Perineural Invasion of Superior and Inferior Laryngeal Nerves in Advanced Stage Squamous Cell Carcinoma of the Larynx: A Case Series and Review

Original Investigation

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Abstract

Objective: To evaluate bilateral superior and recurrent laryngeal nerves for tumor spread in patients of advanced-stage laryngeal carcinoma undergoing surgical resection.

Methods: A prospective study was conducted including biopsy-proven cases of laryngeal squamous cell carcinoma (SCC) that were planned for total laryngectomy. Patients with metachronous or synchronous SCC were excluded from the study. All patients underwent total laryngectomy, where both superior and recurrent laryngeal nerves were harvested along with the specimen, and the proximal ends of the nerves were marked for reference. Perineural invasion (PNI) was assessed in nerves within the tumor and in bilateral extra-laryngeal nerves.

Results: The study included 22 patients with a mean age of 58 years. Intra-tumoral PNI was found in 7 of the 22 cases (32%). The free nerve margins of superior and recurrent laryngeal nerves, which were examined from proximal to distal orientation, showed no tumor infiltration in any of the cases.

Conclusion: Perineural invasion of minor nerves constitutes a major pathway of spread. On the contrary, invasion of superior or recurrent laryngeal nerves does not constitute a route for tumor spread. Hence, there is no need to extend the surgical boundary for total laryngectomy to include these major nerves separately.

Keywords: Larynx cancer, squamous cell carcinoma, laryngectomy, recurrent laryngeal nerve, perineural spread

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Introduction

In India, laryngeal cancers account for 3–6% of all cancers in males. The age-adjusted incidence rates of laryngeal cancer vary from 1.26 to 8.18 per 100,000 populations (1). The inconspicuous symptomatology of laryngeal cancers is responsible for late presentation and diagnosis at advanced stages. The treatment for laryngeal cancers has advanced over the last few decades, still, the 5-year survival rates are dismal. Loco-regional recurrence (LRR) rates vary between 30–50% for these advanced laryngeal cancers (2). Various risk factors have been cited for high LRR failure rates, including age, smoking index, initial T stage, tumor grade, nodal metastasis, surgical suitability, and residual disease post treatment (2).

The invasion of the perineural space by tumor cells is an important risk factor for LRR (3). The involvement of the nerve occurs at the terminal endings and may progress to involve the major trunks proximally. Tumor spread along the perineural space has been reported to occur for long distances, which may preclude obtaining a clear surgical margin (4). Perineural invasion (PNI) is an important component of the Brandwein–Gensler et al. (5) pathological risk assessment model for LRR and survival in patients of squamous cell carcinoma (SCC) of the head and neck. Involvement of the major nerves (>1 mm) has been given a score of three and directly places the patient in the high-risk category for LRR, hence, the recommendation of adjuvant therapy in such cases. The larynx is a site where nerve supply is through paired superior and recurrent laryngeal nerves, which are easily identified during surgical resection (6). The tumor may spread along these major nerves distant from the tumor micro-environment constituting perineural tumor spread. We hypothesized that recurrences may, in part, be attributed to the residual tumor along these major nerves.

We conducted a prospective study in a tertiary care hospital in India to find out the incidence of PNI in patients of advanced-stage laryngeal carcinoma undergoing surgical resection. We also aimed to evaluate bilateral superior and recurrent laryngeal nerves for perineural tumor spread in these patients.

Methods

A prospective study was conducted in the Department of Otorhinolaryngology and Head-Neck Surgery of All India Institute of Medical Sciences, New Delhi, India. The study received ethical clearance from the Institute Ethics Committee of All India Institute of Medical Sciences, New Delhi, India (Ref. No. IEC-287/02.06.2017, RP-58/2017, date: 04.07.2017). The study included biopsy-proven cases of laryngeal SCC that were planned for total laryngectomy. Informed written consent was obtained from the participants. The clinical and demographical details of all the patients were collected in the proforma. All patients underwent physical examination and radiological evaluation in the form of contrast-enhanced computed tomography of the cervical and thoracic regions with or without contrast-enhanced magnetic resonance imaging of the cervical region followed by biopsy from the lesion. All patients with biopsy-proven laryngeal SCC were referred to a multidisciplinary head and neck tumor team for treatment planning. Disease staging was done according to the staging system proposed by the American Joint Committee on Cancer, eighth edition. The patients who underwent total laryngectomy during the study period were included. The patients with metachronous or synchronous SCC were excluded from the study. All patients underwent total laryngectomy using a standardized protocol, where both superior and recurrent laryngeal nerves were harvested along with the specimen, and the proximal ends of the nerves were marked for reference (Figure 1). The specimens were sent for histopathological examination. The tissues were fixed in 10% neutral formalin and then embedded in paraffin. The formalin-fixed paraffin-embedded specimen was sectioned using microtome to obtain 4–5 µm thick paraffin sections. These were stained with hematoxylin and eosin. Perineural invasion was defined as more than 33% of circumferential involvement of the nerve by malignant cells or the presence of tumor cells in the three layers of nerve sheaths. Similarly, the sections of both superior and inferior laryngeal nerves were also examined to investigate perineural tumor spread.

Statistical Analysis

Descriptive statistics were used to describe the data. Statistical analysis was done using Stata/MP 16 (StataCorp LLC, Texas, USA). A chi-square test was used to compare PNI between primary and residual/recurrent cases of advanced-stage laryngeal SCC and survival between PNI-positive and PNI-negative cases of laryngeal SCC.

Results

The study included 22 patients with advanced-stage laryngeal carcinoma. The clinical and demographical details are summarized in Table 1. The most common presentation was voice change (100%) followed by dysphagia (46%).

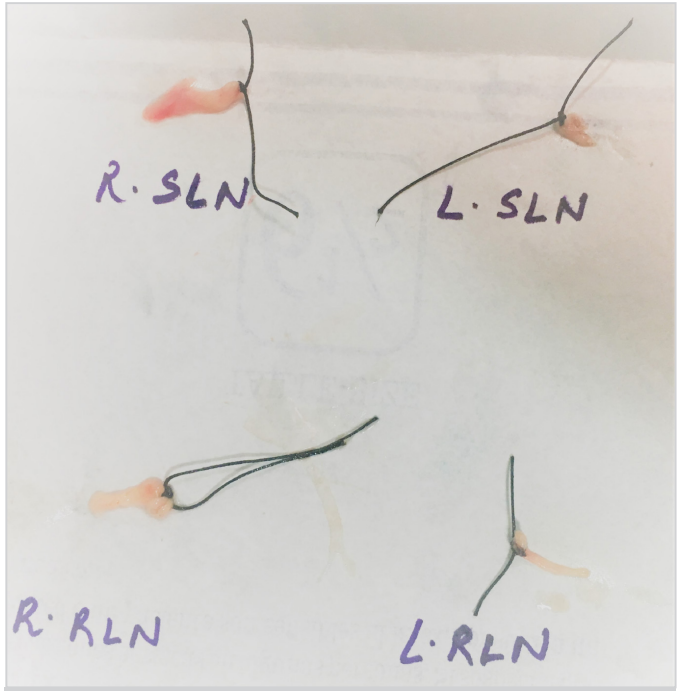

Figure 1. Harvested specimens of bilateral superior laryngeal nerves (SLN) and recurrent laryngeal nerves (RLN) with proximal ends tagged
R: Right, L: Left

Table 1. Clinical and demographical details of the cases

	Number (percentage)
Total patients	22
Age in years (mean, range)	58, 33 to 84
Sex	
Male	20 (90.9%)
Female	2 (9.1%)
Stage distribution	
Stage 3	4 (18.2%)
Stage 4	18 (81.8%)
Case distribution	
Primary cases	14 (63.6%)
Residual/recurrent cases	8 (36.4%)
Histopathological surgical margins	
Free of tumor	13 (59.1%)
Close	8 (36.4%)
Involved	1 (4.5%)
Post-operative adjuvant treatment	
Radiotherapy	18 (81.8%)
Chemo-radiotherapy	1 (4.5%)
None	3 (13.7%)
Recurrence	
Loco-regional	3 (13.7%)
Distant	1 (4.5%)

Ten patients had undergone preoperative tracheostomy as an emergency airway procedure. Preoperative biopsy showed that 19 patients had moderately differentiated SCC, while three patients had poorly differentiated SCC. TNM staging, subsite distribution, and PNI data are detailed in Table 2.

Intra-tumoral PNI was found in seven of the 22 cases (32%). Of these, five had primary laryngeal malignancy and two had residual/recurrent disease post radiotherapy/chemo-radiotherapy. The difference in PNI between primary and residual/recurrent cases was not found to be statistically significant (p=0.49). The free nerve margins of superior and recurrent laryngeal nerves, which were examined from proximal to distal orientation, showed no tumor infiltration in any of the cases.

The patients were followed-up for a median duration of 54 months (range, 2 to 74 months). Five patients were lost to follow-up (one in the PNI-positive group and four in the PNI-negative group). Overall survival at five years was 58.8% (10 out of 17). In the PNI-positive group, 2/6 (33.3%) patients were alive and disease-free, while in the PNI-negative group, 8/11 (72.7%) patients were alive and disease-free at five years. The difference was not found to be statistically significant (p=0.14).

Table 2. Details of the patients regarding TNM staging, tumor subsites, prior treatment and perineural invasion within the larynx and nerves

Case no.	Age/sex#	Stage	Subsite	Prior treatment	PNI larynx	PNI nerves^
1	61/M	T3N3bM0	Supraglottis	No	Yes	No
2	60/M	T3N0M0	Transglottis	No	No	No
3	45/F	T4aN0M0	Supraglottis	No	Yes	No
4	50/M	T4aN1M0	Transglottis	No	No	No
5	59/M	rT4aN0M0	Supraglottis	CT/RT	Yes	No
6	59/M	rT4aN0M0	Transglottis	CT/RT	No	No
7	65/M	rT3N0M0	Glottis	RT	No	No
8	84/M	T4aN0M0	Transglottis	No	No	No
9	57/M	rT4aN0M0	Transglottis	CT/RT	No	No
10	80/M	rT3N0M0	Glottis	RT	No	No
11	60/M	T4aN0M0	Transglottis	No	No	No
12	66/M	T4aN1M0	Supraglottis	No	Yes	No
13	42/M	T4aN0M0	Supraglottis	No	No	No
14	53/M	rT3N0M0	Glottis	RT	Yes	No
15	57/M	rT4aN0M0	Transglottis	CT/RT	No	No
16	59/F	T4aN3bM0	Supraglottis	No	Yes	No
17	33/M	T4aN0M0	Transglottis	No	No	No
18	59/M	T4aN2bM0	Supraglottis	No	No	No
19	58/M	rT4aN0M0	Transglottis	RT	No	No
20	48/M	T4aN0M0	Transglottis	No	Yes	No
21	62/M	T4aN0M0	Supraglottis	No	No	No
22	59/M	T4aN0M0	Transglottis	No	No	No

CT: Chemotherapy, F: Female, M: Male, PNI: Perineural invasion, RT: Radiotherapy

Discussion

Perineural invasion is difficult to assess preoperatively by clinical examination. Even though radiological evaluation may give some clue about the PNI of major nerves in the form of changes in signal intensity, contrast enhancement, or widening of the foramen, such is observed only where involved nerves are quite large (4). Mesolella et al. (7) have found the incidence of PNI at 15.8% in their retrospective study of 40 patients with advanced-stage laryngeal SCC. Zhu et al. (8), in their retrospective study, have evaluated 1,272 laryngeal SCC patients undergoing surgical treatment. The authors found that 118 patients (9.28%) had PNI. In their matched-pair analysis, they have concluded that PNI-positive laryngeal SCC had significantly worse overall survival compared to their PNI-negative group. Our data also shows a similar trend with 72.7% survival in PNI-positive group as compared to 33.3% survival in the PNI-negative group. However, the difference was not found to be statistically significant which may be because of the small sample size.

Ten out of the fifteen laryngeal SCC patients (66.6%) evaluated by Vural et al. (4) were found to have PNI in the histopathological evaluation. The study by Chirilă et al. (6) included 246 patients of laryngeal and hypopharyngeal SCC. The authors found that 35.59% of the patients had evidence of PNI on histological evaluation. Similar to the study by Chirilă et al. (6), we found the incidence to be 32% in our study. The wide variation in the reported values of PNI suggests the geographical differences in the population included in the studies.

The evaluation of PNI in superior and recurrent laryngeal nerves has been done in two previous studies, albeit, in a different geographical setup. Vural et al. (4), in their evaluation of 15 patients, did not find PNI of any of these nerves. Similarly, the study by Chirilă et al. (6) was unable to find evidence of PNI of these nerves in any of the cases of laryngeal SCC. Our findings were consistent with those of the previous studies suggesting that perineural tumor spread through superior and recurrent laryngeal nerves did not constitute a pathway of spread in laryngeal SCC, even in locally advanced stages. Hence, there is no need to extend the surgical resection boundaries of total laryngectomy to include the bilateral superior and recurrent laryngeal nerves.

Conclusion

Perineural invasion of minor nerves varies widely in laryngeal SCC but constitutes a major pathway of spread. On the contrary, invasion of superior or recurrent laryngeal nerves does not constitute a route for tumor spread. Hence, there is no need to extend the surgical boundary for total laryngectomy to include these major nerves separately.

Ethics Committee Approval: The study received ethical clearance from the Institute Ethics Committee of All India Institute of Medical Sciences, New Delhi, India (Ref. No. IEC-287/02.06.2017, RP-58/2017, date: 04.07.2017).

Informed Consent: Informed written consent was obtained from the participants.

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Authorship Contributions

Surgical and Medical Practices: K.S., A.T., H.V., Concept: S.B., K.S., A.T., H.V., Design: S.B., Sh.B., K.S., A.T., H.V., Data Collection and/or Processing: A.S.J., S.B., Sh.B., S.K., Analysis and/or Interpretation: A.S.J., S.K., Literature Search: A.S.J., S.K., A.T., H.V., Writing: A.S.J., S.B., Sh.B., S.K., K.S., A.T., H.V.

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Main Points

- Risk of recurrence in advanced-stage laryngeal carcinoma varies between 30–50%.
- Perineural invasion is an important risk factor for loco-regional recurrence.
- Perineural invasion of minor nerves in the tumor micro-environment contributes a major pathway of spread for laryngeal cancers.
- However, invasion of superior or inferior laryngeal nerves does not form a pathway of spread for laryngeal squamous cell carcinoma.
- Hence, there is no need to extend the surgical boundary for total laryngectomy to include these major nerves separately.

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