The Journal of Laryngology & Otology

cambridge.org/jlo

Non-surgical organ preservation in laryngeal and hypopharyngeal cancers: an audit from the clinic

S Sood[1], S Sinha[1], A Balaji[2], S R Mundhe[4], N Mummudi[1], A Budrukkar[1], M Swain[1], K Prabash[3], V Noronha[3], A Joshi[3], V Patil[3] and S G Laskar[1]

Departments of [1]Radiation Oncology, [2]Speech and Therapy and, [3]Medical Oncology, Tata Memorial Centre, Homi Bhabha National Institute, Mumbai, and [4]Department of Radiation Oncology, Krupamayi Cancer Hospital, Aurangabad, India

Abstract

Background. There is increasing concern regarding efficacy of organ preservation protocol in laryngeal and hypopharyngeal cancers.

Method. This study retrospectively assessed disease-related and functional outcomes of 191 patients with non-metastatic laryngeal or hypopharyngeal squamous cell carcinoma treated with curative intent (radiotherapy with or without chemotherapy).

Results. Seventy-six patients (39.8 per cent) had a primary cancer in the larynx, and 115 patients (60.2 per cent) had a primary cancer in the hypopharynx. The median follow up was 39 months. The 3-year time to progression, overall survival, local control and laryngectomy free survival was 56.2 per cent, 76.3 per cent, 73.2 per cent and 67.2 per cent, respectively. At the time of analysis, 83 patients (43.5 per cent) were alive and disease free at their last follow up and did not require tube feeding or tracheostomy. The laryngo-oesophageal dysfunction-free survival was 61 per cent at 3 years.

Conclusion. Organ conservation protocols remain the standard of treatment in appropriately selected patients with laryngeal and hypopharyngeal cancers.

Main Article

Dr S Laskar takes responsibility for the integrity of the content of the paper

Cite this article: Sood S *et al*. Non-surgical organ preservation in laryngeal and hypopharyngeal cancers: an audit from the clinic. *J Laryngol Otol* 2023;**137**:448–454. https://doi.org/10.1017/S002221512200113X

Accepted: 29 April 2022
First published online: 9 June 2022

Key words:
Larynx; Hypopharynx; Organ Preservation

Author for correspondence:
Dr S Laskar, Department of Radiation Oncology and Head and Neck Disease Management Group, Tata Memorial Centre, Homi Bhabha National Institute, Parel, Mumbai 400012, India
E-mail: sarbanilaskar@gmail.com

Introduction

Laryngeal and hypopharyngeal cancers account for approximately one third of all head and neck cancer cases. As per The Global Cancer Observatory 2020, the number of new laryngeal and hypopharyngeal cancer cases worldwide was 184 615 and 84 254, respectively.[1] In India, the projected incidence for laryngeal and pharyngeal cancers was 30 462 and 4131, respectively, for the year 2020.[2] Smoking and excessive alcohol intake constitute the most common aetiologies.

The Department of Veterans Affairs Laryngeal Cancer Study group trial[3] paved the way for organ preservation in locally advanced laryngeal cancers. Subsequently, the European Organisation for Research and Treatment of Cancer 24891 trial proved the feasibility of organ preservation in hypopharyngeal cancers too.[4,5] The contemporary standard of care for locally advanced laryngeal and hypopharyngeal cancers is concurrent chemoradiation in appropriately selected patients (T_3 and some T_{4a} patients with a functional larynx).[6] Upfront total laryngectomy should be preferred in patients with gross destruction of laryngeal cartilages and those with a dysfunctional larynx.[7]

Although results of multiple clinical trials have demonstrated acceptable outcomes in terms of both survival and preservation of the larynx with the organ preservation approach, questions have been raised regarding implementing this approach in the clinics (non-trial setting). In 2005, a retrospective National Cancer Database and Surveillance, Epidemiology, and End Results database analysis of the past three decades by Hoffman *et al.* reported that the survival of patients with locally advanced laryngeal cancers has gradually declined from 68.1 per cent in 1985 to 62.8 per cent in 1993.[8] The authors ascribed this to improper patient selection for organ preservation in routine clinical practice. Similarly, outcomes of T_3 laryngeal and hypopharyngeal cancers treated with organ preservation approaches in a non-trial setting have been questioned by some authors.[9,10] The results of these studies have emphasised that appropriate staging and case selection upfront are the cornerstone for the success of organ preservation approaches. Salvage laryngectomy post-concurrent chemoradiation,[11] in addition to being an extremely morbid procedure, is associated with significantly inferior outcomes when compared with upfront surgery.[12]

We conducted this audit to investigate these concerns, optimise selection of cases for organ conservation and look into the success of salvage treatments offered post-organ conservation, aiming to report the survival outcomes of patients with organ conservation protocol at a tertiary cancer care centre in India.

Materials and methods

Study design

The study included patients with stage III and non-metastatic stage IV (American Joint Commission on Cancer 7th edition) squamous cell carcinoma (SCC) of the larynx and hypopharynx treated with curative intent radiotherapy (RT) with or without chemotherapy between January 2009 and December 2017. Patients with a second primary neoplasm of the head and neck region, patients who received re-irradiation, patients who did not complete the planned RT schedule and those treated with palliative intent were excluded from analysis. Patients' clinical history, examination details, treatment details, toxicity and outcomes were obtained from the institutional electronic medical records.

Treatment details

After a detailed history and clinical examination, disease mapping was performed prior to the start of treatment with indirect or direct laryngoscopy (or both) and biopsy or fine needle aspiration cytology. Most patients were staged with contrast-enhanced computed tomography (CT). Magnetic resonance imaging (MRI) was utilised for patients with equivocal findings on contrast-enhanced CT. Additionally, systemic staging with a CT scan of the lungs or F^{18}-fluoro deoxyglucose positron emission tomography CT (FDG PET-CT) was performed for all patients with laryngeal cancer and hypopharyngeal cancer, especially those with N_3 nodes or multiple nodes with extra nodal extension. Baseline functionality of the larynx was established for all patients subjectively by the physician or speech swallowing therapist. Objective methods of assessment including modified barium swallow, functional endoscopic evaluation of swallowing and video fluoroscopy were carried out as deemed appropriate by the physician or speech swallowing therapist. A prophylactic nasogastric tube was inserted for patients at a high risk of aspiration.

All patients were discussed at a multidisciplinary clinic comprising head and neck surgeons, radiation oncologists, medical oncologists, radiologists and pathologists before deciding on organ preservation. Radiotherapy was delivered with either conventional techniques with individualised tissue compensators or with intensity modulated radiation therapy and related techniques (volumetric modulated arc therapy or helical tomotherapy). The primary tumour with adequate margins and gross nodes was treated with 70 Gy in 35 fractions or equivalent dose while the elective nodal levels were treated with 50 Gy in 25 fractions or equivalent dose. The target volume selection and delineation was as per standard guidelines.[13–15]

In patients deemed fit, concurrent weekly cisplatin at a dose of 30–40 mg/m^2 was administered concurrently along with RT. However, certain other concurrent systemic therapy schedules such as 3 weekly cisplatin at 100 mg/m^2, weekly carboplatin (area under curve 2) and weekly nimotuzumab (200 mg) with or without cisplatin were used in certain patients as deemed suitable by the medical oncologist. All patients were regularly reviewed at least once a week in the out-patient department for toxicity assessment and tolerance during RT. Nasogastric tube insertion was undertaken in patients with significant weight loss (more than 10 per cent of baseline) or in patients with severe mucositis precluding adequate oral intake.

Post-completion of treatment, clinical follow up was undertaken every three months for the first two years, every six months from three to five years and yearly after five years. At the first follow up post-treatment (8–12 weeks post-RT completion), FDG PET-CT was performed. Subsequent radiological investigations were performed at clinical suspicion of a recurrence. Speech and swallowing rehabilitation exercises were encouraged at every follow up. Nasogastric tube removal was performed after patients could have an adequate oral intake.

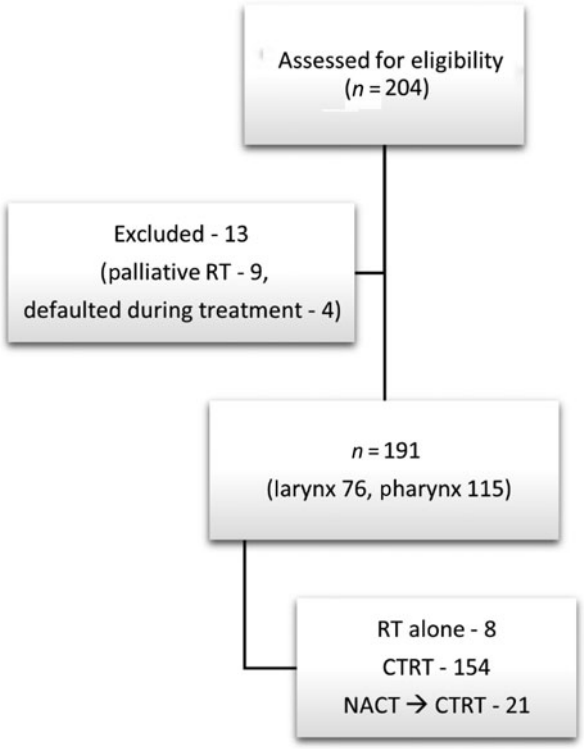

Fig. 1. Consort diagram. RT = radiotherapy; CTRT = concurrent chemoradiation; NACT = neo adjuvant chemotherapy

Statistical analysis

Statistical analyses were performed using SPSS® (version 25.0) and R Studio statistical computing software.[16] The study's primary endpoint was time to progression, which was defined as the time in months between the date of diagnosis until the date of persistent locoregional disease or locoregional or distant recurrence or death because of disease. The secondary endpoints of the study were overall survival, laryngectomy free survival and local control. Descriptive statistics were used to describe the clinico-demographic and treatment variables. Kaplan–Meier survival method was used to estimate the various survival endpoints. Difference in survival with respect to variables known to impact outcomes was assessed by log-rank test (univariate analysis). A p-value of ≤ 0.05 was considered as statistically significant. Multiple regression analysis was performed for variables that were significant on univariate analysis using the Cox proportional hazard method.

Results

A total of 204 patients were screened for the study. Out of them, 13 were ineligible for analysis (9 received palliative RT, 4 defaulted during treatment; Figure 1).

Therefore, a total of 191 eligible patients were included for this analysis. Median age at diagnosis was 60 years

https://doi.org/10.1017/S002221512200113X Published online by Cambridge University Press

Table 1. Demographic data

Parameter	Value
Age (median (range); years)	60 (21–87)
Sex (*n* (%))	
– Male	167 (87.4)
– Female	24 (12.6)
Site (*n* (%))	
– Larynx	76 (39.8)
– Hypopharynx	115 (60.2)
Stage: larynx* (as per AJCC 7th edition) (*n* (%))	
– II	2/76 (2.6)
– III	49/76 (64.5)
– IVA	25/76 (32.9)
– IVB	0
Stage: hypopharynx† (as per AJCC 7th edition) (*n* (%))	
– II	1/115 (0.9)
– III	54/115 (47)
– IVA	51/115 (44.3)
– IVB	9/115 (7.8)
Histology (*n* (%))	
– WDSCC	1 (0.5)
– MDSCC	30 (15.7)
– PDSCC	36 (18.8)
– SCC	123 (64.4)
– Undifferentiated	1 (0.5)
Karnofsky Performance Scale (*n* (%))	
– ≥80	187 (98)
– 70	4 (2)

*$n = 76$; †$n = 115$. AJCC = American Joint Committee on Cancer; WDSCC = well differentiated squamous cell carcinoma; MDSCC = moderately differentiated squamous cell carcinoma; PDSCC = poorly differentiated squamous cell carcinoma; SCC = squamous cell carcinoma

Table 2. Types of chemotherapy used

Parameter	Frequency (*n*)	Percentage (%)
No concurrent chemotherapy	16	8.4
Weekly cisplatin	120	62.8
Three weekly cisplatin	1	0.5
Carboplatin	14	7.3
Others	11	5.8
Nimotuzumab	12	6.3
Nimotuzumab + concurrent weekly cisplatin	13	6.8
Cetuximab	3	1.6
Taxanes	1	0.5
Total	191	100.0

(interquartile range, 21–87). Out of the 191 patients, 167 (87.4 per cent) were male and 24 (12.6 per cent) were female. A total of 76 patients (39.8 per cent) had a primary in the larynx, and 115 patients (60.2 per cent) had a primary in the hypopharynx. The demographic features are summarised in Table 1.

At baseline functional assessment, aspiration was present in 3 cases (1.6 per cent), and 8 cases (4.2 per cent) had undergone tracheostomy. Nasogastric tube insertion prior to starting treatment was performed in 12 patients (6.3 per cent). Four out of the 12 patients with nasogastric tube also underwent tracheostomy. So, a total of 181 patients (94.7 per cent) had intact laryngeal functions at baseline. Of the three patients who had aspiration, one patient had disease reaching the vallecula and tonsil and therefore was considered for organ preservation protocol. The reason for the organ preservation approach in two other patients was not known. Reasons for doing tracheostomy for patients planned for organ preservation were: (1) three patients presented with stridor with bulky hypopharyngeal mass, (2) one patient presented with stridor and the disease was reaching the tonsil; (3) elective tracheostomy had been performed in three patients at a different centre, and (4) another patient was operable but was a high risk in view of angioplasty and therefore did not undergo operation. However, the reason for tracheostomy in this patient was not known.

A total of 175 patients (91.6 per cent) were treated with RT with concurrent CT, and 16 patients (8.4 per cent) received definitive RT alone (in view of age, co-morbidities or as they had borderline suitability for concurrent chemotherapy). Twenty-nine patients (15.2 per cent) received neoadjuvant chemotherapy followed by concurrent chemoradiation. Neoadjuvant chemotherapy was advised in 8 patients (4 per cent) with laryngeal cancer and 21 patients (11 per cent) with hypopharyngeal cancer because of the following reasons: exolaryngeal spread, bulky disease and patient presenting with stridor.[17]

A total of 160 patients (83.8 per cent) were treated with conventional technique, and 31 patients (16.2 per cent) were treated with intensity modulated RT. The median overall treatment time was 51 days (interquartile range, 49–55). Concurrent chemotherapy was used in 175 patients (91.6 per cent). Various chemotherapy drugs used were as follows: (1) weekly cisplatin, 120 patients (68.6 per cent); (2) three weekly cisplatin, 1 patient (0.6 per cent); (3) carboplatin, 14 patients (8 per cent); (4) nimotuzumab, 12 patients (6.9 per cent); (5) nimotuzumab + cisplatin, 13 patients (7.4 per cent); and (6) others, 15 patients (8.6 per cent) (Table 2).

The median follow-up period was 39 months (interquartile range, 27–69 months). Forty-one patients (21.5 per cent) were lost to follow up. At the time of analysis, 83 patients (43.5 per cent) were alive and disease free at their last follow up and did not require tube feeding or tracheostomy; 15 patients (7.9 per cent) were alive with disease, 43 patients (22.5 per cent) had died of disease and 9 patients (4.7 per cent) had died of other causes.

The 3-year and 5-year time to progression was 56.2 per cent (95 per cent confidence interval (CI): 49.2–64.2) and 48.8 per cent (95 per cent CI: 41.1–57.9), respectively (Figure 2a). The 3-year and 5-year overall survival was 76.3 per cent (95 per cent CI: 70–83) and 64.4 per cent (95 per cent CI: 55.9–74.2), respectively (Figure 2b). Local control at 3 years and 5 years was 73.2 per cent (95 per cent CI: 66.7–80.4) and 71.2 per cent (95 per cent CI: 64.3–78.8), respectively (Figure 2c). The laryngectomy free survival at 3 years and 5 years was 67.2 per cent (95 per cent CI: 60.4–74.7) and

https://doi.org/10.1017/S002221512200113X Published online by Cambridge University Press

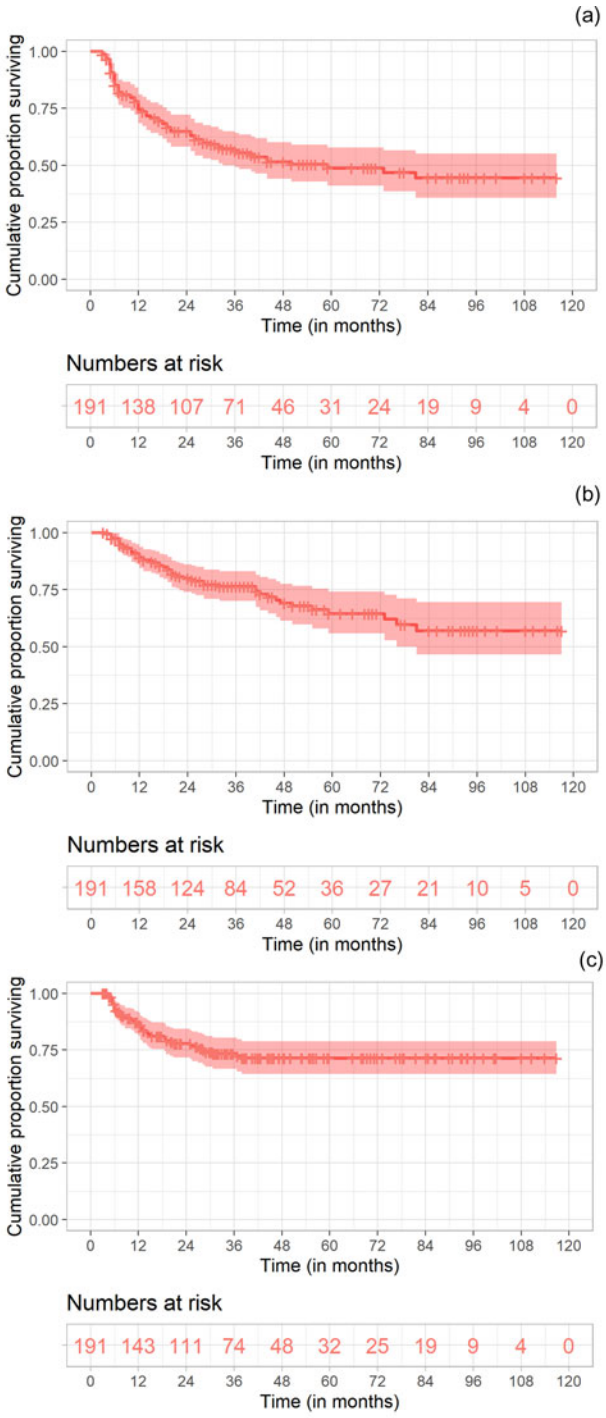

Fig. 2. Graphs showing (a) time to progression, (b) overall survival and (c) local control.

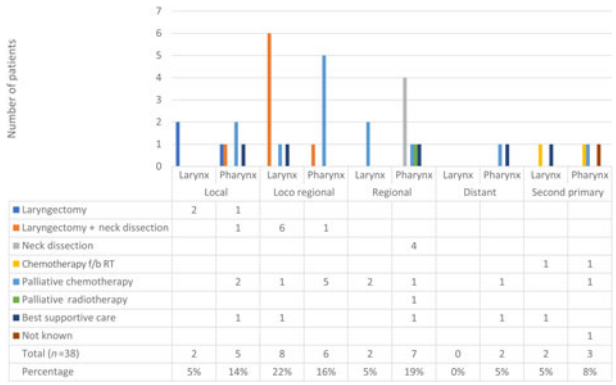

Fig. 3. Recurrence pattern and salvage treatment. f/b = followed by; RT = radiotherapy

57.2 per cent (95 per cent CI: 45.6–48.9). The 3-year time to progression and overall survival post-laryngectomy for these 22 patients was 37.6 per cent (95 per cent CI: 17.2–82.2) and 45.9 per cent (95 per cent CI: 24.1–87.4), respectively. The laryngo-oesophageal dysfunction-free survival was 61 per cent (54.1–68.8) and 52.5 per cent (44.5–62) at 3 years and 5 years, respectively.

For patients who had baseline aspiration or tracheostomy ($n = 11$), the 3-year overall survival and disease-free survival was 52.5 per cent (95 per cent CI: 27.2–100) and 16 per cent (95 per cent CI: 14.3–85.8), respectively, compared with 180 patients with no aspiration (3-year overall survival and disease-free survival, 77.5 per cent (95 per cent CI: 71.3–84.3), $p = 0.21$ and 57.3 per cent (95 per cent CI: 50.2–65.5), $p = 0.31$, respectively).

Thirty-three (17.2 per cent) patients had residual disease at 10–12 weeks post-completion of treatment. Of these, 7 (3.7 per cent) had residual disease at the index primary site, 7 (3.7 per cent) had disease at the index primary site as well as the nodal region, 10 (5.2 per cent) had disease at the index nodal site alone, and 1 patient (0.5 per cent) had disease at the index primary site and a new nodal region. Of these 33 patients, 1 patient (3 per cent) underwent salvage laryngectomy, 6 patients (18 per cent) underwent salvage neck dissection, 3 patients (9 per cent) underwent salvage laryngectomy with neck dissection, 8 patients (24 per cent) received palliative chemotherapy and 6 patients (18 per cent) were declared best supportive care. Details for 9 other patients (28 per cent) were not known.

Thirty-eight patients (19.8 per cent) had a recurrence. Patterns of recurrence and the salvage treatments offered are highlighted in Figure 3. Of the 7 patients (19 per cent) with recurrence at the index primary site, 3 (8 per cent) underwent salvage laryngectomy and 1 (2.5 per cent) underwent salvage laryngectomy with neck dissection. Of another 14 patients (38 per cent) who had a recurrence at the index primary site as well as the index nodal area, 7 (19 per cent) underwent salvage laryngectomy with neck dissection. Another 9 (24 per cent) patients had a nodal recurrence (4 at the index nodal region and 4 at a new nodal region), and only 4 (10 per cent) underwent a salvage neck dissection.

The univariate analysis for various factors is given in Table 3. The 3-year time to progression, overall survival and local control for laryngeal cancers versus hypopharyngeal cancers was 65.3 per cent (95 per cent CI: 55–77.5) versus 49.8 per cent (95 per cent CI: 40.9–60.6, $p = 0.067$), 90.2 per cent (95 per cent CI: 83.5–97.4) versus 66.2 per cent (95 per cent CI: 57.3–76.5; $p = 0.0019$) and 81.2 per cent (95 per cent CI: 72.3–91.1) versus 67.3 per cent (95 per cent CI: 58.3–77.6, $p = 0.098$), respectively (Figure 4a and Figure 4b). For patients who had baseline aspiration or tracheostomy ($n = 11$), the 3-year time to progression and overall survival was 16 per cent (95 per cent CI: 14.3–85.8) and 52.5 per cent (95 per cent CI: 27.2–100), respectively, compared with patients with no aspiration; 3-year time to progression and overall survival was 57.3 per cent (95 per cent CI: 50.2–65.5) and 77.5 per cent (95 per cent CI: 71.3–84.3), respectively. The difference in survival however was statistically non-significant ($p = 0.81$ for time to progression and $p = 0.21$ for overall survival).

In multivariable analysis, initial site of disease (larynx *vs* pharynx, hazard ratio, 2.72, $p = 0.002$, 95 per cent CI: 1.42–5.19) and

https://doi.org/10.1017/S002221512200113X Published online by Cambridge University Press

Table 3. Univariate analysis for prognostic factors for three-year overall survival

Variable	Three-year overall survival (%)	*P*-value
Age group		
– <60 years	69.5	0.175
– ≥60 years	79.9	
Sex		
– Female	53.1	0.029*
– Male	79.8	
Site		
– Larynx	90.2	0.002*
– Pharynx	66.2	
T-stage		
– T_1–T_2	83.3	0.14
– T_3	77.8	
– T_4	64	
Concurrent chemotherapy		
– Radiotherapy alone	42.9	0.004*
– Concurrent chemoradiation	78.8	
Neoadjuvant chemotherapy		
– Yes	81.1	0.261
– No	75.5	

*Statistically significant

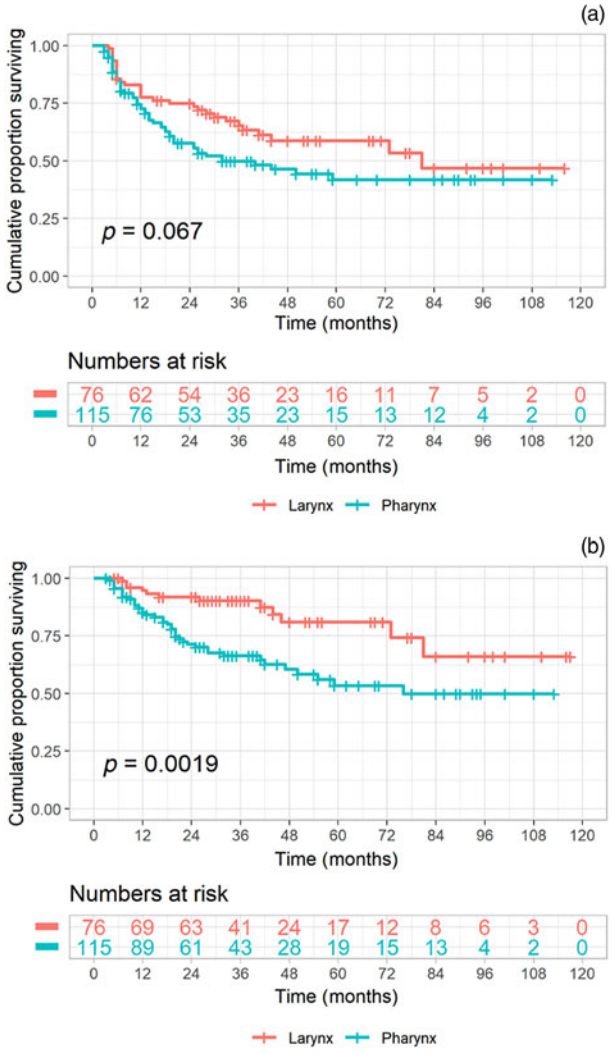

Fig. 4. Graphs showing (a) time to progression site wise and (b) overall survival site wise.

concurrent chemoradiation versus RT alone (hazard ratio, 2.97, $p = 0.01$, 95 per cent CI: 0.14–0.76) were associated with a better prognosis.

Discussion

Despite more than 25 years since the publication of the Veterans Affairs trial, organ conservation for laryngeal and hypopharyngeal cancer remains one of the most contentious issues in clinical oncology. Reassuringly, the reports of this study in a real world scenario (non-trial setting) in relation to the outcomes of organ conservation were acceptable (5-year time to progression, overall survival, laryngectomy free survival and local control of 48.8 per cent, 64.4 per cent, 57.2 per cent and 71.2 per cent, respectively), with results comparable with those reported in the landmark clinical trial involving laryngeal (Veterans Affairs trial[3] with 2-year overall survival of 68 per cent; Radiation Therapy Oncology Group 9111[6] with 10-year local control of 69 per cent and 10-year overall survival of 28 per cent) and hypopharyngeal cancers (European Organisation for Research and Treatment of Cancer[4] with 5-year overall survival of 33 per cent).

At least four large retrospective population database studies[8,10,18,19] have raised questions regarding utilisation of RT or concurrent chemoradiation as the primary local modality instead of surgery in T_3 and T_4 laryngeal cancers. A review of the National Cancer Database by Hoffman *et al.* showed 158 426 cases of laryngeal SCC diagnosed between the years 1985 and 2001.[8] They reported a trend towards decreasing survival among patients with $T_3N_0M_0$ laryngeal cancers of all sites in patients who were treated with chemoradiation (59.2 per cent) or irradiation alone (42.7 per cent) when compared with those of patients after surgery with irradiation (65.2 per cent) and surgery alone (63.3 per cent). However, there was no decrease in survival when only $T_3N_0M_0$ glottic cancers were considered.

Similarly, Grover *et al.* identified 969 patients from 2003 to 2006 with T_{4a} laryngeal cancer using the National Cancer Database, 64 per cent of whom had been treated with organ conservation protocol.[10] Median survival for total laryngectomy versus chemoradiotherapy was 61 versus 39 months ($p < 0.001$). Chemoradiotherapy showed an inferior overall survival compared with total laryngectomy (hazard ratio, 1.31; 95 per cent CI: 1.10–1.57) after potential confounders were controlled.

Another analysis of the National Cancer Database from 2004 to 2015 was performed for 16 832 patients by Bates *et al.*[18] For $T_3N_{0\text{-}3}$ laryngeal cancers, chemoradiotherapy showed benefit in overall survival (51.4 per cent) when compared with total laryngectomy (46.3 per cent; hazard ratio, 0.9; 95 per cent CI: 0.8–0.9; $p < 0.01$). Among those with $T_4N_{0\text{-}3}$ disease, chemoradiotherapy (38.0 per cent) was associated with worse overall survival relative to total laryngectomy (44.3 per cent; hazard ratio, 1.2; 95 per cent CI: 1.1–1.2; $p < 0.01$). However, upon analysis by node stage, a statistically significant decrement in overall survival with

https://doi.org/10.1017/S002221512200113X Published online by Cambridge University Press

chemoradiotherapy was seen only in T_4N_0 patients (42.8 per cent *vs* 49.4 per cent; hazard ratio, 1.2; CI: 1.1–1.3; $p = 0.002$) and not in patients with T_4N_+ disease (35.1 per cent *vs* 38.5 per cent; hazard ratio, 1.1; 95 per cent CI: 1.0–1.2; $p = 0.16$). The author concluded that only those with T_4N_0 disease experienced a decrement in overall survival relative to total laryngectomy among patients receiving optimal chemoradiotherapy. Finally, in an analysis of the Alaska Cancer Registry between 1998 and 2008, overall survival for T_{4a} cancers at 2 and 5 years for total laryngectomy-radiotherapy or chemotherapy was 60 per cent and 49 per cent, for RT was 12 per cent and 5 per cent, and for concurrent chemoradiation was 32 per cent and 16 per cent, respectively.

The results of these retrospective population-based studies emphasise that case selection for organ preservation in T_3 and T_4 laryngeal cancers should be undertaken with caution. Moreover, the heterogeneity in staging of these cancers by different physicians (T_3 *vs* T_4), the imaging modality used (contrast-enhanced CT *vs* MRI) and the treatment given (RT dose, fractionation, technique and use of concurrent chemotherapy) make the results of these studies not applicable across all settings and scenarios. Moreover, it is impossible to differentiate which of the patients included in these studies were offered organ preservation despite not being suitable because of age, co-morbidities, being medically unfit or having unresectable or extensive disease.

Our results of laryngeal preservation are better than those reported in these population-based studies and are more in line with those reported in a clinical trial setting. At our institute, patients with gross erosion or lysis of the thyroid cartilage and those with a baseline dysfunctional larynx are treated with upfront total laryngectomy followed by appropriate adjuvant therapy unless unresectable because of the mucosal extension of disease or being medically unfit. This is in accordance with the recent American Society of Clinical Oncology guidelines for organ preservation.[20] Patients with an exo-laryngeal disease through breech of the thyrohyoid membrane only without involvement of cartilaginous framework are offered organ preservation protocols either with concurrent chemoradiation or neoadjuvant chemotherapy followed by concurrent chemoradiation, provided the larynx is functionally preserved.

Interestingly, a high proportion of patients (60 per cent) were those with hypopharyngeal cancers. In most parts of the world, incidence of laryngeal cancers is significantly higher than it is for hypopharyngeal cancers.[1] Most trials of organ conservation have focused on laryngeal cancers alone or have clubbed together laryngeal and hypopharyngeal cancers. Hypopharyngeal cancers are known to be highly aggressive tumours compared with laryngeal cancers, with a higher nodal stage at presentation as well as higher nodal incidence of distant metastasis.[4] Moreover, hypopharyngeal cancers have a rather morbid presentation with significant weight loss. Surgery for hypopharyngeal cancers also requires construction of a neopharynx along with a total laryngectomy. Taken together, these factors can account for the lower time to progression and overall survival seen in our cohort of patients (3-year time to progression for larynx *vs* hypopharynx: 65.3 per cent (95 per cent CI: 55–77.5) *vs* 49.8 per cent (95 per cent CI: 40.9–60.6); $p = 0.067$), although laryngectomy rates were acceptable for hypopharyngeal primary cancers (39.1 per cent). This also suggests that the criteria for patient selection for laryngeal and hypopharyngeal cancers should probably be defined separately. This may also call for revisiting neoadjuvant chemotherapy in hypopharyngeal cancers because of a difference in the natural history and biological behaviour.

In our opinion, one of the main reasons of acceptable outcomes of larynx preservation was that our centre is a high-volume tertiary cancer centre in India registering approximately 1000–2000 new cases of laryngeal or hypopharyngeal cancers annually. Clinico-radiological staging of the tumour is the mainstay of treatment decision-making and should be performed preferably by a radiologist specialising in head and neck cancers. Another strength of our study was the uniform treatment protocols of RT despite this being an audit of patients treated across 8 years. We could also differentiate between patients who were offered organ preservation on the basis of clinico-radiological suitability ($n = 180$) versus inability to undergo surgery ($n = 11$). On the other hand, the study comes with the biases associated with a retrospective study including a significant proportion of patients (approximately 15 per cent) who were lost to follow up. However, out of them, 45 per cent of patients had a follow up duration of at least 2 years. Additionally, there was a heterogeneity in terms of chemotherapy protocols (i.e. the drugs used as well as the timing (neoadjuvant chemotherapy *vs* concurrent). Finally, there was no objective assessment of functionality post-treatment in many patients. However, as none of the patients who were alive without any evidence of disease had tube dependence (feeding tube or tracheostomy), clinically significant aspiration or dysfunction (if present) would be expected in a small proportion of these patients.

A new composite endpoint for assessing the laryngeal survival and function, the laryngo-oesophageal dysfunction-free survival,[21] has been laid down by the consensus panel for future studies on laryngeal dysfunction so as to account for heterogeneity of results in studies of laryngeal preservation. This endpoint is measured as the time from randomisation, and events would include: death, local relapse, total or partial laryngectomy, tracheostomy at two years or later, or feeding tube at two years or later. This should be used as a composite endpoint in further organ preservation trials. Moreover, as discussed above, there is probably a need for further differentiating the organ conservation protocols for hypopharyngeal versus laryngeal cancers. The role of neoadjuvant chemotherapy and other systemic therapies like targeted therapy or immunotherapy continues to evolve and should be further explored especially in hypopharyngeal primary cancers in the setting of a prospective clinical trial.

- Baseline functional and clinico-radiological assessment are the cornerstone of the protocol for case selection for organ conservation in laryngeal and hypopharyngeal cancers
- In cases of dysfunctional larynx or gross thyroid cartilage erosion, surgery should be considered
- Hypopharyngeal cancers tend to be more aggressive and carry worse prognosis compared with laryngeal cancers
- Patients who receive concurrent chemoradiotherapy carry a better prognosis compared with patients who receive radiotherapy alone
- The laryngo-oesophageal dysfunction-free survival was 61 per cent at 3 years

To summarise, organ conservation for advanced laryngeal or hypopharyngeal cancer can be considered as a standard option in routine clinical practice with proper case selection. Baseline assessment of functionality and clinico-radiological assessment are the cornerstone for case selection.

https://doi.org/10.1017/S002221512200113X Published online by Cambridge University Press

Conclusion

Organ conservation protocols remain the standard of treatment in appropriately selected patients with laryngeal and hypopharyngeal cancers. Enough evidence from trials exists that despite the stringent criteria followed, significant morbidity is associated with non-surgical organ conservation especially chemoradiotherapy, which again highlights the importance of choosing the right candidates. In case organ conservation cannot be offered, such as with dysfunctional larynx or gross thyroid cartilage erosion, or where the patient is not a candidate for chemotherapy, surgery remains a viable option and should be considered.

Competing interests. None declared

References

1 Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A *et al.* Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin* 2021;**71**:209–49

2 Mathur P, Sathishkumar K, Chaturvedi M, Das P, Sudarshan KL, Santhappan S *et al.* Cancer Statistics, 2020: report from National Cancer Registry Programme, India. *JCO Glob Oncol* 2020;**6**:1063–75

3 Department of Veterans Affairs Laryngeal Cancer Study Group, Wolf GT, Fisher SG, Hong WK, Hillman R, Spaulding M *et al.* Induction chemotherapy plus radiation compared with surgery plus radiation in patients with advanced laryngeal cancer. *N Engl J Med* 1991;**324**:1685–90

4 Lefebvre J-L, Andry G, Chevalier D, Luboinski B, Collette L, Traissac L *et al.* Laryngeal preservation with induction chemotherapy for hypopharyngeal squamous cell carcinoma: 10-year results of EORTC trial 24891. *Ann Oncol* 2012;**23**:2708–14

5 Lefebvre J-L, Chevalier D, Luboinski B, Kirkpatrick A, Collette L, Sahmoud T. Larynx preservation in pyriform sinus cancer: preliminary results of a European Organization for Research and Treatment of Cancer phase III trial. *JNCI J Natl Cancer Inst* 1996;**88**:890–9

6 Forastiere AA, Zhang Q, Weber RS, Maor MH, Goepfert H, Pajak TF *et al.* Long-term results of RTOG 91-11: a comparison of three nonsurgical treatment strategies to preserve the larynx in patients with locally advanced larynx cancer. *J Clin Oncol* American Society of Clinical Oncology: 2013;**31**:845–52

7 ASCO clinical practice guideline for the use of larynx-preservation strategies in the treatment of laryngeal cancer: guideline summary. *J Oncol Pract* 2006;**2**:258–61

8 Hoffman HT, Porter K, Karnell LH, Cooper JS, Weber RS, Langer CJ *et al.* Laryngeal cancer in the United States: changes in demographics, patterns of care, and survival. *The Laryngoscope* 2006;**116**:1–13

9 Nair SV, Mair M, Sawarkar N, Chakrabarti S, Qayyumi B, Nair D *et al.* Organ preservation vs primary surgery in the management of T3 laryngeal and hypopharyngeal cancers. *Eur Arch Otorhinolaryngol* 2018;**275**:2311–6

10 Grover S, Swisher-McClure S, Mitra N, Li J, Cohen RB, Ahn PH *et al.* Total laryngectomy versus larynx preservation for T4a larynx cancer: patterns of care and survival outcomes. *Int J Radiat Oncol Biol Phys* 2015;**92**:594–601

11 Sinha S, Agarwal JP, Mahajan A, Chaturvedi P, Balaji A, Juvekar S *et al.* Implications of limited exolaryngeal disease and cricoarytenoid joint involvement in organ conservation protocols for laryngopharyngeal cancers: Results from a prospective study. *Head Neck* 2021;**43**:1289–99

12 Putten L, Bree R, Doornaert PA, Buter J, Eerenstein SEJ, Rietveld DHF *et al.* Salvage surgery in post-chemoradiation laryngeal and hypopharyngeal carcinoma: outcome and review. *Acta Otorhinolaryngol Ital* 2015;**35**:162–72

13 Grégoire V, Coche E, Cosnard G, Hamoir M, Reychler H. Selection and delineation of lymph node target volumes in head and neck conformal radiotherapy. Proposal for standardizing terminology and procedure based on the surgical experience. *Radiother Oncol* 2000;**56**:135–50

14 Grégoire V, Levendag P, Ang KK, Bernier J, Braaksma M, Budach V *et al.* CT-based delineation of lymph node levels and related CTVs in the node-negative neck: DAHANCA, EORTC, GORTEC, NCIC, RTOG consensus guidelines. *Radiother Oncol* 2003;**69**:227–36

15 Grégoire V, Ang K, Budach W, Grau C, Hamoir M, Langendijk JA *et al.* Delineation of the neck node levels for head and neck tumors: a 2013 update. DAHANCA, EORTC, HKNPCSG, NCIC CTG, NCRI, RTOG, TROG consensus guidelines. *Radiother Oncol* 2014;**110**:172–81

16 RStudio Team. *RStudio: Integrated Development Environment for R RStudio, PBC.* Boston: RStudio Team, 2020

17 Joshi P, Joshi A, Norohna V, Chaturvedi P, Patil V, Agarwal JP *et al.* Role of neoadjuvant chemotherapy in advanced carcinoma of the hypopharynx and larynx. *South Asian J Cancer* 2017;**6**:15–9

18 Bates JE, Amdur RJ, Morris CM, Hitchcock KE, Dziegielewski PT, Boyce BJ *et al.* Curative-dose chemoradiotherapy versus total laryngectomy for stage T3-T4 squamous cell carcinoma of the larynx: an 'apples-to-apples' analysis of the national cancer database. *Am J Clin Oncol* 2019;**42**:527–33

19 Dziegielewski 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

20 Forastiere AA, Ismaila N, Lewin JS, Nathan CA, Adelstein DJ, Eisbruch A *et al.* Use of larynx–preservation strategies in the treatment of laryngeal cancer: American Society of Clinical Oncology clinical practice guideline update. *J Clin Oncol* 2018;**36**:1143–69

21 Lefebvre J-L, Ang KK, Larynx Preservation Consensus Panel. Larynx preservation clinical trial design: key issues and recommendations--a consensus panel summary. *Head Neck* 2009;**31**:429–41

https://doi.org/10.1017/S002221512200113X Published online by Cambridge University Press