Role of neck dissections in patients undergoing salvage laryngectomy with a clinically and radiologically negative neck

Study Submitted for the partial fulfillment of M.D. Degree in Otorhinolaryngology (Thesis)

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Abbreviations

2D XRT	Conventional external beam radiation therapy
3D CRT	Three dimensional conformal radiation therapy
5 FU	5 Fluorouracil
ADC	Apparent diffusion coefficient
AT	Auger therapy
ATP	Adenosine triphosphate
b-values	Brownian motion of water protons in biological tissues
Ca Lx	Cancer larynx
CCRT	Concurrent chemo-radiation therapy
CHART	Continuous hyper-fractionated accelerated radiotherapy
cN0	Clinically N0
COX	Cyclooxygenase
CPU	Central processing unit
CRT	Chemo-radiotherapy
CT	Computed tomography
DNA	Deoxyribonucleic acid
DW	Diffusion weighted
EBRT	External beam radiation therapy
EGFR	Epidermal growth factor receptor

ELISA	Enzyme linked immunosorbent assay
END	Elective neck dissection
FDA	Food and drug administration
FGD	Fluoro-deoxy-glucose
fGNP	Functionalized gold nanoparticles
FNAC	Fine needle aspiration cytology
GNPs	Gold nanoparticles
Gy	Gray (unit)
HER2	Human epidermal growth factor
HOX 1	Homeobox protein 1
HPV	Human papilloma virus
IGRT	Image guided radiation therapy
IMRT	Intensity modulated radiotherapy
MLS	Micro-laryngeal surgery
MRI	Magnetic resonance imaging
MRND	Modified radical neck dissection
MRSA	Methicillin resistant staph aureus
ND	Neck dissection
NFK	Nuclear factor kappa
PCF	Pharyngo-cutaneous fistula
PET	Positron emission tomography
pN0	Pathologically negative neck nodes
pN+	Pathologically positive neck nodes
qRT PCR	Real time quantitative polymerase chain reaction
ras	Rat sarcoma viral oncogene
RND	Radical neck dissection
RT	Radiotherapy
SCC	Squamous cell carcinoma
SLN	Sentinel lymph node

S/L ratio	Short to long axis ratio
SND	Selective neck dissection
SPECT	Single photon emission computed tomography
STL	Salvage total laryngectomy
SUV	Standardized uptake value
TP53	Tumor protein 53
VEGF	Vascular endothelial growth factor
VMAT	Volumetric modulated arc therapy
US	Ultrasound
U.S.A	United States of America
USG	Ultrasonography
USg FNAC	Ultra sound guided fine needle aspiration cytology

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Introduction

Cancer larynx is common in head and neck with a percentage of ***17%*** *of head and neck carcinomas. It was calculated that every 1,000,000 of population have 14 patients with cancer larynx. Cancer larynx is more common in males however; the difference between both genders is decreasing* ***(Brandstorp-Boesen et al., 2014).***

Management of various stages of cancer larynx in terms of total cure is considered the top goal in treatment. On the other hand, tumor recurrence risk should be balanced with the benefits of organ preservation ***(Ganly et al., 2009).***

Before 1990, total laryngectomy was the preferable line of management. New advances in chemotherapy paved the way for concurrent chemo-radiotherapy to become the standard of care in many institutions. The last twenty years have improved non-surgical management dramatically in treatment of advanced tumors. The development of taxanes and epidermal growth factor receptor monoclonal antibodies in conjunction with high advances in nanotechnology are building the future, supporting organ preservation ***(Horn et al., 2012).***

The best line of treatment of both clinically and radiologically negative neck N0 and a local failure after radiotherapy performing salvage laryngectomy still needs more study. Although occult metastasis may be present in regional lymph nodes, the incidence rate of pathologically positive nodes is low and described in literature ranging from ***0.0% to 28.3% (Dagan et al., 2010).***

Before the last two decades, neck dissection (ND) to be included with any salvage laryngectomy in local failure was the prevailing concept. Elective neck dissection (END) in such patient was hilarious with elongated operative time, more complications and poor life quality. The low percentage of occult regional metastasis in N0 patients with local failure in hands with disadvantages of neck dissection in previously irradiated neck stand against the past concept which should be revised ***(Dagan et al., 2010).***

The aim of this study is to verify the necessity of neck dissection with salvage operation in N0 cancer larynx after failure of radiotherapy or chemo-radiotherapy, and to compare it with the watchful waiting protocol in management of neck in these cases as regard regional recurrence, morbidity and survival rate.

Review of literature

Non surgical laryngeal preservation in management of cancer larynx: History, nowadays and upcoming

The larynx is a highly valuable organ. It provides marvelous tasks in respiratory airway protection, swallowing and vocalization. Treatment of cancer larynx (Ca Lx) entails successful survival balanced with function preservation. Studies during previous century have transformed this cancer from the greatest nightmare to the utmost treatable tumor as shown in figure (1) ***(Nakayama et al., 2012).***

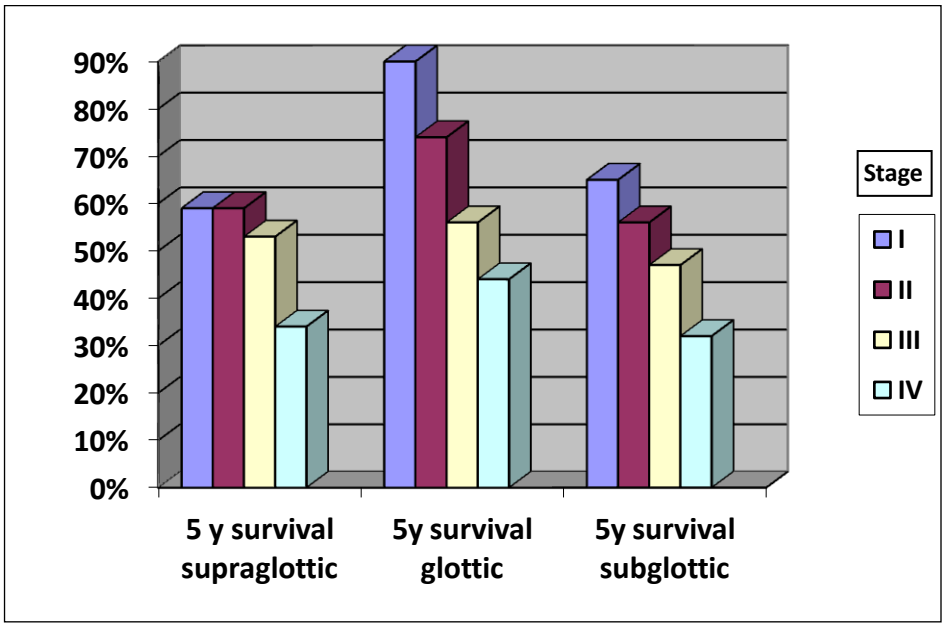

Figure (1): a chart of laryngeal cancer 5 years survival rate according to stage. **Quoted from American joint cancer committee (AJCC) cancer staging manual, seventh edition.**

Total laryngectomy, invented in the late 18th century, kept on being an efficient operation, particularly for advanced stages. The deviation of normal air route by generating an everlasting opening and damage of laryngeal purpose always has a catastrophic influence on patients. Those patients continuously experience disastrous psychosis on mislaying their voices ***(Terrell et al., 2011).***

Numerous organ preservation operations were designed as a replacement for the hilarious operation as horizontal or vertical laryngectomy, supra-cricoid laryngectomy and trans-oral laser micro-laryngeal surgery.

These operations were familiarized to manage early tumors in the seventies and nowadays are being used to manage also advanced tumors ***(Laccourreye et al., 2012).***

Radiotherapy was mainly presented to treat small tumors, but advancements of chemotherapeutic drugs, 5 Fluorouracil (5 FU), cisplatin and taxane (spindle or mitosis poison) in the nineties have progressed the idea of laryngeal preservation. Concurrent chemoradiation therapy (CCRT) has developed to be the major line of treatment in USA as shown in fig. (2) ***(Lambert et al., 2010).***

Throughout the former 20 years, chemo-radiotherapy has saved many larynges and improved the quality of survival, mainly in advanced stages. This methodology was capable to accomplish laryngeal preservation in **64%** of patients with a comparable overall survival **(Mitali and Anil , 2014).**

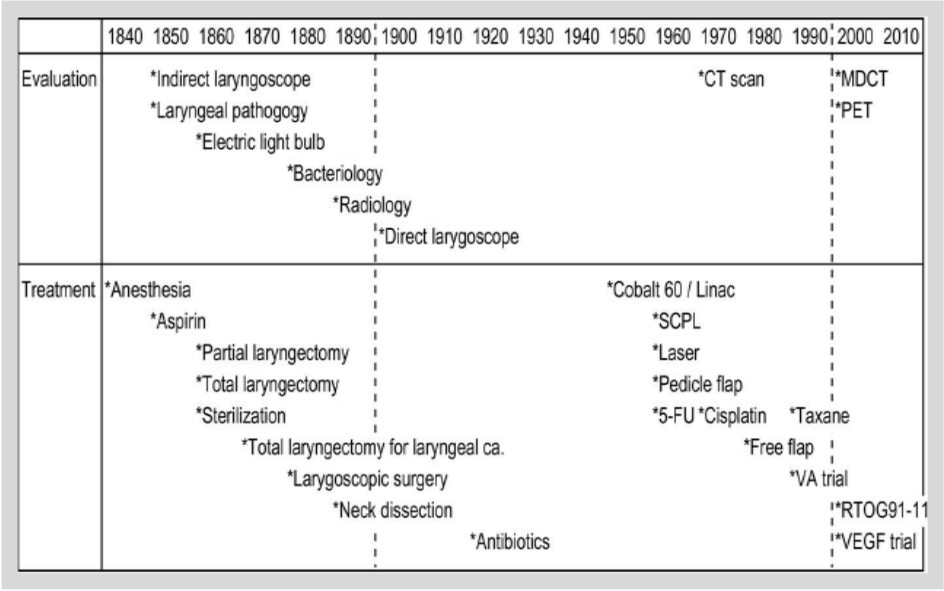

Figure (2): history of management in cancer larynx.
Quoted from Nakayama et al., 2012.

Appraising development of organ preservation approaches, patients' opinion should be kept in advance. This concept has been rising as Western civilization necessitate that patients contribute in choosing their therapeutic plans. Are they ready to trade a theoretical decrease in their life expectancy for the opportunity to reserve their life quality? ***(Laccourreye et al., 2012).***

In Egypt total laryngectomy is the commonest modality of treatment for primary Ca Lx, as most of patients are diagnosed at late stages. For lymph node management, the selective neck dissection is the commonest treatment as most of cases have N0 and N1as shown in fig. (3,4) ***(Hazem et al., 2014).***

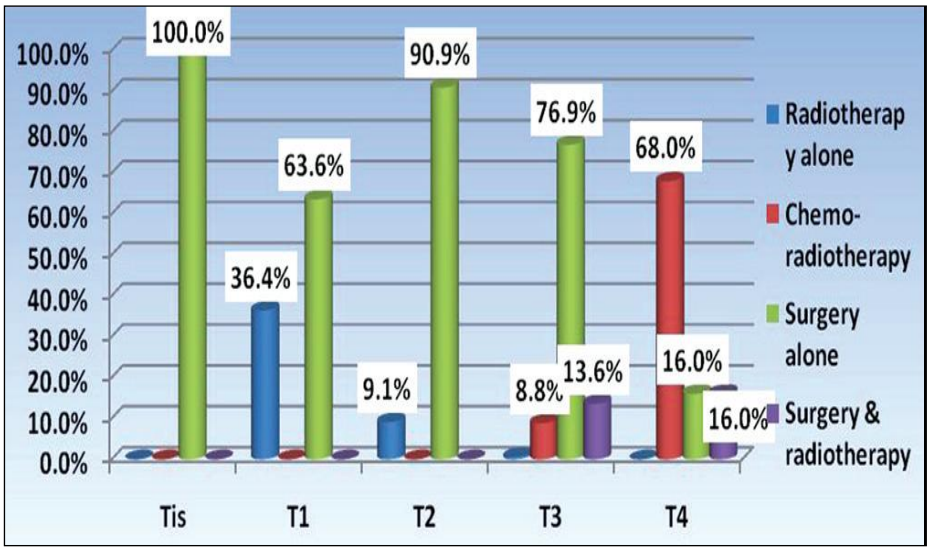

Figure (3): chart showing association between the T stage of the tumor and the treatment modalities in Egypt.
Quoted from Hazem et al., 2014.

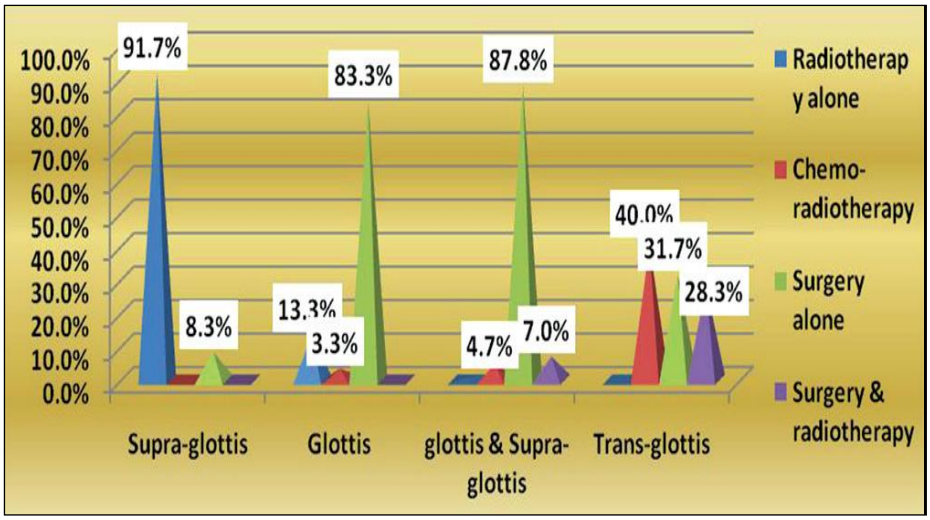

Figure (4): chart showing association between the tumor site and the different treatment modalities in Egypt.
Quoted from Hazem et al., 2014.

A- Radiotherapy (RT)

Radiotherapy is the utilization of ionizing radiation, to control or destroy tumor cells and generally provided by a linear accelerator. High energy electron beams, particle beams (including protons and boron, carbon, and neon ions) and gamma rays are also included clinically ***(Bomford et al., 2012).***

Radiotherapy could be curative or a part of adjuvant therapy preventing recurrence post-surgery. Radiotherapy is synergistic with chemotherapy, and is being used in advance, throughout and afterwards chemotherapy ***(Bomford et al., 2012).***

In order to save healthy tissues, fashioned radiation rays are designed at numerous angles to transect at the targeted tumor cells with a higher radiation dose at targeted area than tissues in neighborhood ***(Bomford et al., 2012).***

There are diverse methods of radiotherapy, comprising 3D conformal radiotherapy, intensity modulated radiotherapy (IMRT), particle-beam therapy and brachy-therapy. Furthermost patients who are managed in the U.S.A and Europe are managed by IMRT via highly energized photons ***(Mahmood and Nohria, 2016).***