Concurrent chemotherapy and radiotherapy in patients with locally advanced head and neck cancer: single institutional experience, Ain-shams university.

Presented by:

Nancy Emad Halim

M.B, B.Ch,

Faculty of Medicine, Ain Shams University

Supervised by:

Dr/Mahmmoud Ellithy

Assistant Professor of Clinical Oncology and Nuclear Medicine,

Faculty of Medicine, Ain Shams University

Dr/Dalia Abd-el-Ghany

Assistant Professor of Clinical oncology and Nuclear Medicine,

Faculty of Medicine, Ain-Shams University

Faculty of Medicine
Ain Shams University
2015

List of contents

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

2DTwo-dimensional

3D Three-dimensional

3D-CRT Three-dimensional conformal radiotherapy

5-FU 5- Flurouracil

AJCC American Joint Committee on Cancer

ASCO American society of clinical oncology

AUC Area under the concentration

CR Complete response

CRT Concurrent chemo-radiotherapy

CT Cross-sectional imaging

DM Distant metastasis

DNA Deoxyribonucleic acid

ECOG Eastren Cooperative oncology group

EGFR Epidermal growth factor

FDG Fludeoxyglucose

FNA Fine needle aspiration

HDTV High-definition television

HNC Head and neck cancer

HPV Human Papilloma Virus

IC Induction chemotherapy

ICRU International Commission on Radiation Units and Measurements

IGRT Image-guided radiotherapy

IMRT Intensity-modulated radiation treatment

KPS Karnofsky performance score

LAHNC Locally advanced head and neck cancer

LRC Loco-regional control

MACH-NC Meta-analysis of Chemotherapy on Head and Neck Cancer

MDT Multidisciplinary Teams

MDCT MultidetectorCross sectional imaging

MECC Middle-East Cancer Consortium

MRI Magnetic resonance imaging

NBINarrow Band Imaging

NCICTC National Cancer Institute Common Terminology Criteria for Adverse Events

NCCN National Comprehensive Center Network

OAR Organs at risk

OS Overall survival

PD Progressive disease

PEG Percutaneous endoscopic gastrostomies

PF Platinol, 5-fluronracil.

PET Positron Emission Tomography

PR Partial response

PTV Planning treatment volume

RNA Ribonucleic acid

RT Radiation therapy

SCCSquamous cell carcinomas

SD Stable disease

SEER Surveillance, Epidemiology and End Results

SEQ Sequential

SIB Simultaneous integrated boost

SPSSStatistical program for social science

TNM Tumor node metastases

TPF Docetaxel , cisplatin , 5-fluorouracil

QOL Quality of life

Introduction

World-wide, the head and neck cancers form the sixth most common cancer.Head and neck cancer (HNC) is the most common cancer in developing countries (**Joshi *et al* .,2014).**In the United States, head and neck cancer accounts for 3 percent of malignancies, with almost 60,000 Americans developing head and neck cancer annually and 12,000 dying from the disease (**Seigel*et al* ., 2015**). Registry done by national cancer institute of Egypt in the year 2005, HNC squamous cell carcinoma (SCC) represent about 7% of all cases presented to the center**.** The majority of cases are diagnosed at advanced stages (**Ibrahim *et al*.,2009).**On 2009, about 4 % of cases were from middle Egypt, while from 2009-2011, 2% of cases were from lower Egypt (**Samy*et al* ., 2014).**

Because the upper aerodigestive tract is lined mainly by squamous epithelium, the most common tumors in the head and neck are squamous cell carcinomas. However,other tumors, such as adenocarcinomas, lymphomas,and melanomas are also seen **(Curado*et al*.,2009).**

More than 50% of patients who die from head and neck cancer have locoregional disease as the only site of failure, and almost 90% of patients with distant failure also have persistent locoregional disease. Therefore, the efficacy of any curative approach is measured by its ability to achieve locoregionalcontrol**(Seiwert*et al.,*2007*).***

During the past 5–10 years, chemo-radiotherapy was shown to markedly improve survival and organ preservation (**Forastiere *et al*., 2003).** Currently, three multimodality treatment approaches are used. The first approach is surgery followed by adjuvant concurrent chemoradiotherapy , which enables precise pathologic staging and identification of high-risk features that influence the choice of adjuvant treatment. This approach can have limitations, such as poor organ preservation, depending on the anatomic location (e.g. larynx), and the majority of locoregionally advanced tumors are unresectable, especially if organ preservation is the goal**(Bernier et *al.*, 2004).**

The second approach is definitive concurrent chemoradiotherapy with surgery as an optional salvage or completion treatment. Although no pathologic information is obtained with this approach, it has the advantage of improved organ preservation. This benefit is most clearly established for laryngeal cancer but is increasingly recognized for other anatomic locations; however, this approach remains controversial for oral cavity tumor**(Guardiola E *et al.,* 2004).**

The third approach is the use of induction chemotherapy followed by definitive local therapy. Advantages include the potential to decrease the risk of distant failure and a rapid reduction in tumor bulk in responders. A response to induction appears to predict responsiveness to chemo-radiotherapy. The role of this approach in the context of concomitant chemo-radiotherapy is currently being investigated in several large, multicenter, randomized trials **(Posner *et al*.,2005*).***

The rationale behind the combination of chemotherapy with radiotherapy has three advantages. Firstly, concomitant chemoradiotherapy can be used with organ preserving intent, resulting in improved cosmesis and function compared with surgical resection with or without adjuvant treatment. Secondly, chemotherapy can act as a radiosensitizer improving the probability of local control and survival, by aiding the destruction of radioresistant clones. Thirdly, chemotherapy may eradicate distant micrometatasis**(Seiwert*et al.,*2007).**

Currently, the most widely used standard regimen is 100 mg/m^2cisplatin every 3 weeks, combined with ~70 Gy radiation delivered in 1.8–2.0 Gy daily fractions. This regimen causes severe toxic effects, such as nephro-, oto- and neurotoxic effects, nausea and vomiting, as well as severe mucositis, which make the treatment suitable only for patients with normal creatinine clearance and a good performance status. Furthermore, locoregional failure rates are 35–65%, depending on tumor location, stage, and resectability(**Cooper *et al.* ,2004)** .

Several other chemotherapy regimens for concurrent chemo-radiotherapy use a different schedule of cisplatin to improve compliance and the toxicity profile. Among these regimens, weekly cisplatin doses ranging from 30 to 40 mg/m^2 are used most widely in the radical and adjuvant settings . Various studies using Cisplatin as a single agent chemoradiotherapy have demonstrated 3 years survival rates ranging from 37–73%(**Adelstein*et al.* ,2003).**

More recently, taxanes as Paclitaxel and Docetaxel, which are another group of radiosensitizers having a unique mechanism of action which leads to the formation of high affinity bonds with microtubules promoting tubulin polymerization and stabilization, have demonstrated single agent activity in patients with SCC of head and neck in several trials(**Fujii*et al*.,2004).**

Carboplatin is not as effective as cisplatin for its direct antitumor effect. The major toxicity of carboplatin is myelosppression ,which limits the total dose that can be given and the frequency of drug administration.The availability of colony-stimulating factors that can lessen the degree and duration of myelosuppression may provide a new avenue for this agent (**Tahir*et al*.,2013).**

The agent 5-fluorouracil (5-FU) has activity in head and neck cancers and, theoretically, is of particular interest because of its activity during the radioresistant S-phase of the cell cycle. Indeed, its radiosensitizing properties are well established and the drug is commonly used for chemoradiotherapy in several diseases **(Cohen et al. ,2005).**

Aim of the work

This is a retrospective study aiming to evaluate the different concurrent chemotherapy and radiotherapy regimens used in management in patients with locally advanced squamous cell head and neck cancers with a radical intent .

Primary objective:.to evaluate tolerability to treatment and response to treatment.

Secondary objective:to determine 3 years progression free survival and 3 years overall survival.

Chapter 1

Epidemiology

Overall, head and neck cancer accounts for more than 550,000 cases annually worldwide (**Jemal *et al*., 2013**). In the United States, head and neck cancer accounts for 3 percent of malignancies, with almost 60,000 Americans developing head and neck cancer annually and 12,000 dying from the disease (**Siegel *et al*.,2015**). World-wide, the head and neck cancers form the sixth most common cancer. Head and neck cancer (HNC) is the most common cancer in developing countries (**Joshi *et al* .,2014).** The highest incidences of HNC in the world are found in South Asia, and parts of central and southern Europe (**Boyle *et al.,*2008).**

Among the 10 most common incident cancers in men worldwide, 90% of HNC is squamous cell carcinomas (SCC) (**Curado et al.,2009).** Males are affected significantly more than females with a ratio ranging from 2:1 to 4:1. The incidence rate in males exceeds 20 per 100,000 in regions of Hong Kong, the Indian subcontinent, central and eastern Europe, France Spain, Italy, Brazil and among African Americans in the United States. The incidence of laryngeal cancer, but not oral cavity and pharyngeal cancer, is approximately 50 percent higher in African American men **(DeSantis et al.,2013**).

Previous hospital-based studies from Egypt showed that HNC constitutes about 17-20% of all malignancies (**El-Bokainy *et al*., 1998).** Registry done by national cancer institute of Egypt in the year 2005, HNC squamous cell carcinoma (SCC) represent about 7% of all cases presented to the center **.**The majority of cases are diagnosed at advanced stages (**Ibrahim *et al*.,2009).** On 2009, about 4 % of cases were from middle Egypt, while from 2009-2011, 2% of cases were from lower Egypt (**Samy *et al* ., 2014).** A report of the Middle-East Cancer Consortium (MECC) of the National Cancer Institute in Bethesda, USA, depicted that Egypt had one of the highest overall incidence rates of cancer of oral cavity and pharynx 5.5 $/10^5$ among the MECC countries (**Freedman et al.,2006).** Registry done in Ain-Shams university oncology and nuclear medicine department, HNSCC represents 12.5% of all oncological cases presented in the period between 2007-2009, with laryngeal carcinoma accounting for 54% **.**

Chapter 2

Staging

Diagnosis and staging of head and neck malignancy will normally include clinical examination by an experienced clinician, fiber-optic endoscopy, fine needle aspiration (FNA)/core biopsy) of any neck masses followed by further examination under anasethetic with additional biopsies if needed. Head and neck tumors are staged by the tumor node metastases (TNM) Classification of Malignant Tumors, which describes the anatomical extent of disease based on an assessment of the extent of the primary tumor the absence or presence and extent of regional lymph node metastasis and the absence or presence of distant metastasis (**Sobin *et al.,*2002**).

The TNM staging system of the American Joint Committee on Cancer (AJCC) and the International Union for Cancer Control (UICC) is used to classify cancers of the head and neck (**Edge *et al.,*2010**). The stage groupings used for head and neck cancer are based on T (primary tumor), N (regional node), and M (distant metastasis) designations as defined by the American Joint Committee on Cancer (***AJCC 7th edition***).Tables (1-8) show staging of HNCSCC except nasopharynx.

Table (1): stage grouping of HNSCC rather than nasopharynx.