RADIOTHERAPY INDUCED TOXICITY FOR OROPHARYNGEAL CANCER PATIENTS: IMPLICATIONS FOR ORAL HEALTH

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ABSTRACT
Radiotherapy is most often used for the treatment of head and neck tumors as an independent method or in combination with surgery and chemotherapy, the multidisciplinary approach being the therapeutically standard in locally advanced cancers. In the group of head and neck cancers, oropharyngeal cancer presents an increased incidence especially in the young population. Unlike head and neck cancers related to smoking cancers that usually occur in the 6th decade of life, oropharyngeal cancers with viral etiology associated with HPV infection have a favorable prognosis. Long time survivals and the curable potential of this entity have led to the necessity of toxicity reduction strategies to improve the quality of life of these patients. Although modern radiotherapy techniques IMRT and VMAT have greatly reduced the dose received by the radiosensitive organs, the oral mucosa is close to the target volumes or even partially included in these volumes irradiated with high doses leading to acute and late toxicities: oral inflammation, loss of taste, dry mouth syndrome caused by xerostomia and secondary infections. Most commons late effects are dental caries, trismus and osteoradionecrosis. The aim of the study is to evaluate the doses received by organs at risk (the oral cavity, the parotid glands and the mandible) for 20 cases of multimodal treated oropharyngeal cancers and to discuss these data in relation to treatment toxicity.
Keywords: head and neck cancers, radiotherapy, oral cavity toxicity

Introduction

Although multimodal treatments of head and neck cancers have made significant progress, the toxicities associated with irradiation of radiosensitive organs from the proximity of the tumor volume are common. Xerostomia, radiation-induced oral mucositis, radio necrosis of the jaw and dental pathologies are just some of the negative effects of treatment. Oral mucositis is one of the most common side effects of head and neck cancer patients occurring during radiotherapy or chemo-radiotherapy, and is often the cause for discontinuation of the optimal radiotherapy delivery, and one cause of severely quality of life impairments. Over the last decade, research has proven that oral mucosal toxicity is not only caused by direct lesions, but is also the consequence of biological events involving sub mucous tissues. Late toxicity to the oral mucosa is relatively unknown, being mainly caused by the reduction in salivary flow. The most frequent late radiation effects on mucosal layers of the upper aerodynamic tract are thinning of the epithelium, loss of mucosal flexibility and sub-mucosal damage [1],[2].

Radiation-induced mucositis is an inflammatory reaction of the mucous membrane of the oral and oropharynx and is an inevitable but transient effect in the case

of irradiation of the head and neck cancers. The first signs and symptoms of oral mucositis include erythema and edema, burning sensation and increased warm and spicy food sensitivity. In the next stage the irradiated mucosa shows redness, inflammation, begins to decompose, with the formation of white or yellow pseudo membranes as a result of basal layer desquamation. The erythematous areas can turn into desquamation patches and later in painful ulcers that are at increased risk of infection. Radiation-induced mucositis has negative consequences to the nutritional capacity and to the fluids intake being a cause of malnutrition and dehydration [3].

The response of the acute mucosa to radiotherapy is due to the basal cell, the death of the mucosal epithelium, compromising the ability of the mucosa to regenerate thus leading to thinning of the epithelium and ulcers, but it also affects the endothelium of the blood vessels. The parenchymal component (salivary acini) is also radiosensitive. Serous cells are more radio-sensitive than mucosal cells, so the parotid glands are more sensitive to xerostomia than submandibular or sublingual glands. The first radiation-induced changes include degeneration or destruction of the acinar tissue with subsequent inflammation and significant loss of salivary secretion during the first weeks of treatment. After months of irradiation, fibrosis occurs due to chronic inflammation but also adiposis, loss of vasculature and degeneration of the parenchyma occurred, all of these physiopathological changes ultimately leading to xerostomia. Low concentration of Ca^{2+} caused by xerostomia leads to greater solubility of tooth structure and demineralization impairments. Dysphagia, a consequence of the edema of structures involved in irradiation, is also aggravated by the loss of lubricating capacity with consistency in affecting mastication and swallowing. It is initially observed as progressive loss of salivary secretion and the mouth becomes dry and tender. Characteristics such as age, sex, salivary gland function at the onset of treatment are factors that influence the risk of xerostomia [4, 5, 6]. Osteoradionectrosis (ORN) of the mandible is one of the most severe chronic side effects of head and neck radiotherapy with significant associated morbidity and subsequent treatment may vary from close observation to radical surgical resection. ORN is a radiation induced fibrosis with histopathological formation phases very similar to chronic wounds, with the activation and regulatory disruption of fibroblast activity substrate [7].

Materials and methods

Our study included 20 patients diagnosed with oropharyngeal cancers and multimodal treated with platinum-based chemotherapy alone or in combination with taxanes or fluorouracil (2-4 cycles) followed by radiotherapy delivered in a total dose of 70Gy/35 fractions to the target volume of the primary tumor, 66Gy/33 fractions on the tumor volume of the high-risk cervical lymph nodes and 50Gy/25 fractions on the target volume of low-risk supraclavicular lymph nodes.

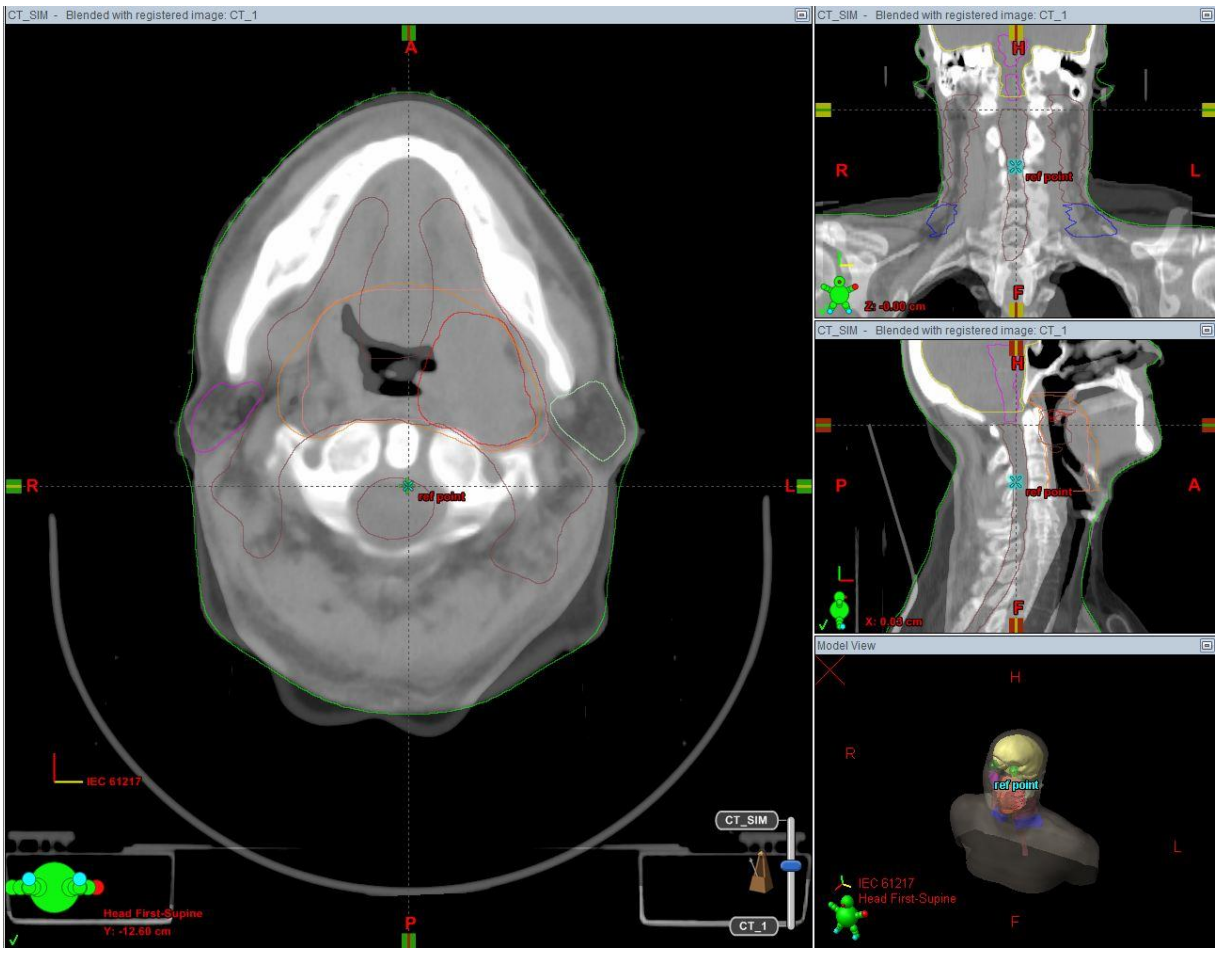

Fig. 1 Registration between contrast agent diagnostic imaging and CT simulation for target volume delineation and 3D reconstruction of OARs - image from Varian Eclipse ™ (TPS)

Using Volumetric Intensity Modulated Arc Therapy (VMAT) technique, the mean doses for parotid glands, oral cavity and mandible considered organs at risks (OARs) was evaluated. For radiotherapy planning, a CT simulation was performed and used for delineation of the target volumes and radiosensitive organs.

For a more precise delimitation of tumor anatomic borders and to identify the maximum tumor volume prior to administration of the chemotherapy, a rigid co-registration algorithm was used between CT imaging (CT or MRI) and simulation CT images (Fig 1).

A two arcs algorithm with a 600cGy /minute dose rate was used to create VMAT (RapidArc®) treatment plans (Fig 2).

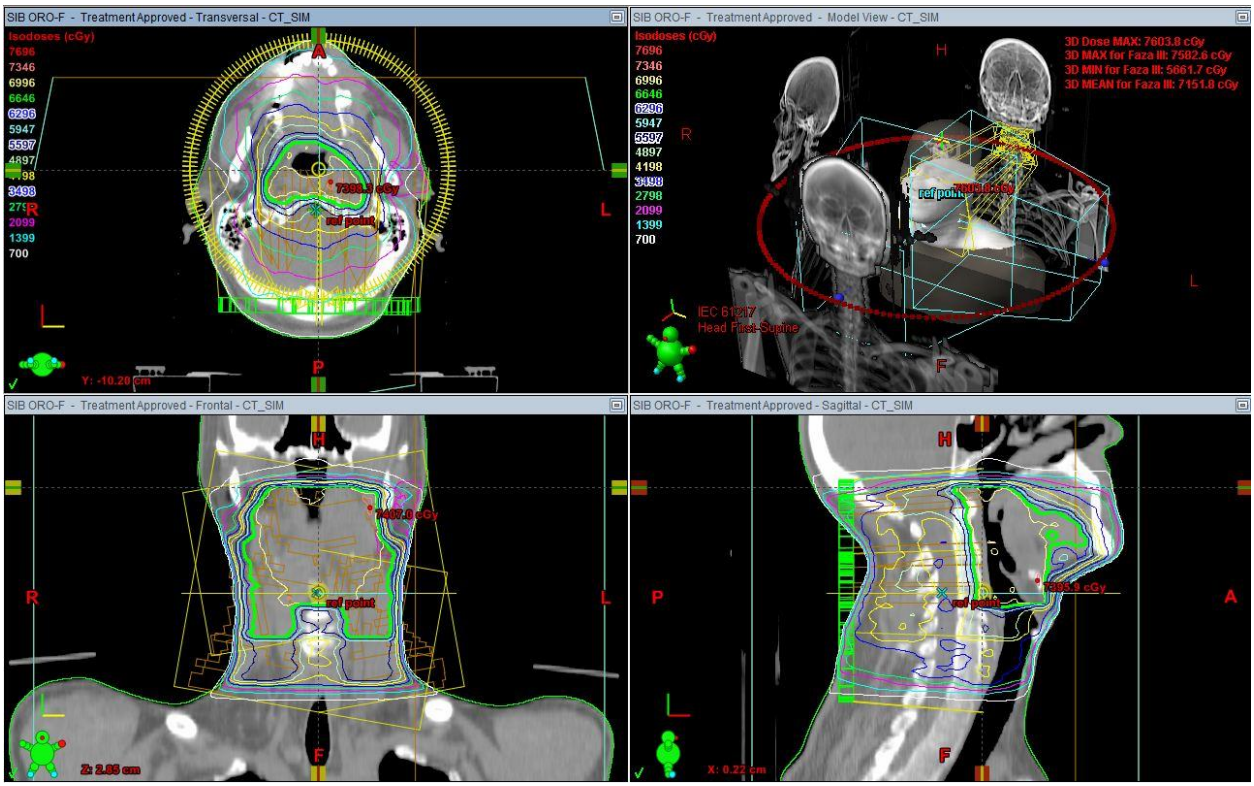

Fig 2. Isodose curves distribution of oral cavity region - image from Varian Eclipse ™ TPS

Results

The maximum dose received by the left parotid exceeded the mean dose of 26Gy for 14 of the 20 cases. In the case of right parotid, the average dose of 26Gy was exceeded in only 12 cases. In 11 out of 20 cases, both parotids received doses greater than 26Gy. Average mean doses obtained by the left parotid and parotid gland respectively were 3256.30cGy respectively 3326.23cGy. In all cases, the average dose received by the oral cavity exceeded 30Gy with an average of 5458.6cGy and the median Dmean received by mandible was 4260.64cGy. The average volume for the target tumor of the primary tumor that received the maximum prescribed dose was 162.23 cmc (Table 1).

Case No.	PTV-T Volume(cmc)	Dmean Left parotid (cGy)	Dmean Right parotidP (cGy)	Dmean Oral cavity (cGy)	Dmean Mandible (cGy)
1	179.63	1979	1947.7	6522	4311
2	118.05	2428	2325	6304	5592
3	176.28	4787	5455	6428	4941.5
4	160.24	2159	2169	5920	4548
5	130.09	2230	222.3	5997	5072.5
6	160.71	2410.1	2032.4	5869.4	4555.8
7	158.43	2120.9	2110.9	4481.4	4061.8
8	176.25	2721.5	2754.4	6043.2	4442.6

9	205.93	3361.6	3951.9	5652.1	4224.4
10	121.56	5097.1	5060.7	5664.4	5079.5
11	148.36	2927.6	3256.3	4019.6	3334.5
12	196.03	6772.7	6732.7	5983.3	4343.1
13	116.95	2800.6	2922.4	5790.9	4376.1
14	191.53	4013.15	4239	5774.2	4000.2
15	157.51	4578.1	4569.5	6036.1	4686.1
16	119.06	2636.4	2416.3	4557.4	3420.5
17	169.78	3241.3	3092	4334.7	3610.5
18	190.66	3380	3506	3938.6	3143.2
19	213.05	2478.8	2616.2	4165	3213.3
20	166.35	3003.1	3146.9	5690.2	4256.2
Average doses (cGy)	162.82	3256.30	3226.33	5458.575	4260.64

Table 1. Doses received by OARs for 20 patients and the volume of the primary tumor target volume (PTV-T)

Discussions: The normal stimulated and unstimulated salivary flow rate averages 1.5–2.0 mL/min respectively 0.3–0.4 mL/min. A stimulated salivary flow rate ≤0.5–0.7 mL/min and the unstimulated salivary flow rate is ≤0.1 mL/min is considered hypo salivation and when saliva flow is less than the rate of fluid absorption and fluid evaporation xerostomia is diagnosed [8].

Due to the anatomical proximity between the tumor and the radiosensitive structures in the head and neck, preserving the function of these organs is difficult in order to maintain the quality of life of the patient. Radiotherapy has an important role in the treatment of head and neck cancers and in recent years techniques that better covered the target volumes and protect radiosensitive organs contribute to reducing toxicity rates. However, the use of systemic chemotherapy and molecular target therapy for locally advanced disease in concomitant or sequential with radiotherapy contributes to a superior loco regional control and survival benefit but also associated with a high rate of toxicity. The introduction of 3D conformational radiotherapy (3D-CRT) and Intensity Modulated Radiotherapy (IMRT) was a major improvement over conventional radiotherapy. These methods are based on treatment planning systems (TPS), using computer tomography (CT) simulation with a careful delineation of target volume and OARs. The spatial relationship between target volume and OARs can be evaluated by 3D volumes reconstruction. The use of IMRT and VMAT techniques offers the possibility of conformation and high-dose irradiation for "banana shape" target volumes without delivering high radiation doses to the OARs. A mean dose on the parotid glands below 26Gy leads to a decrease in xerostomia rate. Not just the mean dose is a predictor of xerostomia. Multiple studies have shown that sub-volumes in the gland that receive certain doses contribute to toxicity, taking into

account the parallel architecture of the parotid from a radiobiological point of view (Fig 3). In the case of locally advanced cancers with bulky tumor volumes, obtaining these doses is difficult, both the parotid glands and the submandibular glands [9],[10].

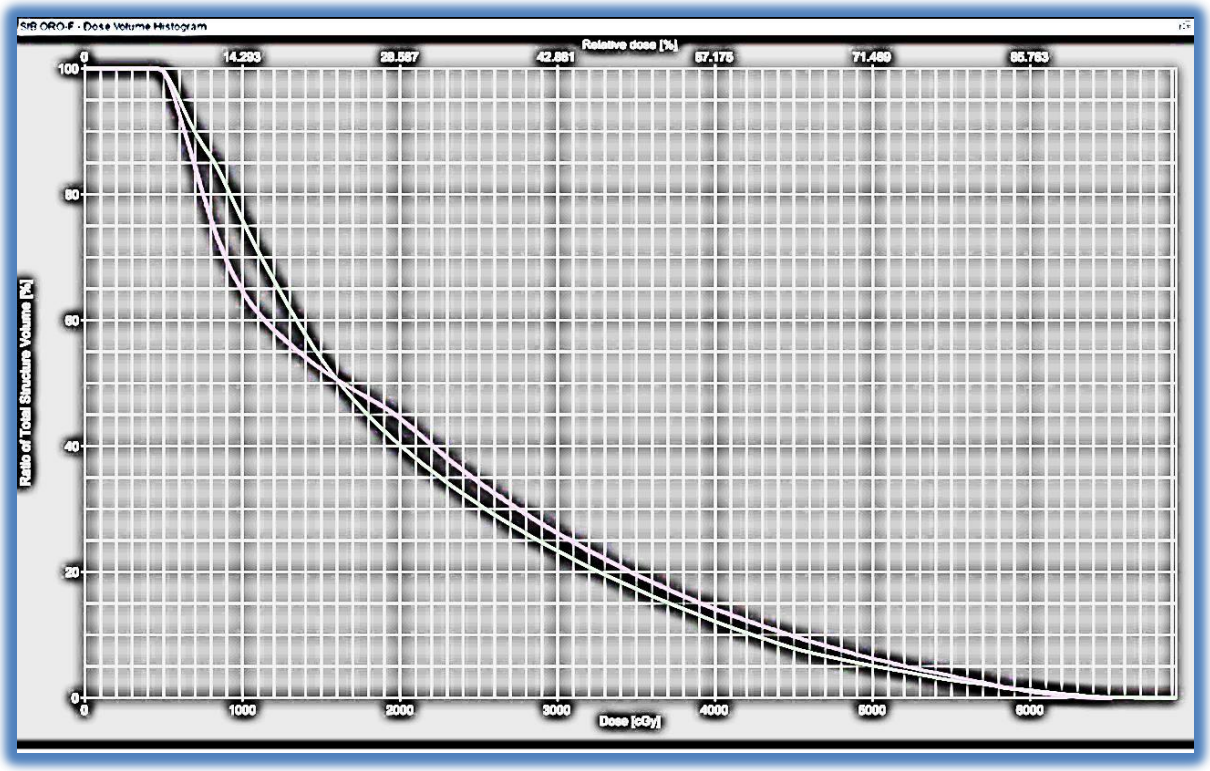

Fig. 3 Dose volume histograms for left (violet) and right (blue) parotid glands - image from Varian Eclipse ™ TPS

70% of the total mucus secreted by the salivary glands is produced by the minor salivary glands which are dispersed in the oral cavity so a dose limitation of the oral cavity could contribute to reducing xerostomia but could also help prevent mucositis and loss of taste. The non-implicated tumor oral cavity should be delineated as OAR and dose constraints should be used for radiotherapy planning if possible, with a dose ≤ 30Gy being recommended. A low priority compared to other radiosensitive organs is recommended to be applied in order not to compromise the correct irradiation of the target volume [11].

Teeth located in the irradiated field during head and neck cancers irradiation are at risk of developing radiation cavities that can progress rapidly to periaptic disease and chemotherapy may worsen subclinical dental pathologies. Effects are potentiated by associated toxicity like xerostomia and rarely by oral lichen planus [12, 13]. Decreased salivary flow and oral microbial

flora change are factors that aggravate the evolution of dental pathologies. Full dental assessment and dental treatment are recommended as a starting point for multimodal therapy. Teeth with advanced carious or periapical lesions and periodontal infections need to be extracted prior to the start of the treatment in order not to affect the delivery of the treatment [14].

The incidence of the ORN jaw is estimated between 2.6% and 44% with a lower ORN incidence to the maxilla because it is more vascular than the mandible. All patients who receive doses greater than 50Gy in the head and neck region are at risk of developing ORN, but dental and jaw trauma and dental surgery treatments or dental surgeries may increase the risk [15,16].

Conclusions

Oral health care assessment, including clinical and radiological evaluations prior to the start of multimodal therapy for head and neck cancers can reduce morbidity and improve the quality of life of these patients. Even if VMAT, a modern radiotherapy technic is used for the radiotherapy treatment delivery, for locally advanced cases, radiosensitive organs involved in oral cavity toxicity and teeth will receive increased radiation doses. In this context, ensuring good hygiene of the oral cavity and including dental control in the therapeutic protocol of multimodal maneuver of head and neck cancers is necessary to minimize toxicity and reduce the risk of severe late onset toxicity.

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