A COMPARATIVE STUDY BETWEEN CONFORMAL AND INTENSITY MODULATED RADIATION THERAPY IN THE TREATMENT OF PRIMARY NASOPHARYNGEAL CARCINOMAS

THESIS

Submitted for the partial fulfillment of the M.D degree in

Clinical Oncology

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2012

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Acknowledgements

First and foremost, my deepest praises are due to Almighty **“ALLAH”** who enabled me to finish this piece of work appropriately.

I would like to express my deep thanks and gratitude to **Prof. Dr. Ehsan Gamal El-Din EL-Ghoneimy** for her continuous meticulous supervision apart from her spiritual support that paved the way to the achievement of this work and remarkable advices removing any obstacle.

I feel deeply indebted to **Prof. Dr. Mohamed Abdalla Hassan** for his precious valuable advices, close supervision. I shall always be proud to have worked under his guidance.

My sincere appreciation to **Prof. Dr. Mahmoud Fawzy El-Bestar** for his ultimate scientific help and continuous encouragement throughout my work. Really had the pleasure to work with him.

Also I would like to express my deep thanks to **Prof. Dr. Omar Moawia Othman** for his continuous unlimited support and help.

I would like to express my deep thanks to the physics team (NEMROCK) for their unlimited help.

Finally, I would like to express my infinite gratitude and my deepest appreciation to my family, all staff members and to my colleagues, at Clinical Oncology Department, for their support.

Karim Mashhour

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List of Abbreviations

3D: Three dimensional

AJCC: American Joint Committee on Cancer

BEV: Beam eye view

CI: Conformity Index

CN: Cranial nerves

CT: Computed Tomography

CRT: Conformal radiation therapy

CTV: Clinical Target Volume

DFFR: Distant failure free rate

DRR: Digitally reconstructed radiograph

DVH: Dose Volume Histogram

EBV: Epstein Barr virus

EGFR: Epithelial growth factor receptor

EORTC: European organization for research and treatment of cancer

EPID: Electronic portal image device

FDG: Fluorodeoxyglucose

FP: Forward planning

FOM: Floor of mouth

GTV: Gross Target Volume

Gy: Gray

HBO: Hyperbaric oxygen

HNSCC: Head and Neck Squamous cell carcinoma

ICRP: International Commission on Radiological Protection

ICRU: International Commission on Radiation Units and Measurements

IGRT: Image guided radiation therapy

IMRT: Intensity modulated radiation therapy

ITV: Internal target volume

LAHNC: Locally advanced Head and Neck Cancer

LC: Local control

LFFR: Local failure free rate

MLC: Multi-leaf collimator

MRI: Magnetic Resonance Imaging

MU: Monitor units

MVCT: Megavoltage computed tomography

NCI: National cancer institute

NPC: Nasopharyngeal carcinoma

OAR: Organ at risk

OME: Otitis media with effusion

PET: Positron Emission Tomography

PRV: Planning at risk volume

PTV: Planning Target Volume

QA: Quality assurance

RECIST: Response evaluation criteria in solid tumours

REV: Room eye view

RLN: Retropharyngral lymph node

RTOG: Radiation therapy oncology group

SCC: Squamous cell carcinoma

SIB: Simultaneous integrated boost

SNHL: sensori-neural hearing loss

TPS: Treatment planning system

TMJ: Tempero-mandibular joint

VEGF: Vascular endothelial growth factor

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) as newer modalities in treating nasopharyngeal carcinomas; evaluating and comparing both techniques as regard their efficacy on tumor response, local control and treatment related toxicity as well as a dosimetric comparison between both techniques.

Patients and Methods: Between February 2010 and December 2011, 20 patients with nasopharyngeal carcinoma were treated by 3D CRT technique (Group A) and compared to another 20 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 based chemotherapy as a weekly sensitizer and post-radiotherapy with cisplatin and 5-FU for 3 cycles. Patients were assessed for treatment related toxicity using the European Organization for research and treatment of cancer, the Radiation Oncology Group (EORTC/RTOG) and the National cancer institute common toxicity (NCI).

Results: Group A showed a higher incidence of treatment related toxicity than in group B particularly xerostomia. IMRT was clearly able to preserve the parotid gland function. Between February 2010 and December 2011 with a median follow up 20 months for both groups, all patients entered in complete remission after treatment except one in group A. Local control rates were 95% and 100% for groups A and B respectively. Results of the dosimetric comparison between both techniques showed that IMRT had a better tumor coverage and conformity index. 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. Also, doses received by the risk structures, particularly parotids, was significantly less in the IMRT plans than those of 3D-CRT. 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 ($p < 0.001$). IMRT reduced mean doses to the cochleae from 53.3 Gy to 46.8 Gy (right side) and 49.16 Gy to 42.72 Gy (left side) with a p-value of 0.008 and 0.013, respectively. 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).

Conclusion: 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.

Key words: Nasopharynx cancer, 3D-conformal, IMRT, xerostomia.

Introduction

Nasopharyngeal carcinoma (NPC) is a malignant tumor of nasopharyngeal epithelium. The median number of nasopharyngeal carcinoma patients in NEMROCK during the period of 2004- 2009 was 15 cases per year; Comprising 10 % of head and neck cancer patients and 0.5 % of all cancer patients **(NEMROCK registration database)**.

Because the nasopharynx is immediately adjacent to the base of skull, surgical resection with an acceptable margin is often not achievable. Nasopharyngeal carcinoma (NPC) is highly sensitive to ionizing radiation, and radiation therapy is the mainstay treatment modality for nonmetastatic disease. Conformal therapy describes radiotherapy treatment that creates a high dose volume that is shaped to closely conform to the desired target volumes while minimizing (as much as possible) the dose to critical normal tissues **(Gunderson et al 2012)**.

Chemo-radiotherapy became the standard of care for non-metastatic nasopharyngeal carcinomas followed by 3 cycles of adjuvant chemotherapy **(Al-Sarraf et al 2001 and Adelstein et al 2003)**.

Intensity- modulated radiation therapy (IMRT) represents one of the major technical advancement in modern radiation therapy. IMRT is an advanced three-dimensional (3D) conformal treatment that uses non-uniform beam intensity patterns with computer aided optimization to achieve superior dose distribution with much higher conformality than those achievable with conventional 3D conformal radiation therapy (3DCRT). Because of this new capability in manipulating the intensities of individual rays within each beam, IMRT allows greater control of dose distributions that, when combined with various image-guided techniques to precisely delineate target volumes and deliver the planned treatments, may improve tumor control and reduce normal tissue toxicity**(Hunt et al 2001)**.

Several institutions have shown a potential dosimetric improvement for IMRT over conventional and 3D conformal techniques in the setting of nasopharyngeal cancer. Cheng et al showed that target coverage of the tumor was maintained and nodal coverage was improved in 17 nasopharyngeal carcinoma patients, as compared with conventional beam arrangements. Also the ability of IMRT to spare parotid gland was exciting **(Cheng et al 2001)**.

In 2002, Lee et al. reported the USCF experience of treating 67 NPC patients using IMRT. Approximately, 70% of all patients had stages III and IV diseases. The prescribed dose was 65–70 Gy (2.12–2.25 Gy/fraction/day) to the gross target volume (GTV) and positive neck nodes, 60 Gy (1.8–2.0 Gy/fraction/day) to the clinical target volume (CTV), 50–60 Gy to the clinically negative neck. Fifty patients received concomitant cisplatin and adjuvant cisplatin and 5-fluorouracil chemotherapy according to Intergroup 0099 trial. With a median follow-up of 31months, 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 estimate of overall survival was 88%. This was one of the first studies that demonstrated an improved tumor control by improved tumor target coverage using IMRT **(Lee et al. 2002)**.

In a randomized trial from Hong Kong, Kwong et al. (2008) compared the disease control and salivary gland dysfunction in stage II NPC patients treated with IMRT vs. three-dimensional radiotherapy (3D-CRT). The 4-year local control 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 between the two arms. Because of the improved treatment outcome and toxicity profile (less than 8% of patients treated with IMRT experienced grade II xerostomia, and no patient had grade III or IV parotid dysfunction), IMRT is recommended for definitive treatment for all patients with nasopharyngeal cancer.**(Kwong et al. 2008)**

One of the major complaints from patients treated with conventional external beam radiation therapy to the nasopharynx is xerostomia because of a high dose irradiation to parotid glands bilaterally. As mentioned above, the probability and severity of xerostomia is largely dependent on the radiation dose and the volume of the parotid gland. IMRT is capable of reducing the dose to the parotid glands while simultaneously delivering high doses to the tumor targets. Reported studies of IMRT for NPC have demonstrated a clear advantage for preserving salivary functions with IMRT **(Peter et al 2004) (Tham et al 2009)**.

The middle ear is exposed to a significant dose of radiation during treatment of nasopharyngeal carcinoma (NPC). This exposure can lead to otitis media with effusion (OME) which is a very common problem during or after the completion of radiotherapy and can persist for many years after treatment.The rate of OME in the IMRT arm was less than the 3D-DRT arm significantly (p-value <0.05)**(Sheng et al 2009)**.

In another report, the frequency of radiation-induced damage to ear function was as high as 54%, second only to xerostomia, as the most common complication associated with the treatment of NPC. The incidence of radiation-induced OME is as high as 26% and is characterized by deafness, tinnitus, and pain in the ear. Eustachian tube (ET) function is the poorest at 6 months after treatment and can last for life **(Yeh et al 2005)**.

Inspite of several dosimetric and functional superiority of IMRT over 3D- CRT, yet there are several concerns regarding this new technique i.e higher doses to undefined tissues, second malignancy, 4 fold increase in monitor units per treatment which is reflected on overload on radiotherapy machines specially in busy departments. Furthermore, the higher cost and longer time required to start treatment are extra-concerns. Longer follow up of large patient cohort is needed to prove the cost-effectiveness of this new technique.

Aim of Work

The study was conducted to compare 3D conformal radiation therapy and intensity modulated radiation therapy as newer modalities in treating nasopharyngeal carcinomas; evaluating and comparing both techniques as regard their efficacy on tumor response, local control and treatment related toxicity as well as a dosimetric comparison between both techniques.