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Role of Organ Preservation in Locally Advanced Hypopharyngeal Carcinoma

Farida Nazeer, Rejnish Ravi Kumar, Malu Rafi, Lekha M. Nair, Kainickal Cessal Thommachan and Kunnambath Ramadas

Abstract

Hypopharyngeal carcinoma is relatively rare and has the worst prognosis of all head and neck cancers. Initially, surgery followed by postoperative radiation was the standard of care for locally advanced disease. In the recent years, various organ sparing approaches have evolved. There are mainly two schools of thought regarding larynx preservation in hypopharyngeal cancers which include either induction chemotherapy followed by response assessment for radical radiotherapy or concurrent chemoradiation. An ongoing trial is comparing the effectiveness between these two established approaches. The role of anti-EGFR therapy and immunotherapy is still being evaluated. Despite all the advancements in treatment, hypopharyngeal cancers are still associated with poor treatment outcomes.

Keywords: organ preservation, hypopharyngeal cancer, locally advanced, induction chemotherapy, concurrent chemoradiation

1. Introduction

Hypopharyngeal carcinoma accounts for about 3% of all head and neck cancers [1]. Anatomically, the subsites include the piriform sinus, the posterior pharyngeal wall, and the post-cricoid region up to the esophageal inlet. Mostly squamous cell carcinoma of the hypopharynx presents as a locally advanced disease which is constituted by Stage III and IVa. Initially, surgery followed by postoperative radiotherapy was the most common treatment modality for these patients. The exploration of organ preservation approaches has opened a new area of research in hypopharyngeal and laryngeal tumors. The role of definitive radiotherapy (RT) was explored since the beginning of the twentieth century. Later, the role of chemotherapy either as induction or concurrent in addition to RT was also investigated. Despite all these available approaches, hypopharyngeal carcinomas still have the worst prognosis of all head and neck cancers with a reported 5-year overall survival rate of about 30–35% [2, 3]. About 50% of patients develop local recurrence within the first year itself and the majority develop distant metastasis too [3].

2. Locally advanced carcinoma hypopharynx

Laryngeal preservation can be explained as the maintenance of the function of the larynx which excludes laryngectomy, long-term tracheostomy, and long-term feeding tube. The definition of larynx preservation was made more accurate in 2009 by a group of experts who defined the term laryngoesophageal dysfunction free survival (LEDFS) which comprised local failure, salvage laryngectomy, tracheostomy or feeding tube at 2 years or thereafter [4]. Major studies of laryngeal preservation were done in laryngeal carcinoma. The promising results of these studies have paved a way to adopt the same modalities in hypopharyngeal cancers also. Even before the publishing of any Phase 3 trials in organ preservation approaches, in a population-based review of hypopharyngeal cancers by Newman et al. [2], it was observed that there is a trend towards using radical radiotherapy than surgery since 1990. Thereafter chemotherapy has been incorporated along with radiation in various combinations in the management. The organ preservation strategies can be either nonsurgical or surgical. The various nonsurgical laryngeal preservation approaches in locally advanced hypopharyngeal squamous cell carcinoma include induction chemotherapy (IC) followed by radical radiotherapy (RT); concurrent chemoradiation (CCRT); IC followed by CCRT and use of anti EFR or monoclonal antibodies along with RT.

2.1 Induction chemotherapy followed by radical radiotherapy

There was a paradigm shift in the management of locally advanced laryngeal cancers with the publishing of the Veterans Affairs Laryngeal Cancer Study Group (VALCSG) [5] which studied the role of induction chemotherapy (IC) followed by radiotherapy (RT) versus surgery followed by RT in Stage III and IV laryngeal cancers. This landmark trial has established IC followed by RT to be the preferred organ preservation approach in locally advanced laryngeal cancers [6]. This trial initiated many studies in organ preservation in hypopharyngeal cancers as well.

The earliest Phase 3 randomized trial that studied the role of organ preservation in hypopharyngeal cancers was the EORTC 24891 trial [7] which included 194 patients who were randomized to receive either IC (Cisplatin 100 mg/m² Day 1 and 5-Fluorouracil [5-FU] 1000 mg/m² infusion over 5 days) for 2–3 cycles followed by RT (N = 100) for patients with a complete response or surgical resection followed by postoperative RT (PORT) (N = 94). The 3-year overall survival (OS) for the IC arm was superior to the surgical arm (57% vs. 43%) but the 5-year OS rates were similar (30% with IC Vs 35% with surgery). The trend for disease-free survival (DFS) was similar to OS with the rates at 3 and 5-years being 43% and 25% for the IC arm versus 32% and 27% for the surgical arm, respectively. The laryngectomy free survival at 3 and 5 years in the IC arm were 28% and 17% respectively. It was also seen that the 3 and 5-year rates of retaining a functional larynx in induction chemotherapy arm were 42% and 35%, respectively. The 10-year update showed that the OS rate at 10 years was 13.8% (surgery arm) and 13.1% (IC arm) and the PFS rates were 8.5% and 10.8%, respectively. The 5- and 10-year rates of survival with preserved larynx were 21.9% and 8.7% respectively, thus confirming the role of IC followed by RT in the larynx preservation approach [8]. Thus, this trial validated the role of IC followed by RT in responders to chemotherapy as an alternative to laryngectomy for locally advanced hypopharyngeal cancers without compromising on survival or disease control.

The EORTC 24954 Phase 3 randomized control trial was done to assess the feasibility of delivering more cycles of chemotherapy [9]. This study compared

alternative chemotherapy with RT versus IC followed by RT in patients with laryngeal and hypopharyngeal tumors. This trial included 450 patients who were randomized to either 2 cycles of IC (Cisplatin and 5-FU) followed by additional 2 cycles in responders followed by radiotherapy (70Gy total) or alternating arm of 4 cycles of chemotherapy (cisplatin and 5-FU) alternating with RT 20Gy during the three 2-week intervals between chemotherapy cycles (total 60Gy). Salvage surgery followed by PORT was offered to patients who did not respond to IC. The 3-year and 5-year rates of survival with a functional larynx were similar in both arms. Acute toxic effects were statistically significantly high in the sequential arm. But in this trial, the radiotherapy doses used were different (median dose for the IC arm was 71.5 Gy and for the alternating arm was 62.8Gy). The 10-year follow-up of the study also showed that the survival with functional larynx and overall survival were similar in both arms (18.7% and 33.6% in IC arm versus 18.3% and 31.6% in alternating arm) [10]. It was also observed there was a small trend for higher larynx preservation and better laryngeal function in the alternating arm. The late toxicities were similar in both arms and there was better tolerance of treatment in the alternating arm which may be explained by the lower doses of chemotherapy and radiotherapy doses in the investigational arm. Though this alternating chemotherapy and radiotherapy has been validated in the literature, this regimen has not been routinely practiced which may be due to the technical difficulty of institutions in delivering such alternating schedules.

In this background, studies investigated the benefit of addition of Docetaxel to IC along with Cisplatin and 5FU (TPF) in laryngeal and hypopharyngeal tumors. The superiority of 3 drug IC with the addition of a taxane to Cisplatin and 5 FU in terms of OS and PFS for advanced-stage head and neck cancers has been established by the TAX 323 [11] and TAX 324 trials [12]. To evaluate the same in locally advanced laryngeal or hypopharyngeal cancers, the GORTEC 2000–2001 trial was conducted [13]. This included 220 patients who were eligible for a total laryngectomy. The randomization was between IC with TPF (docetaxel at 75 mg/m² on day 1, cisplatin at 75 mg/m² on day 1, and 5-FU at a dose of 750 mg/m² continuous infusion over 5 days) Vs PF (cisplatin 100 mg/m² on day 1 and 5-FU given at a dose of 1,000 mg/m² continuous infusion over 5 days). Three cycles of IC chemotherapy were given in each arm and the responders (complete response at the primary site or partial response and recovered normal larynx mobility) received radical RT while non-responders underwent total laryngectomy and postoperative RT. The 3-year laryngeal preservation rate was 70.3% (TPF) vs. 57.5% (PF). The overall response was statistically higher in the TPF arm when compared to the PF arm (80.0% vs. 59.2%, $P = .002$). The acute toxicities to chemotherapy were variable in both arms with the TPF arm having more grade 2 alopecia, grade 4 neutropenia, and febrile neutropenia, while the PF arm had more grade 3 and 4 stomatitis, thrombocytopenia, and grade 4 creatinine elevation. The long-term efficacy and safety of the trial with a median follow-up of 105 months showed that the 5-year and 10-year larynx preservation rates were 74.0% vs. 58.1% and 70.3% vs. 46.5% ($P = .01$) in the TPF vs. PF arm, respectively [14]. Fewer grade 3–4 late toxicities were higher in the TPF arm when compared with the PF arm. (9.3% vs. 17.1%, $P = .038$).

Thus, IC with TPF was found to be superior to PF with respect to laryngeal preservation rates in locally advanced laryngeal and hypopharyngeal cancers hence being a reasonable organ preservation approach albeit the toxicity of chemotherapy.

The major difference between the EORTC 24954 trial and GORTEC 2000–2001 trial was that radical radiotherapy was given to only complete responders to chemotherapy in the EORTC study while RT was given to patients with complete response in primary site or partial response with recovered normal mobility of larynx in the latter study.

Moreover, in the subsite analysis of MACH-NC, induction chemotherapy has shown a 5-year absolute benefit of 5.3% in OS and 3.3% in event-free survival (EFS) in hypopharyngeal cancers [15].

2.2 Concurrent chemotherapy

The role of concurrent chemotherapy along with RT in head and neck squamous cell carcinoma was established in the large MACH-NC meta-analysis and its updates [15–19]. The addition of chemotherapy concurrently to radiotherapy had shown improved survival for all tumor sites with an absolute 5-year OS benefit of 3.9% in the subset analysis of hypopharyngeal cancers. Thus, concurrent chemoradiation is another potential strategy that can be practiced for the organ preservation approach.

The role of CCRT in organ preservation for laryngeal cancers was established in RTOG 91–11 and its update and the study had shown a higher 10-year laryngeal preservation rate in CCRT arm over IC followed by RT when compared to RT alone [20, 21]. This study was only for laryngeal cancers and did not include patients with primary in the hypopharynx. Concurrent chemoradiation in hypopharyngeal cancers was studied in a phase 3 randomized trial by Prades et al. [22]. This trial included 81 patients with T3N0 pyriform sinus tumors only and the randomization arms were either CCRT with Cisplatin or IC with Cisplatin and 5-FU followed by response assessment for RT. The 2-year laryngeal preservation rates were 68% in the IC and 92% in the CCRT arm ($p = 0.016$) and the two-year event-free survival rates were 36% (IC arm) and 41% (CCRT arm) respectively without any difference in overall survival (47% vs. 51%). Even though this trial showed that CCRT is superior to IC followed by RT in responders, it included only a specific subset of patients and the sample size was also less.

To conclude, there are two schools of thought in the organ preservation approach in hypopharyngeal cancers which include either induction chemotherapy followed by response assessment or concurrent chemoradiation. These two approaches are being compared in the ongoing Phase 3 French trial (GORTEC 2014–2103-SALTORL) which randomizes patients with laryngeal and hypopharyngeal cancers into IC with TPF followed by RT vs. CCRT with Cisplatin [23].

2.3 Induction chemotherapy followed by chemoradiation

No trials have evaluated the role of induction chemotherapy followed by chemoradiation in hypopharyngeal cancers alone. Various studies have shown that IC with 3 drugs is not superior to CCRT alone in head and neck squamous cell carcinoma and the meta-analysis by Budach et al. also showed that induction chemotherapy with TPF before CCRT did not improve OS and PFS in locally advanced head and neck cancers compared to chemoradiation [24–27].

2.4 Role of anti-EGFR therapy

Anti-EGFR therapy has been tried in different combinations in the management of various head and neck squamous cell carcinomas. Various trials have compared RT alone vs. RT plus anti-EGFR [28, 29]; CCRT vs. CCRT plus anti-EGFR [30–32]; RT with Cetuximab vs. CCRT with Cetuximab [33]; CCRT vs. RT plus anti-EGFR [34–36] and IC followed by RT with Cetuximab vs. CCRT [37]. But there has been no proven benefit for anti-EGFR therapy in addition to concurrent chemoradiation in terms of overall survival in head and neck cancers.

There are no Phase 3 trials that have evaluated the role of anti-EGFR therapy specifically in hypopharyngeal and laryngeal cancers. Two Phase 2 trials have investigated the role of Cetuximab in these tumors. These include the GORTEC TREMPLIN trial and the DELOS trial which had studied the role of addition of Cetuximab to RT following IC with TPF (38–40). Both studies did not prove any superiority with the addition of Cetuximab and showed an increase in adverse effects in those receiving Cetuximab. Thus, there is no proven data for the use of anti-EGFR therapy in hypopharyngeal cancers and more Phase 3 studies are required to establish its role.

2.5 Role of immunotherapy

Immunotherapy has no established role in the management of locally advanced hypopharyngeal cancers. The JAVELIN trial which included locally advanced cancers of hypopharynx, oropharynx, larynx, and oral cavity studied the role of Avelumab with concurrent chemoradiation [38]. The interim analysis did not show any significant improvement in PFS with the addition of Avelumab to CCRT.

2.6 Surgery

Various partial resection procedures that do not include a total pharyngolaryngectomy are available as organ preservation strategy. They include endoscopic transoral laser microsurgery (TLM), supracricoid partial laryngectomy, and partial pharyngectomy [39].

The ability to get a negative margin in hypopharyngeal cancers makes these procedures challenging. Transoral laser microsurgery (TLM) is a reasonable approach for the treatment of early and even moderately advanced tumors of the hypopharynx. Martin and Steiner et al. reported the results of 172 patients with hypopharyngeal cancer (Stage I-4%, Stage II-11%, Stage III-30% and Stage Iva-55%), mostly with piriform sinus tumors (87%) who underwent endoscopic TLM resections [40]. Even though this study demonstrated that TLM is a valid option to standard radical surgery or standard conservation treatment, it was seen that only 6% could be treated with TLM alone while 42% required TLM and neck dissection; 4% required TLM and adjuvant radiotherapy; and 48% needed TLM, neck dissection, and adjuvant radio- or radio chemotherapy. It was seen that 52% patients required adjuvant radio (chemo-)therapy. Another innovative approach is transoral robotic surgery (TORS). TORS has mainly been applied in the treatment of oropharyngeal carcinoma but has been tried in the treatment of hypopharyngeal and laryngeal cancers. As of now, there are only few case series showing better functional outcomes with TORS in T1-T2 hypopharyngeal tumors [41–44].

Even though various surgical approaches are available, they are mainly indicated in selected subset of patients, especially with early stage well defined lesions. It has to be noted that majority of the patients who undergo primary organ preservation surgery ultimately require adjuvant radiotherapy with or without chemotherapy. Adequate surgical expertise is also required for these procedures. Hence the role of surgery in organ preservation approach in locally advanced hypopharyngeal cancers remains questionable.

3. Hypopharyngeal cancers with cartilage destruction (T4a N0-N2 disease)

Patients with cartilage destruction are not ideal candidates for larynx preservation approaches and surgery followed by RT remains the standard of care in this

subgroup. There is less likelihood of complete response with RT or CCRT and reduced success rates due to increased complications of salvage laryngectomy in these patients.

4. T4b or N3 disease

These subsets of patients are generally treated with palliation. Highly selective patients like those with low volume primary, absence of heavy nodes, good performance status, and younger age group may be considered for radical approach [45].

5. Future directions

Large-scale clinical trials are difficult in hypopharyngeal tumors due to the poor prognosis and uncommon incidence of such tumors. The future direction in the management of hypopharyngeal cancers is the use of immunotherapy [46]. The role of immune checkpoint inhibitors like Pembrolizumab and Nivolumab has shown promising results in recurrent or metastatic head and neck squamous cell carcinomas [47, 48]. New studies must be done to assess the effectiveness of these agents in larynx preservation. The expression of ERCC1 as a predictive biomarker in head and neck cancers including hypopharynx for chemotherapy response to 5-FU/cisplatin for both organ preservation and survival has been identified [49]. Validation of the various biomarkers is required to select the ideal candidates that can benefit from various treatments.

6. Conclusion

T1, T2 N1-N2 tumors are treated with concurrent chemoradiation. T3 N0-N2 can be treated either with concurrent chemoradiation or induction chemotherapy followed by reassessment for radical radiation. Patients with T4a N0-N2 (cartilage destruction) disease are treated with surgery followed by postoperative radiotherapy. The treatment for patients with T4b or N3 should be an individualized approach. The decreased treatment outcomes of hypopharyngeal cancers compared to laryngeal cancers are due to advanced stage at presentation disease, poor response to chemoradiation, and difficulty in salvage surgery. An ongoing trial is comparing the effectiveness between the two established organ preservation approaches. The definite role of surgery in organ preservation in locally advanced hypopharyngeal cancers requires further validation. There is no proven data for anti-EGFR or immune checkpoint inhibitors in the radical treatment of locally advanced hypopharyngeal cancers to date and trials are underway.

Conflict of interest

“The authors declare no conflict of interest.”

Notes/thanks/other declarations

Nil.

Appendices and nomenclature

Nil.

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