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"Rare Head and Neck Tumors"

Systematic Review

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Laryngeal Paraganglioma: A Review Article

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ABSTRACT

Background: This study reviews the published literature related to the condition of laryngeal paraganglioma. Clinical presentation, demographics, treatment, and outcomes of this uncommon disease have been reported.
Methods: A systematic review of studies for laryngeal paraganglioma from 1996 to 2016 was conducted. A PubMed database search, both for articles related to this condition along with bibliographic records of related research, was performed. Articles reporting clinical data of patients who indicated the disease outcome were carefully examined.
Results: Fifty-three journal articles were included in this analysis, comprising a total of 58 reported cases. External surgical approach was the most common treatment modality applied in 47 cases, followed by endoscopic surgical approach, and radiotherapy alone. Following the treatment, the 2-year and 5-year overall survival rates were recorded as 96.9% and 91.5%, respectively; while, the overall local control rates recorded over a period of 2 years and 5 years were 81.2% and 74.4% respectively. The local control rate was significantly higher in patients treated with the external surgical approach.
Conclusion: This review contains the largest pool of information relevant to the patients reporting laryngeal paraganglioma recorded till date and indicates the effectiveness of the external surgical approach as the appropriate treatment modality for this condition.

KEY WORDS: Laryngeal paraganglioma; Head and neck paraganglioma; Laryngeal tumor; Paraganglioma; Radiotherapy; Surgical management.

INTRODUCTION

In 1955, Blanchard et al[1] reported the first case of laryngeal paraganglioma. Since then, around 130 cases of this condition have been reported. In 1994, Ferlito et al[2] suggested that some reported cases of laryngeal paraganglioma were in fact atypical carcinoid tumors, carcinoid tumors or small cell neuroendocrine carcinomas and accepted 62 of the total reported cases as that of paraganglioma. Paragangliomas are rare neuroendocrine tumors that originate from paraganglion cells located in the sub-mucosal layer of the larynx. Paragangliomas are known to appear in two forms: Sporadic and familial. Multi-centric forms of head and neck paragangliomas are usually a result of the familial paraganglioma syndrome. However, laryngeal involvement is very rare, especially in the case of multi-centric type paraganglioma 13.

The purpose of our article is to review the literature investigating the multiple reported cases of laryngeal paraganglioma.

MATERIALS AND METHODS

Search Strategy

A systematic review was conducted for all the reported cases of laryngeal paraganglioma recorded from 1996 to 2016 using the PubMed database. The search criteria was put as "laryngeal paraganglioma", "laryngeal chemodectoma", "laryngeal glomus", and "laryngeal neuroendo-

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crine tumor". Initially, 819 articles were obtained which were then filtered to exclude non-human research. Next, the abstracts were reviewed to search for full-text articles that discussed different cases of laryngeal paraganglioma, and reviewed for the extraction of data relevant to the case. References of the included studies were examined for the additional cases.

Selection Criteria and Data Extraction

All human studies that reported data for individual cases of laryngeal paraganglioma, were included in the study if reported diagnosis, treatment, follow-up, and outcome. Non-human radiologic, cadaveric, anatomical, and histological studies were excluded. Being sources with insufficient or unextractable data, articles with unobtainable full text were also excluded.

Outcome measures extracted included: Demographic data, presenting symptoms, tumor size, angiography results, primary treatment modality, recurrence, and metastasis.

Two and five-year overall survival (OS) and tumor local control were calculated using the Kaplan-Meier method. Differences in the local control rates were assessed by the log-rank test. All *p*-values were two sided, and a *p*-value <0.05 was taken as the standard for recording the threshold for significance (Figure 1).

RESULTS

The final PubMed searches using the keywords yielded 53 studies recording the case of a total of 58 patients yet to be examined. All 53 studies included individual patient data that was extractable and fit the minimum criteria for inclusion (Table 1).

Demographics

Patient demographics for the 85 patients included in this review have been summarized in Table 2. The mean age of patients was 50.21 years, ranging from 5 to 85 years. Males were associated with 29% of the reported cases, whereas females constituted nearly 71% of the reported cases. There was a family history of the reported medical condition in 7% of the patients. 13% of the patients indicated the symptoms of multiple paraganglioma, carotid body tumor being the most common associated form of paraganglioma. The most commonly occurring symptom for this condition was hoarseness for 64% of the cases. Seventy-six percent of the patients had paraganglioma in the supraglottic area whereas 14% of the patients were affected in the subglottic area.

The mean size of the supraglottic tumor was 2.82 cm, while the mean size of subglottic tumor was 1.91 cm. Using *t*-test, the mean size of supraglottic tumor was significantly higher than the mean size of the subglottic tumor ($p<0.05$).

Further demographic information has been summarized in Table 2.

Treatment Modalities and Outcome

The majority of patients, nearly 81% (n=47) were treated with the external surgical approach, 16% of the patients (n=9) were treated with the endoscopic approach. The remaining two patients received only RT (n=2) which constituted nearly 3% of the reported cases. Further information regarding the treatment modality has been summarized in Table 3.

Patient outcomes in this study were classified as either alive with no evidence of disease (ANED), alive with disease (AWD), died of disease (DOD), and died but not due to the disease (D) (Table 2).

Overall outcome was generally favorable, as 42 patients (91%) were alive with no symptomatic evidence of the disease and 2 patients (4%) were reported as alive with the diseased condition after a median follow-up of 27 months. A total of 2 patients (4%) died, among which only one patient (2%) died

Figure 1: Flowchart of the Study Selection Process.

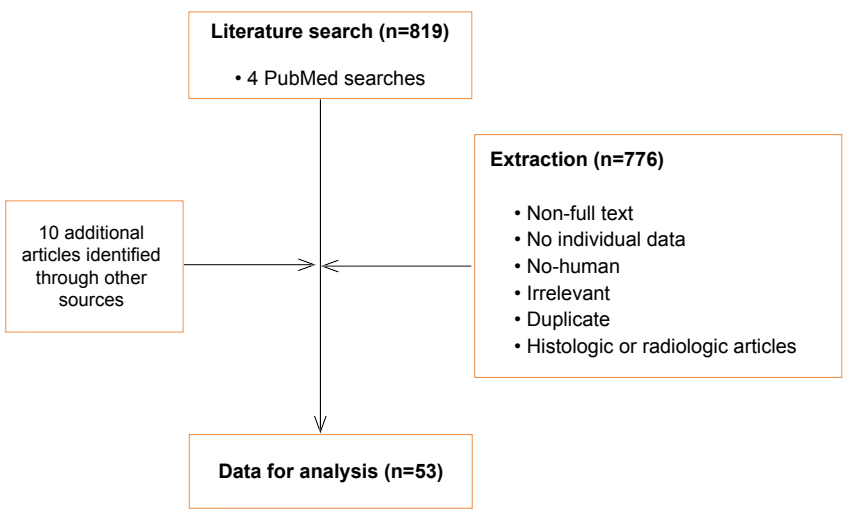

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Table 1: Laryngeal Paraganglioma Articles.

Article (s)	Age/ Sex	Symptoms duration	Symptoms	Location	Size	Surgery	Follow-up	Others
Ozunlu et al[3]	55/F	1 year	Hoarseness Dyspnea Globus Stridor	R Supraglottic R ventricle	3x2.5 cm	External surgery, laryngofissure	Dead 10 days due to MI	
Peterson et al[4]	52/F	3 months	Hemoptysis	Subglottic	1.3x1.5 cm	External surgery. Partial laryngectomy	N/A	
Thirlwall et al[5]	5/M	2 months	Stridor Hoarseness	R Supraglottic	N/A	Endoscopic Laser CO_2	Recurrent 1.6 year, then supraglottic laryngectomy NED 3 months	
Buiret et al[6]	76/M	1 year	Hoarseness	R Supraglottic R Ventricle	3,3x3 cm	External surgery, Lateral pharyngectomy	N/A	Family positive
Berta et al[7]	40/M	6 months	Snoring Hoarseness	L Supraglottic L Ventricle	N/A	External surgery Supraglottic laryngectomy	N/A	
Rubin et al[8]	55/M	4 months	Neck mass Dysphonia Otalgia Hoarse-ness Stridor	L supraglottic L aryepiglottic fold	N/A	External surgery	NED 1 Month	Multifocal carotid tumor
Khan et al[9]	37/M	2 days	Stridor Dyspnea Neck mass	Subglottic	2x2 cm	External surgery, Airway reconstruction	NED 5 year	
Aribas et al[10]	77/M	10 years	Dyspnea Stridor Neck mass	Subglottic	0.8x1.1x1.3 cm	External surgery	NED 2 years	
Solarez et al[11]	67/F	N/A	Hoarseness	Glottis	N/A	External surgery, Total laryngectomy	NED 2 years	
	50/F	N/A		L supraglottic	N/A	External surgery, Supraglottic laryngectomy	Recurrent 8 months, then Total laryngectomy. Metastasis 8 month, Dead 16 months	Malignant
	85/F	2 years	Cough Hoarseness Dysphagia Aspiration	L supraglottic L aryepiglottic, Epiglottis, Fales vocal cord	N/A	Radiation	AWD 5 years	
	39/F	N/V	Dyspnea Stridor	Glottis	2.5x6x3 cm	External surgery, Supraglottic laryngectomy	NED 10 months	
Khademi et al[12]	45/F	6 months	Hoarseness Dyspnea	L supraglottic	4x 3 cm	External surgery Lateral pharyngectomy	NED 2 years	
Dhakhwa et al[13]	60/F	5 months	Hoarseness Globus	R supraglottic	2.5x2.5x2 cm	External surgery, Total laryngectomy	16 month	D/D SMCC
Naik et al[14]	35/M	4 months	Hoarseness Globus Neck mass	L Supraglottic L aryepiglottic fold	3x4 cm	External surgery, Lateral pharyngotomy Partial laryngectomy	NED 2 months	STA main artery
Dogan et al[15]	32/F	1.5 years	Neck mass	R Supraglottic R preepiglottic space	1x1.2 cm	External Surgery	Family history	Family history Multifocal Carotid tumor, STA main artery
Papacharalampous et al[16]	45/F	2 months	Hoarseness Dysphagia	L Supraglottic L aryepiglottic fold	N/A	Endoscopic	NED 16 months	

ISSN 2470-4059 http://dx.doi.org/10.17140/OTLOJ-SE-6-101

Garrel et al[17]	38/F	-----	Incidentally	L Supraglottic L ventricle	N/A	External surgery	NED 2 months,	Succinate dehydrogenase mutation C
Gupta et al[18]	62/F	13 years	Hoarseness Stridor Hemoptysis	Supraglottic Trasnglottic	N/A	External surgery, Total laryngectomy	NED 16 months	
Del Jaudio et al[19]	50/F	6 months	Dysphonia Globus	L Supraglottic L aryepiglottic fold	3 cm	External surgery Laryngeal fissure	NED 2 years	STA main artery
Shilpi Sahu[20]	50/F	1 year	Hoarseness Dyspnea	R Supraglottic R epiglottic, Aryepiglottic fold, False vocal cord	3.2x3.7 cm	External surgery , Total laryngectomy	N/A	
Zhuo et al[21]	40/F	4 years	Hoarseness Globus Snoring	L Supraglottic L arytenoid	3x5x2 cm	External surgery Lateral pharyngectomy	NED 3 months	
Binesh et al[22]	77/F	2 years	Hemoptysis Hoarseness Snoring	R Supraglottic R aryepiglottic	N/A	External surgery, Supraglottic laryngectomy	Ned 7 months	
Shervin et al[23]	34/F	6 months	Hoarseness	L supraglottic epiglottis, Left aryepiglottic fold	1.7x1 cm	External surgery, Through thyrohyoid membrane	Recurrent 1 year	Multifocal Carotid tumor Glomus jugular globus
Pham et al[24]	78/F	1 year	Globus	R supraglottic R aryepiglottic fold extending to the base of the epiglottis	2 cm	Radiation SCC	Recurrent 2 month, then Total laryngectomy, NED 6 months	
Hobson et al[25]	11/F	7 days	Hemoptysis Snoring	L supraglottic L aryepiglottic fold	2 cm	External surgery, laryngofissure	NED 1 month	
Da Santos et al[26]	40/M	6 months	Neck pain Globus Dysphonia	L Supraglottic Left aryepiglottic fold	1 cm	Endoscopic	NED 4 months	
Sesterhenn et al[27]	66/F	5 years	Dysphonia Dysphagia hempoptysis	L supraglottic	N/A	Endoscopic	NED 5 years	
Caplou et al[28]	57/F	6 months	Dysphonia Sore throat Dyspnea	R Supraglottic R areepiglottic	N/A	Endoscopic	N/A	STA main artery
Khalkhali et al[29]	28/M	18 months	Dyspnea	Subglottic	1cm	External surgery, laryngofissure	NED 2 years	
Hahan et al[30]	25/F	N/A	Hoarseness Dyspnea	L Supraglottic L aryepiglottic fold	3 cm	CO2 laser aborted Due bleeding, Supraglottic laryngectomy	NED 1 month	
De Masto et al[31]	30/F	N/A	Hoarseness Dyspnea	Supraglottic	N/A	External surgery, Total laryngectomy	NED 24 months	
Sato et al[32]	41/M	7 years	Sore throat	L Supraglottic L arytenoid, vestibular fold	N/A	Endoscopic	Recurrent 1 year, Then Laryngofissure, Ned 12 year	
Kaytazet al[33]	34/M	6 months	Hoarseness	R Supraglottic R aryepiglottic fold, false vocal cord	N/A	External surgery, laryngofissure	NED 3 years	STA main artery
Samuel et al[34]	51/M	3 months	Pain Globus	R Supraglottic R epiglottis	N/A	Endoscopic	Recurrent 2 timed with 9 year, Last operation Laryngofissure, then NED 1 year	
Sanders et al[35]	69/M	N/V	Hemoptysis	L supraglottic	4 cm	Supraglottic Laryngectomy	Ned 2 months	Multifocal Carotid body tumor
Chol Chang et al[36]	32/F	N/V	Globus	Supraglottic	1x1.6 cm	External surgery laryngofissure	NED	

ISSN 2470-4059 http://dx.doi.org/10.17140/OTLOJ-SE-6-101

Freitas et al[37]	71/F	5 years	Globus	R supraglottic R aryepiglottic	4 cm	Endoscopic	NED 3 years	
García-Martín et al[38]	22/F	3 years	Hoarseness	R Supraglottic R aryepiglottic	3.3x3.2 cm	External surgery	NED 5 months	Multifocal Carotid body tumor
Daza et al[39]	45/F	2 years	Cough Sore throat Dysphonia	L Supraglottic L aryepiglottic	N/A	Supraglottic laryngectomy	N/A	
	47/F	3 years	Dysphonia Dyspnea Stridor	Supraglottic	3x2.5 cm	External surgery laryngofissure	N/A	
DegenMeotti et al[40]	32/F	1 year	Dysphonia Dyspnea Hemoptysis	Supraglottic R ventricle	N/A	Right Hemilaryngectomy	NED 1 Year	Multifocal Carotid body tumor
Caballero et al[41]	58/F	5 years	Hoarseness Dysphagia	L Supraglottic L aryepiglottic	0.3x0.4 cm	External surgery Thyrotomy	N/A	Multifocal Carotid body tumor, STA main artery
Pillson et al[42]	69/F	6 months	Dyspnea Hoarseness	R Supraglottic R aryepiglottic fold, involving the right ven-tricular band	N/A	Supraglottic laryngectomy	NED 3 years	
Arslanoğlu et al[43]	68/M	6 months	Dyspnea Hoarseness	Transglottic R Supraglottic	1.2x2 cm	External surgery, Total laryngectomy	NED 8 years	
Bagii et al[44]	64/F	2 months	Hoarseness Dyspnea	Supraglottic	3x4 cm	External surgery	NED 3 months	
Sharma et al[45]	40/M	6 months	Hoarseness Dyspnea Choking	L supraglottic	2.6x2.3 cm	External surgery, Suraglottic laryngectomy	N/A	
Squillaci et al[46]	48/F	N/A	Hoarseness	R Suprglottic R aryepiglottic, False vocal cord.	2 cm	Endoscopic	NED 66 months	
Roman et al[47]	65/M	N/A	Hoarseness	Supraglottic	N/A	External surgery, Supraglotic Laryngectomy	NED 1 year	
Myssiorek et al[48]	74/F	N/A	N/V	N/V	3 cm	External surgery, Lateral laryngotomy	NED 2 years	
Maisel et al[49]	78/F	4 days	Dyspnea	Subglottic	1.5x2 cm	External surgery, Resection Cricoid split	NED 3 years	
Hinjora et al[50]	51/F	2 years	Dyspnea Stridor Neck mass	Subglottic	3 cm	External surgery, 3 year recurrence Excision Airway reconstruction	NED 4 years	
Brown et al[51]	47/F	N/A	Hoarseness	L supraglottic	2,5 cm	External surgery, Supraglottic laryngectomy	NED 9 years	
	74/F	N/A	Hoarseness	L supraglottic	N/V	External surgery, Lateral thyrotomy	NED 5 years	
Schmit et al[52]	33/M	N/A	Neck mass	Subglottic	3x3x2.5 cm	External surgery	N/V	Family history Multifocal Carotid body tumor, skull base Right ear
Hall et al[53]	50/F	1 year	Neck mass	Glottis	1.6x1.5 cm	External surgery	AWD 6 months	Family history, Lymph node. Multifocal, Carotid body, tumor Skull\ base tumor, Malignant, Succinate hydrogenas c mutation

ISSN 2470-4059 http://dx.doi.org/10.17140/OTLOJ-SE-6-101

Leung et al[54]	40/F	2 weeks	Dyspnea Cough Hemoptysis	Subglottic	1x1.5 cm	External surgery	N/A
Khalil et al[55]	63/F	3 years	Hoarseness Chocking Dysphagia	R supraglottic R aryepiglottic	N/A	External surgery Through Thyrohyoid Membrane	N/A

Table 2: Patient Characteristics.

Cases, n	58
Demographics	
Age, years, mean (range)	50 (5-85)
Gender	
Male	17 (29%)
Female	41 (71%)
Symptoms duration, mean (range)	20 m (2 days - 13 years)
Family history	4 (7%)
Multi-centric paraganglioma	9 (13%)
Succinate dehydrogenase mutation	2 (3%)
Functional tumors	Absent
Presenting symptoms in only 56 article	
Hoarseness	36 (64%)
Dyspnea	19 (34%)
Globus	10 (15%)
Hemoptysis	8 (12%)
Stridor	7 (12%)
Neck mass	7 (12%)
Dysphagia	5 (7%)
Snoring	4 (7%)
Aspiration	3 (5%)
Sore throat	3 (5%)
Neck pain, ear pain, cough	5 (7%)
Tumor size, cm, mean, range	2.62 (0.4-8 cm)
Site	
Supraglottic	44 (76%)
Glottis	3 (5%)
Subglottic	8 (14%)
Transglottic	2 (4%)
N/V	1 (1%)
Follow-up, months, mean (range)	27 (1-156)
Outcome	
NED (no evidence of diseae)	42
AWD (alive with disease)	2
DOD (dead of disease)	1
D (dead of other disease)	1
N/A (Non-Available)	12
Follow-up measures	
Recurrence	7 (12%)
Malignant	2 (3.5%)

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Table 3: Recurrence.

M	F	
3/17 (18%)	4/41 (9%)	
Subglottic	Supraglottic	
0/8 (0%)	7/44 (16%)	
Age>40	Age<40	
2/16 (12%)	5/44 (11%)	
Endoscopic	External	Radiation
3/9 (33%)	2/47 (4.2%)	2/2 (100%)

from the disease. Only two patients showed the symptoms of malignant paraganglioma (3%), one of them was reported as dead from the disease while the other patient was reported alive in spite of the diseased condition. (Table 2)

Using the Kapaln-Meir test, the 2-year and 5-year overall survival rates were recorded as 96.9% and 91.5%, respectively. The 2-year and 5-year disease-specific survival rates were recorded as 100% and 94.4%, respectively. Using log rank test, there was no statistically significant difference in survival due to the influence of gender, location, and age.

The overall local control rates recorded over a period of 2 years and 5 years were 81.2% and 74.4% respectively. Local control rate in patients treated with the external surgical approach was significantly higher than those patients who were treated with the endoscopic approach ($p<0.05$). Recurrence was observed more often in male patients, following radiation therapy, endoscopic approach and in supraglottic tumors (Table 3).

DISCUSSION

Laryngeal paraganglioma are rare benign neuroendocrine tumors that originate from the neural crest-derived cells of the superior or inferior laryngeal paraganglia. The superior laryngeal paraganglia are located near the superior edge of the thyroid cartilage, whereas the inferior laryngeal paraganglia are usually localized between the thyroid cartilage and the first tracheal ring, occasionally inside the thyroid gland capsula. Ninety percent cases of laryngeal paraganglioma have been observed in the supraglottic area, while 12% are subglottic and 3% are found in the glottis. Laryngeal paraganglioma occur mostly in females with a female-male ratio of 3:1 and they have been studied widely through four to six decades of life.[10,42]

Laryngeal paraganglioma may present clinical symptoms due to the compression of surrounding structures if they are non-functional. The most commonly occurring symptoms of laryngeal paraganglioma are characterized by hoarseness, dyspnea, dysphagia, hemoptysis, throat pain, and airway obstruction. However, in secreting tumor, symptoms of a hyperadrenergic state marked by headache, diaphoresis, palpitations, hypertension, paroxysms, and cardiac, gastrointestinal and metabolic manifestations may be observed. Cases of familial paragangliomas and hypertension should be screened even though they are rarely associated with laryngeal paragangliomas.[42]

MRI is the imaging technique of choice for the diagnosis of laryngeal paraganglioma. Laryngeal paraganglioma shows high T1-enhancement of the lesion after gadolinium injection. Some authors have also advocated the application of preoperative arteriography in combination with selective embolization, in order to reduce intraoperative blood loss to assess the blood supply. Laryngeal paraganglioma usually appear as a non-homogenous tumor receiving blood supply from the superior laryngeal artery, which is a branch of the superior thyroid artery. Like other neuroendocrine tumours, paragangliomas express somatostatin receptors, which may be visualized using somatostatin receptor scintigraphy. Performing a In-111 pentetreotide scan can confirm the neuroendocrine characters of the observed mass.[10,11]

A positive diagnosis of laryngeal paraganglioma depends on the results of the histopathological examination and the immunohistochemical assessment of the mass. The histopathological examination usually reveals that paragangliomas are composed of two types of cell: Chief cells and sustentacular cells. Chief cells are arranged in an alveolar or “Zellballen” pattern which is a characteristic but is not pathognomonic of paragangliomas.

Immunochemistry usually shows that paraganglioma tumors express several neuroendocrine markers such chromogranin, synaptophysin and neuron specific enolase, but are usually negative for epithelial markers such as cytokeratin. The sustentacular cells may express S-100 protein. Paraganglioma needs to be distinguished from haemangioma, typical carcinoid, atypical carcinoid, small cell carcinoma, malignant carcinoma and medullary carcinoma of the thyroid gland. No histopathological criteria have been reported for the differentiation of the benign from the malignant paraganglioma. They are usually recognized as malignant when distant metastasis occurs.[11,49]

Paragangliomas are known to be radioresistant therefore, validating surgery as the treatment of choice for laryngeal paraganglioma. Conservative surgical procedure should be the treatment of choice due to the low recorded rate of malignancy (<2%). The open surgical techniques are preferred over the

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endoscopic techniques, because of reduced exposure and more difficult control of hemorrhagic risk during endoscopy. Several other techniques have been described in this regard which includes procedures such as lateral pharyngotomy, laryngofissure, supraglottic laryngectomy, lateral thyrotomy and endoscopic procedure. Chemotherapy is recommended for the un-resectable or recurrent tumor. Recurrence rate is low but has been reported to occur more commonly following the endoscopic surgery approach. The recurrence rate of laryngeal paragangliomas is about 17%, and has been reported to occur in 80% of the cases of endoscopic surgery.[10]

CONCLUSION

Laryngeal paragangliomas are rare benign neuroendocrine tumors located mostly in the supraglottic area. It should be differentiated from other types of neuroendocrine tumors using immunohistochemical techniques. Paragangliomas are radioresistant, thus, partial laryngectomy is the only effective treatment strategy that ensures preservation of voice functions. However, total laryngectomy should be considered for therapy only in case of large and local recurrence following partial laryngectomy.

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