

## **Changes in Survival in Locally Advanced Laryngeal Carcinoma Over Past Three Decades**

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### **ABSTRACT**

**Objective:** To evaluate the treatment outcome in patients with advanced laryngeal carcinoma treated in the Kasr El-Aini Center of Radiation Oncology and Nuclear Medicine (NEMROCK), from 2005 to 2008. **Patients and Methods:** We retrospectively reviewed records of 42 patients who had been diagnosed with advanced laryngeal carcinoma and presented to NEMROCK from January 2005 to December 2008. Inclusion criteria were stage III and stage IV laryngeal carcinoma and histopathological diagnosis of squamous cell carcinoma. Primary surgical treatment was total laryngectomy with or without unilateral or bilateral neck dissection. Positive surgical margins, vascular invasion and extra-capsular nodal extension were considered as high-risk features. Radiation therapy represented the adjuvant therapy following surgery.

Radiation treatment consisted of external beam radiotherapy (EBRT) two-dimensional technique.

Post-operative concurrent chemo-radiotherapy (CCRT) was given when indicated. Loco-regional control (LRC) rate, isolated local relapse nodal, loco-regional recurrences and distant metastases were all reported. Patients, response to systemic chemotherapy together with its side effects were also reported. Reports of computed tomography (CT) scans before and after treatment were compared. **Results:** Surgery was the primary treatment modality in 35 (83.3%) out of 42 patients. Total laryngectomy with unilateral or bilateral neck dissection was made in 32 patients (91.4%) and without neck dissection was performed in 3 patients (8.6%). Radiation treatment representing the adjuvant therapy following surgery was applied to all 35 patients. Post-operative CCRT was given for 33 (94.3%) out of 35 patients. The incidence of laryngeal cancer was 3% in this period. The median overall survival (OAS) for patients in the surgical group was 22 months (range, 6-52 months). The (OAS) rate in the surgical group of patients was 78% at 2 years, 58% at 4 years. While the median disease free survival (DFS) was 18 months (range: 4-52 months) and 75% and 55% at 2 and 4 years respectively. During the follow-up period, among the 35 patients, the loco-regional control rate was 80.1% and the median overall survival (OAS) for relapsing patients was 13 months. The toxicities were all tolerable and no fatal case was recorded. **Conclusion:** 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. We strongly advocate the acceptance of postoperative concurrent chemo-radiotherapy in cases with surgical specimen demonstrating high risk pathological features.**

***Keywords: Chemotherapy; laryngeal carcinoma; radiotherapy***

## **INTRODUCTION**

Laryngeal cancer is the commonest carcinoma of the head and neck region with squamous-cell carcinomas (SCC) in 90 % of cases [1]. The incidence of laryngeal cancer was relatively about 160,000 new cases per year. The disease predominantly affects men; about 2.4% of all cancer cases and 2.1% of all cancer deaths worldwide. The majority of patients with SCC of larynx present with locally advanced (LA) disease [2]. The incidence of laryngeal cancer in Kasr El-Aini Center of Radiation Oncology and Nuclear Medicine (NEMROCK), Faculty of Medicine, Cairo University from year 2005 to 2008 is 3.1% 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 40% to 50% of patients with laryngeal cancer [3]. From the second half of the 20<sup>th</sup> century total laryngectomy combined with neck dissection was considered the treatment of choice for advanced laryngeal cancer [4]. In most institutions, postoperative radiotherapy as an adjuvant treatment following ablative surgery with radiation doses up to 60-66 gray (Gy) has also become the standard approach for patients with stage III-IV laryngeal cancer [5].

However, the treatment of advanced laryngeal cancer seems to be a permanent challenge, and the management of patients with advanced laryngeal cancer has become more complex as other modalities include induction chemotherapy (IC) followed by radiotherapy or concurrent chemo-radiotherapy (CCRT). These modalities have evolved with the goal of preserving the larynx and reserving total laryngectomy as a salvage procedure for cases with less than 50% response to induction chemotherapy or in those who have persistent disease following (CCRT) [6]. The aim of the current work was to evaluate the possible treatment outcome in patients with advanced laryngeal carcinoma treated in NEMROCK in the period between 2005 and 2008.

## **PATIENTS AND METHODS**

The current study was a retrospective study. Records of patients having advanced laryngeal carcinoma who presented to Kasr El-Aini Center of Radiation Oncology and Nuclear Medicine (NEMROCK) from January 2005 to December 2008 were revised to report: age, gender, TNM classification, histopathology, surgical treatment, radiation therapy, chemotherapy, treatment response and recurrence. Inclusion criteria were stage III and stage IV disease and histopathological diagnosis of squamous cell carcinoma. Patients below the age of 18 years, having other malignancy, and those who did not complete treatment and without follow-up records were excluded from the study. The disease was staged according to 2010 criteria of the American Joint Committee on Cancer (AJCC) [3]. Primary surgical treatment was total laryngectomy with or without unilateral or bilateral neck dissection. Positive surgical margins, vascular invasion and extra-capsular nodal extension were considered as high-risk features. Radiation therapy represented the adjuvant therapy following surgery. Radiation treatment consisted of external beam radiotherapy (EBRT) two-dimensional technique. Patients were immobilized in supine position with a thermoplastic head and neck mask and treated with photons with beam energy of 6 megavolts or cobalt and electrons with energies 8-12 megavolts. The radiation technique applied was the classical technique of conventional mixed electron-photon fields consisting of three stages. The first stage referred to the field set-up for 40 Gy (20 fractions of 2 Gy/fraction) and was represented by two opposing lateral fields to irradiate the upper neck and

anterior fields to irradiate the lower neck up to 50 Gy (25 fractions of 2 Gy/fraction). In the second stage 20 Gy over 10 fractions was applied to the lateral fields were reduced from the dorsal side in order to exclude the spinal cord from the fields. An off-cord boost to the posterior neck was delivered by two lateral electron fields. In patients with surgical margins being microscopically involved or metastatic lymph node(s) in the neck with determined presence of high-risk pathological features for regional failure (nodal metastases with extra-capsular extension (ECE), lymph node larger than 3 cm in the greatest diameter and /or two or more positive lymph nodes), the operative bed of the primary lesion or the beds of metastatic lymph node were boosted up to 66 Gy.

Post-operative CCRT was given when indicated. The patients received cisplatin (30 mg/m<sup>2</sup>) once a week for 6-7 weeks, given concurrently with EBRT on an outpatient basis. Cisplatin was infused over one hour, before radiotherapy, diluted in normal saline 500 ml. Supportive pre- and post-hydration with 500 ml normal saline solution and 250 ml monitor 18% in 30 minutes intravenously were also given. Prophylactic anti-emetic therapy and dexamethasone 8 mg intravenously were given before chemotherapy. Loco-regional control (LRC) rate, isolated local relapse nodal, loco-regional recurrences, distant metastases and performance status were reported. Patients' response to systemic chemotherapy together with its side effects was also reported including acute and late toxicities grades [2]. Reports of computed tomography (CT) scans before and after treatment were compared. The protocol of the study was reviewed and accepted by the local ethical committee of clinical oncology department.

#### **Statistical analysis:**

All data were tabulated and statistically studied by descriptive analysis as well as survival analysis in relation to different clinico-epidemiological factors. Survival was defined as a time from presentation to death or date of last follow up. Disease free survival (DFS) was defined as the time from achieving complete remission (CR) to relapse, death or last follow up. Survival analysis was performed using Kaplan Meier method for both overall survival (OAS) and DFS. Univariate and multivariate analysis using COX regression module were performed to test the power of relation between the independent variables and OAS as well as DFS. A probability value (P-value) less than 0.05 was considered to be significant. The statistical calculations were done using computer programs (statistical package for the STATA, release 10.0, STATA Corp, College Station, TX, USA).

## **RESULTS**

#### **Patients' characteristics:**

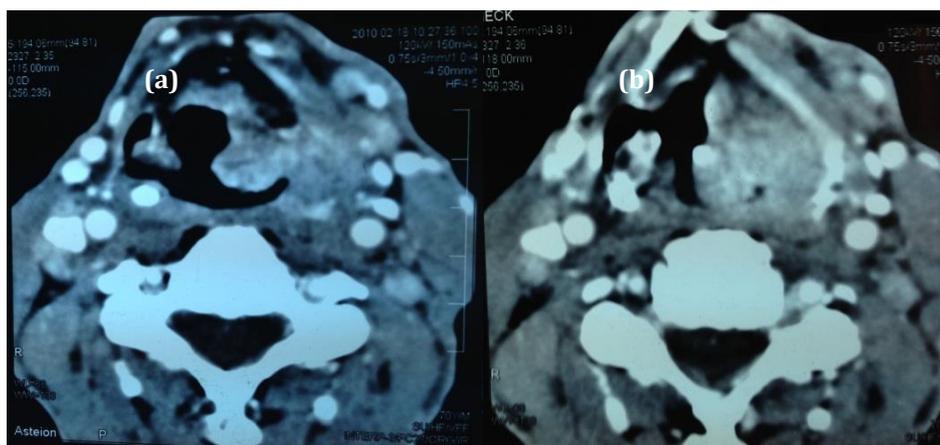
Forty two patients with locally and/or regionally advanced squamous cell carcinoma of the larynx treated at NEMROCK between January 2005 and December 20 were analyzed. In this study, we estimated the incidence of laryngeal cancer to be 3% in this period. There was an evident male predominance (97.6%) with only one female patient present. The median age at diagnosis was 60 years (range: 30-84 year). The performance status grade 1 according to the Eastern Cooperative Oncology Group (ECOG) was scored in 59.5% of patients [2]. The median follow-up for all patients was 41 months (range 11-70 month), and for patients, who stayed alive, was 52 months (range, 34-70 month). Patients' characteristics were summarized in Table (1).

**Table (1): Patients' characteristics**

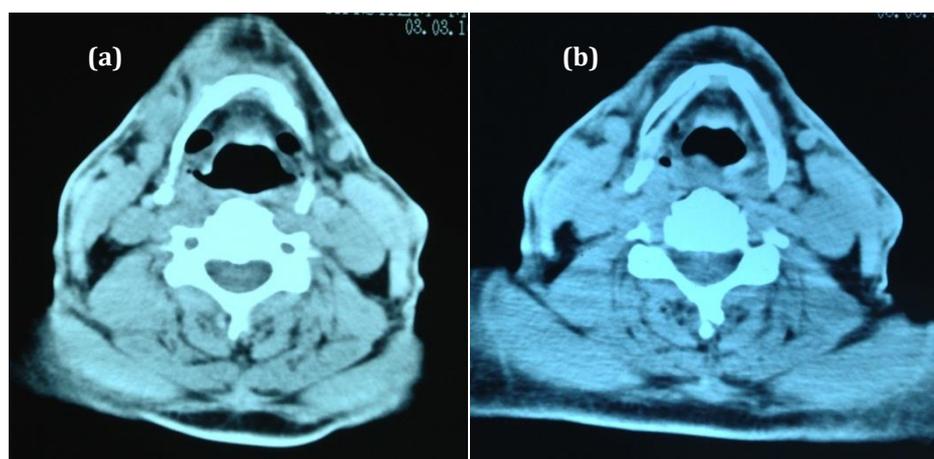
Characteristics		Number of patients (42)	%
<b>Sex</b>	<b>Male</b>	41	97.6
	<b>Female</b>	1	2.4
<b>ECOG<sup>1</sup> (performance status)</b>	<b>1</b>	25	59.5
	<b>2</b>	9	21.4
	<b>3</b>	8	19.1
<b>Site of tumor</b>	<b>Supraglottic</b>	22	52.4
	<b>Transglottic</b>	15	35.7
	<b>Subglottic</b>	5	11.9
<b>Tumor stage</b>	<b>T2</b>	3	7.1
	<b>T3</b>	17	40.5
	<b>T4</b>	22	52.4
<b>Nodal stage</b>	<b>N0</b>	19	45.2
	<b>N1</b>	10	23.8
	<b>N2</b>	8	19.1
	<b>Nx</b>	5	11.9
<b>Unilateral nodes</b>		23	54.4
<b>Bilateral nodes</b>		19	45.2
<b>Stage:</b>	<b>III</b>	20	47.6
	<b>IV</b>	22	52.4

<sup>1</sup>ECOG: Eastern Cooperative Oncology Group

More than one half of the patients (52.4%) had primary tumor classified as T4 (Fig.1), and 18 patients (42.8%) had metastatic lymph nodes in the neck (Fig.2). The overall stage IV was present in 22 patients (52.4%). Supra-glottic region was the most common tumors' site among our patients (52.4%).



**Fig. ( 1 )** CT neck, axial images of a 72 years old man, (a) a soft tissue mass lesion is seen arising from the left aryepiglottic fold .It measures 4.8x4x3 cm.(b) the lesion is seen extending to the level of the left true vocal cord ,with small group V lymph nodes seen . Total laryngectomy was done and the patient received concurrent chemoradiotherapy.



**Fig. ( 2 )** CT neck, axial views of a 47 years old man with (a) a focal right laryngeal nodule seen at the supraglottic region ,(b) Right group V lymph nodes are noted .

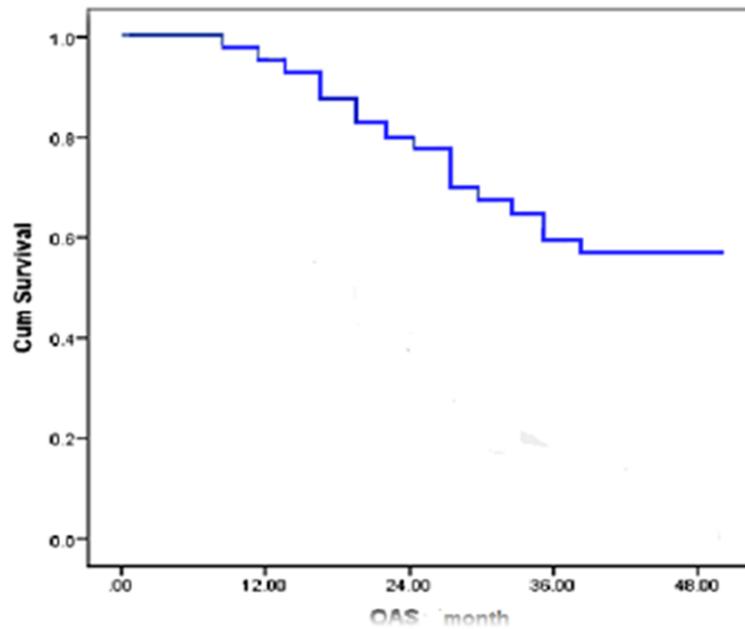
Surgery was the primary treatment in 35 (83.3%) out of 42 patients. Total laryngectomy with unilateral or bilateral neck dissection was done for 32 patients (91. 4%) out of the 35, and without neck dissection in 3 patients (8.6%). Concerning high-risk features, positive surgical margins were detected in 6 patients (17%) out of 35, vascular invasion in 10 patients (28.5 %) and extra-capsular nodal extension (ECE) in 8 (22.8%) out of 35 patients.

Radiation treatment representing the adjuvant therapy following surgery was applied to all of the 35 patients. The median time interval between surgery and onset of radiation treatment was 4 weeks (range 3-8 weeks). Post-operative CCRT was given for 33 (94.3%) out of 35 patients. The median total dose delivered to the primary tumor and involved lymph nodes was 66 Gy (range 60-66Gy), the median overall treatment time was 56 days (range 47-69 days), The median, minimal and maximal doses of cisplatin were 45 mg, 30 mg and 54 mg respectively. The median number of treatment cycles was 4 cycles (range 2-7 cycles). Seventy five percent of patients (25) received the total prescribed cisplatin dose and cycles.

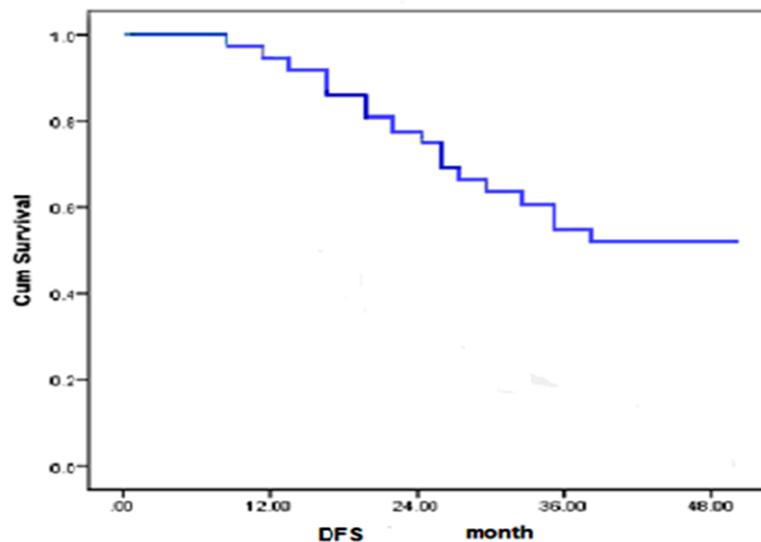
There was no grade 4 acute toxicity observed. The most frequent grade 3 acute toxicities were dysphagia and mucositis in 25% of the cases, neutropenia in 12% of patients. We also recorded grade

3 cutaneous reactions in 15% of patients. No related deaths occurred among the treated patients. The late tolerance of the treatment was acceptable. Grade 3 and grade 4 late toxicities were not observed in any patient.

The median overall survival (OAS) for patients in surgical group was 22 months (range, 6-52 months). The (OAS) rate in the surgical group of patients was 78% at 2 years, 58% at 4 years (figure 3). While the median disease free survival (DFS) was 18 months (range: 4-52 months) and 75% and 55% at 2 and 4 years respectively, (figure 4).

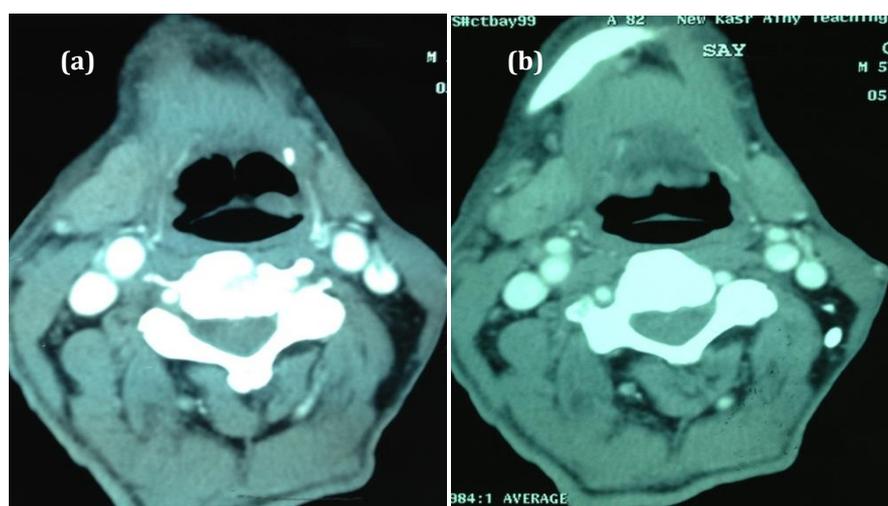


**Figure (3) : Overall survival of patients (OAS) in surgical groups.**



**Figure (4): Disease free survival of patients (DFS) in surgical group.**

During the follow-up period, among the 35 patients who underwent surgery, the loco-regional control rate was 80.1%. Three patients (8.5%) developed isolated local relapse as the first site of failure, while nodal and loco-regional recurrences occurred in another 2 patients (5.7%), (Fig.5).

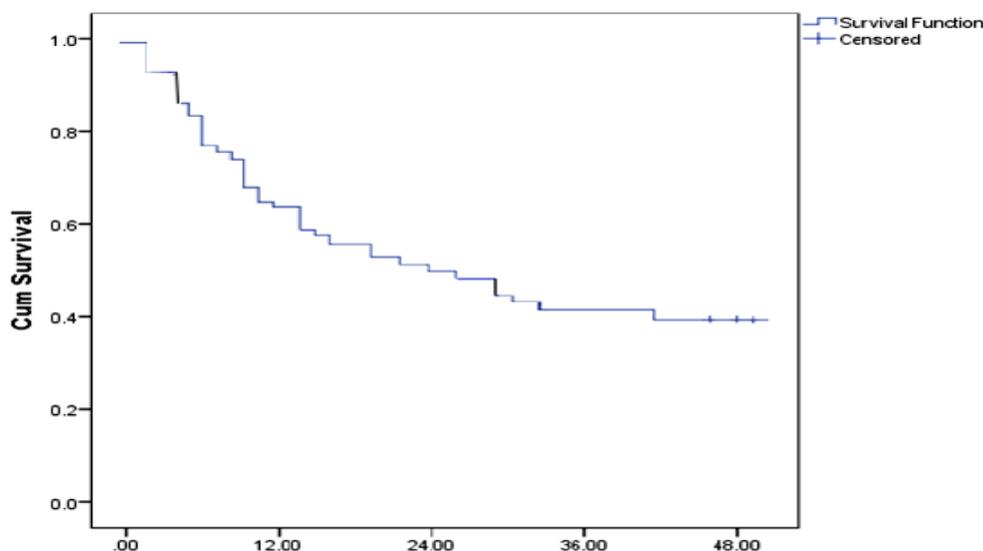


**Fig. 5: (a) CT neck , axial images of a 57 years old man with a left epiglottic nodule , the patient refused total laryngectomy and received radiotherapy, (b) right cervical nodal recurrence is noted at his CT follow up visit.**

Distant metastases in the bone were observed in 2 patients (5.7%). The median time for the occurrence of failure was 18 months (range, 6-28 months). All patients received systemic chemotherapy [5-fluorouracil] and achieved partial response which maintained between 6-21 months (median 10 months), and median OAS for relapsing patients was 13 months.

Seven (16.7%), out of 42 patients, with irresectable tumor underwent only surgical biopsy, their median age was 62 years (range 53-84 years) and the median performance status grade was 2 (range 1-3 ). Four patients (9.5%) were initially treated with induction chemotherapy (IC) in the form of cisplatin and 5-fluorouracil and 3 patients (7.1 %) treated with definite EBRT. The median cycles received were 3 cycles (range 2-3 cycles), after 2 or 3 cycles, all four patients achieved partial response. Two patients underwent total laryngectomy and neck dissection followed by CCRT while the other 2 patients treated with CCRT after IC. The median radiation dose was 60Gy for all patients (range 60 -70Gy).

The toxicities were all tolerable and no fatal case was recorded. Nausea and vomiting were the most common toxicities recorded in all patients during IC. Grade 2 leucopenia was reported in 50% of cases while anaemia and infection in 25% of cases. According to response, 3 (75% ) out of 4 patients showed complete remission (CR), one patient maintained CR for 23 months, 2 patients developed local recurrence after 8 and 10 months . One patient (25%) out of 4 developed bone metastasis after 11 months. The 3 patients who received definite EBRT achieved partial response (PR) with median progression-free survival (PFS) equals to 5 months and their median OAS was 8 months and all died with local disease progression. The OAS rate for all patients was 50 % at 2 years, 40 % at 4 years and the median OAS was 8 months, (Fig.6).



**Figure (6): Overall Survival for all Patients.**

The OAS in all patients at 2 years was significantly influenced by performance status ( $P < 0.05$ ) and receiving adjuvant radiation ( $P < 0.02$ ) but not significantly influenced by stage, nodal involvement and IC.

## DISCUSSION

In the current study, there was an evident male predominance (97.6%) with only one female patient present. This is due to different levels of exposure to the main risk factors of laryngeal cancer, as tobacco smoking and alcohol consumption [7]. More than one half of the patients (52.4%) had primary tumor classified as T4, and 18 patients (42.8%) had metastatic lymph nodes in the neck. The overall stage IV was present in 22 patients (52.4%). This high percent, may be due to the fact that, the large size these tumors usually reach before they are diagnosed. Various therapeutic strategies have been proposed in an attempt to improve outcome results for high-risk resectable locally advanced head and neck squamous cell carcinoma (HNSCC). Because surgery alone might achieve cure in only about one-third of patients, the addition of adjuvant radiation therapy may lead to a detectable loco-regional failure risk reduction (above the clavicles), with an extrapolated absolute survival benefit of 10% [8]. At our center, the treatment of choice for advanced laryngeal cancer is total laryngectomy followed by adjuvant CCRT. In this study, we recorded 83.3% of patients with advanced stage who received post-operative radiotherapy following radical surgery, they achieved a 4-year LRC of 80.1% which is more or less comparable with a 5-year LRC rate of 74% in the retrospective study performed by Nguyen-Tan et al. on 146 patients treated with total laryngectomy and adjuvant radiotherapy [9].

In the phase III study comparing accelerated with conventional fractionated postoperative radiotherapy for advanced head and neck cancer conducted by Sanguineti et al., the reported 2-year LRC in the group of patients treated with conventional fractionation was 80% [10]. Comparison of treatment outcomes based on OAS showed that in our study a 4-year OAS was 58% in the surgical group and this is nearly close to the OAS at five years done by Ampil et al. and proved to be 61% [11]. Attempting to compare the patterns of failure recognized in our study with those observed by other authors, we found that the incidence of distant metastases of 5.7% recorded in our study, and diagnosed by follow up CT scanning, was lower than the incidence of distant metastases development of 7% in the study of Ampil et al. [12]. On the other hand, the reported incidence of

distant metastases of 13% in the study of Idasiak et al. conducted on 267 patients with locally advanced squamous cell laryngeal cancer treated with surgery and postoperative radiotherapy was three-fold higher than the incidence of distant metastases in our study [13].

Analyzing the radiation induced late toxicity in our study, we did not record grade 3 and grade 4 late reactions. Ampil et al. also reported minimal late toxicity in their 14-year review of total laryngectomy and postoperative radiotherapy for T4 laryngeal cancer [12]. The prognosis of stage III and IV HNSCC remained dismal; in fact, in a meta-analysis of 10,000 advanced head and neck squamous cell carcinoma HNSCC patients, Pignon et al. underlined that the 5 year overall survival rate with exclusive adjuvant radiation therapy did not exceed 32%. As a matter of fact, a substantial part of this ineffectiveness might be due to a high probability of developing systemic disease (either directly in the shape of a previously present microscopic spread or indirectly 'following' a prior loco-regional failure) [14]. Hence, the role of the combination of chemotherapy and radiation in setting began to be explored. A two large scale multicentre prospective randomized (EORTC 22931 and RTOG 9501) trials yielded a new standard of care in the adjuvant setting of high-risk locally advanced HNSCC, with the association of EBRT and concurrent 100 mg/m<sup>2</sup> cisplatin given on days 1, 22 and 43. Both trials showed a statistically significant advantage in terms of loco-regional control and DFS if compared with exclusive adjuvant radiation; the European trial showed a significant improvement in OAS too.

The chemotherapeutic regimen used in our center was chosen in order to minimize acute and late treatment related side-effects; the slight reduction in dose intensity was believed not to, supposedly, affect the effectiveness. In our experience, severe acute toxicity was relevant but manageable at the same time, with 25% mucositis and 12% neutropenia; these data are at least comparable with previous mentioned studies reported by Porceddu et al [15,16]. In our study, late effects were mild if compared with the other weekly cisplatin studies. This comprehensive permissive toxicity profile allowed even generally 'unfit' patients to be treated. No apparent detrimental effect has been observed concerning local control or survival due to the reduction in cisplatin dose intensity. In fact, we observed an encouraging rate of LRC (80.1%) consistent with the data reported by the two large randomized trials ,82% for the EORTC study, and 81% for the RTOG study[15,16]. This is considered to be as one of the strengths in our study due to the fact that the OAS and LRC had not been evaluated and compared with the international levels in locally advanced laryngeal carcinoma previously in Egypt, and the assessment of the outcome gives a good indication of our successful treatment modalities. In our centre IC was not practiced as a standard protocol in the treatment of advanced laryngeal cancer till 2008 may be due to inadequate renal function in most of our elderly patients and that was evidenced in small number of patients treated with IC (9.5%) and this may be considered as a weakness in the current study. However, in the meta-analysis, the difference in survival and LRC between the patients who received IC compared to those that did not receive IC is not significant [17].

Therefore, for further identification of the clinical response to different IC regimens, we recommend to proceed with further investigation to identify the subset of patients that are most likely to respond to IC, targeting improvement in their survival outcomes. If this population can be identified, IC will definitely provide a survival benefit for these HNSCC patients.

## **CONCLUSION**

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 overall survival, 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 chemo-radiotherapy in cases with surgical specimen demonstrating high-risk pathological features.

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