Changes in Survival in Locally Advanced Laryngeal Carcinoma over Past Three Decades

Thesis

Submitted for Fulfillment of Master Degree in

Clinical Oncology

By

Ibrahim Mohamed Sherif EL-Zawahry

M.B.,B.Ch., Faculty of Medicine

Supervised By

Prof. Dr. Eman Abdul Hady

Professor of Clinical Oncology

Faculty of Medicine, Cairo University

Assistant Prof. Dr. Hanan Seleim mosalum

Assistant Professor of Clinical Oncology

Faculty of Medicine, Cairo University

Assistant Prof. Dr. Tamer EL-Nahas

Assistant Professor of Clinical Oncology

Faculty of Medicine, Cairo University

Dr. DINA EL HUSSIENY

Lecturer of Radiology

National Center for Radiation Research and Technology, Atomic Energy Authority

٢٠١٣

Acknowledgement

First and foremost, Thanks are to ALLAH,

The most Beneficent and Merciful of All

I would like to express my deep thanks and gratitude to **Prof. Dr. Eman Abdul Hady, Professor of Clinical Oncology, Faculty of Medicine, Cairo University**, for her continuous supervision, support and advice. I shall always be proud to have worked under her guidance.

I would like to express my deep thanks and appreciation to **Assistant Prof. Dr. Hanan Seliem Musallam, Assistant Professor of Clinical Oncology, Faculty of Medicine, Cairo University,** for her excellent supervision, creative criticism, guidance, support and her hard competent effort that made this work and removing any obstacle. I am always be proud to have worked under her supervision.

Also I would like to express my deep thanks and appreciation to **Assistant Prof. Dr. Tamer EL-Nahas, Assistant Professor of Clinical Oncology, Faculty of Medicine, Cairo University** for his continuous support and help.

I am greatly indebted to **Dr. Dina El Hussieny, Lecturer of Radiology-National Center for Radiation Research and Technology–Atomic Energy Authority** for her support, advice and valuable guidance.

Finally to the soul of my father **Dr. Mohamed Sherif El-Zawahry**, and I would like to express my infinite gratitude and my deepest appreciation to my **dear mother, my brother and my sisters** for their help and support.

Ibrahim El-Zawahry

Abstract

According to the results of our study and taking into account the possibility of existence of dysfunctional larynx following radiotherapy as primary treatment modality in patients with advanced laryngeal cancer, we can conclude that total laryngectomy and ipsilateral or bilateral neck dissection followed by postoperative radiotherapy should be considered as a recommendable treatment approach in patients with resectable advanced laryngeal cancer.

In order to improve treatment results in terms of LRC and OS and following evidence-based treatment recommendations for patients with advanced laryngeal cancer whose initial treatment is radical surgery, we strongly advocate the acceptance of postoperative concurrent chemoradiotherapy in cases with surgical specimen demonstrating high-risk pathological features.

Key Words:

Epidemiology, Therapeutic Approach in Locally Advanced Cancer Larynx, Future Challenges in Head and Neck Cancer.

Contents

List of Figures and Tables

INTRODUCTION

Laryngeal cancer is the commonest carcinoma of the head and neck region with squamous-cell carcinomas (SCC) in ٩٠ % of cases (**Birchall et al., ٢٠٠٨).**

The incidence of laryngeal cancer was relatively about ١٦٠,٠٠٠ new cases per year. The disease predominantly affects men; about ٢.٤% of all cancer cases and ٢.١% of all cancer deaths worldwide, also in United States in ٢٠١٢ the estimated new cases is ١٢,٣٦٠ and deaths from laryngeal cancer is ٣,٦٥٠. The majority of patients with SCC of larynx present with locally advanced (LA) disease (**American Cancer Society, ٢٠١٢**).

The incidence of laryngeal cancer in the Kasr El-Aini Center of Radiation Oncology and Nuclear Medicine (NEMROCK), Faculty of Medicine, Cairo University from year ٢٠٠٥ - ٢٠٠٨ is ٣.١%per year.

Advanced laryngeal cancer is generally considered as the disease in stages III and IV based on the primary tumor extension and/or the presence of metastatic lymph node(s) in the neck and it accounts for roughly ٤٠% to ٥٠% of patients with laryngeal cancer (**Chen AY, et al ٢٠٠٦).**

From the second half of the ٢٠th century total laryngectomy combined with a neck dissection was considered a treatment of choice for advanced laryngeal cancer **(Genden EM et al, ٢٠٠٧**).

In most institutions, postoperative radiotherapy as adjuvant treatment following ablative surgery with radiation doses up to ٦٠-٦٦ Gy has also become the standard approach for patients with stage III-IV laryngeal cancer (**Corvo R, ٢٠٠٧).**

However, the treatment of advanced laryngeal cancer seams to be a permanent challenge, but the management of patients with advanced laryngeal cancer has become more complex as other modalities including induction chemotherapy followed by radiotherapy or concurrent chemo-radiotherapy have evolved with the goal of preserving the larynx and reserved total laryngectomy as a salvage procedure for cases with less than ٥٠% response to induction chemotherapy or in those who have persistent disease following concurrent chemo-radiotherapy (**Diaz FI et al** ٢٠٠٥).

The Aim of Work

It is a retrospective study performed to evaluate the possible treatment outcome in patients with advanced laryngeal carcinoma treated in Kasr El-Aini Center of Radiation Oncology and Nuclear Medicine(NEMROCK) from (٢٠٠٥ to ٢٠٠٨) and to compare them with the outcome recorded in the thesis of laryngeal carcinoma conducted at NEMROCK during the past ٣ decades.

Epidemiology

The incidence of laryngeal carcinoma is relatively low in comparison to that of carcinomas of all organs. Laryngeal cancer comprises ٢ to ٥% of all malignant diseases diagnosed annually worldwide. There are areas where the incidence is higher (greater than ١٠ per ١٠,٠٠٠) including Spain, Italy, France, Brazil, India and the Afro-Caribbean populations in parts of the USA. Low incidence areas (less than ٢ per ١٠٠,٠٠٠) include Japan, Norway and Sweden. Worldwide, the peak incidence of laryngeal cancer is highest in men aged between ٥٥ to ٦٥ years. The male-to-female ratio varies from ٥ to ٢٠:١, however the last decades there is a decrease in this ratio, because of an increase of laryngeal cancer in women. There is a notable social class difference, in that laryngeal cancer is twice as common in men with low socioeconomic status. It is also more common in people residing in cities than in rural areas. Most studies show that inhabitants of the most industrialized cities have an incidence of laryngeal cancer ٢ to ٣ times higher than that of rural inhabitants. These racial, social and urban variations may be reflect different lifestyle and habits and also confirm the already recognized harmful effects of tobacco and alcohol (**Jemal A, et al ٢٠١٠).**

Risk factors:

Smoking and alcohol

Smoking is the most important risk factor for laryngeal cancer. Death from laryngeal cancer is ٢٠ times more likely for heaviest smokers than for nonsmokers. Heavy chronic consumption of alcohol, particularly alcoholic spirits, is also significant. When combined, these two factors appear to have a synergistic effect **(Jemal A, et al ٢٠١١).**

Human papillomavirus and helicobacter pylori

An increased risk of laryngeal cancer has been shown for people with evidence of human papillomavirus-١٦ (HPV-١٦) infection in the larynx (up to ١٩-fold risk increase), or in blood samples (up to a three-fold risk increase) (**Rees L, et al ٢٠٠٤**). It has been estimated that more than ١٠% of laryngeal cancers in the UK are linked to HPV infection. A meta-analysis showed a doubling in risk of laryngeal cancer in people infected with helicobacter pylori **(Chaturvedi AK, et al ٢٠١١).**

Gastro-oesophageal reflux disease

Meta-analysis concluded that a diagnosis of gastro-oesophageal reflux disease increases risk of laryngeal cancer by two–three times **(Qadeer MA, et al ٢٠٠٥).**

Immunosuppression

A meta-analysis reported an almost three-fold increased risk of laryngeal cancer in people with HIV/AIDS and a two-fold risk increase in transplant recipients, suggesting a role of immunosuppression in the disease **(Grulich AE, et al ٢٠٠٧)**.

Previous cancer

A six-fold increased risk of laryngeal cancer has been shown for people with a previous head and neck cancer **(Chuang SC, et al ٢٠٠٨**).

Occupation and indoor air pollution

Occupational exposure to coal dust increase laryngeal cancer risk, with a risk ratio of more than six for the most highly exposed (**Shangina O, et al ٢٠٠٦**).

It has been estimated that around ٣% of laryngeal cancers in the UK are linked to occupational exposure to asbestos or sulphuric acid **(Parkin DM, et al ٢٠١١).**

Family history

A pooled analysis of case-control studies showed a doubling in risk of laryngeal cancer in individuals with a history of head and neck cancer in first-degree relatives, after adjusting for the main lifestyle risk factors for laryngeal cancer. A ٣٠% risk increase has been shown for people with a first-degree family history of non-head and neck smoking-related cancers (**Negri E, et al ٢٠٠٨).**

Pathology:

Ninety five percent of laryngeal carcinoma **is squamous cell carcinomas,** other laryngeal malignancies include: Carcinoma in situ, Verrucous, spindle cell and basaloid SC, Undifferentiated carcinoma, Adenocarcinoma and other Miscellaneous carcinomas such as (adenoid cystic, neuro-endocrine carcinomas ,etc.). Glottic carcinomas represent the majority of laryngeal cancers (٥٠%-٦٠%), followed by the supraglottic carcinomas (٣٠%-٤٠%), while the subglottic carcinomas are uncommon (٥% or less). Squamous cell carcinoma vary according to their degree of differentiation to well, moderate and poor carcinomas. Glottic cancers are generally well

differentiated and have a less aggressive behaviour in comparison with carcinomas at the other sites of the larynx (**Christopouls TA et al ٢٠٠٨).**

Cytogenetics and molecular markers:

Various chromosomal alterations have been observed in laryngeal SCC, such as ٩p٢١ loss which contains the p١٦ gene, ١١q١٣ which contains the CCND١ locus, ١٧p١٣ where the p٥٣ gene is located, ٣p with at least three putative tumour suppressor loci, ١٣q٢١, ٦p and ٨. Some of these alterations have been demonstrated to precede the development of cancer by several years, while others may be also detected as late-occurring cytogenetic events. A few of them could be proposed targets for preventive strategies. Among the most frequent and relevant cellular changes in laryngeal carcinogenesis are those involving p٥٣, cyclin D١ (CCND١), p١٦ and EGFR **(vynios DH, et al ٢٠٠٨)**.

The nuclear phosphoprotein p٥٣ is involved in gene transcription, DNA synthesis and repair, cell cycle co-ordination and apoptosis. Disruption, or perturbation of p٥٣ function have been detected not only in the laryngeal but almost in all head and neck cancers. P٥٣ point mutations or deletions (also by LOH at ١٧p١٣) are frequent and p٥٣ inactivation occurs in the transition from the preinvasive to the invasive state **(Anwar K, et al ١٩٩٣)**.

Cyclin D١ is involved in cell cycle progression and interacts with cyclin-dependent kinases. When Cyclin D١ gene (CCND١) amplification is observed in precancerous and cancerous lesions, cyclin D١ is always overexpressed. In turn, cyclin D١ overexpression does not determine, but

always anticipates gene amplification, which probably represents a more stable **(Bellacosa A, et al ١٩٩٦).**

Early in the cancerous process altered p٥٣ gene function and CCND١ gene overexpression increase genetic instability and promote further genetic and chromosomal alterations, such as CCND١ amplification which is considered as the ultimate transforming event by the selection of a malignant subclone from a genetically altered field.

EGFR is frequently and early overexpressed in LSCC, mainly by post-translational mechanisms. EGFR expression retains a strong predictive value independently of treatment (surgery, chemotherapy and radiation) and adversely influences overall relapse-free and metastasis-free survival in LSCC. At present, EGFR is the most reliable biological marker for molecular characterisation, aggressiveness and invasiveness of LSCC, non-reversible, alteration in tumor cells **(Papageorgakopoulou N, et al ٢٠٠٧).**

Telomerase activity often is present at high levels in most laryngeal cancer cells. It can at least partly depend on h-TERT gene (coding for catalytic subunit of telomerase) overexpression. It can be used for molecular epidemiology, diagnostics and targeting **(Almadori et al ٢٠٠٥).**

An overexpression of metalloproteases, hyaluronidases and cathepsin D is often detectable in tumor cells. These molecules are responsible for degradation of extracellular matrix and thus play an important role in tumor growth, invasion and metastasis, as well as in tumour-induced

angiogenesis. In addition**,** overexpression of CD٤٤ hyaluronan receptor in a less glycanated form is observed **(Christopoulos TA, et al ٢٠٠٧).**

Among the extracellular matrix components, the proteoglycan versican appeares to be overexpressed becoming the macromolecule characteristic of the tumour state and being another marker of aggressiveness. Similarly, hyaluronan is found in increased amounts and of rather smaller molecular size. Alterations, also, in the sulphation pattern of chondroitin/dermatan sulphate are observed, indicating different expression of sulpho-transferases **(Vynios DH, et al ٢٠٠٨).**

Route of spread :

The incidence of occult lymph node metastases in laryngeal cancer increase with T– stage and is correlated with the tumor subsite , showing higher incidence in supraglottic (٤٠%) than in subglottic (٣٠%) and glottis carcinoma(١٠%) **(Bohannon IA, et al ٢٠١٠).**

Clinical Presentation

Hoarseness is the most common presenting symptom of laryngeal carcinoma. Sore throat, otalgia, localized pain resulting from cartilage invasion, and dyspnea are symptoms of advanced disease **(Brady Lw, et al ٢٠١٠).**

Diagnostic Evaluation:

Initial Evaluation

careful history and physical examination are mandatory in the evaluation of a patient with carcinoma of the larynx. The neck should be