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COMPARATIVE EVALUATION OF THE RISK OF XEROSTOMIA USING RADIOBIOLOGICAL MODELS FOR PATIENTS WITH LOCALLY ADVANCED NASOPHARYNX AND OROPHARYNX NEOPLASM, IRRADIATED WITH IMRT AND VMAT TECHNIQUES

BY

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Abstract. Xerostomia is a frequent cause of damage of the quality of life of a patient treated with radiotherapy for head and neck neoplasm. Prevention is the most recommended attitude because the management of xerostomia is rarely effective. Several strategies have been developed to avoid radiation-induced salivary dysfunction. They imply radiation techniques know to spare salivary glands: intensity modulated radiotherapy (IMRT) and volumetric modulated arc therapy (VMAT). For 20 patients with oro- and nasopharyngeal cancer, treated with IMRT/VMAT, the risk of xerostomia was computed with the radiobiological models Lyman, Kutcher, Burman (LKB) and EUD (Equivalent Uniform Dose)-based. These models’ inputs are the dose-volume histograms (DVH) calculated by the treatment planning system (TPS). The values obtained vary from one model to the other, for the same technique and patient.

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Radiobiological models are not implemented as a standard in clinical practice but may provide predictive values for irradiation-related toxicity.

Keywords: xerostomia; radiobiological models; IMRT; VMAT; head and neck neoplasm.

1. Introduction

Xerostomia is one of the most common complications during and after radiotherapy for head and neck cancer, because irreparable damage is caused to the salivary glands included in the radiation fields. Xerostomia can be permanent, leading to severe damage to deglutition function, taste and to oral cavity infections and dental caries because of the altered composition and salivary pH. Parotid glands produce 60% of total saliva, submandibular glands 20% and the rest is produced by sublingual and accessory salivary glands. The acute effects can be reversible if the allowed doses are not overcrossed for the parotid glands. QUANTEC dosimetric recommendations for reducing xerostomia are a mean dose lower than 26Gy for bilateral parotid gland, and lower than 20Gy for unilateral ones. If it is not possible to follow dosimetric constrains, the next step is to reduce dose to only one of the parotids to less than 26Gy, in order to save at least one of two. The clinical benefit of protecting the submandibular glands is controversial. Maintaining them at a mean dose less than 39Gy could preserve their function (Ortholan *et al*., 2010; Buzalaf *et al*., 2012; Deasy *et al*., 2010).

Xerostomia is a frequent cause of damage of the quality of life of a patient treated with radiotherapy for ORL neoplasm. Prevention is one of the most important recommended attitude because the management of xerostomia is rarely effective. Several strategies have been developed to avoid radiation-induced salivary dysfunction without definitively compromising the oncologic treatment. These strategies imply salivary gland-sparing radiation techniques: IMRT (intensity modulated radiotherapy) and VMAT (volumetric modulated arc therapy). For complex dose distribution differing from that provided by the 3D-CRT radiotherapy technique, radiobiological models may have a predictive value superior to univariate assessment for prediction of high grade xerostomia (Abel *et al*., 2017).

2. Materials and Methods

For 34 patients treated with definitive radiotherapy using IMRT or VMAT techniques for oro- and nasopharynx cancer, the risk of xerostomia was calculated with the help of mathematical models: Lyman Kutcher Burman and EUD-based. They are centered on several parameters such as TD50, n, m, etc. These models come into shape with the help of the dose-volume histogram

(DVH). The values obtained vary from one model to another, for the same technique and patient (Gabryś *et al*., 2017).

CT scans with a slice thickness of 3 mm were acquired from the aortic arch to the vertex. Weekly during treatment, following the initial setup, an orthogonal pair of kV radiographs were acquired using the Varian On Board Imaging (OBI) system (Varian Medical Systems, Palo Alto, CA), and manually by the therapists using the Varian OBI application and the necessary (manual 2D-2D). The registering of acquired images to the simulation DRRs was made by the radiation therapist to determine setup errors and corrective couch shifts (Kang *et al*., 2010).

GTV (gross tumor volume) was delineated using image fusion and a rigid registration algorithm. CT (computer tomography) and MRI (magnetic resonance imaging) with contrast agent as well as clinical examination data and endoscopic evaluation were used to delineate the anatomical limits of GTV volume (Fig. 1). Three CTVs (clinical target volumes) with a risk for microscopic dissemination are defined: a high dose CTV70 disease; a high risk CTV66 reflecting the high risk of local spread in and adjacent to the nasopharynx and oropharynx and a prophylactic CTV50 to treat the at risk but uninvolved nodes. A CTV-PTV margin is applied (3–5 mm) based on set-up errors, assuming no tumor motion (Dobbs *et al*., 2009).

Doses of 70Gy/35 daily fractions in 7 weeks plus concomitant cisplatin or 3-4 cycles of platinum based induction chemotherapy, 66Gy/33 fractions on high risk lymph nodes PTV and 50Gy/25 fractions on low risk lymph nodes levels were administrated in three treatment phases (sequential boost) (Brouwer *et al*., 2015).

VMAT plans using the Varian RapidArc technique (Varian Medical Systems, Palo Alto, CA) were planned using Eclipse Version 11.0.31 treatment planning software using the same CT-dataset and contoured volumes as the IMRT plans. A single arc technique was used with the gantry set to rotate through 360° in a clockwise direction from a starting position of 181° to a final position of 179°, and a double arc technique with the gantry set to rotate through 360° in a clockwise direction from a starting position of 181° to a final position of 179°, and through 360° in a counterclockwise direction from a starting position of 179° to a final position of 181° according to the complexity of the phase being treated. The collimator rotation was individually optimized for each patient but generally set at 30° and 330° to reduce the effect of tongue and groove leakage (Figs. 2 and 3).

Radiobiological models can be divided into two categories: empiric and theoretical. Empiric models are based on the fitting curves to the actual clinical data. These models are valid only if they are described by initial clinical data. On the other hand, theoretical models are described with the help of radiation interaction with cells and DNA, and also with the help of the processes involved. When using radiobiological models, you have to take into

consideration the fact that they do not have a wide applicability due to the fact that there are no sufficient laboratory data.

Normal tissue complication probability (NTCP) is defined as the percentage of radiotreated patients which develop certain reactions, at a certain dose, at a tissue located near the tumor mass. Manifestation of a specific effect of a normal tissue is also known as clinical endpoint. These endpoints can be divided into two groups. The first one includes functional changes such as paralysis and death, which occur at a narrow dose range. The second one refers to physiological and extensive reactions, and these ones can be developed for a wider dose range, with a direct relation between dose and severity of the reaction.

There are two models that were used to calculate the risk of xerostomia, Lyman-Kutcher Burman and EUD.

The first one, LKB model, is described by the following formula:

$$NTCP=\frac{1}{\sqrt{2\pi}}\int_{-\infty}^{t} e^{\frac{x^2}{2}}\,dx \tag{1}$$

where

$$t=\frac{D_{ef}-TD_{50}}{mTD_{50}} \tag{2}$$

and

$$D_{ef}=(\sum_i v_i {D_i}^{1/n})^n \tag{3}$$

D_{ef} is the dose that, administrated uniformly to the entire volume will lead to the same *NTCP* as the real unevenly distributed dose, and D_i is the dose given to the sub volume v_i. The volume dependence of complication probability is given by parameter *n*, and the complication probability slope comparing to the dose curve is given by *m*. TD_{50} is the dose given to the entire organ which would lead to a complication probability of 50%.

EUD based model is defined as the equivalent biological dose, which when unevenly distributed, will lead to the same biological effect as the real distribution of the unevenly dose distribution.

$$EUD=(\sum_i v_i D_i^a)^{\frac{1}{a}} \tag{4}$$

D_i is the dose received by a subvolume v_i and *a* is a parameter that has no dimension and it's specific for every tissue

NTCP can be calculated with the help of formula

$$NTCP=\frac{1}{1+(\frac{TD_{50}}{EUD})^{4\gamma_{50}}} \tag{5}$$

Where γ_{50} is also a dimensionless parameter, specific for every tissue, describing dose-response curve.

3. Results

NTCP obtained using the EUD radiobiological model provided values between 0 and 26.46% with an average value for the right parotid of 7.38% for IMRT and 3.89% for VMAT. For the left parotid, the average value is 9.08% for IMRT and 3.75% for VMAT. For the LKB model, the NTCP values ranged between 7.23 and 37.49% with an average value for the right parotid of 24.33% for IMRT and 20.74% for VMAT. For the left parotid 25.27% for IMRT and 22.49% for VMAT (complete values in Table 1 and 2, see also the diagram from Fig. 4).

Higher values were obtained using the LKB model than the EUD model.

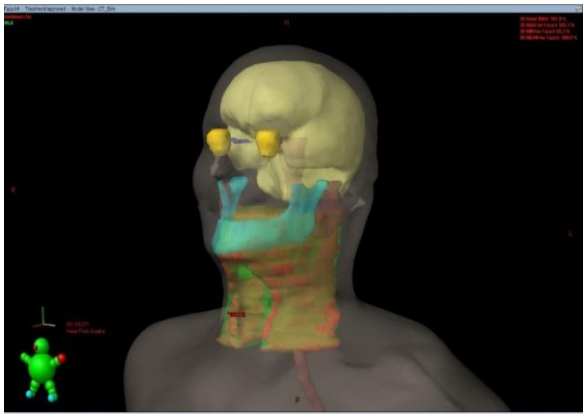

Fig. 1 – Organs at risk and target volume, 3D reconstruction using VARIAN Eclipse TPS.

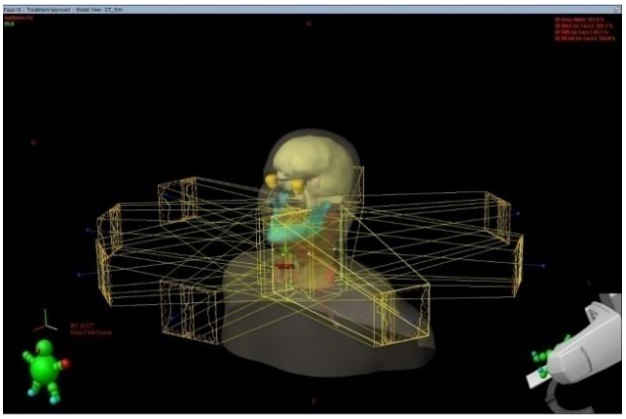

Fig. 2 – IMRT field orientation.

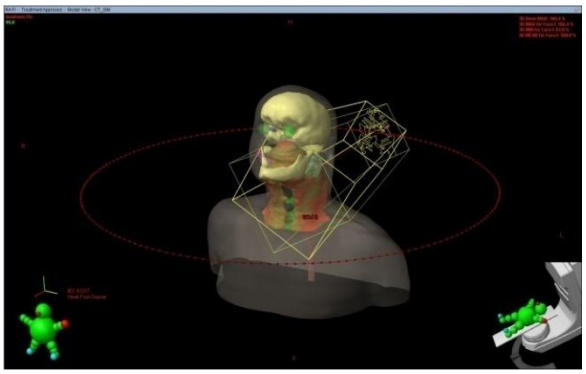

Fig. 3 – VMAT field orientation.

Table 1
NTCP Calculated for Patients Treated with VMAT Techniques

Patient	Left parotid (%)		Right parotid (%)	
	LKB	EUD	LKB	EUD
1	27.97	7.35	29.47	9.43
2	16.49	0.49	14.38	0.19
3	23.77	3.24	25.41	4.84
4	34.03	17.93	32.26	14.22
5	26.64	5.76	23.52	3.05
6	27	6.17	26.77	5.9
7	15.99	0.36	14.96	0.24
8	24.53	3.81	23.35	2.95
9	18.06	0.72	20.63	1.51
10	25.91	5.03	29.03	8.77
11	24.06	3.46	18.3	0.78
12	20.52	1.52	25.31	4.57
13	21.51	1.98	23.32	3.01
14	21.06	1.73	19.36	1.1
15	25	4.2	26.56	5.7
16	27.68	6.99	30.18	10.53
17	27.23	6.45	31.19	12.3

Table 2
NTCP Values Calculated for Patients Treated with IMRT

Patient	Left parotid (%)		Right parotid (%)	
	LKB	EUD	LKB	EUD
1	36.43	23.73	37.49	26.46
2	32.98	15.71	35.28	20.88
3	11.5	0.04	13.6	0.11
4	12.25	0.06	7.23	0
5	28.56	8.1	23.52	3.08
6	36.39	23.65	32.07	13.99
7	33.73	17.49	31.64	13.35
8	26.64	5.78	29.66	9.7
9	17.92	0.72	17.22	0.57
10	21.65	2.04	25.94	5.13
11	22.02	2.21	20.39	1.46
12	25.56	4.7	25.63	4.79
13	32.72	15.19	26.66	5.83
14	20.23	1.38	25.03	4.24
15	36.67	24.43	28.75	8.44
16	9.12	0.01	9.16	0.01

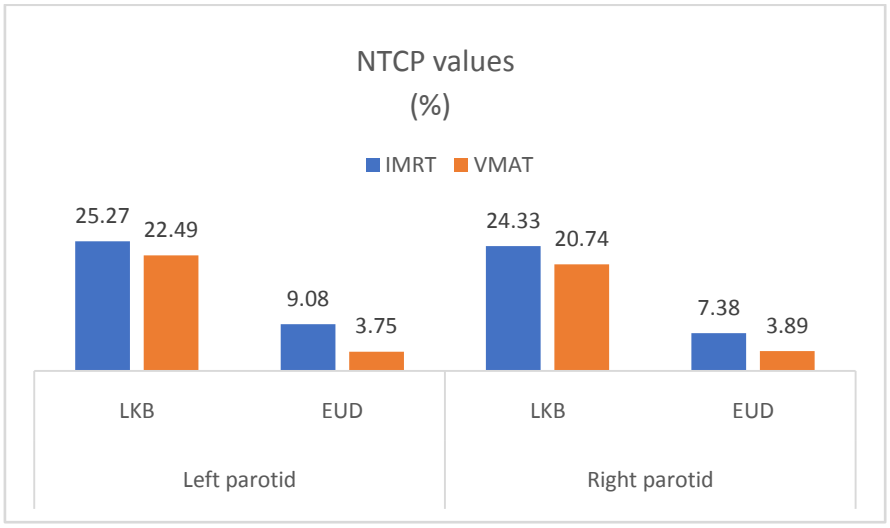

Fig. 4 – Diagram with average values for NTCP.

4. Discussion

White *et al*. demonstrates the equivalence or even superiority of VMAT technique to IMRT technique in target volume coverage and OAR protection with a considerable benefit in reducing the treatment time with possible positive radiobiological consequences. Doses to parotid glands and their NTCPs were significantly lower for VMAT plans (White *et al*., 2013).

The reduction of the salivary flow rate causes functional impairment and patient discomfort including the inability to articulate, a dry mouth, the inability to chew and swallow food and halitosis with an important impact on the patient's social life. The Common Terminology Criteria for Adverse Effects (CTCAE) was used to describes gradually possible side effects (Grade 2 effects are moderate, Grade 3 effects are considered severe and are associated with possible treatment disruption) (Hanley and Leech, 2016).

Some authors have shown that the LKB model has the advantage of differentiating the risk of severe xerostomia for cases where QUANTEC recommendations are exceeded. Unfortunately, radiobiological models have not shown a predictive value for low or moderate grade xerostomia (Houweling *et al*., 2010).

In a thirty-two patients cohort with non-metastatic nasopharyngeal cancer curatively treated using VMAT (RapidArc), Layla *et al*. reported a 9.4% grade 3 xerostomia, concluding that the VMAT technique offers a good sparing of organs at risk especially the nervous structures and salivary glands and an excellent target volume coverage (Lalya *et al*., 2017).

On a radiobiological model trained on the PARSPORT trail date, Gabryś *et al*. considered that the LKB model predicts quite correctly the risk of xerostomia between G1 and G2 grade, from moderate to severe xerostomia, but it does not provide accuracy for cases where the parotid mean dose is in the low-dose domain. The same predictive limit value is also proven if the parotid mean dose exceeds the QUANTEC tolerance recommendations (Gabryś *et al*., 2017).

5. Conclusions

Radiobiological models are ideal mathematical models, not clinically validated but have orientative value in therapeutic decision and radiotherapy plan optimization. The risk of xerostomia is influenced by different factors such as age, sex, smoker status, chemotherapy treatment, personal medication for comorbidities. Concluding values individually tailored can be reached by multivariate analysis including clinical, biological and dosimetric variables.

Values obtained for the two techniques are similar, proving that VMAT technique is not inferior to IMRT, which is considered to be standard in head & neck radiotherapy.

Higher values of NTCP lead to the necessity of optimizing treatment plans in order to reduce/lower doses to parotids. They have a guiding purpose when DVH curve analysis can not provide an intuitive risk of xerostomia due to complex dose distribution.

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EVALUAREA COMPARATIVĂ A RISCULUI DE XEROSTOMIE CU AJUTORUL MODELELOR RADIOBIOLOGICE PENTRU PACIENȚII CU NEOPLASME DE NAZOFARINGE ȘI OROFARINGE LOCAL AVANSATE, IRADIATE PRIN TEHNICILE IMRT ȘI VMAT

(Rezumat)

Xerostomia este o cauză frecventă a afectării calității vieții unui pacient cu neoplasm al capului și gâtului radiotratat. Prevenția este una dintre cele mai importante atitudini recomandate, deoarece administrarea xerostomiei este rareori eficientă. Au fost dezvoltate mai multe strategii pentru a evita disfuncțiile salivare induse de radiații. Aceste strategii implică tehnici de iradiere care știu să ocolească glandele salivare: IMRT (radioterapia modulată în intensitate) și VMAT (terapie în arc modulată volumetric).

Pentru 20 de pacienți diagnosticați cu cancer oro- și nazofaringian, tratați cu tehnicile IMRT sau VMAT, riscul de xerostomie a fost calculat cu ajutorul modelelor radiobiologice: Lyman Kutcher Burman (LKB) și bazate pe EUD (Doză Uniformă Echivalentă). Datele de intrare ale acestor modele sunt histogramele doză-volum (DVH) calculate de sistemul de planificare a tratamentului (TPS). Valorile obținute variază de la un model la altul, pentru aceeași tehnică și acelasi pacient. De obicei, se obțin valori mai mari utilizând modelul LKB decât modelul EUD. Modelele radiobiologice nu sunt implementate ca standard în practica clinică, dar oferă o valoare predictivă pentru toxicitățile asociate iradierii.