

Recurrence Rate in Post Irradiated T1 and T2 Supraglottic and Glottic Carcinoma of the Larynx

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Abstract

Background: T1 and T2 carcinoma of the supraglottis and glottis can be treated by radiation or conservative surgery. Our aim was to study the recurrence rate following treatment with radiation alone, the sites of involvement, the risk factors involved and to assess the hemoglobin (Hb) levels in relation to the prognosis and treatment outcome.

Materials and Methods: A total of 61 patients with T1 and T2 laryngeal carcinoma were enrolled for this purpose. One succumbed to death due to unrelated cause. All the patients were given external beam radiation and followed up for 3 years. Association of risk factors like smoking and alcohol were recorded and the pretreatment Hb levels were checked.

Results: Local control rate at the end of 3 years was as follows: 53.57% for T1 and T2 supraglottic cancer and 87.5% for T1 and T2 glottic cancer. A maximum number of recurrence was found to be with infrahyoid supraglottic cancer. Parameters such as tumor extent and TNM staging, pretreatment Hb levels, histological differentiation, and continuance of risk factors significantly influenced the recurrence rate on univariate analysis, but by logistic regression table, significant *p* value was obtained only in the higher recurrence rate for infrahyoid supraglottic carcinoma, when compared to the other sites of the larynx.

Conclusion: Early T1 and T2 laryngeal cancers can be treated by radiotherapy or surgery. The choice of therapy is dependent on both patient and treatment institution related factors. While T1 and T2 glottic cancers had a control rate by radiotherapy comparable to that by surgery, infrahyoid supraglottic cancers had a higher rate of recurrence by radiotherapy. Conservative partial laryngectomy, transoral laser surgery or other alternative techniques in radiotherapy may be considered in treating these tumors.

Key words: Carcinoma, Glottis, Radiotherapy, Recurrence, Supraglottis

INTRODUCTION

Laryngeal cancers are considered to be the 11th most common malignancy of the head and neck cancers¹ and constitute about 25% of all head and neck malignancies. Adult males are more commonly affected, but the male to female ratio has come down significantly, over the recent past from 15:1 to less than 5:1.² More than 90% of these cancers are squamous cell carcinomas (SCC). Tobacco smoking and alcohol consumption are important risk factors for SCC of the larynx.³

The larynx is divided into the following three anatomical regions.⁴

- The supraglottic larynx includes the epiglottis, false vocal cords, ventricles, aryepiglottic folds, and arytenoids.
- The glottis includes the true vocal cords and the anterior and posterior commissures.
- The subglottic region begins 5 mm below the free margin of the true vocal cords or 10 mm below the apex of the ventricle and extends to the lower border of the cricoid cartilage.

The incidence and the preferential involvement of the site varies geographically. Glottic tumors predominate in the Anglo-Saxons, while the glottic cancers and supraglottic tumors equal in number approximately among the Indians and French populations.¹

Early laryngeal cancers are treated with either radiation or transoral laser surgery or conservative partial laryngectomy

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procedures, while advanced tumors require combined modalities of treatment.⁴

In the present study, patients who had undergone radiation alone were selected to determine the recurrence rate in the post irradiated cases of T1 and T2 supraglottic and glottic laryngeal cancer lesions. The influence of risk factors, the hemoglobin (Hb) levels, and the surgical options in the treatment of early laryngeal carcinoma are discussed.

OBJECTIVES

1. To study the incidence of recurrence in early supraglottic and glottic carcinoma of larynx following treatment with radiation
2. To assess the effectiveness of radiation therapy in early laryngeal carcinomas.
3. To study the risk factors and to assess the Hb levels in relation to the prognosis and treatment outcome.
4. To study the treatment modalities that are presently used in the management of early supraglottic and glottic carcinoma of the larynx.

Inclusion Criteria

1. T1 and T2 N0 supraglottic and glottis carcinoma of the larynx.
2. Patients in the age group between 30 and 80 years were included in this study. Below 30 years incidence of laryngeal malignancy is less. Above 80 years, the treatment options may differ due to associated comorbidities. Both sexes were included.

Exclusion criteria

1. Suspected cases of benign lesions and tumors are excluded after tissue diagnosis.
2. Those presenting with neck lymph node metastasis as the staging of cancer becomes advanced.
3. Patients who developed a second primary during the study period to be excluded.
4. Subglottic cancer patients due to the rarity in presentation in early stages.

MATERIALS AND METHODS

The present study was approved by the Ethical Research Committee of the institution.

A prospective study of 3 years, between April 2010 and March 2014, patients with T1 and T2 N0 supraglottic and glottis laryngeal cancers, who attended the ENT and Radiology Departments, at MCH, Vandanam, Alappuzha, Kerala, India were enrolled after getting the informed consent to participate in this study. The patients were

divided into subgroups according to the TNM classification and to the site of involvement.

Staging of laryngeal cancer was according to the TNM classification designated by the American Joint Committee of Cancer.⁴

Supraglottis T1 - Tumor limited to one adjacent subsite of the supraglottis without fixation of the larynx.

Supraglottis T2 - Tumor invades mucosa of more than one subsite of supraglottis or glottis or region outside the supraglottis (e.g. mucosa of the base of tongue, vallecula, medial wall of pyriform sinus) without fixation of the larynx.

Supraglottic lesions were further classified into T1 and T2 suprahoid and T1 and T2 infrahyoid lesions.

Glottis tumor limited to vocal cord(s) (may involve anterior and posterior commissure with normal mobility.

T1a - Tumor limited to one vocal cord

T1b - Tumor involves both vocal cords

T2 - Tumor extends to supraglottis and/or subglottis and/or with impaired vocal cord mobility.

61 patients were enrolled for the study purpose. 1 patient had succumbed to death due to an unrelated cause during the study. The patients were categorized under T1 and T2 suprahoid, T1 and T2 infrahyoid supraglottic cancers, and T1a T1b and T2 glottic cancers.

Risk factors in the personal history of the patients were recorded, notably alcoholism, smoking and the duration of the abuse. Pretreatment Hb levels were recorded. All the patients were subjected to indirect laryngoscopy and flexible pharyngolaryngoscopy. Computed tomography (CT) neck was taken for all patients. Magnetic resonance imaging (MRI) was done in patients who needed further evaluation on submucosal invasion, cartilage infiltration, involvement of anterior commissure, pre-epiglottic and paraglottic space invasion, which were mandatory for the staging of the tumors. Direct laryngoscopy was done and biopsy specimen was sent to our Pathology Department for histopathological confirmation of SCC.

External beam radiation therapy was administered by standard fractionation modality.⁴ Telecobalt radiation therapy of 66-70 gray in 33-35 fractions for 5 days a week were administered to the patients. The radiation therapy portal extended from the thyroid notch to the inferior border of the cricoid cartilage, the field ranging from 4 cm × 4 cm. The follow-up during the first 6 months was

carried out both at the ENT OP and Radiotherapy OP to assess the post radiation edema and any residual lesion at the primary site. Patients were evaluated at 3 months intervals during the first 1 year and at 6 months intervals during the subsequent period of follow-up or earlier if the patient had any specific complaints after completion of the external beam radiation therapy. Return of hoarseness, pain, increase in edema at the radiation site, fixity of a previously mobile vocal cord, metastatic lymph node were all considered suspicious of recurrence.

Clinically, all patients were assessed by indirect laryngoscopy and flexible pharyngolaryngoscopy. Those who presented with suspicious lesions were sent for radiological studies like CT scan and or MRI to know if there was deep infiltration and also to differentiate between post radiation edema and the mass lesion. As MRI gives a much better soft tissue contrast than with CT and has a higher sensitivity than CT, it is a better choice when it comes to imaging doubtful cases of cartilage and submucosal invasion.³ Though positron emission tomography is most helpful to differentiate between a recurrent tumor and post irradiation sequelae, it was not advocated, being not cost effective⁵ and locally not available.

As the incidence of distant metastasis from laryngeal carcinoma is related to the N stage, screening was not done in these patients for distant metastasis with early laryngeal carcinoma.⁵

Patients with suspected recurrent lesions were subjected to direct laryngoscopy and biopsy for histopathological confirmation. Continuation of the risk factors even after radiotherapy treatment was recorded. A statistical analysis was performed using SPSS software version 16.6.

RESULTS

Among the 60 patients, the maximum number of cases presented between 61 and 70 years of age group, 10 with supraglottic cancer and 16 with glottis cancer, the total number being 26 (Table 1).

28 cases had supraglottic T1 and T2 malignancy, 8 with suprahyoid T1 lesions, 5 with suprahyoid T2, 5 infrahyoid T1 lesions and 10 infrahyoid T2 lesions. 32 patients had T1 and T2 glottic malignancies, 18 T1a, 12 T1b and 2 T2 malignancy (Table 1).

On histopathology, 34 patients presented with well differentiated and 26 with moderately differentiated SCC.

A total of 19 cases had recurrence in the first 3 years giving a local recurrence rate of 31.6%. 78.9% ($n = 15$) cases

were supraglottic and 21% cases ($n = 4$) were glottis cancer recurrence. Out of 13 T1 and T2 suprahyoid supraglottic cancer patients, 2 cases had a recurrence. Whereas, 13 out of 15 T1 and T2 infrahyoid supraglottic cancer patients went on to recurrence, giving an overall recurrence rate of 53.57% for supraglottic cancers. The recurrence rate of T1 and T2 glottic malignancy was only 12.5%.

The first case of recurrence was noted at the 9th month, which was of a T2 infrahyoid supraglottic cancer. A maximum number of recurrence cases ($n=8$) was noted at 18 months among whom, 6 were supraglottic and 2 were glottic laryngeal cancer (Table 2).

The subsite which had maximum recurrence was T2 infrahyoid cancer ($N = 8$) (Table 2). Among the 19 cases of recurrence, 11 were of moderately differentiated and 8 were of well-differentiated SCC.

All the patients were smokers and alcoholics for years with an average of 33.8 years. Among the 19 patients with recurrence, 15 had continued the risk factors of smoking and alcohol throughout the study. Poor Hb levels were found in 15 cases of recurrence.

Association of the recurrence positive and negative cases with the sites of lesions, risk factors, Hb levels, and histopathology were calculated by univariate analysis using Chi-square's test and Fisher's test. Results are given in Tables 3 and 4.

Out of the 13 cases of suprahyoid supraglottic cancer, only 15.4% ($n = 2$) had recurrence, while 86.7% ($n = 13$) of patients out of 15 with infrahyoid supraglottic cancer showed recurrence which was found to be significant. Furthermore, there was a significant increase in the rate of recurrence in supraglottic cancers when compared to glottis cancers (Table 3).

Continuing smoking and alcohol intake significantly increased the rate of recurrence in laryngeal cancer in this study (Table 4). Association between Hb levels with recurrence is given in Table 4. Poor Hb levels at the time of radiotherapy had an increased rate of recurrence. Histopathologically well-differentiated carcinoma had less recurrence than moderately differentiated carcinoma (Table 4) which was not found to be statistically significant.

But when the above factors which were found to be significant from univariate analysis (Chi-square and Fisher's exact test) when put into the logistic regression model, only the fact that recurrence was higher in infrahyoid tumors than suprahyoid tumors of supraglottic carcinoma was significant at a p value of 0.025, odds ratio 0.03 (confidence interval, 0.001-0.65).

Table 1: Age group distribution of carcinoma of the larynx in relation to the different subsites of the supraglottis and glottis

Age group	Number of patients with supra glottic suprahyoid T1	Number of patients with supra glottic supra hyoid T2	Number of patients infra glottic infra hyoid T1	Number of patients with infra glottic infra hyoid T2	Number of patients with glottic T1a	Number of patients with glottic T1b	Number of patients with glottic T2	Total number of patients with supraglottic malignancy	Total number of patients with glottic malignancy
31-40	Nil	Nil	Nil	1	Nil	Nil	Nil	1	
41-50	1	Nil	Nil	Nil	3	Nil	Nil	1	3
51-60	2	2	2	3	5	1	Nil	9	6
61-70	4	2	1	3	8	6	2	10	16
71-80	1	1	2	3	2	5	Nil	7	7
Total number	8	5	5	10	18	12	2	28	32

Table 2: Correlation of the associated factors in patients of T1 and T2 carcinoma of the larynx who developed recurrence after radiotherapy

Age in years	Site of lesion	Risk factor Tobacco and Alcohol	Duration in years of exposure to risk factor	Hb level	Whether exposure to risk factor was continued	HPE type Squamous cell carcinoma differentiated	Recurrence period in months
54	1	Present	31	Good	Yes	Well differentiated	18
67	7	Present	26	Poor	Yes	Well differentiated	24
39	6	Present	16	Poor	No	Moderately differentiated	24
74	3	Present	38	Poor	No	Well differentiated	36
64	4	Present	31	Good	Yes	Moderately differentiated	9
60	4	Present	40	Poor	Yes	Moderately differentiated	18
68	7	Present	32	Poor	No	Moderately differentiated	18
71	3	Present	43	Good	Yes	Well differentiated	12
68	6	Present	45	Poor	Yes	Moderately differentiated	18
73	2	Present	46	Poor	Yes	Well differentiated	18
56	4	Present	29	Poor	Yes	Moderately differentiated	36
69	3	Present	39	Poor	Yes	Moderately differentiated	18
69	4	Present	40	Poor	Yes	Moderately differentiated	18
58	3	Present	27	Poor	Yes	Well differentiated	24
69	4	Present	40	Poor	No	Well differentiated	36
59	3	Present	39	Poor	Yes	Moderately differentiated	30
73	4	Present	34	Poor	Yes	Moderately differentiated	18
72	4	Present	39	Good	Yes	Well differentiated	12
71	4	Present	43	Poor	Yes	Moderately differentiated	12

Hb: Hemoglobin, HPE: Histopathological examination

Table 3: Association of the recurrence of T1 and T2 laryngeal cancers with the sites of lesion

Site of lesion	Recurrence positive	Recurrence negative	Marginal row totals
Supraglottic	15 (8.87) [4.24]	13 (19.13) [1.97]	28
Glottic	4 (10.13) [3.71]	28 (21.87) [1.72]	32
Marginal column totals	19	41	60 (grand total)
Chi-square=11.6413	P=0.000645		
Supraglottic suprahyoid	2 (6.96) [3.54]	11 (6.04) [4.08]	13
Supraglottic infrahyoid	13 (8.04) [3.07]	2 (6.96) [3.54]	15
Marginal column totals	15	13	28 (grand total)
Chi-square=14.2272	P=0.000162		

DISCUSSION

Glottic cancers are discovered at a relatively early stage with hoarseness being the initial symptom, while supraglottic

cancers may present late with dysphagia, metastatic lymph node or hoarseness with stridor. Glottis of the larynx is devoid of lymphatic drainage, but the supraglottis is rich in lymphatic drainage.⁴

Suprahyoid lesions of the supraglottis usually produce exophytic masses with little tendency to spread. Infrahyoid lesions of the supraglottis tend to invade the porous epiglottic cartilage and thyroepiglottic ligament onto the pre-epiglottic fat space. They can grow circumferentially to involve the false vocal cords, aryepiglottic fold and medial wall of the pyriform sinus and thyroid cartilage. The frequency of nodal metastasis is at least 20-50%.⁴ Bilateral metastasis is also not uncommon, as supraglottis is a midline structure.⁶

The goals in treating the early stages of cancer of the larynx include cure, voice preservation, and minimal morbidity.

Table 4: Association of the recurrence in T1 and T2 laryngeal cancers with the risk factors, Hb levels and histopathology

Parameters	Recurrence positive	Recurrence negative	Marginal row totals
Risk factor			
Risk factor continued	15 (7.92) [6.34]	10 (17.08) [2.94]	25
Risk factor discontinued	4 (11.08) [4.53]	31 (23.92) [2.1]	35
Marginal column totals	19	41	60 (grand total)
Chi-square=15.8995	P=0.000067		
Hb level			
Good Hb level	4 (11.4) [4.8]	32 (24.6) [2.23]	36
Poor Hb level	15 (7.6) [7.21]	9 (16.4) [3.34]	24
Marginal column totals	19	41	60 (grand total)
Chi-square=17.5738	P=0.000028		
Histopathology			
Well-differentiated	8 (10.77) [0.71]	26 (23.23) [0.33]	34
Moderately well differentiated	11 (8.23) [0.93]	15 (17.77) [0.43]	26
Marginal column totals	19	41	60 (grand total)
Chi-square=2.4009	P=0.121264		

Hb: Hemoglobin

Considering the important role the larynx plays in speech, measures have to be taken to preserve the function of the larynx as well treating cancer. Radiotherapy, chemotherapy, conservative laryngeal surgeries, transoral laser surgeries are nowadays being considered against total laryngectomy.⁴

Both radiotherapy and surgery (transoral laser surgery or conservative laryngeal surgery) are advocated in treating T1 and T2 laryngeal carcinoma with equally good results. The selection of treatment usually depends on the location and site of the tumor, occupation of the patient (professional voice users), facility available at the hospital, general medical fitness of the patient and the choice made by the patient.⁶

The local control rates after treatment for T1-T2 laryngeal cancer vary. The most important parameter that influences the local control after RT is the tumor extent and staging. Other factors that are likely to influence are tobacco and alcohol abuse, histologic differentiation, pretreatment Hb, sex and p53 etc.⁶

Tobacco smoking and alcohol intake are the most important etiological factors. Both can act synergistically and independently. Even after stopping the abuse, the chance of developing laryngeal SCC, still remains high when compared to lifelong nonsmokers with a 3 fold risk.⁷ Alcohol might promote carcinogenesis through acetaldehyde exposure, malnutrition, and desiccation of mucosa. Polycyclic hydrocarbons like benzopyrene are the main culprits in tobacco in promoting carcinogenesis.¹

An association between a low Hb-content and a poor response on radiation therapy has been established in patients with SCCs. Pre-treatment poor Hb levels and poor levels at the end of treatment have been found to reduce the disease-free survival period after radiotherapy.^{8,9}

Histologic differentiation also influences the local control rate, with better prognosis for well differentiated than for poorly differentiated carcinoma.⁶

The increasing T stage and N stage are the most important prognostic factors for laryngeal cancers. Tumor bulk, submucosal invasion, deep tissue and cartilage invasion affect the prognosis adversely.¹⁰

Tumors involving the infrahyoid supraglottis tend to be aggressive, with frequent pre-epiglottic space involvement and deep tissue infiltration. Recurrence occurs in 40-50% of cases.^{11,12}

In our study, local control rate of 68.3% was achieved for both supraglottic and glottic T1 and T2 malignancy at the end of 3 years with a local control rate of 53.57% for supraglottic cancer and 87.5% for glottis cancer. Supraglottic infrahyoid cancers had the maximum number of recurrence ($n = 13$). Recurrence of laryngeal cancer was associated with the tumor extent, poor Hb levels, histological differentiation and continuing smoking and alcohol which was significant at univariate analysis. But on logistic regression, recurrence was significantly higher with infrahyoid than suprahyoid suprahglottic carcinoma.

The reasons for irradiation failure in SCC of the larynx may be due to geographical miss due to undiagnosed extensions, inadequate technique to assure daily coverage of the tumor, inadequate dose for larger tumor volume, poor penetration of hypovascular tissue and in deep infiltration with fixation, the possibility of new cancer instead of recurrence.¹³

Standard fractionation was the radiation schedule used in this study. Hyperfractionation and accelerated fractionation with concomitant boost schedule may yield better control of tumor recurrence.^{4,14}

LIMITATIONS

1. A small group of patients were studied. Statistical significance of the risk factors could not be assessed.
2. Prognostic factors like p53 were not included in the study.
3. A comparative study with surgical treatment of T1 and T2 laryngeal cancers could not be done.
4. Only one modality of radiation schedule was

administered for all cases which may have affected the outcome result.

5. The neck was not irradiated in T2 supraglottic carcinoma, which may have led to the increased recurrence due to occult metastasis.
6. The role of concurrent chemoradiotherapy was not explored.

Those patients who had recurrence were advised conservative laryngeal surgery.

Since larger tumor volume ($>5 \text{ cm}^3$), impaired vocal cord mobility and infrahyoid lesions had a better result with conservative surgery in the literature, these patients may be considered for conservative partial laryngectomy or transoral endoscopic laser surgery as the first line of management. Also as supraglottic lesions present with occult nodes, selective neck dissection may also be advised. Poor Hb levels, long duration of smoking and alcohol adversely affect the prognosis. Improvement of nutritional status and cessation of these risk factors will definitely improve the outcome of treatment by radiotherapy.

CONCLUSION

A multidisciplinary approach is necessary for the management of laryngeal cancer. Both radiotherapy and conservative laryngeal surgery can be advised for T1 and T2 supraglottic and glottis lesions of laryngeal malignancy. The choice of therapy depends on patient factors like occupation (professional voice user), duration of treatment, pulmonary reserve status and the place of treatment. Radiotherapy may be preferred for patients who are professional voice users, those with poor pulmonary reserve and with high anesthesia risk. Large tumor volume, deep tissue invasion, impaired vocal cord mobility, infrahyoid supraglottic lesions which have the potential to involve the adjoining pre and paraglottic spaces may be managed with transoral endoscopic laser surgery or with conservative partial laryngectomy. All the patients in this study had undergone external beam irradiation. Other radiation techniques like hyperfractionation may be tried in early laryngeal cancers to improve the local control rate.

Those who continued the personal habits of smoking and consuming alcohol had a higher recurrence rate than those who discontinued. It was also noted that poor Hb levels were a poor prognostic factor in the treatment of laryngeal cancers. Educating patients over these factors can considerably bring up the local control rate, irrespective of the choice of treatment.

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