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Definitive Chemoradiation in Locally Advanced Squamous Cell Carcinoma of the Hypopharynx: Long-term Outcomes and Toxicity

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Abstract. *Background/Aim: Definitive chemoradiation (CRT) is a common approach for locally advanced hypopharyngeal squamous cell carcinoma (SCC) with the goal of organ preservation. Reports on long-term oncologic and functional outcomes have been limited. This study reports on outcomes utilizing this approach at a single institution over 30 years. Materials and Methods: Medical records for patients with stage III-IVB SCC of the hypopharynx were retrospectively reviewed. Patient and disease-related factors were identified and analyzed for impact on overall survival (OS), cancer-specific survival (CSS), disease-free survival, distant failure, and locoregional failure. Results: A total of 54 patients were identified who were treated with definitive CRT to a mean dose of 72 Gy. With a median follow-up period of 49.8 months, 5- and 10-year OS was 62% and 43% respectively. Five and 10-year CSS were 74% and 72% respectively. Ten-year local control was 78%. Of the 37 patients with no treatment failure, 29% experienced a grade 3 or higher late toxicity, with the majority resolving during continued long-term follow-up. Conclusion: This study demonstrates good outcomes with long-term follow-up with acceptable rates of late toxicities. The findings here represent the longest published median follow-up in this population and validate the strategy of organ preservation.*

Squamous cell carcinoma (SCC) of the hypopharynx is a rare malignancy accounting for approximately 3-5% of head and neck SCC cases (1) with a yearly incidence of 3,400 new cases in the United States (2). The management of hypopharyngeal SCC remains complex due to the close proximity of the hypopharynx to the larynx and esophagus and the natural history of the disease. Only 25% of patients with hypopharyngeal SCC present with early-stage disease (T1-T2N0) (3) and in these patients, both surgery and definitive radiation have been associated with similar outcomes in terms of local control and functional outcomes (1, 4). Due to the late presentation of symptoms and rich lymphatic drainage of the hypopharynx, most patients present with locoregionally advanced disease at the time of their diagnosis. Traditionally the standard-of-care for patients presenting with advanced disease has included extirpative surgery followed by adjuvant radiation (RT) (5, 6). The ability to preserve the larynx, and thus help maintain the crucial functions of speech and respiration has increasingly become recognized as an important goal of definitive treatment. Therefore, definitive chemoradiotherapy (CRT) has become a common treatment strategy. Treatment with CRT has indeed noted an annual 2% increase in hypopharynx patients since 1988, with over 70% of patients undergoing this treatment strategy in 2010 (7). Here, we present our long-term institutional experience of patients with locally advanced hypopharyngeal cancer treated with concurrent CRT over the past 30 years and examine the impact of this strategy on oncological outcomes and associated toxicity.

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Key Words: Head and Neck cancer, hypopharynx, organ preservation, radiotherapy, chemotherapy, squamous cell carcinoma.

Materials and Methods

We queried the Cleveland Clinic's Institutional Review Board (IRB)-approved Head and Neck Cancers Registry for patients with hypopharyngeal carcinoma treated at our institution. Patients with histologically confirmed stage III-IVB SCC of the hypopharynx treated with definitive CRT from 1986 through 2013 were included. Patients with a history of prior major surgery of the neck or glottis,

Table I. *Patient characteristics.*

Characteristic	N	%
Gender		
Female	12	22.2
Male	42	77.8
Race		
African American	10	18.5
Caucasian	42	77.8
Other	2	3.7
Smoking history		
≤10 Pack-years	13	24.1
>10 Pack-years	35	64.8

Table II. *TNM stage (AJCC 7th edition) (8) of patients with hypopharyngeal carcinoma.*

	N-Stage, n					
T-Stage	N0	N1	N2a	N2b	N2c	N3
T1	0	0	0	3	1	4
T2	0	4	2	5	4	2
T3	3	5	2	2	0	3
T4a	4	2	1	3	2	1
T4b	1	0	0	0	0	0

Table III. *Characteristics of surgery, chemotherapy, and radiotherapy.*

Factor	N	%
Chemotherapy		
Cetuximab	1	1.9
Cisplatin	2	3.7
Cisplatin + 5FU	49	90.7
Other	2	3.7
Radiation		
3D-RT	47	87.0
IMRT	7	13.0
Radiation fractionation		
BID	21	38.9
Daily	33	61.1
Elective lymph node dissection		
No	40	74.1
Yes	14	25.9
Salvage surgery after LR (n=10)		
No	2	20.0
Yes	8	80.0

5FU: 5-Fluorouracil, IMRT: intensity-modulated radiation therapy, *BID*: twice daily, LR: local recurrence.

metastatic disease, or a synchronous primary in the head and neck region were excluded. The medical chart was abstracted for data regarding patient presentation, demographics, tumor characteristics, and treatment-related outcomes. The collection, storage, and retrieval of data were all carried out in compliance with the hospital's IRB and the Health Insurance Portability and Accountability Act.

The Kaplan–Meier method was used to calculate the time to locoregional failure, distant failure, disease-free survival and overall survival (OS). Actuarial analysis was performed to estimate time-specific rates for these endpoints. Surviving patients were censored at their last clinical follow-up date. Cancer-specific survival (CSS) rates were calculated using competing risk analysis with death from other causes treated as a competing event. Rates for second malignancies were also calculated using competing risk analysis with all-cause mortality treated as a competing event. Cox proportional hazards regression was used to examine the association between locoregional failure and patient demographic, clinical, and treatment factors. A two-sided *p*-value less than 0.05 was considered to be statistically significant. All statistical analyses and plots were performed with SAS version 9.3 (SAS Institute, Cary, NC, USA).

Results

A total of 54 patients were identified [(median age=60 years, range=42-74 years), median KPS=90 (range=70-100)] with hypopharyngeal SCC treated with definitive CRT between 1986 and 2013 (Table I). The median follow-up was 49.8 months (range=1.9-184 months). Pathology confirmed SCC in 96% of samples, with one case identified as papillary SCC and one case identified as basaloid SCC. The majority of patients were Caucasian and male (78% and 78%, respectively) with greater than a 10 pack-year smoking history (65%). All patients presented with American Joint Committee on Cancer [seventh edition (8)] stage III or IV disease. Approximately 46% (n=25) of patients presented with a T1/T2 tumor and approximately 54% (n=29) presented with a T3/T4 tumor (Table II). A minority of patients presented with early nodal disease [cN0: n=8 (4.8%) and cN1: n=11 0.3%)], with 64.8% presenting with cN2 disease and higher (cN2: n=25 (46.2%) and cN3: n =10 (18.5%)].

Radiotherapy was delivered to the primary tumor and the bilateral necks *via* a conventional or 3D conformal RT technique in 87% (n= 47); seven patients were treated with intensity-modulated radiotherapy (IMRT, Table III). The median RT dose was 72 Gy (range=66-74.4 Gy) and daily fractionation was utilized in 61.1% (n=33). Twice-a-day fractionation was used for select patients (generally with T3-4 tumors) in the earlier years (9, 10). Most patients (n=49, 90.7%) received concurrent chemotherapy consisting of cisplatin and 5-fluorouracil and 92.5% (n=50) of all patients received two or more cycles of chemotherapy. Elective neck dissection was performed at the discretion of the treating

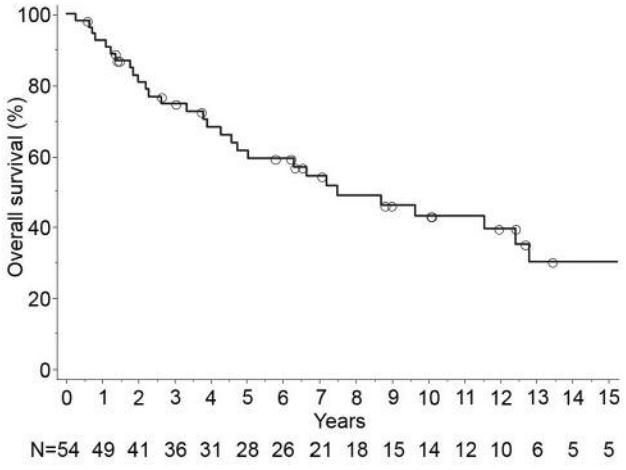

Figure 1. *Kaplan–Meier analysis of overall survival after definitive treatment for hypopharyngeal cancer.*

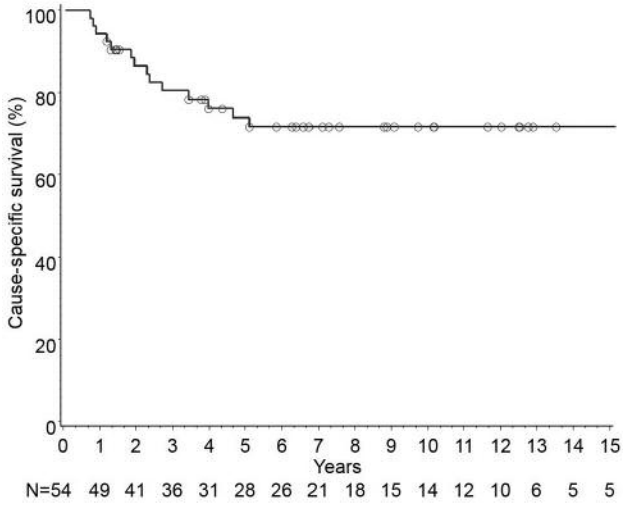

Figure 2. *Kaplan–Meier analysis of cancer-specific survival after definitive treatment for hypopharyngeal cancer.*

surgeon after definitive CRT in 25.9% (n=14) of the population, all of whom had N2 or greater disease.

The median, 5-year, and 10-year OS for the study cohort was 7.5 years, 62% [95% confidence interval (CI)=48-75%], and 43% (95% CI=28-58%), respectively (Figure 1). The 5-year and 10-year CSS for the study cohort was 74% (95% CI=62-86%) and 72% (95% CI=59-84%), respectively (Figure 2). Thirty-nine patients were without evidence of disease at the last follow-up. There were 10 locoregional failures resulting in 5- and 10-year rates of local control

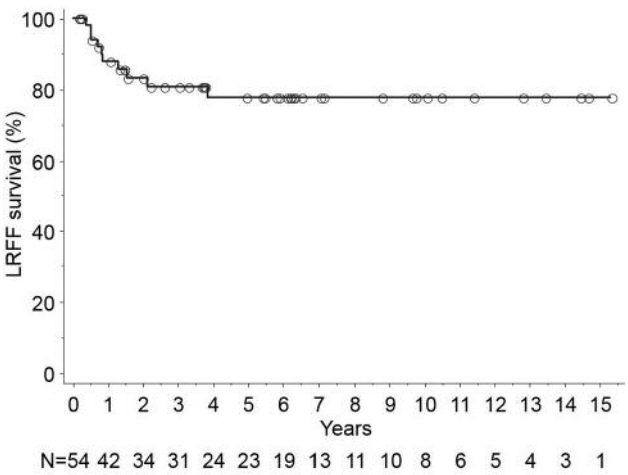

Figure 3. *Kaplan–Meier analysis of locoregional failure-free (LRFF) survival after definitive treatment for hypopharyngeal cancer.*

(Figure 3) both of 78% (95% CI=66-94%). Surgical salvage after locoregional failure was attempted in eight patients, and was successful in three, resulting in a median survival after successful salvage surgery of 11.6 years. The median survival for patients with uncontrolled locoregional disease after salvage surgery was 4.8 months. Ten patients were noted to have distant metastases: one patient developed distant metastases at the time of local regional failure, two patients with locoregional failure subsequently developed distant metastases, and seven patients were noted to develop distant metastases without evidence of locoregional failure. The median survival for the seven patients with distant metastases only was 4.8 months. The 5- and 10-year rate of distant failure-free survival (Figure 4) was 76% (95% CI=63-89%). No examined demographic, clinical, or treatment related parameter was noted to predict for locoregional failure on univariate analysis (Table IV). Twelve patients (22%) developed a second primary cancer, two of whom developed a second primary head and neck cancer. The cumulative 5- and 10- year rate of secondary malignancy was 14% (95% CI=4-24%) and 24% (95% CI=11-38%), respectively (Figure 5).

Maximum toxicities as defined by the Common Terminology Criteria for Adverse Events (CTCAE) (11) are detailed in Table V. Of the 37 patients with no recurrence during the course of follow-up, 16 (29%) patients experienced a grade 3 or higher late toxicity, with the majority (13/16) resolving in long-term follow-up. At the last follow-up of the 24 patients that required a feeding tube, seven remained dependent and nine required a limited diet without feeding tube dependence. Eighteen patients

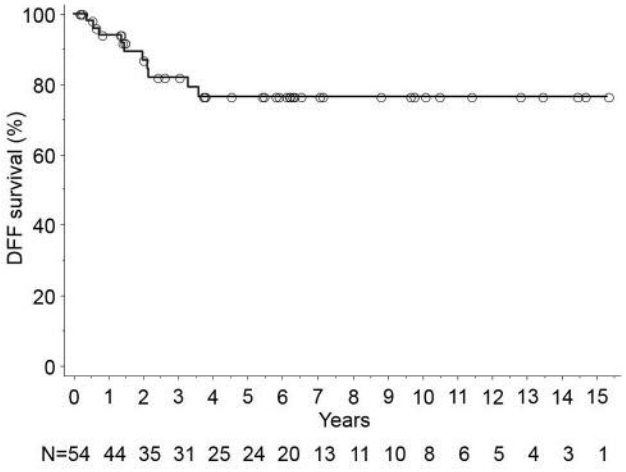

Figure 4. *Kaplan–Meier analysis of distant failure-free (DFF) survival after definitive treatment for hypopharyngeal cancer.*

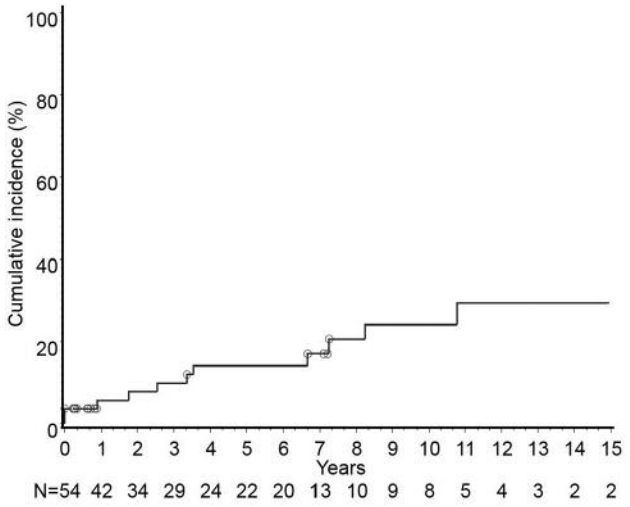

Figure 5. *Cumulative incidence of second primary malignancy after definitive treatment for hypopharyngeal cancer.*

experienced grade 3 dysphagia and 11 patients were noted to have grade 3 stricture requiring dilation. Eleven patients were noted to have grade 2 or higher aspiration. Two treatment-related deaths were noted from renal failure and aspiration pneumonia, resulting in a 3.7% mortality rate.

Discussion

The present study is a unique analysis of long-term survival and toxicity in a cohort of patients with locally advanced hypopharyngeal cancer treated with definitive CRT at a single institution over approximately 30 years. To our knowledge, this study represents the longest published median follow-up after definitive CRT for locally advanced hypopharyngeal cancer. Table VI displays comparative data from other published series showing outcomes for definitively treated patients. Our findings demonstrate that for select patients, CRT is a feasible and efficacious primary treatment strategy associated with excellent locoregional control and organ preservation. Furthermore, our OS and CSS outcomes compare favorably to other published surgical and definitive CRT series.

The 5-year rates of local control and freedom from distant metastases in the present study were 78% and 76% respectively, identical to the 10-year rates, suggesting that a patient's disease course is primarily determined in the early years after treatment. Additionally, we noted equivalent rates of distant and primary failure differing from previous reports in the literature wherein locoregional failures were the main drivers of relapse (12, 13). In the present study, 22% of patients developed secondary primary cancer after treatment, with 5-and 10-year rates of secondary malignancy of 14% and 24% respectively, consistent with previously reported rates of 20-26% in published studies (3, 14). The increased rate of secondary tumors underlines the importance of continued long-term follow-up in this patient population.

As the use of CRT rather than surgery has become the more common primary treatment strategy, there has not been an overall compromise in survival outcomes (7). Previous studies of patients with hypopharyngeal cancer from the Surveillance, Epidemiology and End Results database have demonstrated

Table IV. *Univariate analysis of tumor and patient factors on locoregional failure. On Cox proportional hazards regression analysis, no clinical parameter (including age, T, N, stage, tumor differentiation, smoking status, alcohol use, and the use of hyperfractionation) was predictive of locoregional failure.*

Variable	HR	*p*-Value
Age at RT (continuous)	1.00	0.91
Female *vs.* male	1.57	0.51
Current smoker *vs.* never/former smoker	1.77	0.38
Heavy alcohol use (yes *vs.* no)	1.24	0.74
Poorly differentiated *vs.* moderate or well-differentiated	3.62	0.13
RT dose (continuous)	0.83	0.39
BID Fx *vs.* *QD* Fx	1.38	0.61
Stage T3T4 *vs.* T1T2	2.41	0.2
Stage N2, N3 *vs.* N0, N1	1.28	0.72
IVa *vs.* III	3.41	0.25
IVb *vs.* III	0.96	0.98
IVb *vs.* IVa	0.28	0.23

RT: Radiation therapy, *BID*: twice daily, *QD*: once daily.

that use of definitive radiation (as opposed to patients treated with surgery alone or surgery with radiation) is the only modality in which OS has significantly improved since 1988. Five-year OS for patients treated with definitive radiation improved from 13.5% in 1988-1990 to 23.7% in 2001-2005 ($p<0.001$) (7), likely reflecting improved radiation and imaging techniques over time. Published reports of patients with hypopharyngeal cancer patients treated with surgery alone show 5-year OS ranging from 24% to 33% (15-18).

The delivery and side-effect profile of RT has improved over the years with the development of IMRT, which has been shown to reduce the integral dose delivered to adjacent normal structures with resultant reduction in treatment related toxicities, such as xerostomia (19). Thus, the use of IMRT in the definitive treatment of head and neck carcinomas has become standard in recent years. Even further advances including the use of image-guided radiotherapy (IGRT) may help clinicians further refine their treatment volumes and set-up error. Given the time period over which our study was conducted, most (87%) patients were treated *via* a 3D approach, with only 13% receiving IMRT. Perhaps our good overall outcomes are a result of high treatment compliance and aggressive supportive care.

Due to the close anatomic proximity of the hypopharynx to supraglottic larynx and pharyngeal constrictors, late toxicity, primarily dysphagia, remains a significant concern in patients treated with definitive radiation (20-23). In our series, 43% of patients experienced grade 3 or more late toxicity, with the majority resolving during long-term follow-up. A total of 35% of patients had severe late dysphagia and only 11% of patients who remained free of disease still required tube feeding at the last follow-up. Our Institution has historically utilized aggressive multidisciplinary evaluation and management of toxicity for patients with head and neck cancer, perhaps reducing the rate of long-term feeding tube dependency.

As a single-institution retrospective study, this study is certainly subject to inherent selection and recall bias, as well as being limited by a moderate sample size. The present study is also limited by lack of available data on p16 as human papilloma virus (HPV) tumor status is now widely recognized as an important prognostic factor in head and neck cancer, although the significance in hypopharyngeal cancer remains unclear.

In conclusion, this study demonstrated successful organ preservation with good oncological outcomes in the treatment of locally advanced hypopharyngeal cancer at our Institution over the past 30 years. Our findings underline the fact that some patients in this population will be long-term survivors and that extended follow-up and continued management of long-term toxicity is warranted. Future prospective studies utilizing IMRT, IGRT, dose escalation, and HPV status are needed to further improve therapeutic gains and limit treatment-related toxicities.

Table V. *Toxicities after definitive chemoradiation according to toxicity grade by CTCAE guidelines.*

Toxicity	Grade/subgroup	Incidence	%
Acute			
Febrile neutropenia	0	30	65.2
(n=46)	3	15	32.6
	4	1	2.2
Radiation dermatitis	1	17	37.8
(n=45)	2	15	33.3
	3	10	22.2
	4	3	6.7
Pain (n=45)	0	2	4.4
	1	3	6.7
	2	37	82.2
	3	3	6.7
Feeding tube (n=54)	No	19	35.2
	Yes	35	64.8
Feeding tube type (n=54)	Corpak	10	18.5
	PEG	24	44.4
	Total	34	63.0
Late			
Feeding tube resolution	No	8	22.9
(n=35)	Yes	27	77.1
Diet at last follow-up	Feeding tube	7	13.0
(n=54)	Limited without supplements	9	13.0
	Normal	34	13.0
	Supplements needed	4	13.0
Xerostomia (n=47)	0	3	6.4
	1	8	17.0
	2	36	76.6
Dysphagia (n=50)	0	14	28.0
	1	13	26.0
	2	5	10.0
	3	18	36.0
Fibrosis (n=49)	0	21	42.9
	1	15	30.6
	2	12	24.5
	3	1	2.0
Stricture (n=50)	0	33	66.0
	3	17	34.0
Osteonecrosis (n=49)	0	45	91.8
	1	1	2.0
	2	1	2.0
	3	2	4.1
Trismus (n=50)	0	39	78.0
	1	9	78.0
	2	2	78.0
Voice changes (n=51)	0	14	27.5
	1	28	54.9
	2	6	11.8
	3	3	5.9
Neck pain (n=49)	0	34	69.4
	1	3	6.1
	2	12	24.5
Aspiration (n=49)	0	37	75.5
	1	1	2.0
	2	5	10.2
	3	6	12.2

Table VI. *Studies examining definitive radiation therapy in patients with hypopharyngeal cancer.*

Study (Ref)	Years	Cohort	Median follow-up	Radiation details	Outcomes
Gupta *et al*. (24)	1990-2004	501 Hypopharyngeal; 83% stage III/IV	12 months	Median dose 70 Gy in parallel opposed fields	3-Year: LRC: 47.1%, DFS: 40.9%
Rabbani *et al*. (25)	1964-2003	123 Piriform sinus; 80% stage III/IV (all T1 or T2)	38.4 months	Median dose 74.4 Gy (98% in parallel opposed fields, 2% IMRT)	5-Year: LRC: 70%, OS: 35%
Mendenhall *et al*. (26)	1964-2009	170 Pharyngeal wall; 77% stage III/IV	24 months	93% Conventional RT (median dose 70 and 76.8 Gy in daily and BID schedule); 7% IMRT (72 Gy)	5-Year: CSS: 49% for stage III and 35% for stage IV; OS: 31% for stage III and 21% for stage IV
Studer *et al*. (27)	2002-2008	65 Hypopharyngeal	21 months	70 Gy Using IMRT (SIB technique)	2-Year LRC: 77%, OS: 83%
Mok *et al*. (28)	2000-2010	181 Hypopharyngeal, all stages	60 months	50% 3D-CRT; 50% IMRT	IMRT: 3-Year LRC: 75%; 3-year OS 50% 3D-CRT: 3-Year: LRC: 58%, OS: 52%
Geretschlager *et al*. (29)	2007-2010	50 Patients (26 hypopharyngeal, 24 laryngeal)	50.4 months	Median dose 72 Gy, all IMRT	3-Year LRC: 77%, OS: 63%
Current study	1986-2013	54 Hypopharyngeal; all stage III or IV	49.8 months	Median dose 72 Gy; 87% 3D conformal, 13% IMRT	Median survival: 7.5 years 5-/10-Year: OS: 62%/43%, LRC: 78%/63%

OS: Overall survival, DFS: disease-free survival, LRC: locoregional control; CSS: cancer-specific survival, IMRT: intensity-modulated radiation therapy, SIB: simultaneous integrated boost, BID: twice daily.

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