

# Larynx Preserving Treatments in the Early and Advanced Laryngeal Cancers; A Retrospective Analysis

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## Abstract

**Background:** To assess tumor control and survival of the patients with laryngeal cancers who received chemoradiation or radiotherapy alone as definitive treatment.

**Material and methods:** Patients with laryngeal cancers who received organ-saving treatment were enrolled in this trial.

**Results:** In 147 cases, chemoradiotherapy was administered in 61 patients. Twelve cases were excluded from the analysis because of the treatment interrupt or death. Fifty eight cases had early-staged disease. In median time of follow up (9.9 months), mean overall survival and mean disease free survival were 51 months and 37 months in early lesions, and 30 months and 17 months in locally advanced tumors, respectively. Local control rate was 60% in early-staged and 43.5% in locally advanced cases. The mean total radiation dose significantly affected the tumor control in chemoradiation group.

**Conclusion:** It seems that radiotherapy or chemoradiation can be appropriate alternative to total laryngectomy in laryngeal cancers.

## Introduction

Laryngeal tumors are among the most cancers in head and neck cancers. The incidence of these tumors is increasing due to the worldwide use of tobacco. Nearly all malignant tumors of the larynx arise from the surface epithelium and therefore are squamous cell carcinoma (SCC) or one of its variants (Mendenhall et al., 2005). Carcinoma arising on the true vocal cords or supraglottis produces clinical symptoms at very early stages but the subglottic tumors are diagnosed at the advanced stages.

Squamous cell carcinoma of the head and neck is a debilitating disease. Combined modality treatments with surgery, chemotherapy, and radiation have been evaluated in multiple settings over the past 30 years. Given the fundamental role the larynx plays in human speech and communication, determining the optimal management of laryngeal cancers must involve consideration of both survival and the functional consequences of a given treatment approach. Larynx-preservation options include radiation therapy, chemoradiation therapy, induction chemotherapy followed by radiation therapy, and function preserving partial laryngectomy procedures.

Several studies have been designed to compare laryngeal preserving treatment with total laryngectomy in survival and local

control. Radiotherapy with concurrent cisplatin is the standard alternative to total laryngectomy for patients with locally advanced laryngeal cancer. The value of induction chemotherapy in larynx-preservation therapies remains unknown (Majem et al., 2006).

In most centers, irradiation is the initial treatment prescribed for early lesions, with operation reserved for salvage of irradiation treatment failure. The mainstay of treatment for advanced glottic lesions in most centers is total laryngectomy with or without postoperative irradiation. In some centers, radiation therapy is the initial modality for T3 lesions (Mendenhall et al., 2005).

Early supraglottic tumors are treated with RT or supraglottic laryngectomy. Total laryngectomy or concurrent chemoradiation (CRT) is used for the advanced tumors (NCCN, 2007).

Early lesions in subglottic area are treated with RT and advanced carcinomas are usually managed by total laryngectomy and postoperative RT (Mendenhall et al., 2005).

One of the common complications of laryngeal surgery is the compromising the patients' voice, so they may not accept the treatment. In the recent years, better techniques of radiotherapy and the use of concurrent chemotherapy have been resulted in survival and local control comparable to surgery especially in early laryngeal lesions. These voice sparing treatment modalities have also become more acceptable among the patients who suffer from laryngeal cancers. In this study, we evaluated disease free survival, local control, and toxicity of organ saving treatment (RT or chemoradiation) in early and advanced laryngeal carcinomas.

## Material and Methods

This study was a retrospective trial. From April 1999 to May 2006, the patients with a diagnosis of laryngeal cancer who were referred for definitive RT or CRT were enrolled in this study. The cases who had total laryngectomy before and were referred for adjuvant RT were excluded from analysis.

These variables were evaluated in the patients' files: age, gen-

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**Received** October 17, 2009; **Accepted** February 23, 2010; **Published** February 23, 2010

**Citation:** Shaghayegh K, Mahdi A, Ali K (2010) Larynx Preserving Treatments in the Early and Advanced Laryngeal Cancers; A Retrospective Analysis. J Cancer Sci Ther 1: 008-010. doi:10.4172/1948-5956.1000016

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der, stage of tumor, tumoral involvement site in larynx, pathology of tumor, the previous treatment before referring to the department, total dose of RT, dose per fraction, chemotherapy regimen in CRT group, toxicity during definitive treatment, longterm adverse effect of therapy, local recurrences, distant metastasis, the mean overall survival, the mean disease free survival. The stage of the tumor was recorded according to AJCC staging 2002 (Mendenhall et al., 2005).

In cases that there were not enough information in the files, we connected them via phone or mail.

## Results

There were 147 cases who received definitive organ saving treatment (RT or CRT) between 1999-2006. The average age of the cases was  $61.2 \pm 12.2$  years. There were 136 men (92.5%) in this study. The tumoral involvement sites were: glottic 47 cases (32%), supraglottic 40 cases (27.2%), subglottic 1 case (0.7%). The others had tumoral involvement in more than one site of larynx. The pathology of tumor was SCC in 143 cases (97.3%) and in the last four cases was anaplastic carcinoma, poorly differentiated carcinoma, verrucose carcinoma and undifferentiated carcinoma.

Nineteen patients (12.9%) had induction chemotherapy. In 13 cases cisplatin+5FU and in one case docetaxel was prescribed, and in five patients the regimen was unknown. Laryngeal preserving surgery was done in 36 cases (24.7%) before.

Of 147 cases enrolled in this study, there were 58 patients with early stages disease (52 cases in RT group, 6 cases in CRT group). Eighty nine patients had locally advanced lesions (43 cases in RT group and 55 cases in CRT group). The indication of concurrent chemoradiation in six cases in stage II was positive surgical margins. In the CRT group, there were 61 cases in which cisplatin was prescribed in 50 cases, cisplatin+5FU in 4 cases, paclitaxel in one case. Concurrent chemotherapy was administered weekly or every 3 weeks. The chemotherapy regimen was not mention in the files of other six patients.

There were twelve cases that were excluded from the analysis because of the treatment interrupt by themselves or death within the treatment course.

The mean total dose of RT was  $63.5 \pm 4.6$  Gy in all of the patients. The mean dose per fraction of RT was  $2.04 \pm 0.14$  Gy. The mean total dose of radiotherapy in the RT group who had local tumor control was  $63.3 \pm 4.3$  Gy and in cases who experienced local recurrence was  $62.3 \pm 3.6$  Gy (P.value > 0.05). However, the mean total radiation dose significantly affected the tumor control in the CRT group ( $69.1 \pm 1.7$  Gy in the controlled patients versus  $64.8 \pm 4$  Gy in the recurrent cases; P.value=0.013).

Local control rate was 60% in the early-staged patients and 43.5% in the locally advanced cases. The local recurrences occurred in 12 cases (19.7%) in the CRT group. There were 11 cases (12.8%) in the RT group who had local recurrences and two of them with locally-advanced disease needed salvage surgery. Two cases in the CRT group had distant metastasis to the lungs.

The median time of follow up was 9.9 months. The mean overall survival was 51 months (Standard Error (SE) =4; 95%

CI= 43-59) in early stages and 30 months (SE=4; 95% CI= 22-37) in advanced stages. The mean disease free survival was 37 months (SE=5; 95% CI= 29-48) in early-staged patients and 17 months (SE=2; 95% CI=13-22) in locally advanced cases.

There were four deaths in early stages (one in CRT group, three in RT group) and nine deaths in advanced stages (eight in CRT group and one in RT group) due to the laryngeal cancer.

The common toxicities during the treatment course were dermatitis (70.7%), mucositis (9.8%), hoarseness (4.9%), and sore throat (2.4%). The late effects were observed in 84 patients (62.2%) during follow up. There was no longterm treatment complication in 29 cases (21.5%) and this information was not found in the files of 22 patients. The most common chronic complications were laryngeal edema which was noted in 35 cases (25.9%) followed by xerostomy in 31 cases (23%) and hoarseness in 24 cases (17.8%). The voice quality improved in 25 patients (18.5%) in the follow up. It was worsen in 5 cases (3.7%). The quality of voice was not mentioned in the rest of the files.

## Discussion

In this study, we evaluated only the patients who received definitive treatment for laryngeal carcinomas. There was not a control group who had total laryngectomy. So, the comparison of survival, local control, and treatment toxicity could not be available.

The mean overall survival of 51 months in early stages and 30 months in advanced stages were obtained with organ saving treatment. Also, the mean disease free survival was 37 months in early-staged patients and 17 months in locally advanced cases which is of great value.

Several studies have compared definitive larynx preserving treatment modalities with surgery. Mlynarek et al. (2006) compared radiotherapy versus surgery as treatments for T1-T2 glottic cancers in terms of local and regional control, complications, cost and voice outcome. There were 12 patients in surgery group and 26 cases in RT group. The recurrence rate following primary treatment was 37.5% for surgery group and 22% for RT group. Patients in the surgery group presented with 25% of local complications (vocal fold scars) and no systemic complications. In the RT group, local and systemic complications were 35% and 27%, respectively. Although the cost of treatment with radiotherapy was five times higher than the cost of surgery, vocal fold function assessed by videostroboscopy was superior in the RT group (Mlynarek et al., 2006).

In our retrospective analysis, local recurrence occurred in 40% of the early-staged patients who received larynx saving treatment. As there were 58 patients with early lesions, this local rate could be comparable to the study of Mlynarek et al. (2006).

In the study by Rudat et al. (2004), concomitant radio - chemotherapy (platinum/5FU) led to superior local control and larynx preservation rates compared to induction chemotherapy followed by radiation (Rudat et al., 2004).

The mean total radiation dose significantly affected the tumor control in the CRT group, but it did not affect the recurrences in the RT group. It might be reasonable, because higher total dose of radiation was administered in the CRT group due to more

Stage Treatment modality	Early	Advanced	Total
RT <sup>1</sup> group	52	34	86
CRT <sup>2</sup> group	6	55	61
Total	58	89	147

<sup>1</sup>Radiation therapy only

<sup>2</sup>Concurrent chemoradiation

**Table 1:** The stage of the tumor and the treatment the patients received.

advanced staged lesions.

In Hinerman et al. (2007) published a single institution's 35-year experience in which 109 patients with T3-T4 glottic SCC were treated with external beam irradiation. Locoregional control for stage III and IVA were 62% and 78% and overall survival for stage III and IVA were 52% and 67%, respectively. Severe complications occurred in 13 cases (12%) (Hinerman et al., 2007). In our study, local control rate was 43.5% in the locally advanced cases. As there were only 89 cases with advanced-staged lesions, the statistic analysis results could not be comparable. Also, in our study the tumoral site was not only the glottic region.

The common toxicities during the treatment course were dermatitis, mucositis, hoarseness, and sore throat that were noted in 87.8% of the patients. The late effects were observed in 62.2% of the patients, but they were not life threatening. The most common long term complications were laryngeal edema, xerostomy, and hoarseness. There was no treatment complication in 21.5% of the cases. The voice quality improved in 25 patients (18.5%) in the follow up. Also, only two of the patients with locally-advanced disease in the RT group needed salvage surgery due to the local failure.

Evidence supports the use of larynx-preserving approaches for appropriately selected patients without a compromise in survival; however, no larynx-preservation approach offers a survival advantage compared with total laryngectomy and adjuvant therapy with rehabilitation as indicated (Pfister et al., 2006).

According to American Society of Clinical Oncology (ASCO) clinical practice guideline for the use of larynx-preservation strategies in the treatment of laryngeal cancer, all patients with T1-T2 laryngeal cancer should be treated, at least initially, with intent to preserve the larynx. T1-T2 laryngeal cancer can be treated with radiation or larynx-preservation surgery with similar survival outcomes. Selection of treatment depends on patient factors, local expertise, and the availability of appropriate support and rehabilitative services. Every effort should be made to avoid combining surgery with radiation therapy because functional outcomes may be compromised by combined-modality therapy; single modality treatment is effective for limited-stage, invasive cancer of the larynx (Pfister et al., 2006).

Organ-preservation surgery, concurrent chemoradiation therapy, and radiation therapy alone, all with further surgery reserved for salvage offer potential for larynx preservation without compromising survival for advanced stage (T3, T4) primary site disease. Anticipated success rates for larynx preservation, associated toxicities, and suitability for a given patient will vary among these approaches. Selection of a treatment option will depend on patient factors, local expertise, and the availability of appropriate support and rehabilitation services. All patients should be evaluated regarding their suitability for a larynx-preservation approach, and they should be apprised of these treatment options. Concurrent chemoradiation therapy offers a significantly higher chance of larynx preservation than does radiation therapy alone or induction chemotherapy followed by radiation, albeit at the cost of higher acute in-field toxicities (Pfister et al., 2006).

## Conclusion

It seems that radiotherapy with or without chemotherapy can be an appropriate alternative to total laryngectomy in preserving of the larynx in different stages of laryngeal cancers.

It is important to realize that many management questions have not been comprehensively addressed in randomized trials and guidelines cannot always account for individual variation among patients. There are no validated markers that consistently predict outcomes of larynx-preservation therapy. Selection of therapy for an individual patient requires assessment by a multidisciplinary team, as well as consideration of patient comorbidity, psychosocial situation and preferences, and local therapeutic expertise (Pfister et al., 2006).

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