



Effect of Protracted Radiotherapy Treatment on Outcome of Head and Neck Cancer Patients (NEMROCK experience)

Thesis

Submitted for Complete Fulfillment of Master Degree in
Clinical Oncology

Submitted by

Lina Abdel Fattah Albadawi Ahmed

M.B.B.Ch, Ain Shams University.

Under Supervision of

Prof. Dr. Shawky El-Haddad

Professor of Clinical Oncology and Nuclear Medicine
Faculty of Medicine, Cairo University

Prof. Dr. Tamer El-Nahas

Professor of Clinical Oncology and Nuclear Medicine
Faculty of Medicine, Cairo University

Ass. Prof. Dr. Hanan Seleem

Assistant Professor of Clinical Oncology and Nuclear Medicine
Faculty of Medicine, Cairo University

Faculty of Medicine

Cairo University

2015

Acknowledgment

First, thanks are all due to Allah for Blessing this work until it has reached its end, as a part of his generous help throughout our life.

It was an honour to work under the supervision of eminent professors, who lent me their whole hearted support and immense facilities as is their usual with their juniors. To them, I owe more than I can record.

I would like to express my deepest gratitude and highest appreciation to Prof.Dr. Shawky El-Haddad, Professor of clinical oncology and nuclear medicine, faculty of medicine, Cairo University, for his continuous encouragement, generous support.

I would like to express my sincere gratitude to Prof. Dr. Tamer El-Nahas, Professor of clinical oncology, faculty of medicine, Cairo University, who supervised this work with great interest.

Many thanks to Ass. Prof. Dr. Hanan Seleem Mosalam, Assistant Professor of clinical oncology, faculty of medicine, Cairo University, for her unlimited help, valuable suggestions,

continuous support, guidance and encouragement during the progress of this work, no words can express my gratitude.

I would like to express my extreme gratitude to all my professors, staff members and colleagues in Kasr Al Ainy center of oncology and nuclear medicine for their help and support.

*Finally, No words can express my deepest appreciation and gratitude to **my family** for their never ending support and care.*

CONTENTS

	<i>Page</i>
List of Abbreviations	IV
List of Figures.....	V
List of Tables	VI
INTRODUCTION AND AIM OF THE WORK	1
REVIEW OF LITERATURE:	
▪ Chapter I: Overview of Head and Neck Cancer	4
▪ Chapter II: Radiobiological Concepts	19
▪ Chapter III: Unplanned Radiation Therapy Interruption: "Causes, Effects and Management	31
PATIENTS AND METHODS	39
RESULTS	42
DISCUSSION	61
SUMMARY	66
CONCLUSION	68
REFERENCES	69
ARABIC SUMMARY	

List of Abbreviations

CART	: Classification And Regression Tree.
CCRT	: Concomitant Chemo-radiotherapy.
Cdk	: Cyclin-dependent kinase.
CI	: Confidence Interval.
CRT	: Chemo-radiotherapy.
DI	: Dose Intensity.
ENS	: Extranodal Spread.
Gy	: Gray.
HNC	: Head and Neck Cancer.
HNSCC	: Head and Neck Squamous Cell Carcinoma.
HR	: Hazard Ratio.
HRR	: Homologous Recombination Repair.
ICRU	: International Commission on Radiation Units.
LC	: Local Control.
LCR	: Local Control Rate.
LQ	: Linear Quadratic.
MV	: Mega Voltage.
NCI	: National Cancer Institute in Egypt.
NEMROCK	: Kasr Al-Aini Center of Radiation Oncology and Nuclear Medicine.
NHEJ	: Non-Homologous End Joining.
OAS	: Overall Survival.
OER	: Oxygen Enhancement Ratio.
OTT	: Overall Treatment Time.
PRT	: Post-operative Radiotherapy.
RCT's	: Randomized Controlled Trials.
RPA	: Recursive Partitioning Analysis.
RT	: Radiotherapy.
SCC	: Squamous Cell Carcinoma.
SE	: Standard Error.
TTP	: Total Treatment Package.

LIST OF FIGURES

Fig. No.	Title	Page
1.	Percentage of Patients with HNC/Year at NEMROCK.	5
2.	Update of the phases of the cell cycle, showing how they are regulated by the periodic activation of different members of the cyclin-dependent kinase family. Various cyclin-dependent kinase-cyclin complexes are required to phosphorylate a number of protein substrates, which drive key events, including the initiation of DNA replication and the onset of mitosis.	20
3.	Relative Therapeutic Ratio as a function of dose rate, normalized to a dose rate of 0.1 Gy/hour.	25
4.	Effect of fractionation (a) on tumor (b) on late-responding normal tissue.	27
5.	Effect of changing dose rate (a) on tumor (b) on normal tissue.	27
6.	Patients' Distribution according to Treatment Interruption Days.	46
7.	Distribution of Gaps Position throughout Radiation Treatment Course.	49
8.	Patients' Distribution according to Early and Late Treatment Gaps.	50
9.	Locoregional Recurrence-Free Survival according to Dose Intensity of Radiation Treatment (DI).	54
10.	Recurrence Free Survival according to Treatment Gap.	55
11.	Overall Survival according to Overall Treatment Time.	58
12.	Overall Survival according to Treatment Gap.	59

List of Tables

Table No.	Title	Page
1.	Patient and Tumor Characteristics.	43
2.	Treatments Factors.	45
3.	Prevalence of Interruptions in Radiotherapy according to Tumor Site.	47
4.	Causes of Unplanned Interruptions (in 116 patients).	51
5.	Locoregional Recurrence-Free Survival according to Dose Intensity of Radiation Treatment (DI).	54
6.	Recurrence Free Survival according to Treatment Gap.	55
7.	Overall Survival according to Overall Treatment Time.	58
8.	Overall Survival according to Treatment Gap.	59
9.	Multivariate Analysis of Overall Survival.	60

INTRODUCTION

Radiation oncology plays a central role in the treatment of many cancers. **(Burnet, et al., 2000)**

The basis of this treatment lies in the different susceptibility and repair capacity of tumour and normal tissues. **(Dörr, 1998)**

Radiobiological factors influencing the resistance of cancers to radiotherapy treatment include among others: repopulation, reoxygenation, repair of sublethal damage and reassortment of cells within the cell cycle. Treatment breaks due to technical problems, patient-related issues, holidays or even side effects of treatment may arise. These treatment interruptions are usually not accounted for sufficiently when treatment is simply continued with the originally planned fractionation. If a sub-optimal compensatory regime is chosen the tumour control rate may be jeopardized or unacceptable side effects risked. **(Withers, et al., 1988)**

For head and neck squamous cell carcinoma (HNSCC) there appears to be little lag time in tumor repopulation during adjuvant RT. Consequently, breaks or gaps in treatment could result in faster tumor growth or regrowth, requiring higher radiation doses or the addition of active chemotherapy to maintain cancer control. This challenge to effective tumor control may also increase the probability of developing higher-grade therapy-related toxicities, such as mucositis, fibrosis, and dysphagia. RT may result in a dose-response threshold, effectively

increasing the dose needed for tumor control. **(Suwinski and Withers, 2003)**

Treatment interruptions usually had an adverse effect on outcomes. For example, a 1-week break in conventional fractionation was estimated to reduce local control rates by 10%-12%. Thus, a 1-day interruption could result in a 1.4% decrease in control for patients with HNC. This reduction presumably reflects repopulation by remaining tumor cells during the treatment interval; particularly for HNCs that often have high growth fractions and the increased ability for clonogen repopulation. **(Bese, et al., 2007)**

Treatment breaks were associated with decreased long-term survival: 5-year survival was 5.8% for patients with treatment breaks compared with 11.4% for those without. **(Tomiak, et al., 2000)**

AIM OF THE WORK

To highlight the clinical significance of treatment breaks and dose reductions in head and neck cancer patients receiving RT or CRT and their impact on disease free survival and overall survival in NEMROCK.

CHAPTER I

Overview of Head and Neck Cancers

Head and neck cancer (HNC) is the 6th most common cancer worldwide and includes cancers of the oral cavity, larynx, oropharynx, sinonasal tract, hypopharynx, and nasopharynx. **(Attar; et al., 2010)**

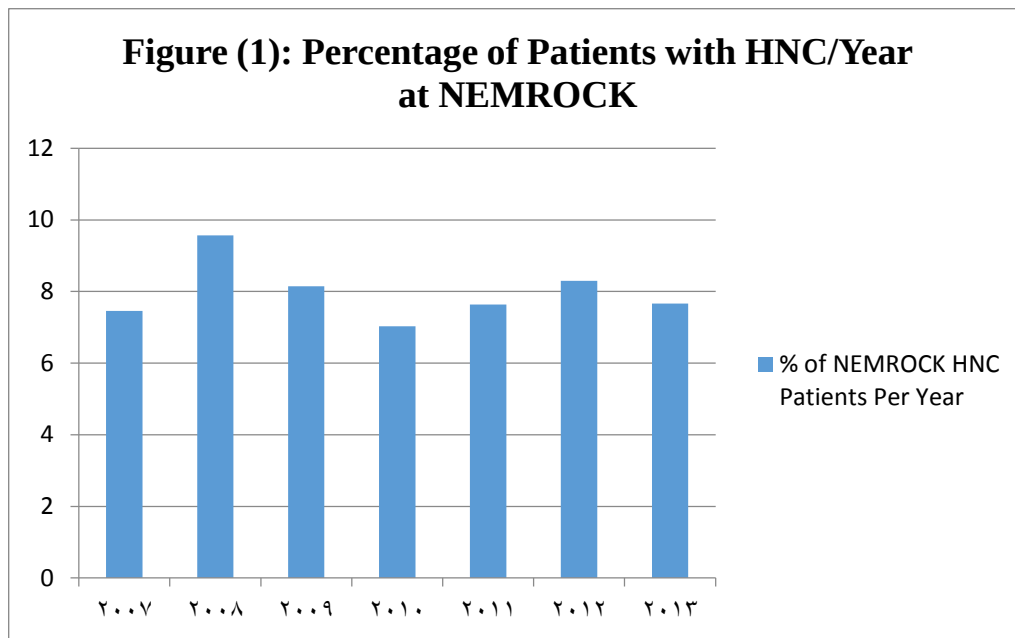
Incidence:

The incidence of head and neck squamous cell carcinoma (HNSCC) has increased over the last 30 years. Patients with HNSCC usually present with advanced metastatic disease leading to higher mortality. **(Upile; et al., 2012)**

In 2014, it is estimated that about 55,070 new cases of oral cavity, pharyngeal and, laryngeal cancers will occur, which account for about 3% of new cancer cases in the united states. An estimated 12,000 deaths from HNC will occur during the same time period. **(Jemal; et al., 2014)**

In NCI-Egypt, HNC represents about 17% of all malignant tumors. **(El-Bolkainy; et al., 2005)**

At NEMROCK, the total patients of HNC presented to the center between 2005 and 2013 was about 8% of all patients presented to the center during the same period with median range equal to 211 head and neck cancer patients per year, figure (1).



In Gharbiah (Egypt), the age adjusted incidence of HNSCC is 8.65 per 100,000. **(Ismail; et al., 2007)**

The incidence of HNSCC is significantly higher in males than in females with a ratio 3:1. The discrepancy in the male to female ratio is even more pronounced in laryngeal tumors, in which carcinoma is 4-5 times more common in men. This ratio has declined in the last 20 years, possibly reflecting the increased number of women using tobacco products during this period. **(Jemal; et al. 2014)**

In Gharbiah (Egypt), the age adjusted incidence for laryngeal cancer with male to female ratio of was 2:0.1. **(Ismail; et al., 2007)**

Pathology and Risk Factors:

Most head and neck malignant neoplasms are squamous cell carcinoma (SCC) or one of its variants, including lymphoepithelioma, spindle cell carcinoma, verrucous carcinoma, and undifferentiated carcinoma. Lymphomas and a wide variety of other malignant and benign neoplasms make up the remaining cases. **(Mendenhall; et al., 2011)**

The most important established risk factors are chronic use of tobacco and alcohol. They are two independent risk factors that have been shown clearly to act in a multiplicative way when used in combination. The carcinogens in tobacco are nitrosamines, polycyclic aromatic hydrocarbons and aldehydes. Nitrosamines are alkylating agents that induce mutational events that predispose to carcinogenesis. **(Benjamin and Jurgen, 2006)**

The annual incidence of second primary cancer following successful treatment of a squamous cell carcinoma in the head and neck area is 3%–7%. A known feature in HNSCC is the observation of field cancerization of the upper aerodigestive tract: several synchronous and also metachronous primary carcinomas, areas of moderate to severe dysplasia and carcinoma in situ are observed with areas of normal mucous membranes in between. This is caused by exposure of the entire upper aerodigestive tract to the same carcinogens, usually combined alcohol and tobacco. Patients are especially at risk of developing lung cancer, esophageal and gastric cancer, and a new localization of HNSCC. **(Rafferty, 2002)**

Treatment:

At present, treatment of an individual cancer is typically determined in a multidisciplinary setting, with the histological subtype, staging information, patient fitness, baseline swallow and airway function guiding management decisions. Approximately one-third of patients present with early-stage disease and these patients are treated with either surgery or radiotherapy depending on the primary tumor site, with cure rates of 70–90%. **(Argiris; et al., 2008)**

The majority of patients, however, present with locally advanced stage disease. Radical treatment in this situation requires multimodality therapy with surgery, commonly followed by postoperative radiotherapy or chemo radiotherapy, or organ preserving primary radiotherapy, with or without chemotherapy, with reduced cosmetic compromise. **(Pignon; et al., 2009)**

Postoperative RT is considered when the risk of recurrence above the clavicles exceeds 20%. The operative procedure should be one stage and of such magnitude that RT is started no later than 6 to 8 weeks after surgery. The operation should be undertaken only if it is believed to be highly likely that all gross disease will be removed and margins will be negative. **(Mendenhall; et al., 2011)**

Benefits of Adjuvant Radiation Therapy in HNSCC Patients:

Historically, curative treatment of head and neck cancer consisted of radical resection. Radiotherapy was reserved for the treatment of tumor recurrence or palliation of disease where surgery was not indicated. In the mid-1950s, the basic principles of radiation biology were discovered, such as the steep dose–Response curve whereby small changes in radiation dose could have large effects on tumor cells, as well as on the extent of damage to normal tissues. The need for molecular oxygen to be present for radiation to affect cells, and the relationships between tumor volume, hypoxia and disease control were also recognized at that time. Over the next 20years, techniques were developed to optimize radiotherapy dose distribution on the basis of tumor concentration, areas at risk for subclinical disease, and improvement of locoregional control. **(Fletcher, 1978)**

Unlike most other solid tumors, the majority of head and neck squamous cell carcinomas (HNSCC) recur at the primary site or in the neck lymph nodes. The primary goal of all head and neck cancer therapies has, therefore, been to reduce locoregional failure rates as an essential step towards improved survival. In the 1970s, surgeon and radiation therapists reported data analyses of large cases series from major centers in the US in order to define the pathologic features associated with an increased risk of recurrence after surgery. For example, in a series of 1,775 patients with HNSCC of various primary sites, the incidence of primary site recurrence was 31.7% if surgical margins were negative and 71% if they were positive. This high recurrence rate did not differ whether carcinoma in