Pan Arab Journal of Oncology

Original Article

3D-Conformal versus Intensity Modulated Radiation Therapy in Locally Advanced Head & Neck Carcinoma; Parotid Glands Sparing Attempt

Karim N. Mashhour, Wedad B. Hashem

Department of Clinical Oncology, Kasr Al Einy School of Medicine, Cairo University, Egypt

Received 12 Dec 2016
R1 received 21 Mar 2017
Accepted 25 Jun 2017
Available online 22 July 2017

Corresponding Author

Karim Nabil Mashhour

E-mail krim.mashour.81@gmail.com
Address:
Clinical Oncology Department
Kasr Al Einy School of Medicine,
Cairo University
Cairo 11553, Egypt

Keywords:
Head and neck carcinoma,
3D-Conformal,
IMRT,
Xerostomia

ABSTRACT

Objectives: The study is a comparative randomized study between two groups of patients, the aim of which is to compare 3D conformal radiation therapy (3D-CRT) and intensity modulated radiation therapy (IMRT) in treating non-metastatic locally advanced head & neck squamous cell carcinoma; evaluating and comparing both techniques as acute and late treatment related toxicity. **Patients and Methods:** Between June 2014 and March 2016, 30 patients with locally advanced head & neck carcinoma were treated by 3D-CRT technique (Group A) and compared to another 30 patients treated by IMRT (Group B). Both groups were treated at Kasr El-Ainy Center of Clinical Oncology and Nuclear Medicine (NEMROCK). The two groups were treated concurrently with platinol as a weekly sensitizer. Patients were assessed for treatment related toxicity using the European Organization for research and treatment of cancer, the Radiation Oncology Group (EORTC/RTOG). **Results:** Group A showed a higher incidence of treatment related toxicity compared to group B, particularly xerostomia. IMRT was clearly able to preserve the parotid gland function. **Conclusion:** IMRT technique was clearly able to increase the dose delivery to the target volume and spare at least one of the parotid glands.

INTRODUCTION

A variety of neoplasms arise in the relatively small body region of the head and neck; it represents around 4% of cancers. [1] Advances in computerized radiotherapy technology offered the possibility of conforming irradiation to an irregular tumor target volume. [2] It is feasible to minimize the radiation dose to the critical normal tissues surrounding the tumor without compromising dose delivery to the intended target volume. Three dimensional conformal radiation therapy (3DCRT) is a precise technique of radiotherapy that can be accomplished by the use of an array of x-ray beams individually shaped to conform to the target. Technology is also available to modify the intensity of the beams across the irradiated field. This irradiation technique is called intensity-modulated radiation therapy (IMRT); which is an advanced form of 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. [3]

The study was conducted to compare 3D conformal radiation therapy and intensity modulated radiation therapy in treating non-metastatic locally advanced head and neck Squamous cell carcinoma (HNSCC);

METHODS AND MATERIALS

Between June 2014 and March 2016, 30 patients with locally advanced head and neck squamous cell carcinoma were treated by 3D-CRT technique (**Group A**) and compared to another 30 patients treated by IMRT (**Group B**) evaluating and comparing both techniques as regard acute and late treatment related toxicities; both groups were treated at Kasr El-Ainy Center of Clinical Oncology and Nuclear Medicine (NEMROCK). The two groups were treated concurrently with cisplatin as a weekly sensitizer. Each group of patients was treated with a different radiotherapy technique and a different fractionation. Group A were treated by conventional fractionation 2 Gy per fraction while group B was treated with simultaneous integrated boost technique (SIB) using 2.12 Gy per fraction.

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.

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 Table1.

Table 1. Patients and tumor characteristics

Patient Characteristics	Group A No. (%)	Group B No. (%)
Age		
≤ 40	3 (10)	6 (20)
41-50	9 (30)	12 (40)
51-60	12 (40)	9 (30)
> 60	6 (20)	3 (10)
Median (range)	56 (36-74)	49 (17-68)
Sex		
Male	18 (60)	15 (50)
Female	12 (40)	15 (50)
T stage*		
T1	0 (0)	0 (0)
T2a	0 (0)	0 (0)
T2b	6 (20)	3 (10)
T3	15 (50)	18 (60)
T4	9 (30)	9 (30)
N stage*		
N0	0 (0)	0 (0)
N1	0 (0)	3 (10)
N2	9 (30)	9 (30)
N3	21 (70)	18 (60)
Tumor Grade**		
WHO 2	3 (10)	6 (20)
WHO 3	27 (90)	24 (80)
Primary Site		
Nasopharynx	20 (66.6)	22 (73.3)
Oropharynx		
Base of tongue	3 (10)	2 (6.66)
Oropharyngeal wall	0 (0)	2 (6.66)
Tonsillar region	1 (3.33)	1 (3.33)
Oral Cavity		
Tongue (ant. 2/3)	4 (13.33)	2 (6.66)
Buccal mucosa	2 (6.66)	0 (0)
Gingiva	0 (0)	1 (3.33)

Pre-treatment evaluation, response criteria and assessment

Patients with distant metastases at diagnosis and those who had received prior treatment were excluded. Pretreatment evaluation included a complete history and physical examination including weight, performance status and nutritional status. Complete dental examination and any required dental repair was done prior to radiotherapy. Laboratory studies included a complete blood picture (CBC), Liver function tests (LFT) and Kidney function tests (KFT). Radiological studies included Chest X-ray (CXR) or Computed Tomography of the chest (CT), CT and Magnetic Resonance Imaging (MRI) of the head and neck and bone scan (if bony symptoms, elevated alkaline phosphatase or a clinically advanced disease). Full endoscopic examination was done. Salivary gland function was assessed using Tc^{99} salivary scintigraphy. Patients were assessed for treatment related toxicity (acute and late normal tissue effects) using the European Organization for research and treatment of cancer and the Radiation Therapy Oncology Groups criteria (EORTC/RTOG). [4]

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 will be used to delineate the site of involved lymph nodes. CT scan of the head and neck with IV contrast will be taken with 5 and 3 mm sections for the 3-D conformal and IMRT respectively down to the infraclavicular region. CT is then transferred to the planning system (Eclipse) for volume definition. Simulation will be done before plan approval to identify the laser marks for the isocenter of treatment. For the 3D planning: 3 fields technique were used; the initial large field irradiation is delivered using two lateral photon portals isocentric technique covering the primary tumor & the neck and a 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 postero-superior neck electron fields. The dose prescribed in both the photon and electron fields is 20Gy/10F/2weeks reaching 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 will receive 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. The IMRT volumes were 1) GTV: gross disease including the primary tumor and enlarged lymph nodes as demonstrated on imaging modalities. 2) CTV1 (high risk disease) : includes areas at high risk of harboring microscopic disease, including high risk lymph nodes as defined by the radiation oncologist. 3) CTV2 (low risk disease) includes low risk nodal regions. The dose prescriptions in IMRT were; GTV: 70Gy/2.12 per fraction, CTV1: 59.4Gy/1.8 per fraction and CTV2: 54Gy/1.64 per fraction in 33 fractions. Dose constraints used in IMRT planning are outlined in Table 2.

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. This treatment plan uses the beam fluencies and energies, MUs, gantry angles and other

Table 2. Dose constraints for IMRT planning

Structure	Constraint	Priority
Spinal Cord	Max. < 48 Gy	High
Brainstem	Max. < 54 Gy	High
Temporal Lobe	Max. < 60 Gy	High
Optic Chiasma	Max. < 50 Gy	High
Optic Nerve	Max. < 54 Gy	High
Retina	Max. < 45 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
Brachial Plexus	Max. < 66 Gy	Intermediate
Mandible	Max. < 70 Gy	Intermediate

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

delivery parameters that are selected for the patient plan and calculates the dose to the CT scan of the phantom. The phantom is subsequently irradiated and the measured dose is compared against the calculated dose distribution. During radiation delivery, the accelerator MLC 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 conformal 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.

Statistical methods

Data were statistically described in terms of mean ± standard deviation (± SD), median and range. Comparison between groups A and B in the present study was done using Mann Whitney U test for independent samples. Survival analysis for the local control was calculated and represented using the Log rank test. A probability value (p-value) less than 0.05 was considered statistically significant. All statistical calculations were done using computer programs Microsoft Excel version 15 (Microsoft Corporation, NY, USA) and SPSS (Statistical Package for the social Science, SPSS Inc., Chicago IL, USA) statistical program.

RESULTS

At a median follow up of 30 months for both groups , the following acute and late toxicity profile were recorded;

Toxicity profile

a) Acute effects

Almost all patients in both groups had G2 to G3 mucositis, grade 4 toxicity was observed in 6 patients in group A but was not observed in group B. A major difference between both groups is that in the IMRT arm mucositis was localized to the high dose region which is less painful and more tolerable. Complete healing was the rule which occurred 6 to 8 weeks post treatment in all patients. G1 dermatitis was more common in group B (21patients), (p=0.01), G2 and G3 were common in group A; however it didn't affect the treatment course. G2 xerostomia was the rule, in group A; 18 patients experienced G2 xerostomia while in group B they were 23 patients, however according to the RTOG/EORTC grading system G2 contains a group of patients complaining of moderate or complete xerostomia, 18 of the 23 patients in group B had the moderate type.

Dysphagia G1 occurred in 7 patients of Group B (p=0.001). Dysphagia G3 was remarkable for group A occurring in 23 patients (76.66%) compared to 12 patients (40%) in group B. A temporary feeding gastrostomy was introduced in three patients in group A. The use of analgesics was a common practice to decrease pain of mucositis and Dysphagia. Upper gastrointestinal manifestations in the form of anorexia and weight loss were almost equal between the 2 groups with 6 patients (20%) in group A and 7 patients (23.33%) in group B had shown G2 toxicity in the form of 5 to 15 % loss of their body weight.

b) Late effects

Grade 3 xerostomia was a common finding in group A occurring in 20 (66.66%) of patients and didn't occur in group B (p=0.002). On the other hand, G1 xerostomia occurred in half of the patients in group B in the form of slight dryness of the mouth and good response on stimulation. The skin, mucous membrane and subcutaneous tissue toxicity were mild with no significant problems for the patients throughout their treatment. Two patients in group A complained of L'Hermitte's syndrome which is a momentary electric like shock that is triggered by flexion of the cervical spine. The condition started 3 to 5 months post radiation therapy and was self limited with no sequalae. No specific treatment was given apart from vitamin B complex injections. The temporo-mandibular joint was affected in only 3 patients (10%) in group A with mild joint stiffness (G1) however it did not prevent normal feeding. On the other hand, the TMJ was not affected in

group B patients (p=0.002).

Table 3: RTOG/EORTC Acute maximum toxicity during RT among the 60 patients treated by 3D conformal (Group A) and IMRT (Group B).

Toxicity	Grade	Group A n (%)	Group B n (%)	P value
Mucositis	G1	0 (0)	0 (0)	-
	G2	6 (20)	9 (30)	0.155
	G3	18 (60)	21 (70)	0.045
	G4	6 (20)	0 (0)	0.5
Xerostomia	G0	0 (0)	0 (0)	-
	G1	2 (6.66)	4 (13.33)	0.16
	G2	18 (60)	23 (76.66)	0.1
	G3	10 (33.33)	3 (10)	0.15
	G4	0 (0)	0 (0)	-
Dermatitis	G0	0 (0)	0 (0)	-
	G1	3 (10)	21 (70)	0.01
	G2	15 (50)	7 (23.33)	0.001
	G3	12 (40)	2 (6.66)	0.122
	G4	0 (0)	0 (0)	-
Dysphagia	G0	0 (0)	0(0)	-
	G1	0 (0)	7 (23.33)	0.001
	G2	7 (23.33)	11 (36.66)	0.001
	G3	23 (76.66)	12 (40)	0.292
	G4	0 (0)	0 (0)	-
Larynx	G0	0 (0)	0 (0)	-
	G1	25 (83.33)	21 (70)	0.235
	G2	5 (16.66)	7 (23.33)	0.432
	G3	0 (0)	2 (6.66)	0.362
	G4	0 (0)	0 (0)	-
Upper GIT	G0	7 (23.33)	7 (23.33)	0.5
	G1	17 (56.66)	16 (53.33)	0.019
	G2	6 (20)	7 (23.33)	0.04
	G3	0 (0)	0 (0)	-

(-) test statistics couldn't be done because there was no event, n: number. GIT **:** gastrointestinal tract

Table 4: RTOG/EORTC late maximum toxicity during RT among the 60 patients treated by 3D conformal (Group A) and IMRT (Group B) techniques

Toxicity	Grade	Group A n (%)	Group B n (%)	P value
Skin	G0	10 (33.33)	29 (96.66)	0.001
	G1	18 (60)	1 (3.33)	0.001
	G2	1 (3.33)	0 (0)	0.432
	G3	1 (3.33)	0 (0)	0.362
	G4	0 (0)	0 (0)	-
Subcutaneous tissue	G0	14 (46.66)	21 (70)	0.153
	G1	12 (40)	4 (13.33)	0.150
	G2	4 (13.33)	5 (16.66)	0.153
	G3	0 (0)	0 (0)	-
	G4	0 (0)	0 (0)	-
Mucous membrane	G0	21 (70)	25 (83.33)	0.117
	G1	7 (23.33)	5 (16.66)	0.344
	G2	2 (6.66)	0 (0)	0.349
	G3	0 (0)	0 (0)	-
	G4	0 (0)	0 (0)	-
Salivary gland	G0	0 (0)	6 (20)	0.362
	G1	0 (0)	15 (50)	0.01
	G2	10 (33.33)	9 (30)	0.241
	G3	20 (66.66)	0 (0)	0.002
	G4	0 (0)	0 (0)	-
Spinal cord	G0	27 (90)	30 (100)	0.003
	G1	3 (10)	0 (0)	0.574
	G2	0 (0)	0 (0)	-
	G3	0 (0)	0 (0)	-
	G4	0 (0)	0 (0)	-
Joint (TMJ)	G0	27 (90)	30 (100)	0.2
	G1	3 (10)	0 (0)	0.002
	G2	0 (0)	0 (0)	-
	G3	0 (0)	0 (0)	-
	G4	0 (0)	0 (0)	-

DISCUSSION

Two dimensional radiation therapy was the most commonly used technique of RT planning in our country. Treatment planning is done on the simulator using standard orthogonal field arrangements and lead blocks based on anatomic landmarks rather than actual tumor geometry. 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 is far from satisfactory and will inevitably lead to suboptimal target coverage and inclusion of large volumes of normal tissues. This can, at least, accounts for the unsatisfactory local control in advanced T stage disease, as well as the high rate of Xerostomia and other late toxicities. [5]

3D-CRT allows manual optimization of beam orientation, beam weighting and beams eye view (BEV) shaping. It represents a major step forward in modern treatment planning. 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 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. [5]

Our Study is a comparative randomized study between two groups of patients, the first group (group A), treated by 3D CRT technique and the second group (group B) treated by IMRT with SIB. Chemotherapy was offered to both groups in the form of weekly Cisplatin sensitizer.

The acute toxicity during radiation therapy was tolerable in both groups and reversible after a period of 3 to 4 weeks post-

treatment. The commonest toxicity was G3 mucositis. Mucositis interfere with the patients' ability to chew and swallow this in addition to the substantial pain. Mouth gargles antiseptic and sometimes anesthetics were offered to patients, as it delays the occurrence of mucositis by decreasing the mouth flora. [6] Oral bicarbonates mouth wash and olive oil and Tahina was common practice for patients in both groups. Intravenous fluids was used whenever there was marked decrease in the oral intake to ensure patients adequate hydration. Non steroidal anti-inflammatory drugs (NSAIDs) were used to decrease pain, however in some patients Tramadol oral tablets was used to alleviate pain in order to avoid treatment interruption. Interruption of radiotherapy treatment in patients with head and neck squamous cell carcinoma has proved to affect local control and eventually survival. That's why every attempt should be done to avoid treatment interruption even during national holidays and machine related problems. [7]

The upper GIT manifestation according to RTOG/EORTC toxicity criteria taking into consideration the degree of anorexia and weight loss was almost equal in the two groups. G1 anorexia (with < 5% weight loss from the pre-treatment baseline) was observed in 17 patients (56.66%) in group A and in 16 patients (53.33%) in group B. The xerostomia complaint during radiation therapy usually started after 30 Gy even in the IMRT group although it was to a mild degree and it improved 2 months after treatment. Hoarseness of voice and dermatitis usually resolve after treatment with no long term sequalae.

One of the most important achievements for IMRT in the head and neck cancer region is its capability to spare the parotid glands, which was obvious in group B. Long-term grade 3 xerostomia was a common finding in group A occurring in 20 (66.66%) of patients and didn't occur in group B. On the other hand, long-term G1 xerostomia occurred in half of the patients in group B in the form of slight dryness of the mouth and good response on stimulation. This may be explained by the suggestion of Eisbruch at al 2001, saying that sparing the minor salivary gland in the oral cavity mucosa help in moistening the mouth especially without eating (the major stimulant for the parotid gland). [8] Salivary gland scintigraphy was done for all patients in both groups. In group A, the parotid gland function decreases post radiation therapy with irreversible recovery. As for group B, the parotid gland excretory function decreased 2 months after radiation and improved at 6 to 8 months in most of the patients.

Dental caries was not a major problem in both groups. All patients were advised for using toothpaste following each meal which also helped in reducing xerostomia and Mucositis. The skin, mucous membrane and subcutaneous tissue toxicity were mild with no significant problems for the patients throughout their treatment. The temporo-mandibular joint was not affected in group B patients; yet only 3 patients (10%) in group A had mild joint stiffness (G1), however it did not prevent normal feeding.

Single-institution studies testing the role of IMRT in the management of NPC and oropharyngeal cancers have yielded exciting results. In patients with NPC, IMRT was given alone or, for locally advanced stages, in combination with chemotherapy consisting of concurrent cisplatin and adjuvant cisplatin plus 5-fluorouracil. In a series of 67 patients , studied by Lee et al, with a median follow-up of 31 months, the 4-year estimates of local progression-free, locoregional progression-free, distant metastasis-free, and OS rates were 98%, 97%, 66%, and 88%, respectively. The worst acute toxicity was grade 1 to 2 in 51 patients (76%), grade 3 in 15 patients (22%), and grade 4 in 1 patient (2%). The worst late morbidity was grade 1 in 20 patients (30%), grade 2 in 15 patients (22%), grade 3 in 7 patients (10%), and grade 4 in 1 patient (2%). Xerostomia was less reported than after 3DCRT and decreased with time. At 3 months after IMRT, 8% of patients had no dry mouth, 28% had grade 1 xerostomia, and 64% had grade 2 xerostomia. Of the 41 patients evaluated at 2 years, 66% had no dry mouth and 32% had grade 1 xerostomia, and only 1 patient had grade 2 xerostomia. [9]

Chao and his colleagues had studied IMRT in 74 patients with Oropharyngeal carcinoma; [10] 14 received IMRT alone, 17 had IMRT combined with cisplatin-based chemotherapy, and 43 underwent surgery followed by postoperative IMRT. With a median follow-up of 33 months, the 4-year estimates of locoregional control, distant metastasis-free, disease-free survival (DFS), and OS rates were 87%, 90%, 81%, and 87%, respectively. Grade 1 and 2 of late xerostomia were seen in 32 and 9 patients, respectively. Late skin toxicity was reported in three patients (two had grade 1 toxicity, and one had grade 2 toxicity), mucositis in three patients (all had grade 1 toxicity), and trismus in three patients.

Inspired by encouraging single-institution data, a number of prospective multi-institutional trials addressing the role of IMRT in the treatment of head and neck carcinomas were completed. RTOG 0022 studied the efficacy of IMRT in the treatment of 69 patients with T1 to T2, N0 to N1, M0 oropharyngeal cancer. The patients received bilateral neck irradiation without concurrent chemotherapy. A dose of 66 Gy in 30 fractions of 2.2 Gy each was administered to the gross tumor planning target volume (PTV), 60 Gy in 30 fractions of 2 Gy each to the intermediate-risk PTV, and 54 Gy in 30 fractions of 1.8 Gy each to the low-risk elective lymph node region PTVs. With a median follow up of 2.8 years, the 2-year estimated locoregional failure rate was 9%. The maximal late grade 2 or higher toxicity was skin 12%, mucosa 24%, salivary 67%, esophagus 19%, and osteoradionecrosis 6%. The incidence of grade 2 or higher xerostomia was 55% at 6 months, 25% at 12 months, and 16% at 24 months. The authors concluded that IMRT for early-stage oropharyngeal cancer yields to high local and regional tumor control rates with lower salivary toxicity when compared with patients treated in previous RTOG clinical trials. [11]

RTOG 0225 studied IMRT in the treatment of 68 patients with stage I to IVB NPC (94% were WHO type 2 or 3). The PTV for the gross tumor at the primary tumor site and within involved lymph nodes received 70 Gy in 33 fractions of 2.12 Gy each. Regions at risk for subclinical disease and electively treated lymph nodes received 59.4 Gy in 33 fractions of 1.8 Gy each to the PTV. Patients with T2 to T4 primary tumors, or who had nodal disease beyond stage N1, received concurrent cisplatin chemotherapy followed by adjuvant cisplatin and 5-fluorouracil chemotherapy. The estimated 2-year local progression-free survival (PFS) rate was 92.6%, regional PFS rate was, 90.8%, local and regional PFS rate was 89.3%, and the distant metastasis-free survival rate was 84.7%. The estimated 2-year PFS rate was 72.7%, and the OS rate was 80.2%. The incidence of late grade 3 toxicity was esophageal toxicity in 4.7% of patients, mucous membrane toxicity in 3.1%, and xerostomia in 3.1%. The incidence of grade 2 xerostomia at 1 year was 13.5%. Only two patients developed grade 3 xerostomia. No patient developed grade 4 xerostomia. The authors established the feasibility of IMRT administration, with or without chemotherapy to patients with NPC and that such treatment is effective with a 90% locoregional progression-free survival rate and minimal grade 3 xerostomia. [12]

The effectiveness of IMRT in the treatment of NPC has been repeatedly reported in retrospective studies. Results from recently published single institutional experiences are encouraging. IMRT has been found to improve toxicity profile, especially in saving parotid function**.** Furthermore, treatment outcome regarding loco -regional control and survival rates were reportedly improved when compared with historic data. In 2002, Lee et al. reported the USCF experience of treating 67 NPC patients using IMRT. Approximately, 70% of all patients were stages III and IV diseases. The prescribed dose was 65–70 Gy (2.12–2.25 Gy/fraction/day) to the GTV and positive neck nodes, 60 Gy (1.8–2.0 Gy/ fraction/day) to the CTV, 50–60 Gy to the clinically negative neck. Fifty patients received concomitant cisplatin followed by adjuvant cisplatin and 5-fluorouracil chemotherapy following Inter-group 0099 trial. With a median follow-up of 31 months, the 4-year estimates of local progression-free, local-regional progression-free and distant metastases free rates were 97%, 98%, and 66%, respectively. The 4-year overall survival was 88%. This was one of the first studies that showed an improved tumor control by improved tumor target coverage using IMRT. [9, 13-16]

In a randomized trial from Hong Kong, Kwong and his colleagues compared the disease control and salivary function in stage II NPC patients whom were treated with IMRT vs. three-dimensional radiotherapy (3DRT). The 4-year local control rate was 90.5% with IMRT vs. 71.7% with 3DRT ($p = 0.019$). Neck control, distant metastasis, failure-free, and disease-specific survival were not significantly different comparing the two arms. The most commonly observed acute toxicity in IMRT for NPC was radiation-induced mucositis and dermatitis. Owing to the reduction of dose in the non-target tissues, a reduction in acute toxicity during IMRT is expected and has been reported. Kwong et al. observed a lower incidence of acute toxicity in NPC patients treated with IMRT. RTOG grade 3 mucositis and pharyngitis were reported in 22% patients. Furthermore, compared with the Inter-group 0099 Trial by Al-Sarraf and his colleagues in 1998, compliance to adjuvant chemotherapy was better in patients treated with IMRT. Using IMRT, nearly all patients completed their three cycles of adjuvant chemotherapy consisting of 5-fluorouracil and cisplatinum in addition to the three cycles of cisplatinum during radiotherapy, whereas in the Inter-group trial, only 55% of the patients finished three courses of the adjuvant chemotherapy and 45% of the patients received two cycles or less adjuvant chemotherapy due to toxicity. [17]

One of the major complaints of patients treated with conventional external beam radiation therapy to the head and neck region is xerostomia because of a high dose irradiation to parotid glands bilaterally. The probability and severity of xerostomia is largely affected by the radiation dose and the volume of the parotid gland. IMRT is capable of minimizing the dose to the parotid glands while at the same time delivering high doses to the tumor targets. Reported studies of IMRT for head and neck neoplasms have demonstrated an advantage for preserving salivary functions with IMRT. Most patients experienced xerostomia had mild symptoms (grade 2 or less). Furthermore, patients treated with IMRT regain their salivary flow faster and more completely than those treated with conventional radiotherapy. Kam et al has performed a randomized trial comparing the rates of delayed xerostomia between two-dimensional radiation therapy (2DRT) and IMRT in the treatment of patients with early-stage NPC. At 1 year after treatment, patients in IMRT arm had lower incidence of observer-rated severe xerostomia when compared to patients in the 2DRT arm (39.3 vs. 82.1%; $p = 001$), parallel with a higher fractional stimulated parotid flow rate (0.90 vs. 0.05; $p < 0001$), and higher fractional stimulated whole saliva flow rate (0.41 vs. 0.20; $p = 001$). In the study of Hsiung et al., the mean parotid dose ranged from 33.2 to 58.8 Gy (average, 43.9 Gy). However, recovery of salivary flow was noticed despite of a higher mean dose to the parotid glands. [18-21]

DISCUSSION

IMRT technique was clearly able to increase the dose delivery to the target volume and sparing at least one of the parotid glands.

REFERENCES

1. Leonard L. Gunderson- Joel E. Tepper: Clinical radiation oncology- Elsevier Churchill livingstone- 2007
2. Eisbruch A, Ten Haken RK, Kim HM, et al (1999): dose, volume, and function relationships in parotid salivary glands following conformal and intensity-modulated irradiation of head and neck cancer. Int J Radiat Oncol Biol phys 45:577-587
3. Hunt MA, Zelefsky MJ, Wolden S, et al (2001): Treatment planning and delivery of intensity-modulated radiation therapy for primary nasopharynx cancer. Int J Radiat Oncol Biol Phys49:623-632
4. 4Erik B, Dieren V, Nowak P ; EORTC/RTOG acute and late toxicity criteria, www.estro.be/education Int J Radiat Oncol Biol Phys 47:1299-1309 (2000)
5. Kam MK, Chau RM, Suen J, et al (2003) Intensity-modulated radiotherapy in nasopharyngeal carcinoma: dosimetric advantage over conventional plans and feasibility of dose escalation. Int J Radiat Oncol Biol Phys 56:145 –157
6. Trotti A., Bellmb L., Epsteine J., Framee D., Zilberberge M (2003)., Mucositis incidence, severity and associated outcomes in patients with head and neck cancer receiving radiotherapy with or without chemotherapy.;66: 253-262
7. Fowler J., and Lindstrom M. (1992): loss of local control with prolongation in radiotherapy, Int Radiat Oncol Biol Phys ; 23: 457-467
8. Eisbruch A, Kim HM, Terrell JE, Marsh LH, Dawson LA, Ship JA (2001) Xerostomia and its predictors following parotid sparing irradiation of head-and-neck cancer. Int J Radiat Oncol Biol Phys 50(3):695–704
9. Lee N, Xia P, Quivey JM, et al (2002) Intensity-modulated radiotherapy in the treatment of nasopharyngeal carcinoma: an update of the UCSF experience. Int J Radiat Oncol Biol Phys 53:12–22
10. Chao Ksc, Ozyigit G, Blanco AI, et al (2004): Intensity-modulated radiation therapy for oropharyngeal carcinoma: impact of tumor volume. Int J Radiat Oncol Biol phys 59:43-50.
11. Tejpal G, JaiPrakash A, Sandeep J, et al (2012): Three-dimensional conformal radiotherapy (3D-CRT) versus intensity modulated radiation therapy (IMRT) in squamous cell carcinoma of the head and neck: A randomized controlled trial. Radiotherapy and Oncology; vol.104 (3): 343-348
12. Shu-Zhen L, Wen-Fei L, Lei C, et al (2011): How does intensity-modulated radiotherapy versus conventional two -dimensional radiotherapy influence the treatment results in nasopharyngeal carcinoma patients? Int J Radiat Oncol Biol Phys; vol. 80 (3): 661-668.
13. Kam MK, Leung SF, Zee B, et al (2007) Prospective ran-

domized study of intensity-modulated radiotherapy on salivary gland function in early-stage nasopharyngeal carcinoma patients. J Clin Oncol 25(31):4873–4879

14. 14. Kwong DL, Pow EH, Sham JS, et al (2004) Intensity-modulated radiotherapy for early-stage nasopharyngeal carcinoma: a prospective study on disease control and preservation of salivary function. Cancer 101:1584–1593
15. 15. Liu WS, Lee SP, Lee JK, et al (2006) Factors influencing the parotid function in nasopharyngeal carcinoma treated with parotid-sparing radiotherapy. Jpn J Clin Oncol 36: 626–631
16. 16. Lin S, Pan J, Lu H, et al (2009) Apr 11. Nasopharyngeal carcinoma treated with reduced-volume intensity-modulated radiation therapy: report on the 3-year outcome of a prospective series. Int J Radiat Oncol Biol Phys. 2009 Apr 11
17. 17.Kwong DL, McMillan A, Pow E, et al (2008) A randomized trial comparing intensity modulated radiotherapy versus 3-dimensional radiotherapy for stage II nasopharyngeal carcinoma. Int J Radiat Oncol Biol Phys 72(Suppl):S98
18. 18. Kam MK, Leung SF, Zee B, et al (2007) Prospective randomized study of intensity-modulated radiotherapy on salivary gland function in early-stage nasopharyngeal carcinoma patients. J Clin Oncol 25(31):4873–4879
19. 19. Wolden SL, Chen WC, Pfi ster DG, et al (2006) Intensity modulated radiation therapy (IMRT) for nasopharynx cancer: update of the Memorial Sloan-Kettering experience. Int J Radiat Oncol Biol Phys 64:57–62
20. 20. Tham IW, Hee SW, Yeo RM, et al. (2009) Treatment of nasopharyngeal carcinoma using intensity-modulated radiotherapy ;The National Cancer Center Singapore Experience. Int J Radiat Oncol Biol Phys. 2009 Apr 20.
21. 21. Hsiung CH, Ting HM, Huang HY, et al (2006) Parotid-sparing intensity-modulated radiotherapy (IMRT) for nasopharyngeal carcinoma: preserved parotid function after IMRT on quantitative salivary scintigraphy and comparison with historical data after conventional radiotherapy. Int J Radiat Oncol Biol Phys 66:454–461