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Definitive radiotherapy in laryngeal cancer patients - retrospective study from single institution

Thesis
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*In the name of **Allah**, the all mighty god, the one and only one, I hereby start my thesis.*

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Abstract

Aim: Clinico-epidemiological study for laryngeal cancer patients, treated by radical radiotherapy (RT) ± chemotherapy (CT). Prognostic factors, treatment modalities, and their effect on loco-regional (LRC) and overall survival (OS) were studied.

Patients and methods: Files of 141 patients treated at the National Cancer Institute, Cairo University, during the period from 2007 to 2013 were studied retrospectively.

Results: mean age was 60 years. Squamous cell carcinoma was the most common pathological type (93%). Glottic carcinoma represent 57.4% while supraglottic carcinoma represent 38.3%. T1 represents 58.6% of early stage, while T3 represents 56.4% of advanced stage. Node negative disease represented 71.6%, while node +ve represented 28.4% of patients. 61% of patients were treated by radical RT, while 39% received chemoradiotherapy. Forty seven patients with advanced stage (33.3%) received CCRT while 35.2% received induction CT. Out of 141 patients, 116 patients completed the RT course (82.2%). The majority of patients (63.8%) achieved complete remission (CR). Locoregional failure was affecting 14 patients, and salvage surgery was done for 13 patients. The 5-year LRC and OS rates for all studied patients were 53.4% and 60% respectively, compared to 65.1% and 71.5% for early stage laryngeal cancer and 47.3% and 46.3% for advanced stage respectively. The 2, 3, and 5 year laryngectomy free survival (LFS) for advanced stage was 41.7%, 34%, and 31% respectively. Adverse prognostic factors affecting OS included; pathological grade, prolongation of overall RT treatment time and RT course discontinuation, while adverse prognostic factors affecting LRC were the pathological grade and disease subsite.

Conclusion: radical RT is the main treatment for early stage, while CCRT is the mainstay of treatment of locally advanced laryngeal cancer in properly selected patients.

Keywords: Larynx, Radiotherapy, larynx preservation.

List of abbreviations

5-FU	5-fluorouacil
AJCC	American Joint Committee on Cancer
ASCO	American Society of Clinical Oncology
CCRT	Concurrent Chemoradiotherapy
CIS	Carcinoma in situ
CR	Complete response
CT	Computed Tomography
CTV	Clinical target volume
DAHANCA	Danish Head and Neck Cancer Study Group
DFS	Disease Free Survival
ECOG	The Eastern Cooperative Oncology Group
EGFR	Epidermal Growth Factor Receptor
EORTC	European Organization for Research and Treatment of Cancer
FDG	Fluorodeoxyglucose
GORTEC	Radiotherapy Oncology Group for Head and Neck
GTV	Gross target volume
Gy	Gray
HNSCC	head and neck squamous cell carcinoma
HPV	Human Papilloma Virus
IC	Induction chemotherapy
IHC	immunohistochemistry
IMRT	Intensity-modulated radiation therapy
LC	Local control
LI	labeling index
LFS	Laryngectomy free survival
LP	laryngeal preservation
LRC	Locoregional control
MDACC	MD Anderson Cancer Center
MRI	Magnetic Resonance Imaging
OS	Overall Survival
PET	Positron Emission Tomography
PL	Partial laryngectomy
PTV	Planning target volume
RT	Radiotherapy
RTOG	Radiation Therapy Oncology Group
SCC	Squamous cell carcinoma
SCL	supracricoid laryngectomy
SPECT	single photon emission computed tomography
TH-3DCRT	TomoHelical 3-Dimensional Conformal RT
TL	Total Laryngectomy
TLM	Transoral CO_2 laser microsurgery
TLR	Transoral laser resection
TPF	Docetaxel, platinol, and fluorouracil
Teff	effective doubling times
Tpot	median potential doubling times

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Introduction:

The larynx produces speech (phonation) and protects the airway. Treatment-related compromise of either of these functions can dramatically affect patients' quality of life after treatment for their cancer. In fact, the loss of one's voice is one of the most feared adverse effects in all of oncology.

Early-stage disease is typically treated with either surgery or radiotherapy (RT) alone, whereas advanced disease is typically treated with a combined modality approach **(Trotti et al, 2006)**.

Moderately advanced lesions (T3 and early T4) that were traditionally treated by laryngectomy (with or without pharyngectomy) and postoperative radiation therapy are now known to be potentially suitable for larynx-sparing therapies with close posttreatment observation and salvage surgery when needed. Five years Local control (LC) after radiotherapy with or without chemotherapy is 35–75 % and 5 years overall survival (OS) is 25–55 % **(Forastiere et al, 2003)**.

Aim of Work:

- Study clinical and epidemiological characteristics of the patients.
- Study patient management and its outcomes.
- Analyze potential prognostic factors influencing locoregional control and overall survival.

2.1.1. Epidemiology:

Laryngeal cancer represents about 2% of the total cancer risk and is the most common head and neck cancer **(Jemal et al., 2010).**

In 2012 the estimated worldwide incidence of laryngeal cancer is 156877 new cases, while estimated mortality about 83376 cases **(Ferlay et al., 2013; Bray et al., 2013).**

According to **Ibrahim and colleagues (2014)** who described cancer incidence in Egypt during the period from 2008 to 2011, the head and neck cancers represent 4.85% of all tumors. The laryngeal cancer represent 0.9% of all tumors and 18.7% of the head and neck cancer, being the most common head and neck cancer in Egypt. The male to female ratio is 7:1. The incidence rate of laryngeal cancer in Egypt is 1.1/100,000.

In Egypt, the estimated incidence of cancer larynx in 2012 is 1431 new cases, while in the United States in 2010, there were approximately 12,720 new cases of cancer larynx (10,110 men and 2,610 women), while estimated mortality in Egypt is about 593 cases, compared to about 3,600 deaths from laryngeal cancer in the United States in 2010 **(Jemal et al., 2010; Ferlay et al., 2013; Bray et al., 2013).**

Glottic cancers are roughly two times more common than supraglottic cancers, whereas subglottic cancers are rare and consist of fewer than 5% of laryngeal malignancies **(Cosetti et al., 2008).**

2.1.2. Etiology:

More than 85% of larynx cancer can be attributed to tobacco use and alcohol consumption, with smoking being the predominant etiology and alcohol being an independent and synergistic factor **(Sadri et al., 2006).**

Other risk factors include environmental exposure to asbestos, nickel compounds, wood dust, leather products, paint, diesel fumes, and glass-wool **(Muscat, 1992).**

Gastroesophageal reflux has also been identified as a risk factor for larynx cancer **(El-Serag et al., 2001)**, with alkaline reflux as the causative factor **(Galli et al., 2002).** Although Human Papilloma Virus (HPV) infection (particularly types 16 and 18) may play a role in the development of larynx cancer, there does not appear to be as strong a causal association as in oropharynx cancer **(Gillison et al., 2000; Smith et al., 2000).**

2.1.3. Anatomy (Olivetti and Cuffari, 2015):

The skeleton of the larynx consists of the epiglottis, thyroid cartilage, cricoid cartilage, and arytenoid cartilages (Fig. 1).

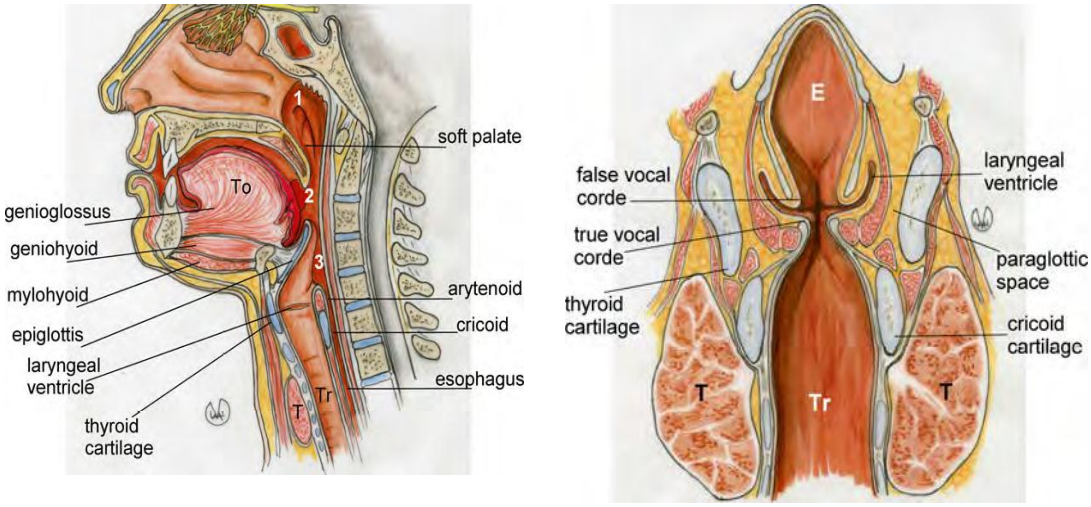

Fig. 1: Anatomy of the larynx. Nasopharynx (1), oropharynx (2), hypopharynx (3), tongue (To), trachea (Tr), thyroid gland (T), epiglottis (E) **(Olivetti and Cuffari, 2015).**

The epiglottis, a leaf-shaped cartilage, is the anterosuperior flexible part of the larynx; it is connected to the oropharynx by the pharyngoepiglottic folds and to the tongue by the glossoepiglottic fold. The thyroid cartilage, the largest laryngeal cartilage, is a median and

unequal element, divided into two even and symmetric laminae, forming an acute posterior corner**.**

The cricoid is the most caudal cartilage of the laryngeal skeleton; it is compared to a ring having an anterior arch and a posterior high lamina, it is the junction between larynx, above, and the trachea, below.

The arytenoid cartilages, located behind, on the cricoid lamina, are symmetrical and pyramidal; their function is to allow the vocal cords mobility, which are attached to the homonymous processes, located at the base of the arytenoid cartilage.

The larynx is generally divided into three parts: supraglottis or laryngeal vestibule, from the laryngeal opening to the false vocal cords; the glottis, where we found the false and true vocal cords delimiting the larynx ventricle (Fig. 2); the subglottis, going from the inferior surface of the true vocal cords to the inferior margin of the cricoid cartilage**.**

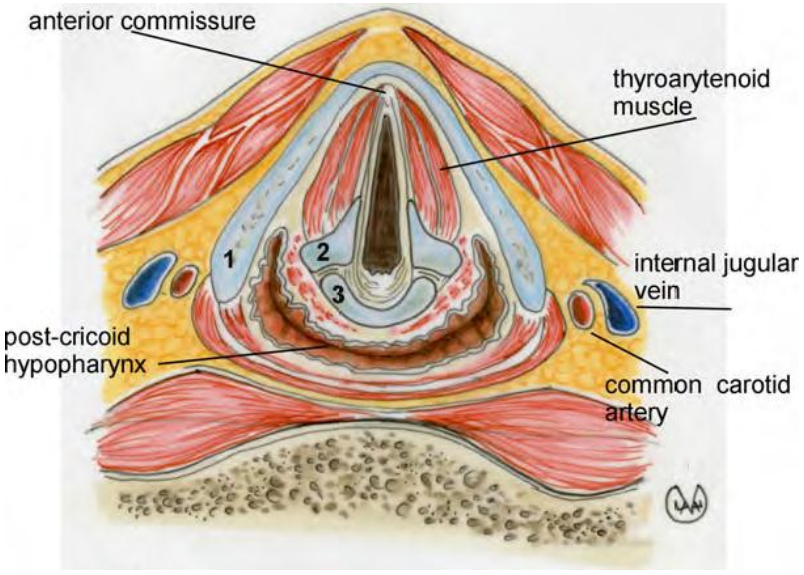

Fig. 2: Anatomy of the glottis, axial section. Thyroid cartilage (1), arytenoid cartilage (2), cricoid cartilage (3) **(Olivetti and Cuffari, 2015).**

2.1.4. Histology (Lingen, 2015):

2.1.4.1. Sequence of Hyperplasia-Dysplasia-Carcinoma:

A spectrum of epithelial alterations is seen in the larynx. They range from hyperplasia, atypical hyperplasia, dysplasia, and carcinoma in situ (CIS) to invasive carcinoma. Grossly, the epithelial changes vary from smooth, white or red focal thickenings, sometimes roughened by keratosis, to irregular verrucous or ulcerated white-pink lesions

The development of an overt carcinoma is directly proportional to the grade of dysplasia when the lesion is first seen. Orderly hyperplasia have almost no potential for malignant transformation, but the risk rises to 1% to 2% during the span of 5 to 10 years with mild dysplasia and 5% to 10% with severe dysplasia.

The epithelial alterations described above are most often related to tobacco smoke, the risk being proportional to the level of exposure.

Indeed, up to the point of cancer, the changes often regress after cessation of smoking.

2.1.4.2. Morphology:

About 95% of laryngeal carcinomas are typical squamous cell tumors. The tumor usually develops on the vocal cords, but it may also arise above or below the cords, on the epiglottis, or in the aryepiglottic folds.

Squamous cell carcinomas (SCC) of the larynx follow the growth pattern of other SCCs. They begin as in situ lesions that later appear as pearly gray, wrinkled plaques on the mucosal surface, ultimately ulcerating and fungating. The degree of anaplasia of the laryngeal tumors is highly variable. Sometimes massive tumor giant cells and multiple bizarre mitotic figures are seen. As expected with lesions arising from

recurrent exposure to environmental carcinogens, adjacent mucosa may demonstrate squamous cell hyperplasia with foci of dysplasia or even CIS**.**

2.1.5. Molecular factors:

Molecular markers predicting radio-sensitivity, chemo-sensitivity, and finally chances of larynx preservation (LP) are being investigated. Selection criteria for patients who may benefit from combining chemotherapy with RT or from induction chemotherapy (IC) remain an unresolved problem **(Rewari et al., 2009).**

The analysis of causes of RT failure in retrospective series of patients with head and neck cancer and cervix cancer, suggests a loss of LC as the overall treatment time increases for the same total dose **(Taylor et al., 1990; Lee et al., 1994).** This is attributed to tumor cell proliferation during fractionated RT. As longer treatment times lead to loss of LC, it has been suggested that shorter treatment times could lead to an increase in LC. For this reason, accelerated treatment regimens have been designed **(Maciejewski et al., 1996; Saunders et al., 1997).** However, these treatments cause severe acute reactions, so lower total doses are sometimes given. Slowly proliferating tumors may therefore do worse when treated with accelerated schedules compared with conventional schedules. In addition, it is not desirable to subject all patients to the intense acute reactions of the accelerated schedules. It would thus be useful to predict which tumors could show rapid proliferation during treatment and would be likely to benefit from accelerated RT **(Begg et al., 1999).**

The median potential doubling times (Tpot), determined in tumors before treatment, seem to be similar to the average values of effective doubling times (Teff) which actually take place during treatment as a

response to therapy-induced cell depletion. The cell birth rate and therefore, the potential doubling time (Tpot), can be calculated knowing the labeling index (LI; proportion cells incorporating the DNA precursor) and Ts (the DNA synthesis time). Tpot is defined as the time within which the cell population of a tumor would double if there were no cell loss **(Steel, 1977).** The hypothesis is thus that Tpot measured before treatment may correlate with Teff during treatment **(Begg et al., 1999).**

Several studies have employed such methods to assess the predictive value of pre-treatment cell kinetic parameters after RT **(Bourhis et al., 1996; Zackrisson et al., 1997).** Results have been variable, some showing positive association with outcome **(Awwad et al., 1992; Zackrisson et al., 1997),** and some not **(Bourhis et al., 1996; Hoyer et al., 1998).**

Almost all the studies have included relatively few patients, limiting their power. In multicentre analysis done by **Begg and colleagues (1999)**, from 11 centers, a total of 476 patients conforming to the inclusion criteria were analyzed. The study revealed that pretreatment cell kinetic measurements provide a relatively weak predictor of outcome after RT in head and neck cancer **(Begg et al., 1999).**

In a retrospective study by Małecki, a lack of Epidermal Growth Factor Receptor (EGFR) was the only independent factor predicting response to IC **(Małecki et al., 2010).**

Low EGFR and high p16 (or higher HPV titer) expression are markers of good response to LP and positive outcome. Tumor angiogenesis and high Vascular Endothelial Growth Factor expression are associated with decreased responsiveness to IC for LP and with poorer OS **(Lagha et al., 2013).**