Low Survival of Advanced Laryngeal Cancers: Time to Change the Treatment Regime?

Sandeep Vijay, Sajith Babu Thavarool, S Manu, Naveen George, Raveena R Nair

Department of Surgical Oncology, Malabar Cancer Centre, Thalassery, Kerala, India

Address for correspondence: Dr. Sajith Babu Thavarool, Department of Surgical Oncology, Malabar Cancer Centre, Kodiyeri, Thalassery - 670 103, Kerala, India. E-mail: drsajith@gmail.com

ABSTRACT

Background: This study aimed to detect the survival outcome of patients who underwent primary laryngectomy in comparison to the salvage total laryngectomy at our institution. Methodology: A retrospective analysis of patients who underwent laryngectomy in our institution from 2009 to 2016 either as primary surgery or as salvage surgery was done. Results: Fifty-four patients were assessed in the current study. Primary laryngectomy was done in 33 (60.4%) patients and salvage laryngectomy in 21 (39.6%) patients. The common complication following laryngectomy was wound infection (68.5%) followed by pharyngocutaneous fistula (29.6%). The 5 year disease free survival in primary and salvage laryngectomy patients were 46% and 32 % respectively, DFS showed a decreasing trend with increase in T-stage and also node positivity. The overall survival (5 years) was found to be 52% for primary laryngectomy cases and 37% for salvage cases. Conclusion: Salvage laryngectomy was found to have higher incidence of postoperative complications. The overall survival and DFS was found to be lesser for salvage cases than primary laryngectomy. T- and N-stage have an important role in determining survival. The survival of advanced laryngeal cancers is dismal with surgery and radiotherapy.

Key words: Complications, laryngeal cancer, laryngectomy, survival

INTRODUCTION

Cancer of the larynx is the seventh most common malignancy affecting males in India. The estimated incidence is 1.26–8.18/100,000 population in our country.[1]

Laryngeal cancers are treated with the main goal of functional organ preservation whenever possible.[2] Early-stage laryngeal cancer patients (Stage I/II) are treated by either radiation therapy only or conservative surgical procedures, and advanced-stage patients (Stage III) are treated by a combination of radiotherapy and chemotherapy.[3] Some of the patients treated with organ preservation may have recurrence or residual disease after radiotherapy/chemoradiotherapy for which surgery is the salvage procedure (salvage laryngectomy). Organ preservation is not possible when the tumors erode thyroid/cricoid cartilages and hyoid bone or when the tumor infiltrates into extralaryngeal tissues (T4 stage, AJCC 8th edition), wherein total laryngectomy (primary laryngectomy) with neck dissection followed by radiotherapy is the treatment of choice in these T4 stage cancers.

The 5-year disease-free survival (DFS) of T4 stage patients after treatment with surgery and radiotherapy is found to be around 60%.4] Whereas, the 5-year DFS after salvage laryngectomy is around 55%.4] This study aims to detect the survival outcome of patients who underwent primary laryngectomy in comparison to the salvage total laryngectomy at our institution.

METHODOLOGY

This study was a retrospective analysis of patients who underwent laryngectomy in our institution from 2009 to 2016 either as primary surgery or as salvage surgery. The hypothesis was that the patients who progressed to an advanced stage of T4 stage are biologically aggressive and are similar to those patients who did not respond to radiotherapy or chemoradiotherapy. Hence, these two biologically aggressive types of laryngeal cancers would have similar outcome in terms of survival. Patients who underwent conservation laryngectomy and those patients with hypopharyngeal cancers who underwent laryngectomy were excluded from the study.
The demographic and clinical details were collected from the patient records. The last date of follow-up and status of the patients were retrieved from the files. Statistical analysis was done using EpiData Analysis software 2.1.0.73 (EpiData Odense, Denmark). For survival analysis, Kaplan–Meier estimates and plots were applied.

RESULTS

There were 62 patients who underwent laryngectomy during the study period, of which the records of eight patients could not be retrieved. Hence, analysis of 54 patients was done in the current study. Primary laryngectomy was done in 33 (60.4%) patients and salvage laryngectomy in 21 (39.6%) patients. Of the salvage laryngectomy patients, 7 had undergone chemoradiation earlier and 14 had undergone radiation therapy alone. The demographic details are given in Table 1. The median age of the patients was 60 years (range, 40–73 years), of which 51 (94.3%) were male.

Among the salvage laryngectomy group, 14 (26.4%) patients had been treated with radiotherapy only and 7 (13.2%) with chemoradiation. Conventional cobalt teletherapy was used till 2011 and intensity-modulated radiotherapy was used from 2012 to 2016. The dose of radiation delivered to the primary was up to 70 Gy. In node-negative patients, the nodal stations at risk were delivered with 56 Gy, and in node-positive patients, the dose of radiation delivered was 66–70 Gy. When the salvage patients developed recurrence following their primary treatment, they were reassessed and found to have Stage III in 38% of cases, Stage IV in 33.5%, and Stage II disease in 28.5%. All the patients in the salvage group who underwent total laryngectomy were included in the study.

Among the primary laryngectomy group, 94% of patients had Stage IVA disease. The different types of laryngectomies done were total laryngectomy (67.9%), total laryngectomy with partial pharyngectomy (26.4%), and total laryngo-pharyngo-esophagectomy (5.7%). Regional flap like pectoralis major myocutaneous flap was used in 12 (22%) patients and supraclavicular flap was used in 2 (3.8%) patients.

The most common complication following laryngectomy was found to be wound infection. Wound infection was defined as all the wounds with erythema, wound edge discoloration, and wound gape in addition to frank infection. All these patients needed prolongation of antibiotics and longer wound care. It was found in half of the primary laryngectomy cases and all of the salvage cases ($P = 0.0001$). Postradiation skin changes and fibrosis were seen in all patients. Pharyngocutaneous fistula formation was also a significant morbidity (29.6%) following laryngectomy, but in most cases, they were treated by conservative measures alone. Only two among the salvage laryngectomy patients required secondary repair of the fistula with local flaps. Furthermore, the incidence of systemic complications was found to be higher in salvage laryngectomy cases [Table 2].

### Table 1: Demographic profile of patients undergoing primary and salvage laryngectomy during 2009 to 2016 at a tertiary cancer centre

| Variable             | Category                  | Laryngectomy |
|----------------------|---------------------------|---------------|
|                      | Primary, $n$ (%)          | Salvage, $n$ (%)|
| Age category (years) | <65                       | 8 (24)        | 2 (9)  |
|                      | Above 65                  | 25 (76)       | 19 (91)|
| Sex                  | Male                      | 31 (94)       | 20 (95)|
|                      | Female                    | 2 (6)         | 1 (5)  |
| Co morbidity         | Absent                    | 1 (3)         | 2 (90) |
|                      | Present                   | 32 (97)       | 19 (10)|
| Tobacco use          | Absent                    | 9 (27)        | 7 (33) |
|                      | Present                   | 24 (73)       | 14 (68)|
| Primary treatment    | Surgery                   | 33 (100)      | 0      |
| modality             | Radiation                 | 0             | 14 (67)|
|                      | Chemoradiation            | 0             | 7 (33) |
| Sub site of laryngeal cancer | Supraglottis       | 20 (61)       | 12 (57)|
|                      | Glottis                   | 13 (39)       | 9 (43) |
|                      | Subglottis                | 0             | 0      |
| T-stage of patients  | T1                        | 0             | 6 (28) |
|                      | T2                        | 0             | 6 (28) |
|                      | T3                        | 1 (3)         | 8 (38) |
|                      | T4a                       | 32 (97)       | 7 (34) |
| N-stage of patients  | N0                        | 21 (64)       | 20 (95)|
|                      | N1                        | 7 (21)        | 1 (5)  |
|                      | N2a                       | 0             | 0      |
|                      | N2b                       | 5 (15)        | 0      |
|                      | N2c                       | 0             | 0      |
| Type of surgery      | Total laryngectomy        | 17 (52)       | 19 (91)|
|                      | TL + partial pharyngectomy| 12 (36)       | 2 (9)  |
|                      | TLPO                      | 3 (12)        | 0      |
| Reconstruction of pharynx | Primary closure       | 20 (61)       | 14 (67)|
|                      | Patch PMMC                | 6 (18)        | 7 (33) |
|                      | Tubed PMMC                | 2 (6)         | 0      |
|                      | Gastric pull-up           | 3 (9)         | 0      |
|                      | Supraclavicular flap      | 2 (6)         | 0      |

TL: Total laryngectomy, TLPO: Total laryngo-pharyngo-esophagectomy, PMMC: Pectoralis major myocutaneous flap

| Complications | Laryngectomy |
|---------------|--------------|
|               | Primary, $n$ (%) | Salvage, $n$ (%) | $P$    |
| Wound infection | 16 (50)       | 21 (100)         | 0.0001 |
| Wound dehiscence | 4 (12.5)      | 13 (62)          | 0.0002 |
| Pharyngocutaneous fistula | 9 (28)       | 7 (33.4)        | 0.4552 |
| Systemic complications | 0            | 3 (14.3)       | 0.0277 |
| Overall        | 20 (62.5)     | 21 (100)         | 0.0014 |
DFS (5 years) following primary laryngectomy and salvage laryngectomy was found to be 46% and 32%, respectively. DFS showed a decreasing trend with increase in T-stage [Figure 1] and also node positivity [Figure 2]. The overall survival (5 years) was found to be 52% for primary laryngectomy cases and 37% for salvage cases [Figure 3].

**DISCUSSION**

The survival of salvage laryngectomy patients after a failure of organ preservation treatment is low in comparison to the patients treated with surgery followed by adjuvant treatment. Moreover, the postoperative complications are higher in salvage laryngectomy group of patients.

Organ preservation treatment by radiotherapy or chemoradiation is usually given for early-stage cancers of the larynx. Some of these patients develop recurrence on follow-up, and these may be in early stage as well. Recurrences following radiotherapy are generally found to develop locally, and in almost 90% of the cases, these occur within 3 years.

The recurrence rate in laryngeal cancers after organ preservation with chemoradiation varies according to the subsite, the T-status, and the N-status of the primary disease, but generally said to be around 25%–50%. Risk factors that have been established as leading to the development of recurrences include higher T-stage disease and N-positivity. Furthermore, the supraglottis subsite is found to produce higher cases of recurrence.

Some of these tumors usually are picked up in early stage as they undergo surveillance with endoscopy. There were 6 (11.3%) early-stage recurrent patients in our group. Conservation laryngectomy is considered in early-stage recurrent laryngeal cancer patients if they had early stage before the organ preservation treatment. Total laryngectomy is considered in patients with dysfunctional larynx even if the disease appears to be early. Other factors that influenced the decision of laryngectomy were presence of tracheostomy, adverse skin condition in neck after radiotherapy, fibrosis of the neck, moderate-to-poor general condition, and advanced age.

Survival analysis of our patients revealed a 5-year DFS of 46% following primary laryngectomy and 32% following salvage surgery. It was found to be influenced by the tumor stage and nodal status. The overall 5-year survival was also found to be higher for primary laryngectomy cases (52%) as compared to salvage cases (37%).

Similar retrospective studies by Stankovic et al., Dziegielewski et al., and Mimica et al. have shown the DFS to be 55%–60% for primary laryngectomy cases and 45%–50% for salvage laryngectomy cases. Studies by Di et al., Varghese et al., and Sankaranarayanan et al. showed overall 5-year survival to be around 45%–50%
for primary laryngectomy and 35%-40% for salvage laryngectomy cases.\textsuperscript{13-15} Varghese et al. cited different reasons for the less number of salvage laryngectomies done and the poorer outcomes in survival. These include high number of treatment dropouts due to complacency following organ preservation procedures (chemoradiation) and delay in the detection of recurrence due to the masking effect of the postchemoradiation sequelae and thus leading to the advanced stage of presentation (III and IV) of the salvage laryngectomy cases. In our study, we have been able to follow-up our laryngeal cancer patients stringently, but the postchemoradiation sequelae (edema and fibrosis) has led to many cases being detected in their advanced stages only.

In our study, we have observed a higher incidence of complications following salvage surgery as compared to primary surgery. This is comparable to the findings of Stankovic et al.\textsuperscript{6} and Ganly et al.\textsuperscript{10} who also found salvage cases to have more complications. Ganly et al. studied and compared the complications of primary (113) and salvage laryngectomy (70) cases and found the wound complications to be 25% versus 45%, and fistula complications to be 12% versus 32%, respectively. Wound infection was found to be the most common complication in our study, which occurred in all cases of salvage laryngectomy. Radiotherapy causes tissue interstitial and perivascular fibrosis following epithelial and endothelial cell damage. This leads to decreased blood flow, delayed wound healing, and higher incidence of infections.\textsuperscript{17} These are the same reasons that lead to higher instances of pharyngocutaneous fistula formation in laryngectomy cases following chemoradiation. The incidence of fistula in our series was 28% following primary laryngectomy and 33.4% in the salvage cases. Mimica et al.\textsuperscript{12} found pharyngocutaneous fistula formation in 28% of their salvage cases, of which 78% were managed conservatively.

Systemic complications were also found to be higher following salvage surgery. Major head-and-neck resections are known to induce a strong risk for myocardial injury, and with the addition of systemic chemotherapy (cisplatin) before surgery, the patient becomes more prone to cardiovascular events.\textsuperscript{18,19}

Our study shows that the T4 patients with primary surgery and the other group of patients who have developed recurrence and undergone salvage surgery show biologically similar characteristics. Their survival rates though different do not show a huge gap. Thus, if we could find out methods to detect the aggressive variants of laryngeal cancer that present early, we could proceed with radical surgery as a part of primary management modality itself. Further prospective studies are required to investigate this factor. Moreover, more aggressive treatment regimens with inclusion of newer chemotherapy or targeted agents may be needed to further improve the outcome.

CONCLUSION
Salvage laryngectomy was found to have higher incidence of postoperative complications which includes minor wound infection to major salivary leak and vessel bleed outs. The overall survival and DFS were found to be lesser for salvage surgery than primary laryngectomy and T- and N-stage have an important role in determining survival. The survival of these advanced laryngeal cancers is low even though treated with the current guidelines of surgery and radiotherapy.

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Conflicts of interest
There are no conflicts of interest.

Disclosure
This material has never been published and is not currently under evaluation in any other peer reviewed publication.

Ethical approval
The permission was taken from Institutional Ethics Committee prior to starting the project. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent
Informed consent was obtained from all individual participants included in the study.

REFERENCES
1. Bobdey S, Jain A, Balasubramaniam G. Epidemiological review of laryngeal cancer: An Indian perspective. Indian J Med Paediatr Oncol 2015;36:154-60.
2. Kelly SL, Jackson JE, Hickey BE, Szallasi FG, Bond CA. Multidisciplinary clinic care improves adherence to best practice in head and neck cancer. Am J Otolaryngol 2013;34:57-60.
3. Gourin CG, Conger BT, Sheils WC, Bilodeau PA, Coleman TA, Porubsky ES. The effect of treatment on survival in patients with advanced laryngeal carcinoma. Laryngoscope 2009;119:1312-7.
4. Stankovic I, Milisavljevic D, Stankovic M. Survival after Salvage Total Laryngectomy: The Influence of Previous Treatment. J Nucl
5. Forastiere AA, Goepfert H, Maor M, Pajak TF, Weber R, Morrison W, et al. Concurrent chemotherapy and radiotherapy for organ preservation in advanced laryngeal cancer. N Engl J Med 2003;349:2091-8.

6. de Visscher AV, Manni JJ. Routine long-term follow-up in patients treated with curative intent for squamous cell carcinoma of the larynx, pharynx, and oral cavity. Does it make sense? Arch Otolaryngol Head Neck Surg 1994;120:934-9.

7. Kothari P, Trinidad A, Hewitt RJ, Singh A, O’Flynn P. The follow-up of patients with head and neck cancer: An analysis of 1,039 patients. Eur Arch Otorhinolaryngol 2011;268:1191-200.

8. Hinerman RW, Mendenhall WM, Morris CG, Amdur RJ, Werning JW, Villaret DB. T3 and T4 true vocal cord squamous carcinomas treated with external beam irradiation: A single institution’s 35-year experience. Am J Clin Oncol 2007;30:181-5.

9. Brandstorp-Boesen J, Sørum Falk R, Folkvard Evensen J, Boysen M, Brøndbo K. Risk of recurrence in laryngeal cancer. PLoS One 2016;11:e0164068.

10. Motamed M, Laccourreye O, Bradley PJ. Salvage conservation laryngeal surgery after irradiation failure for early laryngeal cancer. Laryngoscope 2006;116:451-5.

11. Dziuglewski PT, O’Connell DA, Klein M, Fung C, Singh P, Alex Mlynarek M, et al. Primary total laryngectomy versus organ preservation for T3/T4a laryngeal cancer: A population-based analysis of survival. J Otolaryngol Head Neck Surg 2012;41 Suppl 1:S56-64.

12. Mimica X, Hanson M, Patel SG, McGill M, McBride S, Lee N, et al. Salvage surgery for recurrent larynx cancer. Head Neck 2019;41:3906-15.

13. Di B, Li XM, Shang YD, Song Q, Tao ZF, Cheng JM. Outcomes of salvage laryngectomy after initial radiation failure in laryngeal squamous cell carcinoma. Zhonghua Er Bi Yan Hou Tou Jing Wai Ke Za Zhi 2011;46:495-500.

14. Varghese BT, Sebastian P, Mathew A. Treatment outcome in patients undergoing surgery for carcinoma larynx and hypopharynx: A follow-up study. Acta Otolaryngol 2009;129:1480-5.

15. Sankaranarayanan R, Ramanakumar AV, Yeole BB. Survival from glottic and supraglottic laryngeal carcinoma in Mumbai (Bombay), India. Oral Oncol 2003;39:656-63.

16. Ganly I, Patel S, Matsuo J, Singh B, Kraus D, Boyle J, et al. Postoperative complications of salvage total laryngectomy. Cancer 2005;103:2073-81.

17. Johnson JT, Bloomer WD. Effect of prior radiotherapy on postsurgical wound infection. Head Neck 1989;11:132-6.

18. Nagele P, Rao L, Kallogjeri D, Cavallone L, Piccirillo J. Postoperative myocardial injury after major head and neck cancer surgery. Eur J Anaesthesiol 2010;27:83.

19. Aleman BM, Moser EC, Nuver J, Suter TM, Maraldo MV, Specht L, et al. Cardiovascular disease after cancer therapy. EJC Suppl 2014;12:18-28.