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FULL PAPER

Assessment and quantification of patient set-up errors in nasopharyngeal cancer patients and their biological and dosimetric impact in terms of generalized equivalent uniform dose (gEUD), tumour control probability (TCP) and normal tissue complication probability (NTCP)

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Objective: The aim of this study is to assess and quantify patients' set-up errors using an electronic portal imaging device and to evaluate their dosimetric and biological impact in terms of generalized equivalent uniform dose (gEUD) on predictive models, such as the tumour control probability (TCP) and the normal tissue complication probability (NTCP).

Methods: 20 patients treated for nasopharyngeal cancer were enrolled in the radiotherapy-oncology department of HCA. Systematic and random errors were quantified. The dosimetric and biological impact of these set-up errors on the target volume and the organ at risk (OARs) coverage were assessed using calculation of dose-volume histogram, gEUD, TCP and NTCP. For this purpose, an in-house software was developed and used.

Results: The standard deviations (ISDs) of the systematic set-up and random set-up errors were calculated for the lateral and subclavicular fields and gave the following results: $\sum = 0.63 \pm (0.42)$ mm and $\sigma = 3.75 \pm (0.79)$ mm, respectively. Thus a planning organ at risk volume (PRV)

margin of 3 mm was defined around the OARs, and a 5-mm margin used around the clinical target volume. The gEUD, TCP and NTCP calculations obtained with and without set-up errors have shown increased values for tumour, where Δ gEUD (tumour) = 1.94% Gy ($p = 0.00721$) and Δ TCP = 2.03%. The toxicity of OARs was quantified using gEUD and NTCP. The values of Δ gEUD (OARs) vary from 0.78% to 5.95% in the case of the brainstem and the optic chiasm, respectively. The corresponding Δ NTCP varies from 0.15% to 0.53%, respectively.

Conclusion: The quantification of set-up errors has a dosimetric and biological impact on the tumour and on the OARs. The developed in-house software using the concept of gEUD, TCP and NTCP biological models has been successfully used in this study. It can be used also to optimize the treatment plan established for our patients.

Advances in knowledge: The gEUD, TCP and NTCP may be more suitable tools to assess the treatment plans before treating the patients.

The main goal of radiation therapy planning is to maximize dose to the target while minimizing dose to the nearby healthy organs, in order to improve the control of tumour growth and to reduce side effects. Nasopharyngeal cancer is common in North Africa, especially in Algeria. It is the highest cause of death among head and neck cancer patients according to "Registre du cancer".¹ Recently, a three-dimensional conformal radiotherapy (3D-CRT) technique has been implemented in the radiotherapy-oncology department of the Mohamed Seghir Nekkache hospital (HCA) in Algiers.

In order to evaluate and to achieve the most optimized treatment plans, predictive models that describe the relationship between dose distributions in organs at risk (OARs) and the probability of radiation-induced complications are needed,² especially those resulting from patient set-up errors. Of course, it is an increasingly important part of the clinical radiotherapy process, for which set-up errors consist of both a systematic component and a random component. The former happens when we have the same deviation in the same direction

Table 1. Patient characteristics

Patient	Sex	Age (years)	Tumour classification
1	M	30	T ₂ N ₁ M ₀
2	M	75	T ₃ N ₀ M ₀
3	M	46	T ₂ N ₂ M ₀
4	M	63	–
5	M	36	T ₄ N ₂ M ₁
6	M	43	T ₂ N ₁ M ₀
7	M	37	T ₁ N ₀ M ₀
8	M	66	T ₃ N _{2b} M ₀
9	M	74	T ₂ N ₁ M ₀
10	M	23	T ₂ N ₃ M ₀
11	F	37	T ₁ N ₂ M ₀
12	M	32	T ₂ N ₁ M ₀
13	F	57	T ₂ N ₀ M ₀
14	F	39	T ₃ N ₂ M ₀
15	M	22	T ₃ N ₁ M ₀
16	M	66	T ₃ N _{2b} M ₀
17	M	54	T ₃ N ₂ M ₀
18	M	52	T ₂ N ₁ M ₀
19	M	59	T ₂ N ₀ M ₀
20	M	33	T ₂ N _{3a} M ₀

F, female; M, male.

for each fraction throughout the whole course of treatment, while random errors vary from day-to-day.³ One way to diminish systematic as well as random set-up deviations is to use electronic portal imaging devices (EPIDs). Effectively, the EPIDs have become available in a large number of institutions for the sake of determining the set-up errors over previous years.^{4–6}

In our study, both types of systematic and random errors were investigated for 20 nasopharynx radiotherapy patients by applying EPIDs. Patient set-up error evaluation in head and neck cancers constitute a challenge partly because the planning target volume (PTV) and the planning organ-at-risk volume (PRV) margins must be specified.⁷

Unfortunately, when set-up errors occur and a PTV is surrounding the OARs, the dose distributions are not always uniform. In this case, tools are needed to evaluate treatment plans in 3D-CRT.⁸ One way this can be used consists of converting dose–volume histograms (DVHs) to an equivalent uniform dose (EUD),⁹ and then estimating the tumour control probability (TCP) and the normal tissue complication probability (NTCP).^{10,11}

The concept of EUD, introduced by Niemierko,¹² was originally defined as the absorbed dose, that is, if given uniformly, would lead to the same cell death as the actual non-uniform absorbed-dose distribution. The current definition of EUD is the generalized mean absorbed dose. According to Niemierko who generalized its application to normal structures and tumours, the concept of EUD has been used as one of the several metrics to determine the impact of absorbed-dose heterogeneity on normal tissues and tumours. EUD is also well suited for obtaining the biological effect for the heterogeneous irradiation of a volume of interest,¹³ whereas TCP and NTCP are predictive models that will be affected by set-up errors and organ motion.¹⁴

METHODS AND MATERIALS

Patient selection, treatment planning and radiation dose

This study was carried out on a sample of 20 patients treated for nasopharyngeal cancer between 2010 and 2012 in the radiation–oncology centre of HCA. Table 1 summarizes the studied patients' characteristics. As far as head and neck cancers are concerned, nasopharynx is the part that the disease most frequently strikes.

Figure 1. Reconstructed radiograph: digitally reconstructed radiograph (a) and portal image imaging portal (b) given for the lateral field.

Table 2. Specific parameters given for tumours and organs at risk (OARs) reported from Emami et al²⁹ used as input parameters to calculate generalized equivalent uniform dose (Gy) and tumour control probability

Structures	<i>a</i>	Gamma (γ_{50})	TCD ₅₀ (Gy)	TD ₅₀ (Gy)
Tumour	−8	2	72	–
OARs				
Brainstem	4.6	3	–	65
Optic chiasm	25	3	–	65
Spinal cord	7.4	4	–	66.5
Parotid (left/right)	5	6	–	46

TCD₅₀, dose that yields a tumour control probability of 50%. This model strictly applies to tumours that receive a uniform dose; TD₅₀, tolerance dose for a 50% complication rate at a specific time interval.

Indeed, calculations are based on radiobiological models that can explicitly optimize the trade-offs that must be made between eradicating the tumour and avoiding damage to healthy surrounding tissue. For these models, we have firstly used the EUD's in-house software for tumour and OARs for the sake of taking into account dose inhomogeneity. Secondly, we have used the predictive models such as TCP and NTCP that were computed by the in-house software¹⁵ (the in-house software was elaborated in FORTRAN (Microsoft Developer Studio) from the study of Gay and Niemierko who calculate TCP and NTCP function EUD) using DVH information. The estimation of TCP and NTCP values has been performed in order to enhance tumour control and avoid damage to healthy tissues and structures.

Before treatment, the nasopharynx–RT patients were immobilized using thermoplastic immobilization device of three fixed points (Arplay, Paris, France). A CT scan was acquired with scanner simulator Big Bore (Philips, Amsterdam, Netherlands) using a 2.5-mm slice thickness.

A focal system (Elekta Inc., IMPAC Medical Systems, Maryland Heights, MO) was used to delineate the clinical target volume (CTV), and the PTV was defined as CTV with a 5-mm safety margin. All OARs were delineated with a safety margin. The XIO v. 4.5.1 (Elekta) was used as the 3D treatment planning system. The digitally reconstructed radiographs (DRRs) were generated and stored as reference images.

The PTV was generated according to the recommendations of the International Commission on Radiation Units and Measurements (ICRU) report 62,¹⁶ with an internal margin (IM) and set-up margins. A total prescribed dose of 70.2 Gy was delivered to the

PTV as daily fractionated doses of 1.8 Gy. The protocol used for treatment was applied using six irradiated fields at different gantry angles with a tilt of 5°, one subclavicular field obtained from a 6-MV photon beam and one spinal field given by electron beam (10 MeV) calculated using pencil beam algorithm. The planning strategy was to cover a PTV within 95% of the prescribed dose. The dose distribution was planned using the superposition algorithm, optimized and prioritized to the spine, chiasm and optic nerve. All dose constraints were defined for these OARs with respect to their tolerance, as the dose to the spinal cord must not exceed 45 Gy, to the optic chiasm must be <54 Gy and to the parotid glands must be <30 Gy.¹⁷

Evaluation of patient set-up errors

In this study, the “Record and Verify” system used to support the fully electronic medical record of the patients was MOSAIQ® v. 2.00V1 (Medical Impact System; Elekta, Stockholm, Sweden).

Patient set-up was evaluated and corrected *via* manual matching using the 3D bony anatomy (Figure 1).

The set-up errors were defined as the displacement of the coordinates of the bony landmarks on the beam film from those on the DRR films.¹⁸ The reported *x* and *y* deviations of the isocentre between simulation and treatment were decomposed into appropriate shifts along each body axis based on the orientation of the patient.

The protocol adopted by the therapists in the radiotherapy–oncology department of HCA allows them to fully control the image display contrast. Set-up errors were corrected if they exceeded 5 mm in any direction. Patients were imaged weekly and whenever the therapist thought there might be a problem. A mean number of 10 EPIDs per patient were carried out, so a total

Table 3. Biological parameters *n*, *m*, TD₅₀ given by Emami et al²⁹ for organs at risk

Structures	End points	<i>n</i>	<i>m</i>	TD ₅₀ (Gy)
Spinal cord	Myelitis/necrosis	0.05	0.175	66.5
Brain stem	Necrosis/infarction	0.16	0.14	65
Optic chiasm	Blindness	0.25	0.14	65
Parotids (left/right)	Xerostomia	0.70	0.18	46

TD₅₀, tolerance dose for a 50% complication rate at a specific time interval.

Figure 2. Age (in years) and number of patients with nasopharyngeal cancer during the 2010–12 time interval.

of 228 portal images (PIs) were used to detect positioning errors during this study. If the portal images (PIs) were incorrect, the patient position was corrected within the mask and the additional PI was performed to recheck the positioning. The corrective shifts were applied and kept constant for the subsequent treatment fractions until the next imaging was performed.

Statistical analysis of patient set-up errors

Set-up errors are a combination of systematic and random errors. It may be calculated individually for each patient and each direction (x , y and z) and according to the number of PIs.¹⁹ A patient set-up error was determined as the difference between the real and the intended positions.

Systematic error was calculated as the average deviation of a particular reference structure between simulation and treatment and is given by:

$$\sum = \frac{\sum_{i=1}^N \Delta_i}{N} \quad (1)$$

where N is the total number of PIs acquired for a particular field, and Δ_i is the calculated deviation from the i th treatment fraction.

Random errors, σ_{random} , were calculated for each treatment fraction as the standard deviation (SD) of the systematic error for a given anatomical feature from the average deviation. It may be calculated individually for each patient and each direction, and it was denoted as:

$$\sigma = \sqrt{\frac{\sum_{i=1}^N (\Delta_i - \sum)^2}{(N-1)}} \quad (2)$$

Margin calculation

An optimum margin is the aperture that ensures the dose received by the target with the least possible amount of irradiation to the

normal tissue. In the present study, that margin was calculated according to ICRU 62, $(\sqrt{\Sigma^2 + \sigma^2})$,²⁰ and different authors such as Stroom et al²¹ $(2 \Sigma_{\text{group}} + 0.7 \sigma_{\text{group}})$ who define a margin that covers 99% of the CTV with a dose of 95% and van Herk et al²² $(2.5 \Sigma_{\text{group}} + 0.7 \sigma_{\text{group}})$ that yields a minimal dose to the CTV of 95% for 90% of the patients population.

Owing to the anatomy of the nasopharynx region, the internal target motion was considered negligible ($\text{IM} = 0$). The PRV margin was calculated according to McKenzie et al^{23,24} $(1.3 \Sigma_{\text{group}} + 0.5 \sigma_{\text{group}})$.

The criterion adopted was that the mean position of the edge of OARs in any single direction would be completely encompassed by this margin in 90% of the cases.

On the basis of these protocols, a PTV margin was calculated and compared.

Biological impact of patient set-up errors on gEUD, TCP and NTCP

The dosimetric and biological impact of patient set-up errors was studied by incorporating these errors into the radiobiological plan evaluation. For this purpose, the DVHs were analysed and the generalized EUD (gEUD), TCP and NTCP were calculated. Statistical analysis was performed, and direct comparisons (paired t -tests) were used for the evaluation, with a level of significance set to 5% ($p < 0.05$).

Generalized equivalent uniform dose calculation

To compare the biological impact of patient set-up errors, DVHs were converted into EUDs using the in-house software and the tumour specific parameter " a " that describes the dose–volume effect. The EUD is equal to the maximal dose when $a = \infty$, and for $a = -\infty$, the EUD is equal to the minimal dose. For $a = 1$, the EUD is equal to the arithmetic mean, and for $a = 0$, it is equal to the geometric mean.

Figure 3. The distribution of the interfractional patient set-up errors for the nasopharynx: the displacements (μ) of the co-ordinate of the nasopharynx between the digitally reconstructed radiograph and imaging portals plotted for the left-right (L-R) (a), anteroposterior (A-P) (b) and craniocaudal (CC) (c) directions.

Figure 4. The dose distributions calculated without set-up error corrections.

The expression for gEUD computed in the present study given by Niemierko¹² is:

$$gEUD = \left(\sum_i^N V_i D_i^a \right)^{\frac{1}{a}} \quad (3)$$

The $\sum_i$ is over all dose bins of the differential DVHs. N is the number of voxels in the volume of interest, V_i and D_i are, respectively, the fractional volume and the dose at that volume. During calculations, we first converted the physical dose D_i in each dose bin of the DVH to the equivalent dose in 2-Gy fractions, EQD2Gy, making use of the formulation derived from the linear-quadratic model:²⁵

$$EQD2Gy = D'_i \frac{\frac{\alpha}{\beta} + G D_i}{\frac{\alpha}{\beta} + 2} \quad (4)$$

where G , is the dose protraction parameter described in the literature,^{26,27} and it is expressed as $G = 1/n$, with “ n ” being the number of fractions; in the present work, we used $n = 39$. D'_i is the dose bin extracted from DVH, and (α/β) is the radiobiological parameter describing the response of the tumours to changes in fractionation; the value of ten is chosen for this parameter, which corresponds to a maximum tumour control. As expected, for serial organs such as the spinal cord, the parameter (α/β) was set to two, and it was equal to three for all others OARs.²⁸

This expression overcomes the limitations of all survival models in order to generalize the application of EUD concept to normal structures and tumours. In this study, gEUD has been calculated for tumour and all OARs, using specific parameters reported by Emami et al²⁹ (Table 2).

The impact of patient set-up errors on the tumour and on the OARs was calculated as the percentage of dose error:

$$\%(gEUD) = \frac{gEUD_W - gEUD_{W/O}}{gEUD_W} \times 100 \quad (5)$$

Knowing that $gEUD_W$ is the calculated EUD accounting for the set-up error corrections and $gEUD_{W/O}$ corresponds to the calculated EUD not accounting for set-up errors corrections.

Tumour control probability and normal tissue complication probability evaluation

To calculate TCP, an in-house software based on the gEUD function and different parameters was developed.¹⁵ The expression of computed TCP is given by:

$$TCP = \frac{1}{1 + \left(\frac{TCD_{50}}{gEUD} \right)^{4\gamma_{50}}} \quad (6)$$

where gEUD represents the gEUD calculated by the in-house software, TCD_{50} is the given dose for which we have 50% of tumour control probability; γ_{50} is the slope of the response dose curve, the values are given in Table 2.

To improve clinical toxicity outcomes for the different OARs, we had to decrease the dose to normal structures. To achieve this, we have used the predictive model of the NTCP given by Lyman Kutcher Burman (LKB),³⁰ which is incorporated in the XIO radiotherapy oncology department's treatment planning system. This model describes the NTCP according to:

Figure 5. Optimal treatment plan obtained with set-up error corrections.

$$\text{NTCP} = \frac{1}{2\pi} \int_{-\infty}^u \exp\left(-\frac{x^2}{2}\right) dx \quad (7)$$

where:

$$u = \frac{D_{\text{eff}} - \text{TD}_{50}(v)}{m \times \text{TD}_{50}(v)} \quad (8)$$

$$D_{\text{eff}} = \sum_i \left(v_i D_i^{1/n} \right)^n \quad (9)$$

$$\text{TD}_{50}(v) = \text{TD}_{50}(1) \times V_{\text{eff}}^{-n} \quad (10)$$

TD_{50} is the tolerance dose (TD) for a 50% complication rate at a specific time interval (e.g. years) suggested in Emami et al²⁹ for normal tissue, when the whole organ of interest is homogeneously irradiated (Table 3).

D_{eff} is the dose that, if given uniformly to the entire volume, will lead to the same NTCP as the actual non-uniform dose distribution.

Kutcher and Burman³⁰ developed a volume reduction algorithm for the Lyman model^{11,31} for inhomogeneously irradiated OARs. The resulting model is conventionally referred to as the LKB

model. In this model, for each irradiation, fractional subvolume v_j [$j = 1, \dots, k$ ($\sum v_j = 1$)] irradiated to dose d_j and reference dose d_{ref} corresponds to partial effective volume:

$$V_{\text{eff}} = \sum_{j=1}^k V_{\text{eff}}^j \quad (11)$$

where:

$$V_{\text{eff}}^j = V_j \times \left(\frac{d_j}{d_{\text{ref}}} \right)^{1/n} \quad (12)$$

with d_{ref} defined as the prescribed dose.

RESULTS

Quantification of patient set-up errors and definition of margins

The number and age of the treated patients during the (2010–12) time interval are shown in Figure 2. The medium age is 47.5 years; it concerned 17 males vs 3 females. Table 1 summarizes the studied patients' characteristics.

The quantification of patient set-up errors was given by the determination of the displacement frequency (μ), and it was plotted in different directions: Figure 3a left-right (L-R), Figure 3b anteroposterior and Figure 3c craniocaudal (CC)

Figure 6. Dose-volume histogram (DVH) of nasopharyngeal cancer planning showing the impact of existing set-up errors (the solid lines) and the case where set-up errors were corrected (the dashed lines) in cases of tumour and organs at risks. CTV, clinical target volume; PTV, planning target volume.

Table 4. Dosimetric impact of patient set-up error corrections on D_{mean} , D_{max} and D_{min}

Structures	Volume (cm ³)	Dose-volume index (Gy)	$D_{\text{W/O}}^{\text{Cal}}$	$D_{\text{W}}^{\text{Cal}}$
Clinical target volume	294.51 ± 96.14	D_{max}	76.69 ± 4.20	77.43 ± 4.64
		D_{mean}	66.77 ± 5.92	67.97 ± 2.04
		D_{min}	26.58 ± 14.08	28.72 ± 11.46
Planning target volume	510.49 ± 93.93	D_{max}	78.12 ± 4.07	77.96 ± 4.20
		D_{mean}	66.68 ± 1.91	66.74 ± 2.06
		D_{min}	16.62 ± 10.74	17.41 ± 10.89
Spinal cord		D_{max}	47.65 ± 4.2	45.14 ± 1.70
		D_{mean}	22.24 ± 3.14	22.01 ± 3.26
		D_{min}	0.91 ± 0.65	0.90 ± 0.67
Brain stem		D_{max}	66.56 ± 2.62	66.85 ± 2.16
		D_{mean}	43.86 ± 7.33	43.34 ± 6.59
		D_{min}	8.35 ± 6.01	8.49 ± 6.01
Optic chiasm		D_{max}	51.42 ± 6.93	51.85 ± 7.33
		D_{mean}	39.79 ± 10.90	40.22 ± 11.7
		D_{min}	34.64 ± 13.83	33.90 ± 12.89
Left parotid		D_{max}	72.65 ± 1.55	72.56 ± 1.66
		D_{mean}	65.66 ± 2.83	65.57 ± 2.77
		D_{min}	41.59 ± 8.59	41.11 ± 9.16
Right parotid		D_{max}	72.11 ± 1.45	71.98 ± 1.42
		D_{mean}	64.85 ± 8.33	63.23 ± 4.23
		D_{min}	59.16 ± 13.53	43.28 ± 7.96

D_{max} , maximum dose; D_{mean} , mean dose; D_{min} , minimum dose.

$D_{\text{W/O}}^{\text{Cal}}$ and $D_{\text{W}}^{\text{Cal}}$ are the calculated dose without and with set-up error corrections, respectively.

directions. It demonstrates that the displacement frequency (μ) is very important in the L-R direction. The SDs of the systematic set-up errors ($\Sigma = 0.63$ cm) and random set-up errors ($\sigma = 3.75$ mm) calculated for lateral and subclavicular fields gave the following results: 0.42 and 0.79 mm, respectively.

Adequate CTV to PTV margins were calculated and compared according to different authors cited above and gave these results: 4.0, 3.8 and 4.2 mm, respectively. A PRV margin was calculated also according to McKenzie et al and was found to be equal to 2.69 mm.

Dosimetric impact of patient set-up errors on dose planning

After having quantified the uncorrected set-up errors using MOSAIQ and EPID images, their dosimetric impact on the dose distributions was assessed. Figure 4 displays dose distributions obtained without set-up error correction in different planes: transversal, CC and sagittal.

After having corrected these set-up errors, the dose distributions were recalculated and the optimal treatment plan was obtained as illustrated in Figure 5, which corresponds for 1 of the 20 patients studied.

To improve patient positioning, a 5-mm margin was used in-between (CTV-PTV) and a 3-mm margin was used around the

OARs to create a PRV. The impact of set-up errors on the dose distribution was shown on the computed plans plotted for tumour and OARs. The final DVHs (Figure 6) for both dose calculations were compared. Table 4 depicts all statistical doses obtained on tumour coverage and OARs for all monitored patients with and without set-up error corrections. It was demonstrated that the mean dose delivered to the tumour was lower than the prescribed dose owing to the reduction of the PTV ($\Delta V = 2.62$ cm³), and the plan was calculated without set-up error corrections. An increase of dose of 0.06–1.05 Gy was noticed in the PTV and CTV, respectively, when set-up errors were corrected. The hot spots given by D_{max} over the PTV decreased from 78.12 to 77.96 Gy, where ΔD_{max} was quantified to 16 cGy when set-up errors were corrected. Doses received by the different OARs (the spinal cord, brainstem, lens, right optic nerve and parotids) were higher when calculation was performed without set-up errors corrections. Otherwise, other OARs exhibited a decrease in doses, as was the case for the optic chiasm. For the right and left parotids, the mean dose was very important because it was impossible to spare them from the irradiated volume with the conventional treatment 3D-CRT (Figure 7).

Biological impact of set-up errors on tumour and organs at risk

A plan quality study was conducted by comparing gEUD, TCP and NTCP calculations obtained with set-up and without set-up

Figure 7. Calculated dose for the right and left parotids that were situated in the irradiated field in cases of three-dimensional conformal radiation therapy treatment. DCRT, three-dimensional conformal radiotherapy, DVH, dose-volume histogram; Lt, left; Norm, normalization; ref pnt, reference point; Rt, right.

errors. The absorbed dose increase on tumour where: gEUD (tumour) = (89.93 vs 91.71) Gy and Δ gEUD = 1.94% ($p = 0.00721$) (Table 5). Consequently, an increase on TCP was observed,

Δ TCP = 2.03% (Table 6). Figure 8 displays the expected probability distributions of TCP values at specified doses given by gEUD plotted with and without set-up errors.

Table 5. Generalized equivalent uniform dose (gEUDs) (Gy) values calculated for tumours and organs at risk (OARs) without set-up error (gEUD_{W/O}) and with set-up error (gEUD_W) corrections

Sites	gEUD _{W/O}	gEUD _W
Tumour		
Nasopharynx	gEUD = 89.93 ± 6.39	gEUD = 91.71 ± 6.35
	Min = 81.34	Min = 84.37
	Max = 101.50	Max = 104.54
OARs		
Spinal cord	gEUD = 16.15 ± 1.78	gEUD = 15.92 ± 1.09
	Min = 14.16	Min = 13.48
	Max = 20.84	Max = 19.11
Brain stem	gEUD = 20.57 ± 1.35	gEUD = 20.41 ± 1.25
	Min = 16.72	Min = 17.89
	Max = 22.66	Max = 22.78
Optic chiasm	gEUD = 25.96 ± 7.11	gEUD = 24.5 ± 5.6
	Min = 9.31	Min = 15.17
	Max = 28.56	Max = 29.97

Max, maximum; Min, minimum.

Table 6. Tumour control probability (TCP) (%) and normal tissue complication probability (NTCP) (%) values calculated for tumours and organs at risk (OARs) without and with set-up error corrections

Tumour	TCP _{W/O} (%)	TCP _W (%)
Nasopharynx	TCP = 84.05 ± 6.79	TCP = 86.08 ± 5.76
	Min = 72.64	Min = 78.05
	Max = 93.97	Max = 95.18
OARs	NTCP _{W/O} (%)	NTCP _W (%)
Spinal cord	NTCP = 1.077 ± 0.44	NTCP = 0.887 ± 0.25
	Min = 0.62	Min = 0.48
	Max = 2.54	Max = 1.64
Brain stem	NTCP = 10.86 ± 6.44	NTCP = 10.71 ± 7.2
	Min = 10.51	Min = 0.33
	Max = 23.83	Max = 27.32
Optic chiasm	NTCP = 2.59 ± 3.75	NTCP = 2.06 ± 2.44
	Min = 0	Min = 0
	Max = 14.1	Max = 6.79
Right parotid	NTCP = 97.32 ± 3.74	NTCP = 97.19 ± 3.5
	Min = 88.86	Min = 88.8
	Max = 99.67	Max = 99.7
Left parotid	NTCP = 98.82 ± 1.32	NTCP = 98.51 ± 1.41
	Min = 95.68	Min = 95.73
	Max = 99.71	Max = 99.7

Max, maximum; Min, minimum; W, with; W/O, without.

Despite these positive variations on tumour control, dose distribution is rarely uniform for the OARs. The EUD concept is useful for analysing the dose received by the total volume of these structures (Fogliata et al³² and Seppenwoolde et al³³). The gEUD results obtained for each OAR (Table 6) show lower values of doses, where: gEUD (spinal cord) = (16.15 vs 15.92) Gy; gEUD (brainstem) = (20.57 vs 20.41) Gy; and gEUD (optic chiasm) = (25.96 vs 24.5) Gy. The relative decrease in dose given by ΔgEUD for different OARs vary from 0.78% to 5.95% in cases of the brainstem and optic chiasm, respectively.

Table 6 depicts all expected values of NTCP calculated for different individual patients. An increase in the dose was obtained for all OARs when set-up errors occurred. After correction of set-up errors, the NTCP decreased for all OARs. The results obtained for all studied OARs can be summarized as follows: NTCP (spinal cord) = (1.077% vs 0.887%); NTCP (brainstem) = (10.86% vs 10.71%); NTCP (optic chiasm) = (2.59% vs 2.06%). An additional calculation of NTCP was undertaken in the case of the right and left parotid, for which NTCP values for the right parotid were 97.32% vs 97.19% and for the left parotid were 98.82% vs 98.51%. In Figure 9, the OAR toxicity was quantified by NTCP calculations for each patient. They were plotted for each OAR vs patient index. For example, in the case of the spinal

cord, brainstem, optic chiasm, and the right and left parotids, Figure 9a–d indicates the organ and the end point obtained after irradiation.

DISCUSSION

Patient set-up errors were quantified by the determination of the displacement frequency (μ); Figure 3 depicted deviations that were found to be more important in the L-R direction. For the definition of PTV and PRV margin, the radiotherapy–oncology department chooses 5- and 3-mm margins around the CTV and OARs, respectively. These two margins were sufficient to account for the position uncertainties, they were considered as the optimal ones because they ensure that the prescribed dose is received by the targeted area with the least possible amount of irradiation to normal tissue.

Cho et al¹³ have shown that with adequate treatment margins there is a small effect on the DVH and EUD.

Indeed, Table 4 depicts the dosimetric results given by $D_{\max}$, $D_{\min}$ and D_{mean} . The complexity of the treatment plans established for some patients, owing to the presence of the OARs close to the tumour, requires the therapist to reduce the size of the PTV in order to reduce the dose received by the OARs, such as the brain stem, and to maintain 95% of the prescribed dose to the CTV. This protocol was adopted because most of the patients have advanced cancer, which means a large tumour volume, whereas it is impossible to maximize the dose to the PTV without overdosage to the surrounding organs, such as the optic nerves, brain stem or parotid glands. The results of the present study showed that during treatment planning, the 3D-CRT plans were implemented and also normalized. The D_{95} for CTV was set equal to the prescription dose and the $D_{\max}$ was close to 110%.

The calculation of $D_{\max}$ for the different OARs gave us lower dose values than did the constraints doses ($D_{\max}$) given by the QUANTEC papers.³⁴ This situation demonstrates that the plan is judged to be optimal.

The obtained results also showed that when the plan was calculated without set-up error corrections, dose distributions deliver lower mean dose, otherwise, the delivered mean dose was higher when the plan was calculated with set-up error corrections. This study is similar to the study by Mavroidis et al.³⁵ The exhibited results on D_{mean} were similar to those given by van Haaren et al.³⁶

Concerning OARs, doses were optimized and recalculated without and with set-up error corrections. The mean dose received on the spinal cord and brain stem decreased. They were kept below tolerance during all the planning, except for the case of parotids where xerostomia is unavoidable for all patients.

This fact shows that any uncorrected deviation of a patient from its initial position (as recorded during simulation), will undoubtedly impact the surrounding OARs. This would therefore require finding an alternative method for taking set-up errors into account in this case.

Figure 8. Tumour control probability (TCP) (%) function generalized equivalent uniform dose (gEUD) (Gy) plotted for tumour, calculated with set-up errors (WSEs) and without set-up errors (WOSEs).

In the second part of this study, we have shown that set-up errors in the clinical situation have an impact on the gEUDs received by targets and by critical structures in 3D-CRT

nasopharynx treatment. We have also evaluated the treatment plans using the TCP and NTCP predictive models. Concerning target volume, Table 5 depicts the variation on the values of

Figure 9. (a) Normal tissue complication probability (NTCP) values calculated for spinal cord with set-up errors (WSE) and without set-up errors (WOSE). (b) NTCP values calculated for brainstem WSE and WOSE. (c) NTCP values calculated for optic chiasm WSE and WOSE. (d) NTCP values calculated for left parotid gland WSE and WOSE.

gEUD function when set-up errors were not corrected and the situation when set-up errors were corrected. When set-up error corrections were taken into account, the treatment plan was calculated. It exhibited a higher value of gEUD on the tumour, otherwise all OARs have shown lower values of gEUD. This means that the probability of any complication occurrence is acceptably low. This situation, demonstrates the impact of the daily set-up variation in the treatment of nasopharyngeal cancer patients. The generated cold spots in the target volume can adversely affect the gEUD. In fact, this function allows selective optimization and reduction of the dose for the OARs.

The calculation of TCP shows a better control on the tumour when the plan was corrected for positioning ($\Delta\text{TCP} = 2.03\%$) (Figure 8); this situation leads to a decrease in NTCP. In case of OARs, all the calculated NTCP decrease expectedly, in the case of parotids glands (Table 6). Figure 9 plotted the curves of NTCP for different OARs, with variation in the values of NTCP for different OARs, where ΔNTCP (spinal cord) = 0.19%; ΔNTCP varies from 0.15% to 0.53% in case of the brain stem and optic chiasm, respectively (Table 6).

By calculating TCP and NTCP, it can be assessed whether the treatment has been performed correctly and if complications or a different local control probability might be expected when set-up error occurs.

CONCLUSION

The purpose of this study was to assess the first treatment plans established in case of nasopharyngeal cancer when set-up errors

occur and then assess and quantify their impact on the calculation of gEUD, TCP and NTCP.

Firstly, an in-house software was developed using the concept of EUD and the predictive models TCP and NTCP. The assessment has taken into account the cases when patient set-up errors occur. Their quantification using EPID has allowed us to infer adequate CTV to PTV and PRV margin, which have improved patient positioning and the regular position correction.

The choice of the EUD approach provides better protection of OARs and better dose distributions in the PTV. The TCP and NTCP predictive models were found to be appropriate tools to remind one of both the tumour control and OAR complications. It also demonstrated the unavoidable biological impact of patient set-up errors on tumours and OARs when they were not corrected, especially in the case of the optic nerves and brainstem.

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