A comparative study between the effect of radio-chemotherapy versus surgery with or without postoperative radiotherapy on advanced stage hypopharyngeal carcinoma (stage III and IV)

Submitted for partial fulfillment of master degree

In Otorhinolaryngology

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2019

بسم الله الرحمن الرحيم

(قالوا سبحانك لا علم لنا

الا ما علمتنا انك أنت

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TO

My Professors,

My dear family

Acknowledgment

*First and foremost, thanks to **ALLAH** who gives me everything I had and I will have.*

*It gives me great pleasure to express my deepest gratitude to **Prof. Ossama Abdel Hamid** professor of Otorhinolaryngology Faculty of Medicine - Ain Shams University for his impressive help and great encouragement during the preparation of this Work.*

*I would like to express my gratitude and cordial appreciation to **Prof. Samia Fawaz** Professor of Otorhinolaryngology Faculty of Medicine - Ain Shams University, for his guidance and constant supervision, which have a great help in the performance of this work.*

*I am deeply thanks to **Dr. Osama Mustafa,** Lecturer of Otorhinolaryngology Faculty of Medicine - Ain Shams University, for great help to achieve my goal.*

Finally, I acknowledge my family, colleagues, and all those who helped me in this work.

Contents

List of Abbreviations

RT	Radiotherapy.
IMRT	Intensity-modulated radiation therapy.
CT	Computed topography.
FDG-PET	Fluoro-deoxy-glucose Positron emission tomography.
T	Tumor staging.
N	Lymph node staging.
M	Metastasis staging.
MRI	Magnetic resonance immittance.
AJCC	American Joint Committee on Cancer.
RFFF	Radial forearm fascio-cutaneous free flap.
ALT	Anterolateral thigh free flap.
TLPE	Total laryngo-pharyngo-oesophagectomy.
GPU	Gastric pull-up.
NTLP	Near-total laryngectomy with partial pharyngectomy.
TLP	Total laryngectomy with partial pharyngectomy.
MACH-NC	Meta-analysis of chemotherapy in head and neck cancer
HNSCC	Head and neck squamous cell carcinoma.
NCCN	National Comprehensive Cancer Network.
NS	Non-significant.
HS	Highly significant.

SD	Standard deviation.
U test	Mann-Whitney's Test.
CRT	Chemo-radiotherapy.
OS	Overall survival.
SR	Survival rate.
LP	Larynx preservation.
LRR	Local recurrence rate.
DMR	Distant metastasis rate.
ORR	Overall recurrence rate.
FR	Failure rate.
CR	Complication rate.
MR	Mortality rate.
RR	Rrisk ratio.
DF	Degree of freedom.

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Abstract

Background: The improvement of clinical outcomes for patients with hypopharyngeal SCC has been particularly challenging for head and neck surgeons and oncologists. CRT has been used for patients with advanced hypopharyngeal cancer with the aim of preserving the larynx. The reasons for the un-favorable prognosis of hypopharyngeal cancers are the strong tendency for extensive sub-mucosal spread, the early occurrence of regional lymphatic involvement, and the relatively high rate of distant spread.

Aim: This study was conducted to collect the recent data about the different modalities of management of advanced stage hypopharyngeal carcinoma (stage III and IV), and systematically review the outcomes of each modality either alone or in combination and compare the efficacy of them.

Method:

I- Target determination
II- Identification and location of articles
III- Screening and evaluation of articles
IV- Data collection
V- Reporting and interpretation
VI- Discussion and consultation

Results:

We found 650 record; of them 160 unique records identified (duplicate removed) by the database searches; 490 were excluded based on title and abstract review; 160 article are searched for eligibility by full text review; 119 articles cannot be accessed or obtain full text; 10 studies were reviews and case reports; 3 were not describing functional outcome, overall survival.

Regarding surgery group was reported in 8 studies with total 1657 patients achieved overall survival (46.23%); While in CRT group, it was reported in 18 studies with total 2995patients achieved overall survival (43%).Comparative study between the 2 groups revealed decrease in overall survival rate; in CRT group; compared to surgery group; with significant statistical difference (p = 0.019).

Conclusion: The treatment approach had a significant impact on OS and RR, as described in other series. Given the equivalence between these two strategies suggested in several series, definitive CRT seems to be an advantageous option as it improves organ preservation and, consequently, the functional outcome.

Recent developments in chemo-radiation treatment techniques could hopefully increase tumor management and survival rates.

Keywords: 1-Advanced hypopharyngeal carcinoma management

2- Treatment of hypopharyngeal carcinoma stage III and IV

3-Radio-chemotherapy in advanced hypopharyngeal carcinoma management

4- Surgery in advanced hypopharyngeal carcinoma management

5- Radio-chemotherapy versus surgery in hypopharyngeal carcinoma

6- Pyriform sinus, post cricoid, posterior wall carcinoma management

Introduction

Squamous cell carcinoma of the hypopharynx accounts for about 5% of all head and neck cancers, the most frequent site is the pyriform sinus, representing (70%) of the cases followed by the post-cricoid region (15% to 20%) and the posterior wall (10% to 15%) (**Bahadur et al 2002**).

This tumor typically occurs in individuals who are older than 50 years of age, with a peak incidence in the sixth and seventh decades and their occurrence is extremely rare in children **(Siddiqui et al 2003)**.

More than 90% of patients present with a history of tobacco use. Risk increases with both the quantity and duration of tobacco and alcohol use (**Tuyns et al 1988**). An increased smoking rate in women resulted in narrowing the gap between genders in some countries (**Popescu et al 2010**). Also, the early introduction of smoking in the individual habits could be considered as a factor contributing to a downward readjustment of the age of appearance of hypopharyngeal cancer (**Lefebvre and Chevalier 2004**).

As most of the hypopharyngeal carcinoma presenting with non-specific symptoms and signs, so two thirds of the patients present with locally advanced disease (stage III or IV) (**Chu and Chang 2009**).

The reasons for the remarkably poor prognosis of hypopharyngeal cancers is their aggressive behavior represented by strong tendency for submucosal spread, early occurrence of nodal metastatic involvement, propensity for direct invasion of adjacent structures in the neck and high incidence of distant metastases (**Johansen et al 2000**).

The high rate of synchronous and metachronous primary tumours identified in patients with hypopharyngeal cancer and the concomitant mucosal dysplasia frequently found surrounding primary tumours appear to relate to a field cancerisation effect, which is consistent with widespread exposure to carcinogens (**Shah et al 2008**).

Management of patients with Squamous cell carcinoma of the hypopharynx is complex and multidisciplinary, requiring the multidisciplinary care and expertise of radiologists, pathologists, head and neck surgeons, radiation and medical oncologists, speech and swallowing therapists, dietitians, nurses and social workers. Moreover, the optimal management of this disease has improved over the past two decades, incorporating refined surgical approaches, organ preservation strategies with either altered fractionation radiotherapy or combination of chemotherapy and radiotherapy (**Brockstein et al 2017**).

Management of hypopharyngeal carcinoma have included radical surgery and adjuvant radiotherapy for resectable disease and radiotherapy for un resectable disease, but treatment outcomes with these approaches have been generally poor: most published series report long-term loco-regional failure rates of (30% to 70%), distant failure rates of (20% to 30%) and survival rate of (20% to 60%) (**Mantz et al 2008**).

Radiotherapy (RT) alone, although appearing to have favorable impact on short-term prognosis, it has only moderate long-term benefits (**Fountzilas et al 2009**). These disappointing results have led to new therapeutic strategies that incorporate chemotherapy in combined modality treatment. However, radiotherapy alone doesn't appear to provide a satisfactory outcome in advanced tumors compared to radical surgery and eventual adjuvant radiotherapy, In terms of loco-regional control and survival (**Barone et al 2008)**.

In fact, mean five years survival in patients treated with radiotherapy alone is estimated to be between 12.7% and 13.9%. Survival rates among patients undergoing radical surgery followed by post-operative radiotherapy range from 25% to 60% (**Chu and Chang 2009**).

Moreover, salvage surgery performed after high dose radiotherapy gives poor results and has high co-morbidity rates, especially considering the formation of fistulas (**Bradley 2005**).

The addition of chemotherapy to radiotherapy as a mean of increasing efficacy is to overcome radio-resistance and eradicate any coexistence of field micro-metastasis (**Calais 2010**).

Several phase III studies comparing radio-chemotherapy and surgery with or without postoperative radiotherapy showed significant improvement in loco-regional control with an impact on overall survival rate (**Barone et al 2008)**.