

Prognostic Factors in Advanced Laryngeal Cancer: An Egyptian experience

Original
Article

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ABSTRACT

Background: In recent years, the survival rate of laryngeal carcinoma patients has been demonstrating a decreasing trend from (57.1% to 51.9%) we retrospectively analyze the various prognostic factors in patients with advanced laryngeal cancer. To explore the best options across the continuum of care for patients.

Patients and Methods: A retrospective analytic study evaluating prognostic factors in 110 patients with advanced laryngeal carcinoma. Selected prognostic factors includes age, gender, smoking, tumor subsite, TNM classification, clinical staging, thyroid cartilage invasion, treatment modality, surgical margins, Preoperative tracheostomy, postoperative fistula, associated comorbidities (chronic diseases).

Results: All patients were followed up for at least 36 months, the survival rates 1, 2 and 3 years after the treatment were 91.8%, 81% and 68.1% respectively. The disease-free progression rates were 89%, 81% and 71.8% respectively.

Conclusion: The increase in Age, Trans-glottic tumors, Thyroid cartilage invasion and Stage-IV AJCC; had an independent effect on increasing the probability of mortality occurrence.

Key Words: Advanced laryngeal cancer, prognostic factors, survival rate.

Received: 8 January 2021, **Accepted:** 18 January 2021

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ISSN: 2090-0740, 2021 Vol.22

INTRODUCTION

Head and neck cancers are ranked eighth in the world as frequency, and laryngeal carcinomas represent 30-40%^[1]. Laryngeal carcinoma represents 2.4% of all neoplasms diagnosed annually^[2].

The term advanced laryngeal cancer generally denotes stage 3 or 4 laryngeal cancers according to the Union for International Cancer Control (UICC)/American Joint Committee on Cancer (AJCC) staging.^[3] Laryngeal cancers may attain this advanced stage classification by virtue of advanced T classification (T3 or T4), N classification (N1-3), or M classification (M1)^[4].

Laryngeal cancers attain T3 classification if they have vocal cord fixation, para-glottic space invasion, pre-epiglottic space invasion, post-cricoid extension, or minor thyroid cartilage erosion. T4 classification is attained in tumors with cartilage destruction or extra laryngeal invasion^[5].

Accurate staging of larynx cancers demands careful clinical and radiological assessment. One of the challenges in staging these cancers is the subjectivity which may be involved in the defining criteria for T3 classification. Thus, vocal cord fixation is an important criterion for defining T3

classification and, when present, is generally accepted to have a significant adverse impact on likelihood of control with non-surgical treatment^[6].

In latest years, the rate of survival of laryngeal cancer patients has shown a decreasing rate from (57.1% to 51.9%) although the survival of patients with other tumors has shown increasing rates. Understanding the prognostic factors for patients with advanced laryngeal cancer may reverse the tendency toward decreasing the rate of survival and greatly help to develop both the treatment methods and therefore the life expectancy. However, the prognostic factors are still controversial^[7].

PATIENTS AND METHODS:

1) Study Subjects:

In this study, we retrospectively analyzed the data suggested to be prognostic factors of 110 consecutive patients with advanced laryngeal carcinoma (stage III or IV), their squamous cell carcinoma was confirmed by biopsy and who were treated either by Surgical treatment (Total Laryngectomy ± Neck Dissection) with or without Chemoradiation or by Chemoradiation only as a curative therapy in the period from January 2010 to December 2015.

2) Study Variables:

For the selected patients, prognostic factors of laryngeal squamous cell carcinoma including age, gender, smoking, tumor subsite, TNM classification, clinical staging, thyroid cartilage invasion, treatment modality, surgical margins, preoperative tracheostomy, postoperative fistula, and associated comorbidities (chronic diseases) were collected. We studied the impact of those factors on the prognosis of laryngeal cancer patients.

Staging of laryngeal cancer was based on the American Joint Committee on Cancer Eighth Edition (AJCC) 8.

The duration of follow-up was at least 36 months in all patients. Patients known to have distant spread or non-squamous cell tumors and patients who could not complete the treatment or didn't complete the follow-up period were excluded.

The standards for showing disease-free status and disease evolution were as follows: Flexible laryngoscopy, Direct laryngoscope and imaging including (CT, MRI, PET- CT scan, chest X ray, abdominal ultrasonography) were done to assess doubtful lesions. PET-CT was also available for detection of a possible residual/recurrent disease.

When doubtful lesions were detected, biopsies with consequent pathological examination were done to decide if local recurrence and/or lymphatic or distant spread had occurred. A disease-free status was defined as the absence of tumor showed by imaging examinations, and (if needed) pathological examination and biopsy.

Follow up was done every 3 months for survival rare, disease evolution, date of death (if possible) and post-surgical complications (such as pharyngo-cutaneous fistula).

Statistical Analysis

Data entry, processing and statistical analysis was performed using MedCalc ver. 18.2.1 (MedCalc, Ostend, Belgium). Tests of significance (Mann-Whitney's, Chi square tests, logistic regression analysis, ROC Curve analysis and Kaplan-Meier survival analysis) were used. Data were presented and suitable analysis was done according to the type of data (parametric and non-parametric) obtained for each variable. *P-values* less than 0.05 (5%) was considered to be statistically significant.

RESULTS:

Clinical data:

-The mean age of all patients was (60.4 ± 9.1) years. All patients were smokers, and (60%) had associated comorbidities.

-Regarding gender of the patients, the majority (94.5%) of patients were males; while (5.5%) were females.

-Regarding tumor site, (48.2%) of patients had glottic tumors, (26.4%) had supra-glottic tumors, and (25.5%) had trans-glottic tumors, with (53.6%) had thyroid cartilage invasion.

-Regarding T staging, (42.7%) of patients in T3 stage, and (57.3%) in T4 stage.

Regarding N staging, (81.8%) of patients in N0 stage, (15.5%) in N1 stage, while (2.7%) in N2 stage.

Regarding AJCC staging, (40%) of patients in stage III, and (60%) in stage IV.

Operative and treatment data:

Regarding Treatment modality, (29.1%) of patients had only surgical treatment, (9.1%) had only CRT treatment, and (61.8%) had combined "surgical and CRT" treatment, with (13.6%) had positive surgical margin, and (39.1%) had pre-operative tracheostomy.

Post-operative outcome data:

Regarding post-operative outcome data, (30%) of patients had fistula, (28.2%) had recurrence at average time of (1.9 ± 0.8) years, and the mortality rate was (31.8%) at average time of (2.1 ± 0.8) years.

Survival and Disease-free progress Rates:

Follow up period was at least 36 months, the disease specific survival rates 1,2 and 3 years after the treatment were 91.8%, 81% and 68.1% respectively. The disease-free progression rates were 89%, 81% and 71.8% respectively.

Comparative studies:

The 110 laryngeal cancer patients were classified according to disease specific survival and disease specific mortality rate into 2 independent groups:

- Disease specific mortality group (35 patients)
- Disease specific survival group (75 patients)

Clinical data:

-Comparative study between the 2 groups revealed; highly significant increase in age in mortality group; compared to survival group; with highly significant statistical difference (*p* < 0.01). As shown in (Table 1).

Comparative study between the 2 groups revealed; significant increase in trans-glottic tumors, T4 stage and AJCC stage-IV, in mortality group; compared to survival group; with significant statistical difference ($p < 0.05$ respectively). As shown in (Table 2).

Operative and treatment data:

-Comparative study between the 2 groups revealed; significant increase in CRT modality and decrease in surgical modality in mortality group; compared to survival group; with significant statistical difference ($p = 0.019$). As shown in (Table 2)

-Comparative study between the 2 groups revealed; significant increase in pre-operative tracheostomy in mortality group; compared to survival group; with significant statistical difference ($p = 0.026$). As shown in (Table 2).

Post-operative outcome data:

Comparative study between the 2 groups revealed; highly significant increase in rates of post-operative fistula and recurrence, in mortality group; compared to survival group; with highly significant statistical difference ($p < 0.01$ respectively). As shown in (Table 2).

Correlation studies:

Correlation studies between recurrence and mortality outcomes; and its relative independent predictors (clinical, tumor site, staging, operative and treatment variables) will be conducted with logistic regression analysis, ROC curve analysis and Kaplan-Meier survival analysis (as suitable).

List of predictor variables (included in the regression model):

- 1- Age
- 2- Sex
- 3- Associated comorbidities
- 4- Tumor site
- 5- Thyroid Cartilage Invasion
- 6- T stage
- 7- N stage
- 8- Staging AJCC
- 9- Treatment modality

10- Residual surgical margin

11- Pre-operative tracheostomy

NB: Smoking excluded as all patients were smokers.

Correlation studies regarding recurrence outcome:

Logistic regression analysis shows that; after applying (Backward method) and entering some predictor variables; trans-glottic tumors, thyroid cartilage invasion, stage-IV AJCC and CRT treatment; had an independent effect on increasing the probability of recurrence occurrence; with significant statistical difference ($p < 0.05$ respectively). As shown in (Table 3).

- By using ROC-curve analysis, surgical treatment modality predicted decrease of recurrence, with 65% accuracy, sensitivity = 93% and specificity = 38% ($p = 0.003$).

- By using ROC-curve analysis, CRT and combined treatment modalities showed non-significant predictive values in discrimination of patients with recurrence from patients without ($p > 0.05$). As shown in (Fig 1, Table 4).

Survival analysis of recurrence time shows that, 50% survival probability was markedly decreased in trans-glottic patients (1.5 years); compared to other patients; with highly significant statistical difference in survival curves of the 3 groups (Log-rank test) ($p = 0.0024$). As shown in (Fig 2).

Correlation studies regarding mortality outcome:

Logistic regression analysis shows that; after applying (Backward method) and entering some predictor variables; the increase in age, trans-glottic tumors, thyroid cartilage invasion and stage-IV AJCC; had an independent effect on increasing the probability of mortality occurrence; with significant statistical difference ($p < 0.05$ respectively).

By using ROC-curve analysis, all treatment modalities showed non-significant predictive values in discrimination of patients with mortality from patients without ($p > 0.05$).

Survival analysis of mortality time shows that, 50% survival probability was markedly decreased in trans-glottic patients (1.8 years); compared to other patients; with highly significant statistical difference in survival curves of the 3 groups (Log-rank test) ($p = 0.034$). As shown in (Fig 3).

Table 1: Comparison between the 2 groups regarding basic clinical data using Mann-Whitney's U and Chi square tests:

Variable	Mortality group (35)	Survival group (75)	Mann-Whitney's U test
	Median (IQR)	Median (IQR)	<i>P value</i>
Age (years)	66 (60 – 69.7)	58 (51 – 64.7)	= 0.00016**
Variable	Mortality group (35)	Survival group (75)	Chi square test
			<i>P value</i>
Gender	Female	5 (6.7%)	= 0.4146
	Male	70 (93.3%)	
Associated comorbidities	+ve	43 (57.3%)	= 0.4055

IQR: inter-quartile range. * Percentage of Column Total.

Table 2: Comparison between the 2 groups:

Variable	Mortality group (35)	Survival group (75)	Chi square test
			<i>P value</i>
Tumor site	Glottic	39 (52%)	= 0.014*
	Supra-Glottic	23 (30.7%)	
	Trans-Glottic	13 (17.3%)	
Thyroid Cartilage Invasion	+ve	37 (49.3%)	= 0.1872
T stage	T3	37 (49.3%)	= 0.041*
	T4	38 (50.7%)	
N stage	N0	64 (85.3%)	= 0.2565
	N1	10 (13.3%)	
	N2	1 (1.3%)	
Staging AJCC	III	36 (48%)	= 0.012*
	IV	39 (52%)	
Treatment modality	Surgical	27 (36%)	= 0.019*
	CRT	4 (5.3%)	
	Combined	44 (58.7%)	
Positive surgical margin	+ve	7 (9.3%)	= 0.0553
Pre-operative tracheostomy	+ve	24 (32%)	= 0.026*
Fistula rate	+ve	16 (21.3%)	= 0.0038**
Recurrence rate	+ve	3 (4%)	< 0.0001**

* Percentage of Column Total.

Comparison between the 2 groups as regards tumor site, staging data, operative data, treatment data and post-operative outcome data using Chi square test.

Table 3: Logistic regression model for the Factors affecting recurrence occurrence using Backward method:

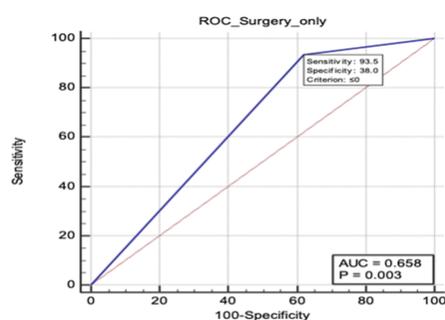
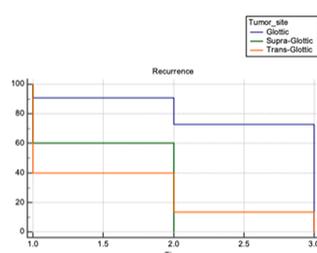
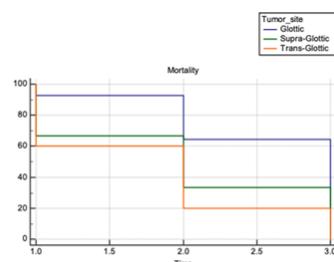
Predictor Factor	Coefficient	Std. Error	<i>P value</i>
(Constant)	-1.42712		
Tumor site = "Trans-Glottic"	1.40940	0.60044	0.018*
Thyroid cartilage invasion	2.34341	0.95219	0.013*
Staging AJCC = "IV"	3.49442	1.03503	0.0007**
Treatment modality = "CRT"	1.92074	0.88528	0.03*

--- excluded from the model if (*p value* > 0.1).

Table 4: Roc-curve of treatment modalities to predict decrease of recurrence:

Variable	AUC	SE	Sensitivity (%)	Specificity (%)	<i>P value</i>
Surgical	0.658	0.0532	93.55	37.97	0.003**
CRT	0.549	0.0632	16.13	93.67	0.4379
Combined	0.609	0.0580	77.42	44.30	0.0611

ROC (Receiver operating characteristic), AUC= Area under curve, SE= Standard Error.

**Figure 1:** ROC curve of surgery (decrease of recurrence).**Figure 2:** Kaplan-Meier survival curve of tumor site (recurrence).**Figure 3:** Kaplan-Meier survival curve of tumor site (mortality time)

DISCUSSION

Although the rate of survival of patients with early cancer larynx are high, the rate of survival of patients with advanced cancer larynx are still relatively low. The survival rate of early stage cancer larynx (Stages I and II) is measured as 73% to 92% and only 35% to 51% for advanced stage cancer larynx (Stage III and IV)^[9].

Our results revealed that the three years survival rate in patients with advanced cancer larynx was 68.1%, which is somewhat higher than that detected in several papers in the literature^[10]. The possible causes may be that most of our patients presented with glottic type of cancer larynx with better outcome, the laryngeal surgeries have developed greatly during last several years, negative margins was guaranteed as much as possible during surgery, a postoperative consistent follow-up scheme was performed.

Whether age affects outcomes is still debatable. In a multivariable analysis, Ramroth *et al.* mentioned that age was the most significant factor affecting outcome of patients with recently detected cancer larynx^[11].

Du and colleagues detected that age was a prognostic factor in the univariable study, but it was not a self-determining prognostic factor^[12]. Our study reinforced the results of Ramroth's study. Our results demonstrated that increase in age had an independent effect on increasing the probability of mortality occurrence.

Laryngeal squamous cell carcinoma is considered to be a male affection, commonly diagnosed between

40-70 years of age, accompanied by increased mortality among them, clearly superior to women^[13].

In recent years, an increase in this pathology has also been identified among female patients most likely due to the habit of smoking or consuming alcohol^[14]. In our study period 5.5% of the patients (6 patients) were women. In the future one might assume that this rate will continue to increase as more women are smokers, A trend also mentioned by Sanderson *et al* in both a Dutch and a UK material^[15].

Our results showed that tumor site had an independent effect on increasing the probability of recurrence & mortality occurrence. This is consistent with Liu *et al.* who mentioned that there are limited lymphatics in the glottic region, therefore, the glottic carcinoma limited to the vocal cord is not liable to regional lymph node spread. On the other hand, supraglottic & trans-glottic carcinomas usually existing with vague symptoms with very common regional lymphatic spread. As a result, supraglottic & trans-glottic carcinoma are liable to regional lymph node spread, especially with occult regional lymphatic spread that makes early diagnosis difficult and with much worse prognosis^[16].

Our study showed that Clinical stage significantly affected the prognosis of patients with laryngeal cancer, and independently influenced the recurrence & survival rates. This is consistent with Raitiola & Pukander who described Clinical stage as significant factor affecting diseases specific survival^[17]. Also consistent with Gonzalez, Rodrigo & Suarez who mentioned that the Clinical stage includes the impact of T and N stages, which shows the important effect of local spread of laryngeal cancer and regional lymph node spread on prognosis generally^[18].

Many of the prognostic features were related to the tumor. T stage and Clinical stage were found to be highly prognostic for both survival and recurrence rates. MacKenzie *et al.* and Marshak *et al.* showed a better recurrence rate with small tumors^[19-20]. Raitiola *et al.* showed a better survival rate in 293 Finnish laryngeal patients^[21].

Our study also showed that T stage and clinical stage significantly affected the outcome of patients with cancer larynx and clinical stage was independent factor affecting both survival and recurrence rates.

Our study showed that recurrence had a highly significant impact on decreasing survival rate in patients with advanced laryngeal cancer. This is consistent with Sessions *et al.* who associated decreased survival with recurrence occurrence^[22].

Many studies suggest that between all the prognostic factors for patients with laryngeal cancer, regional lymphatic spread is the most important^[18,23].

Jose *et al.* showed that the 5 years survival rate decreased by fifty percent in patients with regional lymphatic spread^[24].

Our study results showed no statistically significant difference between positive nodal metastasis and negative nodal metastasis patients as regard to overall survival and diseases free progression rate. that is may be due to small number of positive nodal metastasis patients in our study; Only 20 patients had positive nodes (18%) as the majority of our patients had glottic laryngeal cancer.

Lots of studies that have measured the efficiency of organ preservation protocols for advanced cancer larynx (Stage III & Stage IV). Whereas, no studies have been restricted for T3&T4 cancer and less studies about direct comparisons with total laryngectomy have also been described^[25].

A modern randomized study of 332 patients with advanced stage III/IV cancer larynx was stated by The Veterans Affairs Laryngeal Cancer Study Group. who prospectively compared the results of chemotherapy and total laryngectomy, both followed by radiotherapy and recommended that nonsurgical organ-preservation methods can be as effective in keeping the larynx without affecting the rate of survival^[26].

In disparity to this study that supported the nonsurgical organ-preservation method, another randomized study of 68 laryngeal cancer patients with T3 stage showed that Overall survival rate could be worse between patients accepted organ preservation technique than those underwent total laryngectomy followed by radiotherapy^[27].

Our study showed that overall survival rate was significant decreased among patients who received chemoradiation (CRT) in comparison to those who received surgical treatment only or followed by radiotherapy specially in Stage IV cancer larynx.

Patients who received surgical treatment alone (Stage III) showed significant improvement in survival in comparison to chemoradiation group or combined surgery and radiation group. In addition, our study showed that the nonsurgical organ preservation approach (CRT) had an independent effect on increasing the probability of recurrence occurrence with significant statistical difference specially in Stage IV Laryngeal cancer.

recently, many studies have found that postoperative radiation would not improve the outcome of patients with advanced cancer larynx^[28-29].

This opinion is also reinforced by our study, where the postoperative radiation did not significantly improve patient's prognosis in terms of survival in comparison to Surgical group. However, it was much better in improving survival rate than chemoradiotherapy alone especially in Stage IV cancer larynx. Moreover, we found that post-operative radiotherapy was associated with recurrence rate in comparison to Surgical group.

The probable causes may be the higher clinical stage of the patients in the postoperative radiation group (Stage IV), and their high or moderate differentiated pathological types of cancer larynx, which is not responsive to radiation therapy.

Yotakis *et al.* reported that there was no major difference in the rate of stomal recurrence between patients undergoing emergency tracheostomy (23.3%) and patients undergoing intraoperative tracheostomy (18.2%)^[30].

Our results supported Yotakis results at which there was no significant difference in the rate of stomal recurrence between those undergoing emergency tracheostomy and those undergoing intraoperative tracheostomy. However, our study showed that preoperative tracheostomy was associated with significant decrease in overall survival rate. The probable cause may be the more aggressive tumor stage of the patients in the preoperative tracheostomy section.

Debate exists regarding the link between CT scan showed cartilage invasion in laryngeal carcinoma and bad results after radiation therapy for locally advanced head and neck tumors^[31].

Although clinical sign of cartilage invasion has historically been considered a contraindication for organ preservation technique with radiation therapy, more recent studies have recommended that cartilage abnormalities on CT scan or MRI are not an independent factor for local failure^[32].

However, this subject has become of limited clinical importance because definitive radiotherapy alone is no longer recommended because of results from RTOG 91/11 showing that definitive radiotherapy alone had significantly worse local control, distant spread and larynx preservation rate than chemoradiotherapy^[33]. Therefore, the standard of care for advanced laryngeal cancer is either chemoradiation or total laryngectomy.

Our study showed that thyroid cartilage invasion considered an independent factor affecting both overall survival rate and disease-free progression rate. Therefore, the current study supported the concept of limited role of nonsurgical organ preservation strategy (CRT) in case of thyroid cartilage invasion (Stage IV) with superiority of Total laryngectomy followed by Chemoradiotherapy.

A single meta-analysis established in the literature for pharyngo-cutaneous fistula after laryngectomy was performed by Paydarfar *et al.* and showed that postoperative hemoglobin less than 12.5 g/dL, tracheotomy made prior to surgery and radiation therapy prior to surgery with or without neck dissection were the most important risk factors for the occurrence of pharyngo-cutaneous fistula after total laryngectomy and it was associated with decrease the rate of survival^[34].

Our study also showed that development of postoperative pharyngo-cutaneous fistula associated with highly significant decrease in overall survival rate. Mostly due to risk factors that contributed originally in formation of fistula.

This study had several limitations. First, the number of patients was relatively small. The second limitation of this study was its retrospective nature. Records were incomplete in some cases, limiting our ability to analyze post-operative function, recurrence and cause of death. Finally the clinical data collected from the patients did not include the occupational information, therefore, we could not measure the impact of possible exposure to certain carcinogens at work on the laryngeal cancer incidence and prognosis. That factor may have influenced our study findings to a certain extent.

CONCLUSION

There were eight variables significantly associated with mortality including Age, Tumor site, T stage, Clinical stage, Treatment modality, Preoperative tracheostomy, Postoperative fistula and Recurrence. While, the increase in Age, Trans-glottic tumors, Thyroid cartilage invasion and Stage-IV AJCC; had an independent effect on increasing the probability of mortality occurrence. Trans-glottic tumors, Thyroid cartilage invasion, Stage-IV AJCC and CRT treatment; had an independent effect on increasing the probability of recurrence occurrence.

CONFLICT OF INTEREST

There are no conflicts of interest.

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