Intensity Modulated Radiotherapy with Simultaneous Integrated Boost (IMRT-SIB) in treatment of Nasopharyngeal Carcinoma. Dosimetric Advantage over 3-Dimentional Conformal Radiotherapy (3D-CRT). Clinical impact on Survival, Toxicity and Quality of life

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Abstract: *Aim:* To compare intensity modulated radiotherapy with simultaneous integrated boost (IMRT-SIB) with 3-dimentional conformal radiotherapy (3D-CRT) dosimetrically as well as to evaluate treatment outcome, acute & late toxicities and quality of life in patients with nasopharyngeal carcinoma (NPC) treated by IMRT-SIB. *Patients & methods:* A total of 30 patients of histologically proof of stage II, III, IVb NPC were included in this study, IMRT-SIB plans as well as 3D-CRT plans were generated for every patient, compared dosimetrically with each other. All patients treated with concurrent chemo radiotherapy using IMRT-SIB. Acute and late toxicities were graded using RTOG/EORTC. Chemotherapy related toxicity was scored using CTCAE, 2017. Tumor response was evaluated according to WHO criteria. Quality of life assessed by QLQ-H & N35 module. Kaplan, Meier method estimated OS, LRPF and DMPF at 2 years. *Results:* IMRT-SIB was superior in PTV coverage with more sparing of spinal cord, brain stem and parotid glands compared to 3D-CRT. Acute grade 3 xerostomia, laryngitis, dysphagia, pain and mucositis recorded in 30%, 20%, 16.7%,16.7% and 13.3% respectively. At the 9th month follow up, only one patient suffered from grade 3 xersotomia and another one had grade 3 dysphagia. Deterioration in most QOL scales was observed during RT with recovery at 12 month even below that at baseline except in sticky saliva and dry mouth. The 2-year locoregional progression free rate, metastasis progression free rate and overall survival were 89.3 %, 92.86% and 86.7% respectively. Univariate analysis with respect to PFS and OS showed that N-stage (N1 is better than N2-3, P = 0.001) and AJCC-stage (II is better than III than IV, P = 0.001) were significantly associated with OS. PFS was significantly influenced by AJCC-stage (P < 0.001). However, multivariate analysis showed that AJCC-stage was the only independent prognostic factor for both PFS and OS. *Conclusion:* IMRT-SIB is significantly better than 3D-CRT in terms of PTVs coverage as well as spinal cord, brain stem and parotid glands sparing with reduction of the incidence and severity of toxicity mainly that of xerostomia in nasopharyngeal carcinoma patients with maintenance of tumor control and survival benefits. These benefits persiste on longitudinal follow-up with patients showing significant recovery of QOL over time, SO, strongly supporting the widespread adoption of IMRT-SIB in head and neck radiotherapy practice.

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1. Introduction

Nasopharyngeal carcinoma (NPC) is one of the Epstein-Barr virus associated malignancies; it is endemic in a few areas as Southeast Asia, Southern China, North Africa and the Arctic ***(1)***. Neck masses, nasal obstruction, discharge, epistaxis and headache are the common presentation. About 70% of patients are diagnosed at advanced stage (clinical stages III and IV) ***(2)***. Radiotherapy either alone or with chemotherapy is considered the primary treatment due to its anatomical location of the nasopharynx and its proximity to various risk organs ***(3)***. Radiotherapy has shifted from three-dimensional conformal radiotherapy (3D-CRT) to intensity-modulated radiotherapy (IMRT) ***(4)***. IMRT uses nonuniform radiation beam intensities to maximize radiation delivery to the planned target volume while minimizing irradiation of normal tissue outside the target resulting in highly conformal and more homogenous dose administration to the target volumes, better sparing of the organs at risk (OAR), and therefore less toxicity. This reduction in toxicity does not compromise the probability of tumor control ***(5)***. Simultaneous integrated boost IMRT allows the simultaneous delivery of different doses to different target volumes within the same fraction resulting in shortening of treatment duration and enhancing biologically equivalent dose ***(6)***. IMRT showed non–inferior survival outcomes as well as less acute & late toxicities and better quality of life ***(7)***.

The objective of this study is to compare intensity modulated radiotherapy with simultaneous integrated boost (IMRT-SIB) and a 3-dimentional conformal radiotherapy (3D-CRT) dosimetrically as well as to evaluate treatment outcome, acute & late toxicities and quality of life in patients with nasopharyngeal carcinoma (NPC) treated by IMRT-SIB concurrently with chemotherapy.

2. Patients and Methods

Between June 2015 to June 2017,30 newly diagnosed patients with histopathological proof of nasopharyngeal carcinoma, stages II-IVb according to AJCC 7th edition, age ≥18 year with ECOG PS ≤ 2with no previous radiotherapy, malignancy or comorbidity and had adequate blood chemistry were enrolled in this prospective study in Tanta and Alexandria University hospitals. All patients had careful history taking, clinical examination including cranial nerve examination, direct flexible fiber opticnasopharyngoscopic examination, CT/MRI head and neck, CXR, abdominal ultrasound and dental evaluation. Bone scan & PET-CT were done if indicated. Informed consents were taken from all patients with maintenance of their privacy.

Patients received concurrent chemoradiotherapy using IMRT followed by adjuvant treatment of either chemotherapy or salvage surgery according to site and stage.

Concurrent Chemotherapy details:

Chemotherapy was given in the form of Cisplatin 40 mg/m2 along with standard hydration and antiemetic prophylaxis concomitantly with radiation on a weekly basis for 7 weeks. Patients received chemotherapy on the same day as commencing radiotherapy. The full blood count and biochemistry were checked weekly before chemotherapy.

Skipping chemotherapy was due to leucopoenia (Total lecocytic count < 3.5 x 103 cell/mm3), elevated renal functions (serum creatinine elevation above high normal level) or severe mucositis.

Adjuvant chemotherapy was given in the form of 3 cycles of docetaxel 75 mg/m2 day 1, cisplatin 100 mg/m2 day 1, and fluorouracil 1000 mg/m2/day by continuous infusion on days 1 to 4 or cisplatin 100 mg/m2 day 1, and fluorouracil 1000 mg/m2/day by continuous infusion on days 1 to 4, cycle every 21 days with standard hydration, antiemetic prophylaxis and regular check of blood count and biochemistry before every cycle.

Radiotherapy details:

Simulation, immobilization and treatment planning CT procedures

All patients had proper staging, dental and nutritional evaluation prior to therapy, they underwent CT-scan from skull vertex to the middle of the sternum, with 3 mm slice thickness, in supine position with head hyper extended and immobilized using a custom made thermoplastic mask including the shoulder with 5-point fixation and intravenous contrast was used in some cases in order to help in the definition of cervical nodes.

Delineation of target volume

GTV 69.96 defined as the macroscopic tumor defined after correlative analysis of CT, MRI-scans and/or PET-CT including all involved positive lymph nodes (all nodes ≥ 1 cm in short axis or those with necrotic center).

CTV gross disease is composed of GTV gross disease with a 5mm margin accounting for possible microscopic disease with exception near the brain stem or spinal cord to be 1 mm.

CTV 59.4 subclinical disease included the entire nasopharynx ensuring inferior coverage of soft palate, clivus, skull base to cover foramen ovale where V3 (the mandibular nerve) resides, pterygoid fossae, parapharyngeal space, sphenoid sinus, posterior 1/3 of the maxillary sinuses with coverage of pterygopalatine fossae where V2 (the maxillary nerve) resides, posterior 1/3 of the nasal cavity, posterior ethmoidsin uses as well as retropharyngeal nodal regions, levels IB–V.

CTV low-risk subclinical disease may be outlined. However, in the presence of any pathologic low neck lymph node, the uninvolved low neck lymph nodes are incorporated into the CTV subclinical disease.

PTV is generally a 3-5 mm expansion of all the CTVs to account for potential setup errors and patient motion with limiting the margin to 1 mm around CTV near to the brainstem and spinal cord. A surface clipping margin of 3 mm was used for the PTV.

The main OAR considered for all patients were evaluated including brain stem, spinal cord, optic chiasma, bilateral optic nerves and right and left parotid glands. The objectives in IMRT plans were to maintain Dmax Spinal cord: < 45Gy, Dmax Brain stem:<54Gy, Dmax Optic nerves and Chiasm: Dmax<54Gy, Dmean Parotids: <26Gy (in at least one gland).

Treatment planning and delivery

Treatment planning was done on Electa planning system which has been configured for photons both for 3D-CRT as well as IMRT (step-and-shoot mode) using Siemens Medical Systems as linear accelerator. 3D-Conformal plans as well as IMRT plan were generated for every patient. 3D-CRT was planned in 2–3 sequential phases (summed to get the composite plan) to a total tumor dose of 69.96Gy using a forward planning process. Inverse planning for IMRT was done with 7–9 coplanar beams with megavoltage x-ray beams of 6 MV. Based on RTOG 0225, the prescribed

dose to the PTV gross disease was 69.96 Gy in 2.12 Gy/fraction, the dose to the PTV subclinical disease was 59.4 Gy in 1.8 Gy/fraction, and the dose to the PTV low-risk subclinical disease was 54.12 Gy in 1.64 Gy/fraction. The prescribed doses were delivered in 33 fractions, once daily, five days/ week.

Dose volume analysis of treatment plans

Dose volume histograms (DVHs) of the PTV and CTV and the critical normal structures were obtained. The dosimetric analysis of both plans was evaluated and compared. Plan quality was analyzed from (DVH) data. The treatment goal for each patient was to deliver 95% of the prescribed dose to ≥ 95% of the PTVs. Homogeneity index as well as confirmatory index was calculated for every plan.

- Homogeneity index (HI) = $\frac{D5\%-D95\%}{Prescribeddose}$

– Where D5%, D95 % are the received dose by 5% and 95 % of the target volume

– HI=0 is the most acceptable value. The closer to zero is the better dose homogeneity

- Confirmatory index (CI) =$\frac{V95\%}{\text{Target volume}}$

– Where V95% is the volume of PTV covered by at least 95% of prescribed dose

– CI=1 is the most acceptable value. If CI >1, it means irradiating volume is greater than the target volume and includes healthy tissue

Treatment interruption was avoided as much as possible through close monitoring of the patients and proper medications to overcome any troubles. Interruption occurred due to mucositis, skin reactions, ulceration & machine breakdown. This was compensated by adding extra fraction. Patients were encouraged to maintain oral hygiene & use super soft toothbrush with fluoride containing toothpaste. On occurrence of any fungal infection, topical and systemic anti-fungal were prescribed according to severity. Patients were advised to wear cotton clothes and avoid that made of synthetic materials. Also, they were instructed to avoid tough maneuver to the skin and to keep it dry and clean. In case of occurrence of moist desquamation, gentian violet 1% aqueous solution was applied.

Nutritional support: Throughout the treatment, the patients were advised to stop smoking, avoid spicy food, very cold and hot drinks. Body weight was monitored weekly and patients were encouraged to modify the consistency and texture of their diet using blended meat and vegetables, adding snacks in between meals to increase protein and caloric intake. Whenever there was marked weight loss (10%) and swallowing was significantly impaired, nasogastric tube was encouraged. Total parenteral nutrition was initiated in some patients who couldn't eat due to mucositis and nausea and refusing gastrostomy or nasogastric feeding tube.

Follow up

During radiotherapy, patients were monitored weekly or more frequent if necessary for body weight, blood count, renal function tests. Acute/late radiation toxicities were graded according to RTOG/EORTC ***(8)***. Acute toxicity scoring had been started from the 1st day of radiotherapy and continued till the day 90. A late toxic effect is considered if it occurred after 90 days of starting of radiotherapy. Chemotherapy related toxicity was scored using the common toxicity criteria for adverse events, version 5 ***(9)***. At 4 weeks after completion of CCRT, tumor response was evaluated according to WHO criteria ***(10)***. It was assessed by using endoscopy and head and neck MRI or CT with contrast as well as a biopsy of any suspicions lesion. Patients were followed-up every 2-3 months for the first 2 years. Chest radiographs were taken every 6 months, whereas CT, MRI, bone scanning, or other investigations were performed when clinical suspicions of recurrence were identified Then follow up with three months interval to detect any recurrence or distant metastasis.

Quality of life assessment:

The QLQ-Head and Neck 35 (QLQ-H & N35) module is a head and neck cancer-specific module with 35 questions and comprises 7 multi-item symptom scales—pain, problems with swallowing, sense, speech, social eating, social contact, and reduced sexuality—and 11 single-item symptom scales—problems with teeth, opening the mouth, dry mouth, sticky saliva, coughing, feeling ill, requirement for analgesics, nutritional supplements, use of a feeding tube, weight loss, and weight gain. In the questionnaire, items 1 to 30 are scored on four-point categorical scales (‘‘not at all,’’ ‘‘a little,’’ ‘‘quite a bit,’’ ‘‘very much’’). Items 31 to 35 have a ‘‘no/yes’’ response format. The scores are transformed into 0-to-100 scales, with a high values on the global and functional scores represent better functioning, whereas increases in the symptom scales indicate the presence of symptoms or problems ***(11).*** Quality of life was assessed before starting RT, during radiotherapy (4th or 5th week) and then at one year. Overall survival (OS) was defined as the time from diagnosis to death from any cause. Progression free survival (PFS) was defined as the time from diagnosis to any type of recurrence or metastasis or death from any cause. Locoregional recurrence was defined as recurrence at the primary site or nodal sites.

Statistical methods:

Statistical presentation and analysis of the present study was conducted, using the mean, standard deviation, Standard student "t test” and Chi-square test by SPSS V.20**.** Kaplan, Meier method estimated overall survival, locoregional progression free rate and distant metastasis progression free rate at 2 years ***(12)***.

Univariate and multivariate analysis of prognostic factors were performed using the Cox model and Log rank test with p value ≤ 0.05 considered significant.

3. Results

Patients 'characteristics:

Of the 30 patients in our study, 18 were males, 12 were females. Mean age was 33 years (range 20-46). The histology was moderately differentiated non keratinizing (WHO II) in 14 and Undifferentiated non keratinizingcarcinoma (WHO III) in 16 patients.13 patients were smokers and 17 patients were nonsmokers. The overall stage was stage II in 3 (10%), III in 22 (73.3%) and IV in 5 (16.7%) patients according to AJCC7th edition. ***(Table 1)***

Table (1): Distribution of Patient Demographic and Clinical Tumor Characteristics

Patients (n = 30)			
Age	**Range** (20 – 46)	**Mean ± S. D** 33.03 ± 9.01	
Parameter		**N**	%
Sex	Male	18	60
	Female	12	40
Smoking	Yes	13	43.3
	No	17	56.7
PS	0	16	53.3
	1	14	46.7
Grading	Moderately differentiated non keratinizing (WHO II)	14	46.7
	Undifferentiated non keratinizing carcinoma (WHO III)	16	53.3
T	T 1	4	13.3
	T 2	18	60
	T 3	6	20
	T 4	2	6.7
N	N 1	12	40
	N 2	15	50
	N 3	3	10
Stage	II	3	10
	III	22	73.3
	IV A	2	6.7
	IV B	3	10

SD: standard deviation, PS: performance status, T: tumor size, N: nodal status.

Treatment outcome:

All patients treated with concurrent chemoradiotherpy using weekly cisplatin 40 mg/m2 and IMRT-SIB. Seventeen patients received all seven cycles of weekly concurrent cisplatin, whereas nine patients received six concurrent cycles. Only four patients received five concurrent cycles. Omission of weekly cisplatin was due to neutropenia, anemia and mucositis. With a last follow up on April 2018, median follow up was 26.5 months (range 11-34 months).

Treatment response assessed 4 weeks after end of concurrent chemoradiotherapy, out of the 30 patients, 22 patients (73.33%) achieved complete remission whereas 5 patients (16.67 %) had partial remission, 2 patients (6.67%) had stable disease and one patient progressed. On correlation between tumor response and patients' characteristics, we found that all patients who had T1 or N1 disease achieved CR, whereas worse outcome observed in patients with N2-3. The progressed case was male, had T4 disease and undifferentiated non keratinizing histology.

At 2 years, 3 patients (10 %) had locoregional recurrence, two patients (6.7%) had distant metastasis, one patient had bone metastasis & the other one had lung metastasis and four patients died (13.3%). LRPF, DMPF rates & OS were 89.3 %, 92.86% and 86.7% respectively. On univariate analysis of prognostic factors that may influence PFS and OS, both N-stage (N1 is better than N2-3, P = 0.001) and AJCC-stage (II is better than III than IV, P = 0.001) were significantly associated with OS. PFS was significantly influenced by AJCC-stage (P < 0.001) ***(Table 2)***. However, multivariate analysis showed that AJCC-stage was the only independent prognostic factor for both PFS and OS. ***(Table 3)***

Table (2): Univariate analysis (Cox model) for progression free survival and overall survival with various prognostic factors

Item	2-Year PFS	P-Value	2-Year OS	P-Value
Sex Male Female	` 15 (83.3%) 10 (81.5%)	0.974	16 (88.9%) 10 (83.3%)	0.661
Smoking Yes No	10 (76.9%) 15 (88.2%)	0.410	11 (84.6%) 15 (88.2%)	0.773
Performance status 0 1	14 (87.5%) 11 (78.6%)	0.513	14 (87.5%) 12 (85.7%)	0.886
Histology Modrately differentiated Undifferantiated non keratinizing	12 (85.7%) 13 (81.3%)	0.743	13 (92.9%) 13 (81.3%)	0.351
T T 1-2 T 3-4	19 (86.4%) 6 (75%)	0.460	20 (90.9%) 6 (85%)	0.307
N N 1 N 2-3	11 (91.7%) 14 (93.3%)	0.317	12 (100%) 14 (77.8%)	0.001*
Stage II III IV	3 (100%) 22 (100%) 0 (0%)	0.001*	3 (100%) 22 (100%) 1 (20%)	0.001*

Table (3): Multivariate analysis for progression free survival and overall survival

Item	Multivariate	
	PFS (P-Value)	OS (P-Value)
N	-	0.325
Stage	0.001*	0.001*

Table (4): Dose-volume statistics derived from dose–volume histograms (DVHs) for target volumes

Item		Range (cG)	Mean ± S. D	t. test	p. value
95% of PTV69.96	**IMRT**	65.12 – 71.43	67.49 ± 1.34	28.897	0.001*
	Conformal	40.61 – 67.55	60.22 ± 7.8		
Mean dose of PTV69.96	**IMRT**	60.18 – 80.86	70.98 ± 4.03	27.210	0.001*
	Conformal	60.95 – 70.21	66.27 ± 2.84		
Min. dose of PTV69.96	**IMRT**	10.68 – 71.29	51.59 ± 1.38	0.711	0.403
	Conformal	8.06 – 40.42	39.25 ± 1.77		
Max. dose of PTV69.96	**IMRT**	72.00 – 84.09	77.44 ± 3.21	49.306	0.001*
	Conformal	52.00 – 76.77	69.35 ± 5.42		
95% of CTV59.4	**IMRT**	40.99 – 64.50	56.42 ± 4.74	79.894	0.001*
	Conformal	37.18 – 54.00	44.25 ± 5.64		
Mean dose of CTV59.4	**IMRT**	55.41 – 77.80	62.18 ± 5.57	16.288	0.001*
	Conformal	7.86 – 68.47	51.75 ± 1.30		
Min. dose of CTV59.4	**IMRT**	10.13 – 54.18	39.20 ± 1.17	13.029	0.001*
	Conformal	3.87 – 70.83	25.80 ± 1.67		
Max. dose of CTV59.4	**IMRT**	59.57 – 79.40	70.34 ± 5.34	9.118	0.004*
	Conformal	39.11 – 72.72	64.30 ± 9.58		

Dose-volume analysis

Table 4 shows the dose-volume statistics of both IMRT and 3D-CRT plans based on DVHs of the target volumes in the 30 patients.

Regarding target volumes

IMRT plans provided better coverage of the target volumes. In IMRT plans, 95% of PTV 69.96 was covered by a mean dose of 67.5 ± 1.3 Gy on contrary of 3D-CRT plans that was covered by a mean dose of 60 ± 7.28 Gy with statistically significant difference (p= 0.001). The mean dose to PTV

69.96was 70.98 ± 4.03 Gy in IMRT, while it was 66.27 ± 2.84 Gy in the 3D-CRT with statistically significant difference (p= 0.001). The mean minimum & maximum dose to PTV69.96 was 51.59 ± 1.38 Gy, 77.4 ± 3.22Gy in IMRT, while they were 39.25± 1.77 Gy and 69.35± 5.4 Gy in the 3D-CRT respectively. Statistically significant difference was observed between IMRT and 3D-CRT plans in the maximum dose of PTV69.96 only (p= 0.001). Regarding CTV 59.4, in IMRT plan, 95% of it was covered by a mean dose of 56.4 ± 4.7 Gy in contrary of 3D-CRT plan that was covered by a mean dose of 44.3 ± 5.6 Gy with statistically significant difference (p= 0.001). The mean dose to CTV 59.4 was 62 ± 5.57 Gy in IMRT and decreased to 51.8 ± 1.3Gy in the 3D-CRT with statistically significant difference (p= 0.001). The mean minimum & maximum dose to CTV 59.4 was 39 ± 1.17 Gy, 70 ± 5.34 Gy in IMRT, while they were 25.8 ± 1.67 Gy and 64.3 ± 9.58Gy in the 3D-CRT respectively with statistically significant difference (p= 0.001) & (p= 0.004).

Regarding organs at risk:

IMRT plans provided significant sparing of critical risk organs. The average maximum spinal cord dose decreased from 54.47Gy in 3D-CRT to39.7 Gyin IMRT with statistically significant difference (p=0.001), whereas mean maximum brain stem dose decreased from 54.73 Gy to 51.29Gywith statistically significant difference. (p=0.032). Although maximum doses of optic chiasma as well as Rt & Lt optic nerves in IMRT plans were lower than that in 3D-CRT plans, no statistically significant differences were seen in comparison of both plans. IMRT had a great role in parotid glands sparing, it maintained mean dose of both parotid glands below 26 Gy. Mean doses of Rt & Lt parotid in IMRT plans were20 ± 4.77 Gy & 23 ± 2.16 whereas in 3D-CRT plans, mean doses were61.51 ± 6.75 Gy & 56.44 ± 17.93 Gy respectively with statistically significant difference. (p=0.001). ***(Table 5)***

Table (5): Dose-volume statistics derived from dose–volume histograms (DVHs) for organs at risk

		Range	Mean ± S. D	t. test	p. value
Dmax spinal cord	**IMRT**	**37 – 45**	**39 ± 4.77**	**64.583**	**0.001***
	Conformal	**44.4 – 66**	**54.47 ± 6.30**		
Dmax brain stem	**IMRT**	**43 – 54**	**51.29 ± 2.01**	**3.923**	**0.032***
	Conformal	**37.4 – 67.57**	**54.73 ± 8.02**		
Dmax optic chiasma	**IMRT**	**20 – 52.68**	**24.01 ± 19.65**	**0.077**	**0.783**
	Conformal	**25 – 65.95**	**27.63 ± 18.77**		
Dmax RT optic nerve	**IMRT**	**11 – 40**	**14.41 ± 14.12**	**3.726**	**0.058**
	Conformal	**20 – 67**	**23.09 ± 20.18**		
Dmax LT optic nerve	**IMRT**	**13 – 42**	**17.12 ± 16.08**	**1.692**	**0.198**
	Conformal	**18 – 65**	**23.19 ± 19.86**		
Mean Rt parotid	**IMRT**	**19.2 – 25**	**20 ± 4.77**	**588.948**	**0.001***
	Conformal	**38.63 – 68**	**61.51 ± 6.75**		
Mean Lt parotid	**IMRT**	**13 – 26**	**23.00 ± 2.16**	**90.036**	**0.001***
	Conformal	**6.4 – 67**	**56.44 ± 17.93**		

Regarding plan parameters:

As illustrated in ***Table 6***: IMRT plans showed more homogenous dose distribution than that in 3D-CRT plans with statistically significant difference (p=0.008). However CI didn't show statistically significant difference between both plans. IMRT plans required more monitor units as well as time per fraction in comparison of 3D-CRT with significantly statistically difference. (p=0.001)

Table (6): Different plan parameters

Item		Range	Mean ± S. D	t.test	p.value
CI	**IMRT**	0.2 – 5	1.24 ± 1.03	0.065	0.799
	Conformal	0.18 – 3.4	1.18 ± 0.89		
HI	**IMRT**	0.06 – 0.3	0.11 ± 0.06	7.457	0.008*
	Conformal	0.05 – 0.7	0.19 ± 0.16		
MU/fraction	**IMRT**	377 – 1128	827.9 ± 148.4	88.67	0.001*
	Conformal	211 – 787	443.9 ± 166.9		
Time/minutes	**IMRT**	1.8 – 5.6	4.14 ± 0.74	88.77	0.001*
	Conformal	1.05 – 3.9	2.21 ± 0.83		

CI: Confirmatory index, HI: Homogeneity index

Toxicity profile:

Hematological toxicity

Grade 1 & 2 anemia and neutropenia occurred in 46.67% & 30% respectively. One patient had grade 3 neutropenia. No one had grade 3 anemia or thrombocytopenia. Most of the patients had anemia and neutropenia at the 4th and the 5th week. ***(Table 7)***

Table (7): Hematological toxicity

Adverse event	Grade 0		Grade 1/Grade 2		Grade 3	
	n	%	n	%	n	%
Anemia	16	53.3%	14	46.7%	0	0%
Neutropenia (ANC)	20	66.7%	9	30%	1	3.3%
Thrombocytopenia	29	96.7%	1	3.3%	0	0%

ANC: absolute neutrophile count

Non-hematological acute toxicities

Acute radiation toxicity was well tolerated. High grade 3 mucositis was noticed in 4 patients (13.3 %). Nine patients (30%) suffered from grade 3 xerostomia. Five patients (16.67%) complained from grade 3 oral pain as well as grade 3 dysphagia. Grade 3 laryngitis was observed in 6 patients (20%). Also, grade 3 radiation dermatitis occurred in 4 patients (13.3%). Only one patient had grade 3 weight loss. Patients complained from toxicities on the 4th, 5th and 6th week with the peak incidence on the 5th week. ***(Table 8)***

Table (8): Non-hematological acute toxicities

Adverse events	Grade 0		Grade 1		Grade 2		Grade 3		Time of highest grade
	n	%	n	%	n	%	n	%	
Mucositis	0	0	5	16.67%	21	70%	4	13.3%	4th & 5th weeks
Acute salivary toxicity	0	0	6	20%	15	50%	9	30%	5th & 6th weeks
Thickening of salivary secretions	0	0	17	56.7%	13	43.3%	0	0	5th week
Pain	0	0	5	16.67%	20	66.7%	5	16.67%	5th week
Laryngitis	4	13.3%	5	16.67%	15	50%	6	20%	4th & 5th weeks
Dysphagia	2	6.67%	8	26.67%	15	50%	5	16.67%	5th week
Radiation dermatitis	0	0	11	36.7%	15	50%	4	13.3%	6th week
Weight loss	1	3.3%	18	60%	10	33.3%	1	3.3%	6th week

Late radiation toxicities

Only one patient still had grade 3 xersotomia and one patient had grade 3 dysphagia. No grade 4 toxicities were noticed. However 20 % of patients still had grade 2 xerostomia and one patient had grade 2 dysphagia. Grade 2 hoarseness of voice remained in 2 patients. ***(Table 9)***

Table (9): Late radiation toxicities

Adverse event	Grade 0		Grade 1		Grade 2		Grade 3	
	n	%	n	%	n	%	n	%
Xerostomia	5	16.67%	18	60%	6	20%	1	3.33%
Fatigue	18	60%	12	40%	0	0	0	0
Neck oedema	20	66.67%	9	30%	1	3.33%	0	0
Hoarsence of voice	4	13.3%	24	80%	2	6.67%	0	0
Dysphagia	7	23.33%	21	70%	1	3.33%	1	3.33%
Trismus	24	80%	6	20%	0	0	0	0
Osteonecrosis of jaw	30	100%	0	0	0	0	0	0

Quality of life:

In the acute phase (ie, during radiotherapy), as expected, there was significant worsening of symptoms. About 80 % of patients (24/30) reported mean QLQ score higher than 50 after the 3rd week of RT. The deterioration was clinically significant in swallowing, local pain, sticky saliva, dry mouth. At the 12-month follow-up, a recovery to baseline and even improvement was observed with the exception of the dry mouth and sticky saliva items, which remained in 25 % of patients (7\28). Percentage of patients with mean QLQ score >50 (i.e poorer health) improved

after one year of treatment compared to that before starting RT (25 % vs 53.3%) respectively. ***(Table 10)***

Table (10): QLQ assessment data; Patients with mean scores > 50

Scale name/Item number and description	Number of patients with mean score >50		
	Before RT	During RT	At one year
1-Pain (HNPA) 1 Pain in the mouth 2 Pain in the jaw 3 Soreness in the mouth 4 Painful throat	9	24	4
2-Swallowing (HNSW) 5 Problems swallowing liquid 6 Problems swallowing pureed food 7 Problems swallowing solid food 8 Choked when swallowing	6	23	2
3-Senses (HNSE) 13 Problems with your sense of smell 14 Problems with your sense of taste	16	18	5
4-Speech (HNSP) 16 Been hoarse 23 Trouble talking to other people 24 Trouble talking on the telephone	3	8	2
5-Social eating (HNSO) 19 Trouble eating 20 Trouble eating in front of family 21 Trouble eating in front of others 22 Trouble enjoying meals	2	4	1
6-Social contact (HNSC) 18 Bothered by appearance 25 Trouble having social contact with family 26 Trouble having social contact with friends 27 Trouble going out in public 28 Trouble having physical contact with family or friends	2	3	0
7-Sexuality (HNSX) 29 Less interest in sex 30 Less sexual enjoyment	6	12	4
Single items			
9 Problems with teeth	0	2	1
10 Problems opening mouth	2	5	1
11 Dry mouth	5	24	7
12 Sticky saliva	6	24	7
hn15 Cough	0	1	0
17 Felt ill	5	10	3
31 Using pain killers	8	14	5
32 Using nutritional supplements excluding vitamins	3	11	1
33 Using feeding tube	0	0	0
34 Lost weight	13	16	3
35 Gained weight	0	0	4

4. Discussion

Transition from 2D conventional radiotherapy to 3DCRT achieved a great advance in radiation technology. Intensity modulated radiotherapy (IMRT) is one of highly precision conformal radiotherapy. It allows delivery of increased doses to tumor tissue while limiting the delivered dose to normal organs at risk ***(13).*** In our study, the epidemiological data (Table 1) reflects the general features of the 30 cases. Mean age was 33 years ± 9 SD, which is less than median age of most of literatures ***(14-15). Lee et al.,*** reported that nasopharyngeal carcinoma is common in

Mediterranean and some North African population (8 to 12 per 100,000 people), considering them as endemic areas, and the incidence outside endemic areas is much lower **(16).** More than half of patients (53.3%) had undifferentiated non keratinizing squamous cell that correlated with endemic nasopharyngeal carcinoma, similar correlation was observed by ***Yansu*** and his colleagues ***(17).*** Also, most patients presented at advanced stage III (73.3%) that is consistently with ***Wang et al.,*** where 81.9 % of their patients had stage III–IVb disease ***(18)***. The young age of our patients, their advanced stage at presentation as well as the disease site that is near to a lot of risk organs rendered them more eligible for IMRT-SIB technique to get its benefit with less toxicities. In this study, there was statistically significant difference between both techniques as regard to PTV69.96 coverage, its mean and maximum doses & CTV59.4 coverage, its mean, minimum and maximum doses as well as statistically significant difference on sparing organs at risk as spinal cord, both parotid glands in all cases, brain stem. Similar results were reported by ***Hunt et al.,*** on treating 23 patients with primary nasopharynx cancer using dynamic IMRT with an inverse planning algorithm. On comparison between 3DCRT and IMRT, They found that mean PTV dose had improved in IMRT plans more than that in 3DCRT plans (74.6 Gy and 77.3 Gy with the the 3D and IMRT plans, respectively), resulting in better improvement of PTV coverage in the parapharyngeal region, the medial aspects of the nodal volumes and the skull base using IMRT. Mean maximum Spinal cord dose was decreased from 44 Gy in the 3D plan to 34.5 Gy in IMRT plan. Also, mean parotid gland dose was decreased with IMRT than that with other plans ***(19).***

Also, ***Claus et al.,*** reported on comparing dose plans of IMRT with 3D-CRT on 11 patients with nasopharyngeal carcinoma significant improvement of target volume coverage, significant reduction of the maximum dose to the spinal cord and brain stem as well as significant protection of parotid glands in IMRT plans that achieved with both a forward or inverse plan method. However, lower doses to parotid glans delivered through the inverse plan method with mean parotid dose 25.5 Gyvs 37.1 Gy in patients treated with forward plans ***(20)***.

Our study also showed a statistically significant difference between IMRT and 3DCRT plans regarding monitor units/fraction as well as time/minutes. Comparable results were found by both ***Miles et al.,*** and ***Van de Werf et al.,*** the first study reported that IMRT planning time was significantly longer than for conventional that had included target volume delination by clinician, more physics time specially for patient specific QA. The second one also proved that both increased QA and the delivery of IMRT had to be significant parameters determining daily treatment time resulting in increased treatment costs ***(21-22).***

Also, ***Murthy et al.,*** concluded that IMRT delivery time is about 2.5–4 times longer when compared to 3DCRTin a cohort of 20 patients. The median treatment delivery time/ fraction varied between the two arms, with 3D CRT taking 15.2 min, while IMRT taking 27.8 min (P<0.001). The total treatment time was also significantly longer in the IMRT arm (P<0.001). The monitor units delivered /fraction and the actual beam-on time were also statistically longer with IMRT ***(23)***.

In our series, acute toxicity was recorded in the thirty patients, Grade 1 & 2 anemia and neutropenia occurred in 46.67% & 30% respectively. Only one patient developed grade 3 neutropenia. However, higher grade 3 mucositis, xerostomia, oral pain, dysphagia, laryngitis and radiation dermatitis were noticed in 13.3 %, 30%, 16.67%, 16.67%, 20% and 13.3% of patients respectively. Only one patient had grade 3 weight loss.

The time of highest grade of toxicity in our study was the 4th, 5th, 6th week with a peak on the 5th week which is a well-known radiobiological finding due to different kinetics of the cell populations involved ***(24)***.

On evaluating late toxicity, we focused mainly on late xerostomia and dysphagia as these are the most important toxicities after RT for HNSCC.

In our study, after 9 months of ending radiotherapy, only one patient (3.3%) still had grade 3 xersotomia and one patient had grade 3 dysphagia (3.3%). No grade 4 toxicities were noticed. However 20 % of patients had grade 2 xerostomia and another one had grade 2 dysphagia. Grade 2 hoarseness of voice remained in 2 patients.

Similar results of our study were proved by ***Lee et al.,*** who examined 68 nasopharyngeal carcinoma patients treated with 70 Gy concurrently with cisplatin followed by adjuvant 3 cycles PE for acute toxicity, they reported acute grade 4 mucositis in 4.4%, and late grade 3 dysphagia, mucositis, xerostomia in 4.7%, 3.1%, 3.1% respectively. At one year from the start of IMRT, grade 2 xerostomia was 13.5%, only two patients complained of grade 3 xerostomia, and no one complaind from grade 4 xerostomia ***(25)***.

Also, ***Nutting et al.,*** reported in one of largest, multicentric studies of 94 patients with advanced pharyngeal cancer that at one year, grade 2 xerostomia was 38 %. The difference between our study and Nutting may be due to scoring late toxicity by the late-effects on normal tissues-subjective objective management analytic (LENT-SOMA) ***(26)***.

In our series, no osteoradionecrosis of jaw was observed similarly as shown by ***Chen et al.,*** who studied the incidence of osteoradionecrosis in patients

with paranasal sinuses and nasal cavity cancers treated by either 2DRT or 3DCRT or IMRT, they found that only IMRT treatment was associated with no events ***(27)***.

Similarly, ***Rastogi M et al.,*** evaluated feasibility, toxicity patterns and loco-regional control rates of IMRT-SIB technique in 30 HNSCC patients who aren't candidates for CCRT. Acute grade 3 mucositis, dermatitis, pharyngitis/esophagitis and laryngeal were 56.66%, 30%, 26.67%, and 6.67% respectively at end of the treatment. Neither grade 4 toxicity nor hematological were noticed. Late grade 2 xerostomia was 13.3% whereas grade 2 subcutaneous toxicity was 7%. Thus, IMRT-SIB alone is an acceptable option for patients of HNSCC unfit for CCRT ***(28)***.

In our study, on analysis of QLQ, there was expected worsening of QOL during RT, mainly in swallowing, local pain, sticky saliva, dry mouth. At the 12-month follow-up, a recovery to baseline and even improvement was observed with the exception of the dry mouth and sticky saliva items. Percentage of patients with mean QLQ score >50 (i.e poorer health) improved after one year of treatment compared to that before starting RT (25 % vs 53.3%) respectively.

Similar improvement was reported by ***Nutting et al,*** who demonstrated significant improvements in the clinical grade of xerostomiain patients who were treated with IMRT both after 12 and 24 months in the PARSPORT trial ***(26)***.

Also, a trial by ***Rathod et al,*** had assessed health related QOL outcomes in 60 HNSCC patients. Although the primary endpoint of the study was acute salivary gland toxicity, several symptom scales, such as dry mouth and opening mouth, were significantly improved at 12 months in the IMRT arm ***(29)***.

Also, ***Huang et al.,*** underwent observational, cross-sectional study of QOL and late toxicities on 242 patients with NPC with survival of more than 5 years after treatment with IMRT or non-IMRT methods. They found that The IMRT group had both statistically and clinically better outcome in global QOL, cognitive functioning, social functioning, fatigue, and 11 scales of the head and neck module. Also, late toxicities including xerostomia, dysphagia, neuropathy, hearing loss, and neck fibrosis were significantly less severe in the IMRT group ***(30)***.

Edvard et al, reported that QOL was deteriorated also in the acute phase. Appetite loss, problems with swallowing, local pain, sticky saliva, dry mouth, fatigue, and decreased role functioning were significantly affected. At the 12-month follow-up, significant improvement was observed in most of symptoms excepting dry mouth ***(31)***.

Our study demonstrated that 73.33% of patients achieved complete remission whereas 16.67 % of patients had partial remission, 6.67% of patients had stable disease and one patient got progression. There was statistically significant difference between tumor response and tumor size as well as N stage.

Comparable results were reported by ***Lertbutsayanukul et al.,*** on treating 18 patients with head and neck cancer using IMRT with concurrent cisplatin or carboplatin,77.8% of patients had nasopharyngeal cancer, at 3 months CR and PR were 71.4% & 28.6% respectively ***(32)***.

Montejo et al., evaluated treatment response of CCRT using IMRT in 43 patients with advanced head-and-neck squamous cell carcinoma, they reported that 90.7% completed chemoradiotherapy. The median treatment duration was 43 days (range, 38–55 days). The complete response rate was 74.4 %***(33)***.

Kim et al., analyzed 53 consecutive nasopharyngeal cancer patients who received definitive treatment using IMRT-SIB and cisplatin-based concurrent chemotherapy. 49 patients (92.5%) showed a complete clinical and radiographic response at 3 months after initial treatment. Two patients showed a partial response. The remaining two patients had progressive disease ***(34)***.

At 2 years, within our patients LRPF & DMPF rates and OS were 89.3 %, 92.86 % and 86.7% respectively. 10 % of patients had locoregional recurrence; two patients (6.7%) had distant metastasis. Univariate analysis showed that both AJCC stage and N classification were significant parameter for overall survival while multivariate analysis revealed that the only significant parameter for overall survival was the stage.

Comparable results obtaind from Grouped' Oncologie Radiothérapie Tête EtCou (GORTEC) in France who reported 2-year loco-regional control and survival of 86% and 86.7%, respectively in a cohort of 208 patients treated with IMRT ***(35).***

Lee et al, reported that 2 years LRPF & DMPF rates and OS were 87.5 %, 82.1 % and 76.7% respectively on treating 68 patients with stages IIB through IVB NPC. Higher survival in our series may be due to less patients with stage IV than that in Nancy et al. (16.7 % vs 28 %) ***(25).***

Katano et al, treated 62 NPC patients with 3D-CRT or IMRT with or without CCT. The estimated 5-year OS, LRPF, and DMPF rates were 72.7%, 77.9%, and 84.2%, respectively. The 5-year OS and PFS rates were significantly worse in the advanced clinical stage group in univariate analysis. Multivariate analysis revealed that clinical stage and administration of CCT were independent predictors for both OS and PFS, regardless of other factors ***(36)***.

Conclusion

IMRT-SIB is significantly better than 3D-CRT in terms of PTVs coverage as well as spinal cord, brain

stem and parotid glands sparing with reduction of the incidence and severity of toxicity mainly that of xerostomia in nasopharyngeal carcinoma patients with maintenance of tumor control and survival benefits. These benefits persiste on longitudinal follow-up with patients showing significant recovery of QOL over time, SO, strongly supporting the widespread adoption of IMRT-SIB in head and neck radiotherapy practice.

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Conflict of interest

None.

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