

Postoperative Radiotherapy in Hypopharyngeal Cancer: Single-institution Outcome Analysis

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Abstract

Purpose: To retrospectively review the outcomes of adjuvant postoperative radiotherapy (PORT) following surgery in patients with advanced hypopharyngeal cancer treated at an academic tertiary referral center.

Methods: Data of patients treated with curative intent in a single radiotherapy unit over a 15-year period (1990-2004) with upfront surgery followed by PORT was retrieved from an electronic database. Local control (LC), locoregional control (LRC) and disease-free survival (DFS) were considered as outcome measures.

Results: The study dataset constituted 159 patients with a median age of 55 years (range 30-79 years). Patients underwent either radical surgery (total laryngectomy with or without pharyngectomy) or voice-conserving surgery. All patients underwent appropriate comprehensive neck dissection. The median radiotherapy dose was 60 Gy (inter-quartile range 50-60 Gy). With a mean follow-up of 21 months (inter-quartile range 6-29 months), the 3-year LC, LRC, and DFS was 87.8%, 70.3% and 62.2% respectively. Cut margin negativity and pyriform sinus subsite predicted for improved LRC and DFS on univariate analysis. Cut margin status was the only independent predictor of outcome on multivariate analysis.

Conclusion: Hypopharyngeal cancer characterized by advanced disease at presentation. Definitive surgery (either voice-conserving or radical) followed by adjuvant radiotherapy provides good LRC and DFS and continues to remain a valid upfront treatment option for advanced hypopharyngeal cancer. Cut margin status and primary subsite are important determinants of outcome.

Keywords: Hypopharyngeal cancer; postoperative radiotherapy; and prognosis.

INTRODUCTION

The incidence of hypopharyngeal cancer has witnessed a decreasing trend in the western hemisphere including United States,¹ in contrast to the steady increase in developing countries.^{2,3} Hypopharyngeal cancer is characterized by advanced disease at presentation with extensive submucosal spread, high risk of regional lymphatic involvement and relatively high propensity of distant metastases.⁴ Therapeutic decision-making includes consideration of stage, site, age, performance status, and personal and institutional preferences. The traditional treatment paradigm for advanced hypopharyngeal cancer surgery has been followed by adjuvant postoperative radiotherapy (PORT) with an aim to

maximize the locoregional control and improve survival.⁵ In recent times, definite chemoradiation has been tested to preserve laryngeal and pharyngeal form and function, without compromising survival. The outcome of advanced hypopharyngeal cancer with primary non-surgical approaches^{4,6,7} has been suboptimal and inferior to upfront surgery and adjuvant therapy.⁷⁻¹⁰ While organ-preservation strategies and intensified adjuvant therapies continue to evolve rapidly, contemporary series reporting outcomes of surgery and PORT would continue to serve as benchmarks for future comparisons. This study aims to retrospectively review the outcomes of adjuvant PORT following voice-preserving or radical surgery in a cohort of patients with moderate to advanced hypopharyngeal cancer treated within

a single radiotherapy (RT) unit in a large academic tertiary referral center in a developing country.

MATERIALS AND METHODS

Medical case records of patients registered as carcinoma of the hypopharynx on an electronic head and neck squamous cell carcinoma (HNSCC) database and treated in a single RT unit over a 15-year period (1990-2004) were retrospectively reviewed. Only previously untreated patients, planned for curative-intent treatment with upfront surgery (conservative or radical) followed by PORT were considered eligible for analysis. Patients treated with surgery alone without PORT, split therapy,¹¹ or neoadjuvant chemotherapy were excluded. For the purpose of this report, local control (LC), locoregional control (LRC) and disease-free survival (DFS) were considered as primary outcome measures. Overall survival was not considered as an outcome measure due to high non-cancer related mortality. Due to the combined effects of aging and medical comorbidities, attendant to tobacco and alcohol abuse prevalent in this population.

Staging Work-up and Follow-up Evaluation

Staging evaluation consisted of a detailed clinical, endoscopic (examination under anesthesia and biopsy) and imaging evaluation to ascertain the extent of disease. Computed tomographic (CT) scan of head and neck though not mandatory was increasingly performed in the latter part of the study for better staging and determining resectability. Chest radiography was routinely done to rule out pulmonary metastases. All patients were subsequently evaluated in a multidisciplinary head and neck joint clinic for therapeutic decision-making. From early 2000, the option of organ-preservation with primary non-surgical approaches keeping surgery reserved for salvage was discussed with all suitable patients. Patients planned for upfront surgery were counseled regarding the type and extent of surgery, anticipated post-surgical functional morbidity and cosmetic outcome. They also underwent preoperative evaluation by a dedicated speech therapist for consideration of voice-rehabilitation and lung function tests to assess pulmonary reserves for major surgery and prolonged ventilation.

All patients were required to follow up at 6-8 weeks after completion of PORT. Subsequently patients were evaluated 3-4 monthly for two years and then 6-monthly thereafter for five years. All patients were evaluated clinically

for evidence of locoregional disease. Endoscopic and/or imaging evaluation was undertaken whenever necessary. Patients who did not attend scheduled follow-up clinics were contacted through reply-paid postcards and telephonically to update disease status. Patients not responding to above measures were considered lost to follow-up and censored for statistical analysis.

Surgery

All patients were operated within a single institution by a specialized head-neck surgical oncology and plastic surgery reconstructive team. Whenever feasible a voice-conserving surgery (partial laryngopharyngectomy, near total laryngectomy with tracheoesophageal puncture or endoscopic resection) was attempted for the primary. Total laryngectomy or laryngopharyngectomy with or without tracheoesophageal puncture was considered in patients with apex involvement, cartilage invasion, or extension to postcricoid region. Primary closure of the resultant surgical defect was achieved by raising a mucosal flap, whenever feasible. In patients with large surgical defects, pectoralis major myocutaneous flap or gastric pull-up technique was used. All patients underwent some form of neck dissection with primary surgery. Ipsilateral or bilateral comprehensive neck dissection (modified or radical) was done in most of the patients.

Radiotherapy

Patients with high-risk factors on surgical pathology (pT3-pT4, multiple involved neck nodes, perinodal extension, close (< 5 mm) or positive cut margins, perineural invasion, lymphovascular emboli, and poorly differentiated tumors either alone or in combination) were considered for two-dimensional conventionally fractionated postoperative adjuvant RT. The entire operative bed was treated with a 2 cm margin to a dose of 56-60 Gy/28-30 fractions with megavoltage radiation over 5.5-6 weeks with bilateral parallel opposed beams. Additional anterior neck portal was used in patients where bilateral portals provided inadequate coverage of the stoma. Off-cord reduction was applied after 46 Gy, and posterior neck boosted with appropriate energy electrons whenever necessary. Beam shaping with corner blocks and use of tissue compensators to ensure homogenous dose distribution was at the discretion of the treating radiation oncologist. Patients were reviewed weekly during the course of RT to document acute toxicity and ensure compliance.

Analgesics, anti-inflammatory agents, and local anesthetic gels were prescribed liberally, while narcotic analgesics were used judiciously whenever necessary. Prophylactic nasogastric intubation was not practiced routinely, but patients with feeding tubes *in situ* at the time of referral for RT were advised to continue tube feeding.

Statistical Analysis

Statistical Package for Social Sciences (SPSS® version 15) was used for statistical analysis. Reappearance of disease at the primary site in the laryngopharynx was considered as local failure. Any recurrence of disease either locally or in the neck was considered locoregional failure. Appearance of distant metastases or a second new primary within the upper aerodigestive tract was additionally considered as an event for disease-free survival. LC, LRC, and DFS were calculated using Kaplan Meier method. Log-rank test was used for comparison on univariate analysis and Cox regression (backward conditional) for multivariate analysis.

RESULTS

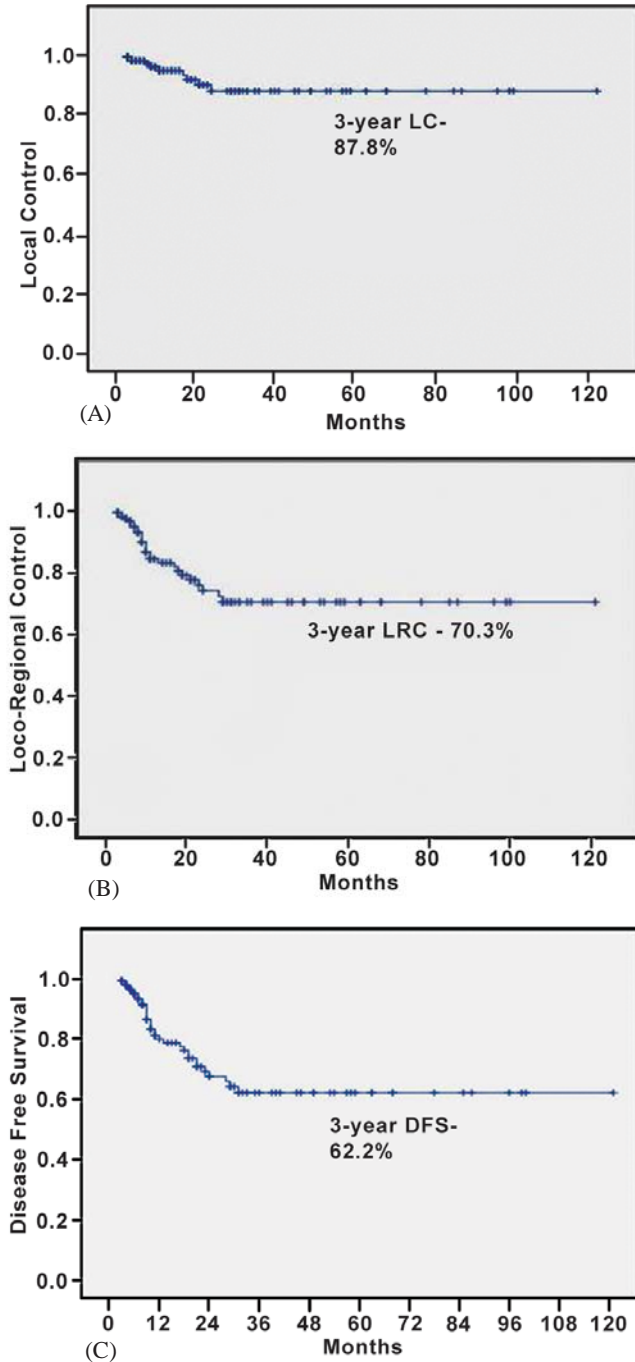
The electronic HNSCC database identified 678 patients with hypopharyngeal cancer treated with radical intent over a 15-year period (1990-2004) in a single RT unit. Among these, 501 patients received primary non-surgical treatment, outcomes of which have been previously reported.⁴ A total of 177 patients underwent upfront surgery. Eighteen of these were treated with either split therapy or neoadjuvant chemotherapy followed by surgery with or without adjuvant RT and were excluded, leaving 159 patients treated with voice-preserving or radical surgery followed by PORT which constitutes the dataset for this report. None of these patients were given postoperative concurrent or adjuvant systemic chemotherapy, as it was not considered standard in those times, even for the high-risk patients.

The demographic characteristics of the study cohort are detailed in Table 1. The median age was 55 years (range 30-79 years) with a male predominance (96%). The median Karnofsky's Performance Status (KPS) was 80 (range 50-90). Tobacco smoking and/or chewing was highly prevalent in the study cohort with 52% smokers and 33% tobacco chewers. Pyriform sinus was the commonest (91%) subsite of primary disease. One hundred thirteen (71%) patients underwent total laryngectomy with or without pharyngectomy whereas twenty four (15%) underwent

Table 1: Clinical, pathological, and treatment characteristics of entire cohort

Characteristics	Number of patients (%)
<i>Primary subsite</i>	
Pyriform sinus	145 (91%)
Non-pyriform sinus	14 (9%)
<i>Surgical Procedure (Primary site)</i>	
Endoscopic Resection/Partial laryngectomy	3 (2%)
Near Total Laryngectomy	21 (13%)
Total Laryngectomy +/- Pharyngectomy	113 (71%)
Not specified / Not known	22 (14%)
<i>Surgical Procedure (Neck nodes)</i>	
Unilateral Modified / Radical Neck Dissection	31 (20%)
Bilateral Modified / Radical Neck Dissection	100 (63%)
Not specified / Not known	28 (17%)
<i>Pathological T-stage</i>	
pT1-T2	17 (11%)
pT3-4	142 (89%)
<i>Pathological N-stage</i>	
pNx	9 (5%)
pN0-N1	47 (30%)
pN2-3	103 (65%)
<i>Pathological stage grouping</i>	
Stage III	9 (5%)
Stage IV	147 (93%)
Not known	3 (2%)
<i>Cut margin status</i>	
Not specified/Not known	8 (5%)
Negative	105 (66%)
Positive	27 (17%)
Close (< 5 mm)	19 (12%)
<i>Perinodal extension</i>	
Present	69 (43%)
Absent/Not known	90 (57%)
<i>Number of risk factors on histopathology</i>	
0	3 (2%)
1	21 (13%)
2-3	86 (54%)
≥4	49 (31%)
<i>Recursive Partitioning Analysis (RPA) Class</i>	
RPA class I	65 (41%)
RPA class II	32 (20%)
RPA class III	62 (39%)

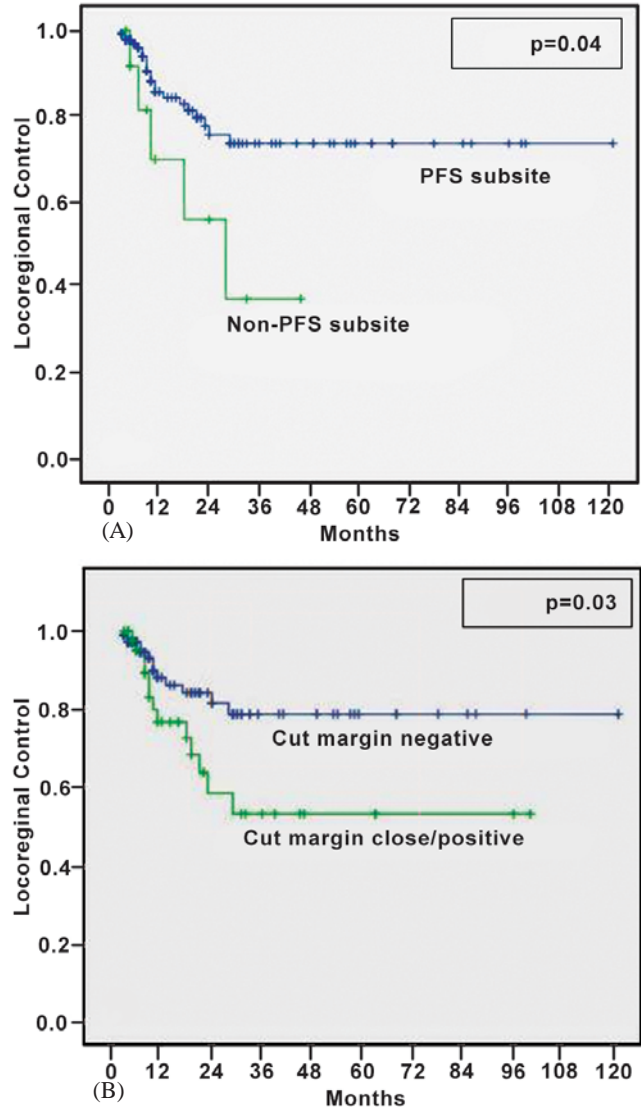
voice-conserving surgery (partial laryngectomy, near total laryngectomy or endoscopic resection). Surgical details were partial or missing in the remaining twenty two (14%) patients. All patients underwent some form of neck dissection along with primary surgery. Comprehensive neck dissection (either unilateral or bilateral modified or radical neck dissection) was done in 131 (83%) patients, whereas details regarding the neck dissection were incomplete in 28 (17%) patients. Primary closure of the post-surgical defect was feasible in majority of patients. Plastic reconstruction either flap reconstruction (10%) or gastric pull-up (7%) was done when deemed necessary. Eighteen (11%) patients had post-surgical leak from the anastomotic site. Most leaks



Figs 1A to C: 3-year local control (A), loco-regional control (B), and disease-free survival (C) in the study cohort of 159 patients of hypopharyngeal cancer treated with definite surgery followed by adjuvant post-operative radiotherapy

were managed conservatively without surgical re-exploration which was needed in just 2 patients. Postsurgical wound infection and stomal stenosis was seen in 8 (5%) and 2 (1%) patients respectively.

The median time from surgery to initiation of PORT was 45 days (interquartile range 34-60 days). Inadvertent



Figs 2A and B: Correlation of locoregional control with primary subsite (A) and cut margin status (B) in the study cohort

delay in initiation of adjuvant treatment was recorded in patients with major surgical complications (requiring re-exploration). The median RT dose and overall treatment time (OTT) was 60 Gy (inter-quartile range 50-60 Gy) and 43 days (inter-quartile range 38-47 days) respectively. One hundred thirty-four (84%) patients completed the planned course of RT without any interruptions or gap. Three (2%) patients needed treatment breaks while another 3 (2%) were hospitalized for symptomatic management of acute radiation reactions. RT was terminated earlier (dose reduction) in 8 (5%) patients at the discretion of treating oncologist.

With a mean follow-up of 21 months (inter-quartile range 6-29 months), the 3-year LC, LRC, and DFS of the entire cohort of 159 patients was 87.8%, 70.3% and 62.2%

Table 2: Univariate analysis of prognostic factors for main outcome measures

Prognostic factor	No of pts	3-yr LC	p-value	3-yr LRC	p-value	3-year DFS	p-value	
Age	≤ 55 years	74	89.8%	0.57	77.8%	0.43	70.1%	0.48
	> 55 years	85	86.2%		63.3%		54.4%	
KPS	≥ 80	99	91.2%	0.47	71.3%	0.67	60.7%	0.45
	<80	60	83.2%		69.3%		65.0%	
Subsite	PFS	145	88.4%	0.86	73.6%	0.04	64.5%	0.15
	non-PFS	14	80.0%		37.2%		37.2%	
T-status	pT1-2	17	93.8%	0.95	80.4%	0.64	80.4%	0.39
	pT3-4	142	87.1%		68.9%		60.1%	
N-status	pN0-1/NX	56	86.0%	0.36	67.5%	0.53	61.9%	0.89
	pN2-pN3	103	89.1%		72.4%		62.7%	
Stage group	pStage III	9	77.8%	0.22	77.8%	0.69	77.8%	0.60
	pStage IV	147	87.8%		68.4%		59.7%	
PNE	Absent/NK	90	88.7%	0.88	69.1%	0.99	59.4%	0.65
	Present	69	86.3%		72.1%		66.5%	
PORT Dose	< 60 Gy	71	85.4%	0.47	66.3%	0.39	56.9%	0.28
	≥ 60 Gy	88	90.4%		74.7%		68.6%	
Cut margins	Negative/NK	113	90.2%	0.50	78.8%	0.03	70.4%	0.08-
	Positive/close	46	82.8%		53.2%		46.4%	
Risk factors	1	21	95.2%	0.86	79.1%	0.52	79.1%	0.75
	2-3	86	85.7%		69.7%		58.0%	
	≥ 4	49	90.9%		67.9%		63.0%	
RPA	Class I	65	88.2%	0.79	75.9%	0.46	67.7%	0.56
	Class II	32	84.7%		59.2%		48.2%	
	Class III	62	89.7%		72.1%		65.8%	
OTT- PORT	≤ 43 days	47	94.1%	0.91	77.5%	0.95	74.1%	0.80
	>43 days	41	86.2%		71.1%		62.0%	
Overall		159	87.8%		70.3%		62.2%	

KPS = Karnofsky Performance Status; PFS = Pyriform Sinus; PNE = Perinodal Extension; NK = Not Known; PORT = Postoperative Radiotherapy; RPA = Recursive Partitioning Analysis; OTT = Overall Treatment Time

respectively (Figs 1A to C). A univariate analysis was done for correlating known prognostic factors with outcome (Table 2). The 3-year LRC (Fig. 2A) for patients with pyriform sinus subsite was significantly better than patients with posterior pharyngeal wall tumors or post-cricoid cancers (73.6% vs 37.2%, $p = 0.04$). Patients with close or positive cut margins fared poorly as compared to patients with negative margins. The 3-year LRC (Fig. 2B) of patients with close or positive margins was significantly inferior to those with negative margins (53.2% versus 78.8%, $p = 0.03$). There was a trend for improved DFS also in patients with negative margins (70.4% versus 46.4%, $p = 0.08$). None of the other prognostic factors were significant for LC, LRC, or DFS. Incomplete documentation regarding lymphovascular emboli precluded assessment of its impact on outcome. Cut margin status was the only independent predictor of LRC (hazards ratio 1.9; 95% confidence interval (CI): 1.2-2.7) and DFS (hazards ratio 1.3; 95% CI: 1.0-1.6) on multivariate analysis. Primary subsite which was a significant predictor of LRC on univariate analysis was found to be only of borderline significance on multivariate analysis. Locoregional failure

was the predominant pattern of relapse (26 patients), whereas distant metastases and second new primary were documented in 10 and 1 patient respectively.

Acute toxicity was determined using Radiation Therapy Oncology Group toxicity criteria. Grade I-II skin and mucosal toxicity was noted in 69% and 84% patients respectively. Grade III skin and mucosal toxicity was noted in 25% and 8% patients respectively. No Grade IV reactions were observed. Analysis of late effects was not done due to missing data in significant proportion of patients. Surgical re-excision was offered to only 3 patients presenting with small volume locoregional recurrence, one of who also received adjuvant re-irradiation. Vast majority of patients with recurrent unresectable locoregional disease or distant metastases were offered either palliative systemic chemotherapy or best supportive care.

DISCUSSION

Hypopharyngeal cancer is generally characterized by advanced stage at presentation with extensive submucosal spread, high risk of regional lymphatic involvement and relatively high propensity of distant metastases, resulting in

poor outcomes.⁴ Optimal therapy is not well-defined and continues to evolve rapidly. Although gaining popularity, the efficacy of organ-preservation approaches have not been tested robustly in hypopharyngeal cancer, unlike laryngeal cancer precluding firm conclusions and evidence-based recommendations. The present study is an outcome analysis of 159 patients with carcinoma hypopharynx treated with primary surgery followed by adjuvant PORT alone within a single academic RT unit at a comprehensive cancer center. The sociodemographic characteristic of the studied population is generally consistent with previously published data from developing countries.^{4,8} Voice-conserving surgery was feasible in only 22% of the patients, mostly in the latter part of the study. Majority of the patients underwent total laryngectomy with or without pharyngectomy. Locoregional control with surgery followed by adjuvant PORT has been reportedly variable in hypopharyngeal cancer ranging from 35-80% at 3 years and 25-70% at 5 years.^{6-10,12-18} A 3-year rate of 70.3% reported herewith lies towards the favorable end of the spectrum. Institutional policy of exhaustive systemic imaging only for symptomatic patients or potentially locoregionally salvageable candidates may have precluded detection of distant metastases, resulting in gross underreporting. Similarly, low rates of second primary cancers may be attributed to a shorter follow-up and high attrition.

Several clinicopathologic factors have previously been demonstrated to impact upon outcome in curative-intent treatment of HNSCC^{19,20} including hypopharyngeal cancer.^{18,21,22} The current study identified cut margin status and primary subsite to be significant predictors of outcome. Many retrospective as well as prospective series have also reported the adverse impact of advancing stage,^{8,18,21,22} increasing level of lymph node involvement,²¹⁻²³ perinodal extension,^{8,14,18,20} perineural invasion,²⁴ and lymphovascular emboli.^{21,24} However, none of these factors were significant in the current study. Time to postoperative radiotherapy and overall treatment time (OTT) have also been important prognostic factors.^{19,25-27} The current study, however, did not report any differences in outcome based on the interval between surgery and initiation of PORT. OTT of RT did not impact upon outcome significantly. A recently proposed Recursive Partitioning Analysis (RPA) classification²⁸ for HNSCC—a composite prognostic index offers better risk-stratification schema for tailoring treatment and predicting outcomes.

In a prospective institutional protocol favoring surgery as initial approach for carcinoma hypopharynx, Eckel et al,¹³ studied 228 consecutive patients to assess surgical mortality, locoregional control, and survival. One hundred thirty six (59.6%) patients were found suitable for initial surgical treatment, 46 of which had larynx-sparing procedures, 54 total laryngectomy and partial pharyngectomy with primary closure, and 36 total laryngopharyngectomy with microvascular pharyngeal reconstruction. PORT was given to 120 of these 136 patients. Actuarial 5-year overall survival was 27.2% for the entire cohort; 39.5% for 136 patients treated with surgery and only 8.7% for patients managed with non-surgical approaches. The 5-year local control was 66.3% in the surgery group. Here it is important to note that the non-surgical group represents a negative selection bias with inherently poorer prognosis and cannot be directly compared. The best outcome (local control-73.4% and survival-61.1%) was seen in the 46 patients treated with conservative surgical approach, reflecting early stage disease. Of all patients treated with surgery, 33% had functioning larynx preserved 5 years after surgery. For patients treated with initial larynx-sparing surgery, the 5-year larynx preservation rate was 92%.

In a more contemporary cohort,²⁹ 202 patients were treated with different approaches as per their own choice without a surgeon's bias, and retrospectively assigned to primary surgery or primary chemoradiotherapy (CT-RT) groups with early CT-RT salvage and early surgical salvage respectively. In 72 patients, the primary treatment was surgery, of which 47 received postoperative chemoradiotherapy for high-risk features. Definitive CT-RT was initial primary treatment in remaining 130 patients, 69 of which received salvage surgery within 2 months of chemoradiotherapy for suspected or visible residual tumor. With a median follow-up of 3 years (range 1.5-10 years), 33 (45.8%) and 3 (4.2%) patients developed loco-regional recurrences and distant metastases in initial surgery group (n = 72), with 30 dying of disease. The corresponding figure was 79 (60.8%) and 14 (10.8%), with 80 deaths in the initial CT-RT group, with statistically significant differences in locoregional recurrence, disease-specific survival and overall survival favoring initial surgery with early chemoradiation salvage.

In a small randomized trial,¹⁶ induction chemotherapy followed by surgery and adjuvant PORT (arm A-47 patients) was compared to induction chemotherapy followed by

definitive RT (arm B-45 patients) keeping surgery reserved for salvage in patients with advanced hypopharyngeal cancer. With a mean follow up of 92 months, 5-year overall survival was significantly better in arm A as compared to arm B (37% vs 19%, $p = 0.04$), because of better local control (63% vs 39%, $p = 0.01$) leading to the conclusion that mutilating surgery improved outcome regardless of response to induction chemotherapy.

The most robust evidence for organ-preservation in hypopharyngeal cancer comes from the European Organization for Research and Treatment of Cancer (EORTC) trial 24891,¹⁷ which randomized patients with advanced cancers of the hypopharynx and lateral epilynx to induction chemotherapy followed by radiotherapy (surgery for non-responders) or surgery followed by adjuvant PORT. The trial had to be closed prematurely after accruing 202 patients due to difficulty in getting consent for surgery. The median survival was 25 months in the immediate surgery arm and 44 months in the induction chemotherapy arm, with an observed death hazard ratio of 0.86 (95% CI: 0.50-1.48), thereby rendering both treatments equivalent. The trend for 3-year DFS was also similar (43% in induction chemotherapy vs 32% in immediate surgery arm). The 3-year estimate of retaining a functional larynx in the induction chemotherapy arm was 42% (95% CI 31-53%), leading to the conclusion that larynx preservation is possible in over one third of patients with advanced hypopharyngeal cancer without compromising survival. Following this, organ conservation approach has been adopted as the standard approach by the EORTC in all subsequent trials in hypopharyngeal cancer.

Though ongoing cooperative group trials continue to assess intensive chemoradiotherapy approaches³⁰ for further improvement in outcome measures, the optimal treatment approach for advanced hypopharyngeal cancer still remains to be defined. In clinical practice, a significant proportion of these patients will continue to be treated with surgery followed by PORT with or without concurrent systemic chemotherapy.

CONCLUSION

Hypopharyngeal cancer is characterized by advanced disease at presentation. Their optimal upfront treatment continues to evolve rapidly. Primary non-surgical approaches with their promise of organ-preservation have gained popularity in recent times, but therapeutic decision making still remains controversial. Definitive surgery (either voice-conserving

or radical) followed by adjuvant PORT provides good loco-regional control and survival and continues to remain a valid upfront treatment option for advanced hypopharyngeal cancer. Cut margin status and primary subsite are important determinants of outcome. Intensification of adjuvant treatment in patients with high-risk features has the potential to improve outcomes further that needs to be tested in appropriately designed randomized controlled trials.

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