), Southeast Asia, Arctic Region, North Africa and Middle East is not taken into account.[1] The etiology of NPC is associated with Epstein-Barr Virus (EBV) infection, occupational exposure to dusts, using of wood fire in cooking and consumption of salted fish and herbal medicine. Especially consumption of salted fish is common in the geographic regions mentioned above.[3]

Clinical manifestation of NPC are; temporomandibular disorders (TMD) with dysfunction and rarely pain, hearing loss, epistaxis, plugged sensation or auditory drainage. These symptoms could warn the patient to consult a physician. Also these manifestations should be well recognized by all medical staff including dentist in order to increase the rate of early diagnosis.[3]

The main treatment of NPC is RT (either convention external beam radiotherapy (EBRT) or intensity-modulated radiation therapy (IMRT)) whereas chemotherapy (CT) and RT is applied together in most cases. The well- established effects of head-neck RT include oral mucositis, infections (fungal and bacterial), salivary gland dysfunction (sialadenitis and xerostomia), taste dysfunction in acute or early phase whereas mucosal fibrosis and atrophy, taste dysfunction (dysgeusia and ageusia), infections (fungal, bacterial and viral), xerostomia, dental caries, soft tissue necrosis, osteoradionecrosis, muscular/cutaneous fibrosis, maturational disturbances, especially in craniofacial bone structure, for young-aged patients are recognized as chronic or long term effects.[5]

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Table I. The grade of the tumors and therapy schedule of patients.

	TNM/ Stage	Therapy	Free of Disease	Dental follow up
Case 1	T3N2M0/Grade III	RT (66Gy) CT (Neoadjuvan 3 courses of PEB*)	28/03/2003	2007-2011 (48 months)
Case 2	T3N2M1/Grade IVC	RT (70 Gy) CT (Concomitan 3 courses of cisplatin+ 2 courses of cisplatin&taxotere for metastasis)	25/05/2005	2007-2009 (24 months)
Case 3	T4N2M0/Grade IVB	RT (68 Gy) CT (Neoadjuvan 3 courses of PEB*)	29/8/2005	2007-2008 (12 months)

Here we report 3 young male NPC patients who were 13,14 and 15 years old at the time of presentation. One of them had stage III and the others had stage IV diseases. All patients were treated with fractionated EBRT and CT. Administered dose of radiation was 66 Gy with 4 years follow up for case I, 70 Gy with 2 years follow up for case II and 68 Gy with 1 years follow up for case III. All of them were disease free in their last visit (Table I). They attended dental clinics with dental and TMJ problems. Teeth were severely affected and they had trismus besides severe xerostomia. Patients received a restorative dental program and supportive therapy for xerostomia.

This report aims to discuss long term effects of radiotherapy in pediatric NPC patients which has a great impact on quality of life, especially in young patients, and the role of supportive care and minimizing the late effects of ionizing radiation.

Case I

A 14 year-old boy was referred to Department of Oral and Maxillofacial Surgery at the University of Istanbul with severe xerostomia, limited mouth opening and caries. The patient reported head and neck RT for NPC when he was 10 years old. On clinical examination, dentition was severely affected with maximal interincisal distance (MID) measured as 14 mm and severe xerostomia. Caries were restored in Department of Operative Dentistry clinics with glass ionomer (14, 16, 24, 26 Black I, 34, 35, Black II, 42, 43 Black IV and 34, 35, 44, 45 Black V) and amalgam based fillings (47 Black II) (Figure 1). Topical neutral fluoride gel applications were performed to avoid new radiation caries in every 3 months for the first year and every 6 months after one-year period in control of patient and GC Tooth Mousse® (Tokyo/Japan) was advised to be used once a week. In order to treat xerostomia mouth moisturizing gel and mouthwash including lysozyme, lactoferrin, lactoperoxidase were advised. Since there was a restriction in mouth opening, we suggested making jaw opening and closing exercises 3x20 times every day and referred the patient to physical therapy clinics for trismus and TMJ problems. The jaw range of motion (ROM) exercise of the TMJ with a hot packs and massage to the masseter muscles were performed. After these therapies, we observed 2-3 mm changes in the amount of MID. Unfortunately the patient did not comply with the notifications and MID regressed back to 14mm again in 6 months. He is still being followed every 6 months.

Case II

A 15 year-old boy was redirected to Department of Oral and Maxillofacial Surgery at the University of Istanbul for caries, severe xerostomia and trismus by his oncologist. He reported that these problems became after RT for NPC when he was 12 years old. On clinical examination, dentitions were severely affected, the maximal interincisal distance (MID) measured was 13 mm (Figure 2) and he presented severe xerostomia. His caries were restored in Department of Operative Dentistry clinics with glass ionomer based fillings (14, 22 Black II, 46 Black III and 14, 15, 17, 24, 25, 26, 27, 35, 36, 37, 46, 47 Black V). Lack of saliva led to new caries and to avoid them, topical neutral fluoride gel applications were performed in every 3 months for the first year and every 6 months after one-year period. GC Tooth Mousse® was recommended to be used once a week. At the same time mouth moisturizing gel and mouthwash including lysozyme, lactoferrin, lactoperoxidase were advised for xerostomia. We suggested making jaw opening and closing exercises 3x20 times every day and he was referred to physical therapy clinic. ROM exercise of the TMJ with a hot packs and massage to the masseter muscles were done. After these therapies we observed 3mm changes in the amount of MID. The patient complied with the notifications properly so MID did not degrade. He is still being followed every 6 months.

Figure 1. Glass ionomer based fillings of Case I

Figure 2. Case II's MID is only 13mm

Figure 3. a) Dental condition of Case III after dental treatment and **b)** one year after without dental follow up.

Case III

A 13 year-old boy referred to Department of Oral and Maxillofacial Surgery at the University of Istanbul with severe xerostomia and severe caries. Parents reported that patient received head and neck RT and CT for NPC when he was 10 years old. On clinical examination, dentitions were severely affected, the maximal interincisal distance (MID) measured 19 mm with severe xerostomia. Mouth moisturizing gel and mouthwash including lysozyme, lactoferrin, lactoperoxidase were advised for xerostomia. Endodontic treatments (11, 14, 21, 24, 25, 36, 43 and 46) were done and the teeth were restored with glass ionomer based fillings (14, 46 Black I, 24, 25, 35 Black II, 36 Black II, 11, 21 ,41 Black IV and 43, 44 Black V) in Department of Operative Dentistry Clinics. Topical neutral fluoride gel applications were performed in every 3 months for the first year in patient's control and GC Tooth Mousse® was advised to be used once a week. We suggested making jaw opening and closing exercises 3x20 times every day. The patient did not continue his control sessions regularly after 1 year and dental problems relapsed. (Figure 3a, 3b).

DISCUSSION

Head and neck RT has well known side effects on oral mucosa as well as oral health in the long term. Especially childhood tumors which are treated with RT affect quality of life significantly. Generally, effects of head and neck radiotherapy are grouped under three headings: early (mucosa, taste and salivary gland), intermediate (taste and salivary gland) and late (salivary gland, dentition, periodontal, bone, muscles and joints) changes.[5] However the quality of life is more important for pediatric patient survivors. New technical developments of RT, like IMRT, seem to decrease the amount of late changes.[6]

Trismus or limited mouth opening may develop due to tumor mass or result of head and neck RT. Most patients result in trismus when RT was performed involving the TMJ, pterygoid muscles or masseter muscle and high dose RT increases the severity of trismus. Trismus occurs about 3 to 6 months after the RT then stabilizes 1 year later, and affects the quality of life. Patients may have serious health problems including malnutrition, difficulty in speaking and compromised oral hygiene.[5-6] Trismus can be graded by MID measurement: grade 1, MID is 20-30 mm; grade 2, MID is 10-20 mm; grade 3, MID is 5-10 mm; and grade 4, MID< 5 mm.[6] Due to our clinical observations not many cases of NPC experience trismus before RT. Only case III had limited mouth opening before RT. Our three patients has experienced trismus grade 2 after RT. We suggested making jaw opening and closing exercises 3x20 times every day and when these exercises were not enough patients were referred to physical therapy clinics. After physical therapy we observed only 2-3 mm changes in the amount of MID, and their problems continued. When the exercises were not done properly, trismus became even severe. Nowadays there is another option for external beam radiotherapy (EBRT) called IMRT. Besides debatable benefits, Chen *et al* reported that IMRT also reduced the incidence and severity of trismus after therapy.[6] IMRT and the exercises, which should start early with the RT and be applied regularly, are important to prevent of fibrosis in the muscles and problems with TMJ Trismus can impact the oral hygiene status, therefore the dental problems caused by xerostomia increase.

Xerostomia is both early and late side effects of head and neck radiation. This problem is probably caused by damaged salivary gland tissue.[5] Developing complex IMRT techniques has been found to protect the parotid glands against the adverse effect of head and neck RT in long term.[7-8] It is well defined in literature that if the parotid glands receive doses of greater than 40 Gy, there is no satisfactory recovery in salivary gland function which is monitored. All three patients had NPC and were treated before IMRT was in use at Radiation Oncology Clinics of Istanbul University so EBRT which is known to lead severe xerostomia, were applied for their therapy. All the received RT doses were over 40 Gy for parotid glands. Tumor size and stage, volume of salivary gland irradiated also act on the salivary gland hypofunction/ damage due to therapy and tumor itself.[5] All patients had advanced diseases: one in grade III and others were grade IV. The tumor size increased the radiation field and major salivary glands except sublingual received 40 Gy and over. Mouth moisturizing gel and mouthwash were started to be used in order to provide oral care and improve the quality of life. In case III he needed to sip water while he was speaking. After 3 months of using mouth moisturizing gel and mouthwash, he was able to speak and sleep (more than 3 hours) without the help of water. All patients had marked relief in xerostomia.

Salivary hypofunction not only affects the oral mucosa and the functions such as speaking, chewing and swallowing but also dentition severely.[5] Hypersensitivity of teeth is common which affect the oral hygiene. Radiation caries usually occur on the cervical and incisal surfaces on the teeth. Restorations should be hygienic, with acceptable esthetics and function.[9] Radiation induced root surface carries restored with more viscous glass-ionomer and fluoride applications were beneficial to prevent carries and hypersensitivity.[9-10] Treatment, done with patients, were consistent with the literature. Dental treatment is important for young aged cancer survivors, to improve their life quality as well as their systemic health.[11]

RT may cause abnormalities in the growth and maturation of craniofacial skeletal structures at younger age.[12] Various factors

such as early age, radiation dose, adjuvant CT, genetic and endocrine factors can change the clinical effect of RT on craniofacial bone growth.[13] Growth hormone deficiency (GHD) is an indirect effect of RT and develops generally within 5 years of treatment.[12-13] Although our patients had both RT and CT in their treatment schedule they were not affected on the basis of growth and maturation of skeletal structures. This thought to be associated with the age of patients in treatment onset. The only effect was on neck structures both in bones and muscles; they were atrophic in all patients.

Hearing loss is another side effect of both head and neck RT and CT. Platinum agents such as cisplatin and carboplatin in chemotherapeutic drugs can cause hearing loss at early ages. RT can influence all parts of the auditory system. Cochlea is more sensitive than auditory nerves. IMRT affects target tissue, so cochlear's exposure is limited.[14] No marked hearing loss was detected in our patient group in follow up period. Its an inevitable effect of EBRT but the percent of hearing loss is not more than %10 in this patient group so there was no social problem detected.

Radiation induced dysphagia is both early and late side affect of head and neck RT. In early stages edema and acute inflammation can lead to dysphagia. Fibrosis damages the skeletal muscles and this situation results to dysphagia in late term of RT.[15] The patients did not experience any dysphagia problem except the issues related xerostomia. They have to take sip of water/liquid in order to eat solid food.

CONCLUSION

In this paper the importance of dental procedures for supportive care for cancer is emphasized. There is an increasing number of grown up children who have had experienced cancer and they have to live rest of their lives with a very low quality of life.

In order to achieve the goal of survival in better quality, a better cooperation is warranted in the oncology team including dentists.

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