A dosimetric comparative study between conformal and intensity modulated radiation therapy in the treatment of primary nasopharyngeal carcinomas: The Egyptian experience

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Key words: 3D-conformal, Dosimetric, IMRT, Nasopharyngeal carcinoma, Xerostomia.

ISSN: 2070-254X

Introduction: The work is a comparative study between two modalities of radiation therapy, the aim of which is to compare 3D conformal radiation therapy (3D-CRT) and intensity modulated radiation therapy (IMRT) in treating patients with nasopharyngeal carcinomas; dosimetrically evaluating and comparing both techniques as regard target coverage and doses to organs at risk (OAR).

Methods: 20 patients with nasopharyngeal carcinoma were treated by 3D-CRT technique and another 20 patients were treated by IMRT. A dosimetric comparison was done by performing two plans for the same patient using Eclipse planning system (version 8.6).

Results: IMRT had a better tumor coverage and conformity index compared to 3D-CRT plans (p-value of 0.001 and 0.004), respectively. As for the dose homogeneity it was also better in the IMRT plans and the reason for this was attributed to the dose inhomogeneity at the photon/electron junction in the 3D-CRT plans (p-value 0.032). Also, doses received by the risk structures, particularly parotids, was significantly less in the IMRT plans than those of 3D-CRT (p-value 0.001).

Conclusions: IMRT technique was clearly able to increase the dose delivery to the target volume, improve conformity and homogeneity index and spare the parotid glands and reduce dose to the risk organs in comparison to 3D-CRT technique

Introduction

Nasopharyngeal carcinoma is a challenge to the radiation oncologist. Patients' survival depends upon local control with high-dose radiation; however, the nasopharynx is surrounded by critical, dose-limiting normal tissues. Each generation of advances in radiotherapy technology carries the promise of improving local control. Historically, patients with early-stage disease had acceptable local control rates, 87–100% for T1 lesions and 89–94% for T2 tumors. Unfortunately, many patients present late with a locally advanced disease. Even with the introduction of combined modality therapy, control rates have remained approximately 62–73% and 44–50% for T3 and T4 lesions, respectively. [1-5]

Definitive radiotherapy plus cisplatin-based chemotherapy is considered the current standard treatment for advanced nasopharyngeal carcinoma. While the recent addition of chemotherapy had shown to improve disease-free survival, the specific impact of chemotherapy on local control has not been well established. [6,7]

Radiotherapy of nasopharyngeal carcinoma traditionally employs parallel opposed lateral photon fields for a significant portion of the treatment. The spinal cord is blocked after 40–45 Gy and the dose to the posterior cervical lymph nodes are supplemented by low-energy electron beam. Intensity-modulated radiotherapy (IMRT) is an advanced form of 3D conformal radiation therapy (3D-CRT) with two key enhancements: (*1*) computerized iterative treatment plan optimization using the inverse planning technique, and (*2*) the use of intensity-modulated radiation beams. [8]

The study was conducted to compare 3D-CRT and IMRT dosimetrically in treating nasopharyngeal carcinomas; evaluating and comparing both techniques as regard their efficacy on tumor coverage and doses received by the organs at risk (OAR) i.e therapeutic ratio.

Methods and Materials

The study design was accepted from our institutional scientific and ethical committees. A written consent was taken from all patients before their recruitment in our study.

Simulation, target volume delineation and dose specification

Regarding pre-radiation therapy preparation, fixation was done with a thermoplastic mask (while patient is lying supine with fully extended neck in the treatment position) over the head and shoulders, a lead marker was used to delineate the site of involved lymph nodes. Computed Tomography (CT) of the head and neck with intravenous contrast were taken with 3 mm sections down to the infraclavicular region. CT is then transferred to the planning system (Eclipse) for volume definition. Dose-volume histograms (DVHs) were calculated for 3D-CRT and IMRT, and all comparative parameters were extracted. Simulation

was done after plan approval to identify the laser marks for the isocenter of treatment. *For the 3D planning:* 3 fields technique was used; the initial large field irradiation was delivered with two lateral portals isocentric technique covering the nasopharynx and the upper neck nodes and low anterior neck field were used. The planned dose to the initial large field is 40 Gy. The field is then divided into a small matching lateral neck field and posterior neck electron fields till 60 Gy. The final cone down is to the gross target volume (GTV) + 2 cm margin to 70 Gy. For the neck nodes N0 =50 Gy, N < 3cm will receive 66 Gy and N > 3cm received 70 Gy. *For the IMRT planning*: 7 fields isocentric technique using isotropic gantry angles which are adjusted when a risk organ could be avoided for adequate target coverage. In accordance with the Radiation Therapy Oncology Group (RTOG 0225) the IMRT volumes were 1) *GTV*: gross disease including the primary tumor and enlarged lymph nodes as demonstrated on imaging modalities. 2) *CTV1* (clinical target volume): a margin of 1 cm around the GTV 3) *CTV2* (high risk disease): defined as areas at high risk of local failure and it includes the entire nasopharynx, sphenoid sinus, cavernous sinus, base of skull posterior ½ of nasal cavity and posterior 1/3 of maxillary sinuses, pterygoid fossa, lateral and posterior pharyngeal walls to the level of mid-tonsillar fossa, the retropharyngeal nodes and bilateral upper cervical nodes including level V and supraclavicular nodes. 4) *CTV3* (low risk disease) defined as areas at low risk of relapse and it includes low risk nodal regions. The planning target volume (PTV) contained an automated 0.3 cm expansion of the CTVs, to account for patient setup error. The dose prescriptions were: PTV1: 70Gy/2.12 per fraction, PTV2: 59.4Gy/1.8 per fraction and PTV3: 54Gy/1.64 per fraction in 33 fractions. The IMRT plans were extended field using simultaneous integrated boost technique (SIB). Dose constraints used in IMRT planning are outlined in table 1.

Table 1: Dose constraints for IMRT planning

Structure	Constraint	Priority
Spinal Cord	Max. < 45 Gy	High
Brainstem	Max. < 54 Gy	High
Temporal Lobe	Max. < 63 Gy	High
Optic Chiasma	Max. < 54 Gy	High
Optic Nerve	Max. < 54 Gy	High
Parotid Gland	Mean < 26 Gy or V30 < 50%	Intermediate
Cochlea/Vestibule	Max. < 50 Gy	Intermediate
Larynx	Mean < 40 Gy	Intermediate
Oral Cavity	Mean < 35 Gy	Intermediate
Nuchal Tissue	Mean < 35 Gy	Low

Abbreviations: IMRT = intensity-modulated radiotherapy; Max =maximum.

Quality assurance

Quality Assurance (QA) for IMRT: For pretreatment patients specific QA, the direct measurement of the IMRT dose distribution is checked using a special phantom. During radiation delivery, the accelerator MLC (Multileaf Collimator) position readout and the record and verify system are checked to verify the start and stop leaf positions of each field for the daily treatments. Off-line Electronic Portal Image Device (EPID) will be done once a week for the 3-D conformal group, and twice weekly for the IMRT group. An isocenter shift of 5mm and 3mm is accepted for the 3-D CRT and IMRT respectively. Treatment was delivered using Linear accelerator, 6 MV photon beam. The step and shoot technique was used for the IMRT treatment delivery.

Dosimetric comparison between conformal and IMRT planning

A dosimetric comparison was done for both techniques regarding:

A) Dose homogeneity within the target volume. Comparison between V95 % (volume of PTV planning target volume receiving 95 % of the prescribed dose) and V107 % (volume of PTV receiving ≥ 107 % of prescribed dose) for each technique and minimum dose in the target volume (D min). Homogeneity index (HI) and conformity index (CI) were calculated for each case using the RTOG equations [9];

$$HI = \frac{\text{Maximum isodose in the target}}{\text{Reference isodose}}$$

$$CI = \frac{\text{Volume of the reference isodose}}{\text{Target volume}}$$

B) Dose received by OAR will be compared for each contoured structure in terms of mean dose and maximum point dose.

Statistical methods

Data were statistically described in terms of mean ± standard deviation (± SD), median and range. Comparison between the study plans was done using Mann Whitney *U* test for independent samples. *p* values less than 0.05 was considered statistically significant. All statistical calculations were done using computer programs SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 15 for Microsoft Windows.

Results

Patient characteristics

Between February 2010 and December 2011, 40 patients with nasopharyngeal carcinoma were enrolled in our study. Two plans were done for each patient; one 3D-CRT and another one IMRT, i.e a total of 80 plans were done. The dosimetric comparison was done using Eclipse planning system (version 8.6).

Patient and tumor characteristics were recorded and all patients were staged using the revised 2002 American Joint Committee on Cancer (AJCC) criteria as shown in table 2.

Table 2: Patient and tumor characteristics for 40 patients with nasopharyngeal carcinoma

Patient Characteristics	Patients number (%)
Age	
≤ 40	11 (27.5)
41-50	11 (27.5)
51-60	9 (22.5)
> 60	9 (22.5)
Median (range)	56 (36-74)
Sex	
Male	21 (52.5)
Female	19 (47.5)
T stage*	
T1	5 (12.5)
T2a	9 (22.5)
T2b	6 (15)
T3	9 (22.5)
T4	9 (22.5)
N stage*	
N0	9 (22.5)
N1	13 (32.5)
N2	12 (30)
N3a	4 (10)
N3b	2 (5)
Tumor Grade**	
WHO 2	3 (7.5)
WHO 3	37 (92.5)

Abbreviations: WHO= World Health Organization

The IMRT plans were significantly better than 3D-CRT as regards the target coverage (V95%), 97.6% (94.6-99.5) and 94.5% (90.3-97.7) respectively, with p value 0.001. Maximum dose in the target (V107%) was nearly the same; 0.05% and 0.068% for the 3D-CRT and IMRT plans respectively (p-value 0.971) (table 3).

The IMRT plans were more conformal than those of the 3D-CRT. The CI was superior with IMRT plans denoting better coverage (p-value 0.004). As for the dose homogeneity it was also better in the IMRT plans (p-value 0.032) (table 3)

Table 3: Dose-volume comparison for target volume coverage in IMRT and 3D-CRT plans.

Parameter	PTV (3D Conformal)	PTV (IMRT)	P-Value
V 95 (%)	94.5 ± 5.844	97.6 ± 2.70	0.001
V 107 (%)	0.05 ± 0.223	0.068 ± 0.306	0.971
D min (Gy)	61.1 ± 9.24	65.9 ± 8.18	0.448
Homogeneity Index	1.08 ± 0.027	1.03 ± 0.40	0.032
Conformity Index	0.91 ± 0.058	0.97 ± 0.029	0.004

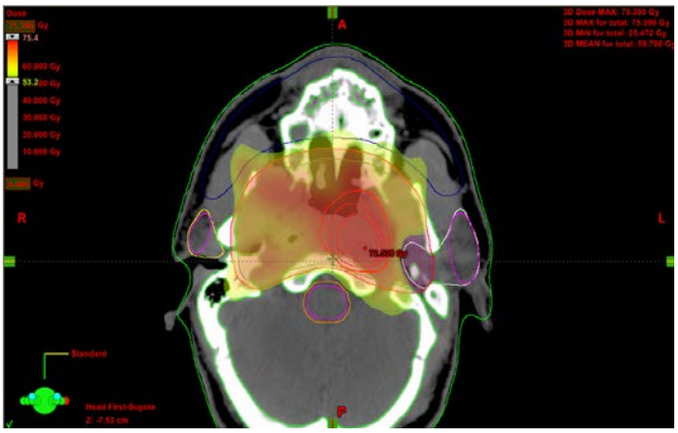
N.B: Data are presented as mean ± SD.

The mean dose to the right parotid gland was 25.21 Gy (range, 21.2–31.4 Gy) among patients treated by IMRT compared with 66.83 Gy (range, 59.3-69.9 Gy) for those treated by CRT (p-value 0.001). As for the left parotid gland, the mean dose was 24.28 Gy (range, 21.8–29.5 Gy) among patients treated by IMRT compared with 63.77 Gy (range, 60.6-71.2 Gy) for those treated by CRT (p-value 0.001). A statistically significant difference was also observed in the V30 to the parotid gland, which was 95.8% and 39.3% with CRT and IMRT, respectively ($p < 0.001$) (table 4). Figures 1 & 2 demonstrate the highly conformal dose distributions achieved with IMRT, particularly with respect to parotid sparing for a patient with nasopharyngeal carcinoma.

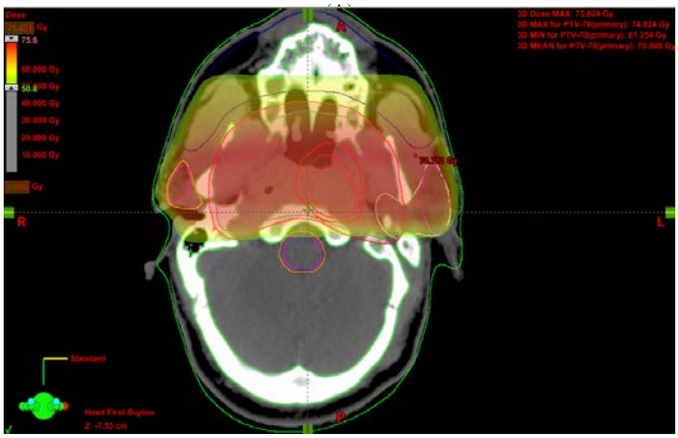
Table 4: Dose-Volume statistics derived from DVH for normal tissues.

Organ At Risk (OAR)	Priority	3D Conformal RT		IMRT		P-value
		Max. Dose (Gy)	Mean Dose (Gy)	Max. Dose (Gy)	Mean Dose (Gy)	
Brainstem	High	54.66 ± 5.10		52.06 ± 2.14		0.052
Brainstem PRV	High	57.9 ± 5.54		55.11 ± 1.97		0.017
Spinal Cord	High	47.34 ± 3.48		44.71 ± 1.92		0.001
Spinal Cord PRV	High	50.49 ± 4.21		47.58 ± 2.10		0.001
Chiasma	High	50.97 ± 7.95		46.3 ± 6.69		0.096
Chiasma PRV	High	53.35 ± 7.95		48.87 ± 5.23		0.035
Rt. Optic Nerve	Intermediate	45.57 ± 12.6		38.11 ± 13.2		0.018
Lf. Optic Nerve	Intermediate	44.25 ± 11.1		38.88 ± 10.9		0.189
Rt. Eye	Intermediate		7.32 ± 3.76		10.94 ± 8.12	0.208
Lf. Eye	Intermediate		9.91 ±5.38		10.31 ± 8.55	0.159
Rt. Temp. Lobe	Intermediate	67.57 ± 2.52		62.23 ± 6.38		0.001
Lf. Temp. Lobe	Intermediate	67.25 ± 2.32		63.29 ± 4.19		0.001
Rt. Parotid	Intermediate		66.83 ± 3.22		25.21 ± 1.98	0.001
Lf. Parotid	Intermediate		63.77 ± 2.98		24.28 ± 9.83	0.001
Rt. Cochlea	Intermediate		53.32 ± 8.18		46.87 ± 5.66	0.013
Lf. Cochlea	Intermediate		49.16 ± 9.11		42.72 ± 8.52	0.008
Mucosa	Intermediate		34.0 ± 4.83		38.79 ± 1.95	0.001
Nuchal Tissue	Low		31.59 ± 3.53		31.35 ± 5.43	0.464

DVH= Dose Volume Histogram; 3D-CRT= 3Dimentional Conformal Radiation Therapy; IMRT= Intensity Modulated Radiation Therapy; Max= Maximum; Gy= Gray; PRV= Planning at Risk Volume; Rt= right; Lf= left;; Temp= Temporal



N.B: Data are presented as mean ± SD.



(B)

Fig. 1: Highly conformal dose distributions achieved with IMRT (plan A), particularly with respect to parotid sparing as compared to 3D-CRT (plan B).

Patients treated by IMRT had lower maximum doses to the auditory structure (cochlea) compared with patients treated by CRT. The currently recommended maximum dose constraint to the cochlea is 50 Gy. The mean dose to the right cochlea was 46.87 Gy (range, 31–55 Gy) among patients treated by IMRT compared with 53.32 Gy (range, 42-69.8 Gy) for those treated by CRT (p-value 0.013). As for the left cochlea, the mean dose was 42.72 Gy (range, 31–52 Gy) among patients treated by IMRT compared with 49.16 Gy (range, 35-65.2 Gy) for those treated by CRT (p-value 0.008) As expected, there was a significant difference in the mean dose to the cochleae between patients treated by CRT vs. IMRT. IMRT reduced mean doses to the cochleae from 53.3 Gy to 46.8 Gy and 49.16 Gy to 42.72 Gy, respectively (table 4).

The maximum doses to the spinal cord, brainstem, chiasma and temporal lobe were greater for patients treated by CRT compared with IMRT ($p < 0.05$, for all). However, IMRT was significantly associated with increased maximum dose to the oral cavity mucosa ($p = 0.001$).

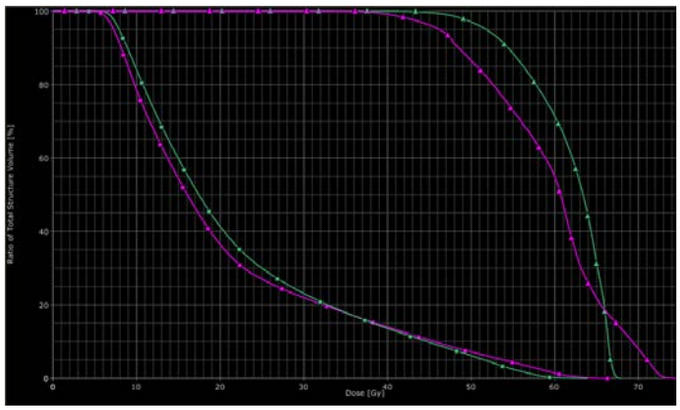


Fig. 2: A comparative Dose-volume histogram for both techniques regarding dose received by parotid glands (right in pink and left in green). The upper lines are of the 3D- CRT plan, while the lower ones are for the IMRT plan.

Discussion

Because of the complex anatomy and large number of sensitive normal structures in the vicinity of a target in the nasopharyngeal region, treatment planning for nasopharyngeal cancers is a challenging task.

With the advent of CT and MRI, now we are able to better visualize the 3D relationship between the tumor and OARs. It became evident that the rectangular shaped dose distribution in 2D-RT is far from satisfactory and will inevitably lead to suboptimal target coverage and inclusion of large volumes of normal tissues. This can, at least, account for the unsatisfactory local control in advanced T stage disease, as well as the high rate of xerostomia other late toxicities.

3D-CRT allows manual optimization of beam orientation, beam weighting and beams eye view (BEV) shaping. However, the problems of dose inhomogeneity and suboptimal conformity to the concave target volume in head and neck cancers are still unresolved. IMRT, compared with 3D-CRT, provides one more degree of freedom by allowing dose intensity modulation within each individual beam. As a result, the dose distribution can conform to the target to an extent that was not previously possible. In addition, the dose constraints assigned to critical structures in the optimization process allow better preservation of organs function than that achieved by conventional 2D RT or 3D CRT.[10]

Pirzkall et al compared the plan quality of 9 patients (plans done with 3D conformal and intensity-modulated radiation therapy). IMRT plans were created for comparison and they compared the target coverage, target conformality, dose homogeneity, monitor units (MU), user interactive planning time and treatment delivery time. Their results showed that IMRT improved target coverage an average of 36% and conformality by 10%. Also IMRT increased mean dose by 4-6 Gy and target coverage by 19% with the same degree of conformality. According to the authors, rotational IMRT was slightly superior to fixed-field IMRT. All IMRT techniques increased integral dose and target dose heterogeneity. IMRT increases MU's significantly.[11]

Our results are in accordance with a planning study involving 6 patients, investigators from Royal Marsden Hospital also showed significant improvements in parotid gland sparing.[15] The mean dose to the parotid gland was, 63.7 Gy, and

24.3 Gy, respectively, among patients treated by CRT and IMRT. These statistics are of relevance considering that Eisbruch et al. have validated the importance of mean dose to the parotid gland in the setting of IMRT and demonstrated a threshold for both stimulated (26 Gy) and un-stimulated (24 Gy) salivary flow rates. [12-16]

Another notable finding in the present study was the ability of IMRT to reduce dose to the ear structures. In view of several recently published studies identifying a dose–response relationship for the inner and middle ear, the importance of minimizing dose to these structures is becoming increasingly recognized among those undergoing irradiation. [17-18] In a prospective study of 40 patients, Pan et al. showed that clinically apparent hearing loss greater than 10 dB (decibel) occurred when the cochlea received mean doses in excess of 45 Gy. [18] Although questions exist regarding the time course of hearing loss after irradiation, general agreement exists that doses to the inner and middle ear should be closely monitored. This may be of increasing relevance because more patients are receiving concurrent cisplatin, which has known ototoxic effects.

It must be recognized that some dosimetric variables (e.g., maximum dose to oral cavity, maximum dose to mandible) were actually worse with the use of IMRT. This is not entirely unexpected, given the multiple beam arrangements leading to moderate doses to areas that would have previously received little if any dose with CRT. Nonetheless, the possibility of IMRT being associated with higher rates of mucositis has also been raised by others and may be due to the multiple beam arrangements and greater volume of non-target tissue in the irradiated volume receiving some dose inherent with this technique. [19]

The results of our study clearly demonstrate the superiority of IMRT in conforming and shaping the doses to the given target volumes, which should also be reflected in significant organs at risk protection, proving better therapeutic ratio. It was possible to decrease the maximum dose to the spinal cord and brainstem and significantly reduce the dose to the parotid glands with IMRT compared to 3D-CRT. Corresponding results were reported in a study by Kristensen et al. who compared dose plans of 11 patients for IMRT and 3D-CRT in patients with nasopharyngeal carcinoma. Their results also concluded superiority of IMRT in improving target volume coverage and critical organ protection. Their mean CI for IMRT was 0.53 (range: 0.39-0.84) as compared to a CI of 0.97 in our study (p-value 0.004). [20]

In another study, Tomita et al. compared radiation treatment plans using IMRT with helical tomotherapy and 3D-CRT for eight patients with nasal natural killer/T-cell lymphoma. It concluded that IMRT achieved significant better PTV coverage compared to 3D-CRT. The HI was better for IMRT compared with 3D-CRT (p-value 0.0001).[21] The results were similar to our study; we had a HI of 1.03 for IMRT and 1.08 for 3D-CRT (p-value 0.032) and the reason for this was attributed to the dose inhomogeneity at the photon/electron junction in the 3D-CRT plans.

Conclusion

IMRT technique was clearly able to increase the dose delivery to the target volume, improve conformity index and homogeneity index and spare at least one of the parotid glands. In addition, IMRT demonstrated delivering less dose to organs at risk including brainstem, spinal cord , chiasma, temporal lobes and cochleae compared to 3D-CRT technique.

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