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Dosimetric analysis of VMAT Irradiation in Nasopharyngeal Carcinoma: A Moroccan Radio Oncology Center's experience

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Abstract

Introduction: Volumetric Modulated Arc Therapy (VMAT) is a technique increasingly used in radiotherapy. It was recently introduced in Morocco. Furthermore, technological advances allow the use of conformal radiotherapy to be phased out and replaced by VMAT technique for some locations. This study aims to evaluate the efficacy and quality of treatment with VMAT of nasopharyngeal cancer.

Methods: Twenty patients with non-metastatic nasopharyngeal cancer treated curatively by VMAT were studied at the Al Kindy Oncology Center in Casablanca. The dose was delivered using two arcs at a dose of 70 Gy in 35 fractions.

The optimization process was performed using the photon optimizer (PO) algorithm, which is available from versions 13.5.35 and beyond of the Varian Eclipse radiotherapy treatment planning system (Varian Medical Systems, Palo Alto, CA). Dosimetric data were collected from dose-volume histograms for target volumes (PTV) and organs at risk (OARs). The homogeneity index (HI) and the conformity index (CI) were calculated. The acute and late toxicities associated with radiotherapy were observed, and the evolution and follow-up of patients were carried out.

Results: For high risk (HR), intermediate risk (IR), and low risk (LR) PTVs, the $D_{95\%}$ was (95.54±1.61), (103.00±1.66) and (100.00±1.90)%, respectively, while the $D_{2\%}$ was (105.15±1.11), (105.20±1.42) and (104.56 ±1.25)%, respectively. For HR PTV, CI and HI were (0.98 ± 0.02) and (0.12 ± 0.03), respectively. For late toxicity, there were no reports of grade IV toxicity or grade III xerostomia. In contrast, a drop in the hearing of grade III was reported in 10% of patients. Patients' evolution was marked by a locoregional recurrence rate of 15% and a specific death rate of 20%.

Conclusion: The VMAT technique allows an excellent coverage of the target volumes while sparing the OARs particularly the nerve structures and the salivary glands.

Keywords: Rhino-pharyngeal cancer, VMAT, Dosimetry, Toxocity

1. Introduction

Nasopharyngeal carcinoma (NPC) is a malignant tumor with a different geographical distribution in the world. A high prevalence is observed in Southern China, Southeast Asia and North Africa. Nasopharyngeal carcinoma is strongly associated with the Epstein-Barr virus [1]. The number of new cases per year has been estimated at 86,700 and the number of deaths per year at 50,800. Remarkably high in certain geographical and ethnic populations, nasopharyngeal cancer is more common in men than in the women with a ratio of 2.3 [1]. Nasopharyngeal carcinoma is highly radiosensitive and chemosensitive. Radiation therapy (RT) is the basis of treatment and is also an essential component of the curative treatment. Stage I NPC is treated with RT alone, while stage II, III, IVA, IVB diseases are treated with concomitant radiochemotherapy [2,3]. Tumor control of the nasopharynx was strongly correlated with the dose delivered to the tumor. A total dose of 70 Gy is required for eradication of the macroscopic tumor and 46-60 Gy for profilactic treatment of lymph node areas at potential risks [2].

Significant progress has been made in the external radiotherapy techniques and equipment. These include the increased improvement of imaging techniques, which has improved the accuracy of the definition and delineation of the target volume and organs at risk. These advances have also led to the sophistication of treatment planning systems, and linear accelerator dose distribution capabilities leading to improved conformity and homogeneity of treatment [4,5].

Volumetric Modulation with Arc Therapy (VMAT) is also a major advance in the field of radiotherapy. It allows irradiation with simultaneous change of the multi-leaf collimator (MLC) position, the gantry positions and the dose rate. These capabilities are extremely valuable in the treatment of nasopharyngeal cancer; given its location and the proximity of the surrounding organs at risk (OARs) [6,7].

In Morocco, new radiotherapy techniques with on-board imaging such as volumetric modulated arc therapy (VMAT) and stereotaxic radiation therapy are increasingly used, but conformal radiotherapy with portal imaging remains the main technique used in external radiotherapy [8-10]. This study aims to evaluate the efficacy and profitability of the VMAT technique in the treatment of nasopharyngeal cancer at the Al Kindy oncology center in Casablanca.

2. Materials and methods

2.1 Population studied

This is a retrospective dosimetric study of 20 patients who were curatively treated for nasopharyngeal cancer between January 2016 and October 2016. However, the sample sizes for this study were randomly selected. The sheet was designed to collect patient data on the basis of comparative study such as demographic data, dose delivered for target volumes and organs at risk. Patients were classified according to the classification (TNM) of American Joint Committee on Cancer (AJCC). All patients received concomitant radiochemotherapy +/- induction chemotherapy. Radiation therapy (RT) was delivered using the VMAT (Rapid Arc) technique.

2.2 Treatment planning

Each patient had undergone a computed tomography simulation with 2.5 mm sections in supine position with immobilization by a 5-point thermoformed mask. Intravenous injection of contrast medium has been—commonly used unless contraindicated. The CT was then transferred to the treatment planning system (Eclipse) for volume definition.

The delineation of the target volumes and organs at risk OAR was the same for all patients in accordance with the recommendations of the ICRU 83. The Gross Tumor Volume (GTV) was defined by the clinic and the MRI. High Risk (HR) CTV uses the isotropic margin of 5 mm around the GTV and is extended to the entire nasopharynx. Intermediate Risk (IR) CTV is defined as the volume that includes the HR CTV with a 3 mm margin all around, with areas at risk of microscopic involvement; including the base of the skull covering the foramen oval, the anterior half of the clivus, the lower half of the sphenoid sinus (the sphenoid sinus was included in all for T3, and the T4), the pterygoid process, pterygopalatine fossae, parapharyngeal spaces and retro-styloids, retropharyngeal ganglia. This volume also includes air with macroscopic lymphadenopathy and adjacent areas. The Low Risk (LR) CTV is delineated by adding a 3 mm isotropic margin around the CTV IR and then extended to include the posterior third of the nasal cavities and maxillary sinuses. It also includes the level of lymph nodes II to V. A safety margin between the CTV and the planning treatment volume (PTV) was set at 3-5 mm for all CTVs. In areas where GTV and CTV were adjacent to critical normal structures (such as the brainstem), the margin was reduced to 1 mm. The organs at risk were also delimited and include: spinal cord, brain stem, chiasma, optic nerves, eyes, inner ears, parotid glands and temporomandibular joints. The near-maximum dose constraint for organs at risk was: partial brain <60 Gy, brainstem ≤ 54 Gy, spinal cord ≤45 Gy, optic chiasm <54 Gy, lens ≤10 Gy. For the parotid, the average dose ≤ 26 Gy in at least one gland, $V_{30\%}$<50% and $V_{40\%}$<33%. For the cochlea D_{mean}<50% and for the temporomandibular joint (TMJ) <60Gy.

The delivered dose was made by two coplanar arcs, one clockwise arc and one counterclockwise, with Simultaneous Integrated Boost (SIB). The PTVs HR, IR and LR received respectively 70 Gy at 2 Gy per fraction, 63 Gy at 1.8 Gy per fraction and 56 Gy at 1.6 Gy per fraction. The patients were irradiated once a day, five times a week. The optimization process, as part of the reverse planning, was performed by the Eclipse software version 13.5 (Varian Medical Systems), using the PO version algorithm. The results obtained were analyzed with the treatment plan evaluation module. At this point, a dose volume histogram is used to display the percentage of the radiation dose received by the volume percentage of a structure.

2.3 Evaluation parameters

The data were collected from dose-volume histograms (DVH). The PTV endpoints included $D_{2\%}$, $D_{5\%}$, $D_{95\%}$, $D_{98\%}$ ($D_{x\%}$ relative dose absorbed by x% of PTV) and $V_{95\%}$ (volume surrounded by isodose 95% of prescribed dose).

The homogeneity index (HI)[HI = ($D_{2\%}$-$D_{98\%}$) / $D_{50\%}$] and the conformity index (CI) (CI = $V_{95\%}$/PTV_{HR}) were calculated according to the formalisms of Radiotherapy and Oncology Group (RTOG) [7]. Ideally, CI should be 1, while HI should be 0.

For OARs data, we have reported dose near to the maximum for the spinal cord, brain stem, chiasma, optic nerves and temporomandibular joint. For parotids, we reported D_{mean}, $V_{30\%}$ and $V_{40\%}$ (the percentage of gland receiving ≥ 30 Gy, 40 Gy). For the eyes we reported D_{mean} and D_{max} for internal eyes and ears.

2.4 Assessment of toxicity

All patients had a weekly clinical evaluation during treatment. Patients were followed up every 3 months for the first 2 years, then every 6 months for the next 3 years and every year thereafter.

Toxicity was classified according to the Common Terminology Criteria for Adverse Events (CTCAE v4.03) for oral mucositis, xerostomia, dermatitis, hearing loss, and cerebral necrosis. The dosimetric data were exploited by the IBM SPSS Statistics system 25.

3. Results

3.1 Characteristics of the patients

Table 1 summarizes the characteristics of the patients. It should be noted that 80% of patients were classified in III and IV.

Table 1 Median age, sex and TNM classification of patients studied.

Items	Number	Percentage (%)	χ^2 -value	*P*-value
Median age (years)	49.50 ±15.42			
Sex				
Men	12	60	0.043	
Women	8	40	0.056	0.385
TNM stage				
II	4	20	0.063	
III	9	45	0.534	
IVA	6	30	0.002	0.118
IVB	1	15	1.813	

3.2 Target Coverage, Homogeneity and Conformity Indices

$D_{98\%}$ was (92.23 ± 2.69), (101.00 ± 3.61) and (101.40 ± 2.07), respectively, for PTV_{HR}, PTV_{IR} and PTV_{LR}, while the $D_{95\%}$ was (95.54 ± 1.60), (103.00 ± 1.67) and (100.00 ± 1.67) for these same volumes, respectively. The $D_{2\%}$ was (105.15±1.11), (105.20 ±1.42) and (104.56 ±1.25) respectively. The HI equivalent to each of these three volumes was very close to 0, (0.12 ± 0.038), (0.18 ± 0.06) and (0.28 ± 0.02) for PTV_{HR}, PTV_{IR} and $PTV_{LR,}$ respectively. For the CI, they were respectively (0.980 ± 0.023), (0.990 ± 0.005) and (0.990 ± 0.008) for PTV_{HR}, PTV_{IR} and PTV_{LR}, respectively. PTV dose coverage parameters are summarized in Table 2.

Table 2 PTV dose coverage parameters.

Plans	$D_{2\%}$	$D_{5\%}$	$D_{50\%}$	$D_{95\%}$	$D_{98\%}$	HI	CI
HR	105.15±1.12	104.51±1.10	101.70±1,01	95.54±1.61	92.23±2.69	0.12±0.03	0.980±0.020
IR	121.90±1.42	120.10±1.38	113.33±4.56	103.00±1.66	101.00±3.61	0.18±0.06	0.990±0.005
LR	130.60±1.25	128.50±1.23	115.25±4.78	100.00±1.90	101.40±2.07	0.28±0.02	0.990±0.008

Note: HR. High Risk ; IR. Intermediate Risk ; LR. Low Risk

3.3 The organs at risk

Dose limits were poorly respected in all nerve structures (optic nerve, brainstem, spinal cord etc.) with maximum doses around 57 Gy. The dose was (57.71 ± 2.29) Gy for the brainstem and (57.01 ± 4.08) Gy for the chiasma. However, the dose absorbed by the contralateral parotid was within the constraints set for doses D_{mean} = (25.01 ± 7.77) Gy, $V_{30\%}$ = (38.80 ± 13.05) Gy and $V_{40\%}$ = (29.21 ± 12.94) Gy. For the homolateral parotid these constraints were only respected for the $V_{30\%}$<50%. The same observation was made for the inner ears where the dose constraints were hardly respected. The results concerning the doses received by OARs are summarized in Table 3.

Table 3 Summary of doses received by OARs.

OAR	D_{max}(Gy)	D_{mean}(Gy)	$V_{30\%}$(%)	$V_{40\%}$(%)
Spinal cord	37.47±5.70	-	-	-
Brainstem	57.71±2.29	-	-	-
Chiasma	57.01±4.08	-	-	-
Optic nerve	56.20±4.12	-	-	-
TMJ	59.66±8.13	38.07±10.92	-	-
Homol eye	38.02±11.36	11.01±3.04	-	-
Control eye	33.13±8.74	10.71±4.18	-	-
Homol parotid	73.12±2.05	30.82±12.01	47.28±14.78	37.53±14.55
Control parotid	69.78±3.71	25.01±7.77	38.80±13.05	29.20±12.94
Homolear	61.78±5.30	50.81±9.92	-	-
Control ear	49.82±7.38	47.87±9.60	-	-

Note: "-" indicates…… . OAR. Organ at risk; TMJ. Temporomandibular joint

3.4 Acute and late toxicity related to radiotherapy

Twenty percent of patients studied had grade III leukopenia, which resulted in a suspension of concomitant chemotherapy. In addition, 15% of the patients presented with mucositis and 5% of the patients followed had grade III dermatitis. For late toxicity, no cases of grade IV toxicity or grade III xerostomia have been reported. In contrast, grade III hearing loss was reported in 10% of patients (Table 4).

Table 4 Acute and late toxicity related to radiation treatment.

Complications	Acute toxicity (grading)[a]					Late toxicity (grading)[a]				
	no	1	2	3	4	no	1	2	3	4
Mucositis	0	2(10)	15(75)	3(15)	0					
Dermatitis	2(10)	4(20)	13(65)	1(5)	0					
Leukopenia	0	1(5)	15(75)	4(20)	0					
xerostomia						0	6(30)	14(70)	0	0
Hearing						0	13(65)	5((25)	2((10)	0

[a] Qualitative variable expressed in n (%)

For a surveillance period of (27.05 ± 12.36) months, 30% of the cases of death were recorded of which 10% of the cases were not related to the cancerous disease. Patients who died of cancer had associated distant metastases, with 75% of cases having locoregional recurrence.

4. Discussion

The proportion of male patients represented 60% of the patients studied. This is consistent with most data in the literature that report a male predominance of this disease [11,12]. The median age was (49.50 ± 15.42) years. This result is of the same order of magnitude as (46.00 ± 30.42) years, (49.90 ± 44.90) years and (44.75 ± 14.63) years respectively reported by Sherif et al.2018 Chen et al.2016 and Lalya et al. 2017 [11,13, 14]. For TNM staging, 80% of patients studied had a stage III or IV tumor. This is similar to 78.2% reported by Lalya et al. 2017 [14] as well as to a 92% and 75.9% of the both arms of the Chen et al. 2016 [13].

VMAT is a technique similar to Intensity Modulated Radiation Therapy (IMRT) that allows irradiation by changing the dose rate, the position of the multileaf collimator (MLC) and the gantry rotation [14, 15] It is a technique that has solved the main limitations of IMRT (large number of MUs, long preparation time and high treatment time).

There are several methods for calculating the CI and the HI, which makes it difficult to compare different series. In addition, most studies evaluate VMAT for head and neck cancers and only a few evaluate VMAT in NPC. A HI value of (1.07 ± 0.01) was reported by Lee et al. 2012 [16] and (1.08 ± 0.02) for the Lalya et al.2017 [14]. Using an equivalent formula to the one we used, Enberger et al. 2009 [17] reported a HI of 0.07 close to 0.12. The CI we found of 0.98 and slightly higher than 0.71 reported by Enberger et al. 2009 [17].

Using VMAT, the proportion of OAR saved is slightly better compared to fixed-field IMRT [18,19]. The main concern when irradiating NPC is the brainstem and the parotid glands. In this study, the maximum dose to the brainstem was (57.71 ± 2.29) Gy, which slightly exceeded its stress dose (54 Gy). In fact, Quantitative Studies of Normal Tissue in the Clinic (QUANTEC) recommend that the entire brainstem can be treated at a dose of 54 Gy using conventional fractionation with limited risk of severe or permanent neurological effects. In

addition, partial irradiation of the brainstem (1-10 cm^3) can be done at doses up to 59 Gy for dose fractions below 2 Gy [20].

VMAT and IMRT reduce the irradiated volume of the salivary glands and thus minimize the risk of xerostomia [21, 22]. In fact, the average dose of the parotid gland appears to be associated with salivary production. A minimal reduction of the flow is observed at the average doses <10-15 Gy, this salivary production decreases gradually for average doses between 20-40 Gy and is significantly reduced above 40 Gy [21, 23]. As a result, the risk of xerostomia is reduced when at least one parotid gland is spared [21]. Portaluriet al.2006 [25] reported that a dose <30 Gy in the contralateral parotid leads to slight subjective xerostomia or no xerostomia at all. In our series, no case of grade III xerostomia was reported for an average dose of (25.01 ± 7.77) Gy.

In a study of 198 stage I-IIB NPCs in patients treated with IMRT alone, Su et al. 2012 [26] reported an incidence of grade III acute mucositis of 13.6%. This is similar to the 15% we found in our series. In a prospective multicentre study, Wang et al. 2012 [27] reported ≥3 grade dermatitis in 4.0% of patients treated with definitive IMRT. In another study, Kong et al. 2014 [28] reported grade III dermatitis in 7.4% of patients and no cases of grade IV skin toxicity. They also showed grade III leukopenia in 17.3% of patients and Grade IV in 13.6% of patients [28]. Our results are similar with grade III leukopenia of 20%. The differences observed between mucosal, skin and hematologic toxicities could be explained by the use of different chemotherapy protocols and/or different dosimetric plans. Hematological toxicity was improved by the routine use of growth factors.

In their studies, Sanda et al. 2016 [29] have reported complete response of 90% of patients treated, a recurrence rate of 16.7% and a mortality rate of 6.67% at 24 months. After a follow-up of 17.78 months, Lalya et al.2017 [14] had a complete response in all patients. Sherif et al. 2018 [12] reported a locoregional recurrence rate of 6.7% and a disease-free survival of 83.9% at 3 years. Our results are consistent with those of the literature, with a locoregional recurrence rate of 15% and specific survival of 80%. However, our center's OS was 80%, which is lower than what others have reported. The difference observed could be due to the use of a different induction chemotherapy protocol depending on the locally advanced stage (IV) of the study population and the small size of our sample.

5. Conclusion

The results obtained showed that the treatment of nasopharyngeal cancer using the VMAT technique allows an excellent coverage of the target volumes as well as good protection of the OARs, in particular nerve structures and salivary glands. The high rate of patients cured and the low incidence of side effects allow us to recommend this treatment plan as an optimal indication for NPCs.

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