

A 13-Year Single Institutional Experience with Definitive Radiotherapy in Hypopharyngeal Cancer

Dear Editor,

Patients with hypopharyngeal carcinoma often present with locally advanced disease. Treatment options are usually multimodality and involve surgery, radiotherapy (RT) and chemotherapy. Definitive RT with or without chemotherapy present a functional organ preservation strategy in selected patients or in patients with extensive inoperable local disease. Whereas upfront surgery followed by adjuvant RT may be more appropriate in patients with disease which limits the adequate recovery of speech and swallowing function with organ preservation strategy. Patients with significant cartilage destruction or bilateral vocal cord destruction may also have better function after laryngectomy and rehabilitation following surgery.

The landmark VA trial investigated the feasibility of organ preservation in laryngeal cancer patients using sequential chemotherapy-RT as an alternative to upfront surgery.¹ More than half of the patients had their larynx preserved with comparable survival to the surgical group. This encouraging result opened new avenues for application of this strategy in patients with locally advanced cancer of other head and neck primary sites. Similar conclusion was also established in the subsequent EORTC 24981 trial which included 152 hypopharyngeal cancer patients.^{2,3}

Concomitant radio-chemotherapy (CRT) strategy arose from the RTOG 91-11 trial and meta-analysis which demonstrated improved loco-regional control (LRC) and laryngeal preservation rates compared to induction chemotherapy followed by radical RT.⁴⁻⁷ This approach is now widely practised in many centres worldwide.

We adopted the concurrent CRT approach as the organ preservation strategy in treating selected patients with hypopharyngeal cancer. The aim of our study was to retrospectively review the outcome following curative intent RT with or without chemotherapy in hypopharyngeal cancer patients treated in our centre and also to determine the prognostic factors on LRC and survival in this group of patients.

Materials and Methods

This is a retrospective analysis of all patients with hypopharyngeal cancer treated with curative intent RT in our Department of Radiation Oncology in National Cancer Centre Singapore (NCCS) between January 2000 and

December 2013. Pretreatment evaluation included history taking, clinical examination, endoscopic examination of the upper aero-digestive tract and computer tomography of the neck and chest. The patients were discussed in a multidisciplinary tumour board and treatment decisions were made based on stage of disease, performance status and the anticipated swallowing and speech outcome. There were a total of 58 eligible patients during this period.

Radiotherapy

All patients were immobilised with customised thermoplastic mask and treated with 6MV photon encompassing the primary bearing area and regional lymph nodes. Patients who received upfront radical RT were treated with 66-70 Gy delivered in 33-35 fractions, whereas patients who received adjuvant RT were treated with 60-66 Gy in 30-33 fractions.

The gross tumour volume (GTV) was defined as any visible gross disease based on radiological and clinical findings. High risk clinical target volume (CTV) is an expansion of 5-10 mm margin around the GTV, and with editing off natural tumour barriers. This volume was treated with 66-70 Gy. Intermediate risk CTV included the possible local subclinical infiltration of the primary site as well as first echelon nodal stations and was prescribed 60 Gy. Low risk CTV included regional nodal stations which are not first echelon nodes and were not adjacent to the levels of involved nodes and was prescribed 50 Gy. In the adjuvant setting, the tumour bed and involved nodal stations were treated to 60 Gy with a further 6 Gy boost to areas of extracapsular extension or close/positive margin.

Twenty-nine of 58 patients were treated using a 2-dimensional (2D) technique and the other 29 with intensity modulated radiotherapy (IMRT). In the IMRT technique, all dose levels were delivered within the same plan with the higher doses effected through a simultaneous integrated boost. In the 2D technique, the RT was delivered via 2 shaped lateral parallel opposed fields with a low anterior neck match in 2 or 3 phases using shrinking field technique.

Follow-Up

Patients were reviewed at least once a week during RT. Thereafter, patients were reviewed once a month for the first year, 2-monthly for the second year, 3-to-4

monthly for the third year and 6-monthly after the third year. Treatment response was assessed by clinical and endoscopic examination, aided by computed tomography (CT) or magnetic resonance imaging (MRI) at 3 months post-RT, and repeated when warranted.

Statistical Analysis

Kaplan-Meier curves were generated for all the survival analysis. The Cox proportional hazards regression was used to analyse the prognostic factors for overall survival (OS), progression-free survival (PFS) and LRC. A two-sided P value <0.05 was considered statistically significant. Duration of all types of survival analysis was computed from the date of diagnosis of hypopharyngeal cancer. Prognostic factors identified were age, gender, T stage (T1/2 vs T3/4), N stage (N0/1 vs N2/3), group stage (stage II/III vs IVA/B), RT technique (IMRT vs 2D), surgery (yes vs no), chemotherapy (yes vs no), smoking status (yes vs no), and tumour subsite (pyriform fossa vs others). Statistical analyses were performed using the STATA 12.0 software (Stata Corp, College Station, 2012, TX, USA).

Results

Patient Characteristics

Out of 58 hypopharyngeal cancer patients who had definitive RT treatment, 51 (87.9%) were male and the median age of all hypopharyngeal cancer patients in this study was 66.5 years; 70.7% of hypopharyngeal cancer patients in this study had stage IVA disease (Table 1).

Fifteen patients underwent surgery followed by adjuvant RT. Out of the 15 patients, 14 had neck dissection, 4 had total laryngectomy, 6 had laryngopharyngectomy, 2 had partial pharyngectomy and 3 had pharyngo-laryngo-esophagectomy. The remaining 43 patients received upfront radical RT.

Concurrent chemotherapy was administered to 33 patients and consisted of mainly cisplatin monotherapy. The median RT dose delivered was 70 Gy in 35 fractions, with a median overall treatment time of 47 days. Half of the patients were treated with IMRT, and the other half were treated with 2D RT. Other demographics and clinical characteristics together with their treatment characteristics are summarised in Table 1.

Response to Treatment

Fifty-one patients achieved complete response at 3 months post-RT whereas 7 patients had persistent/residual disease (3 in the primary site only, 3 in the primary and regional nodes and 1 in the regional nodes only). Out of these 7 patients, 2 patients were inoperable or unfit for salvage surgery and received palliative treatment. The remaining

Table 1. Demographics and Clinical Characteristics of Hypopharyngeal Cancer Patients in National Cancer Centre Singapore

Variable	No.	%
Total	58	100
Age at diagnosis		
Median (range)	66.5 (44 – 87)	
Age, years		
≤70	38	65.5
>70	20	34.5
Gender		
Male	51	87.9
Female	7	12.1
Subsite		
Posterior wall	18	31.0
Pyriform fossa	32	55.2
Postcricoid space	8	13.8
Cancer stage		
II	3	5.2
III	7	12.1
IVA	41	70.7
IVB	7	12.1
T stage		
T1	2	3.5
T2	16	27.6
T3	9	15.5
T4	31	53.4
N stage		
N0	15	25.9
N1	8	13.8
N2	32	55.1
N3	3	5.2
Chemotherapy		
Yes	33	56.9
No	25	43.1
Surgery		
Yes	15	25.9
No	43	74.1
RT technique		
Conventional	29	50.0
IMRT	29	50.0
Smoking status*		
Yes	43	74.1
No	9	15.5
Unknown	6	10.3
Number of pack-years (n = 43)		
<10	39	90.7
>10	4	9.3

IMRT: Intensity modulated radiotherapy; RT: Radiotherapy

*Inclusive of current and ex-smoker.

5 patients proceeded to salvage surgery. One of these 5 patients underwent a salvage neck dissection for isolated nodal recurrence and has subsequently remained disease-free from hypopharyngeal carcinoma, although he died at 20 months post-RT from a second primary lung cancer. The rest of the patients died of disease recurrence despite salvage surgery.

Patterns of Failure

Median follow-up was 15.9 months for all patients. In those alive, the median follow-up was 21.7 months (range:

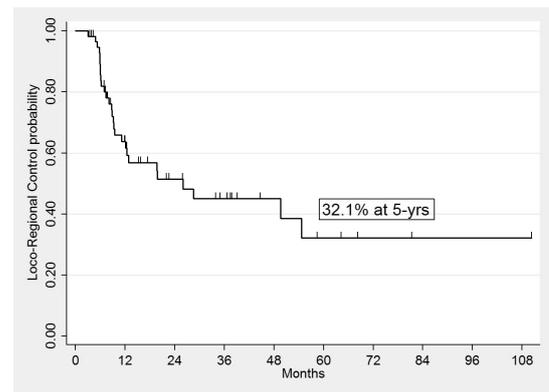


Fig. 1. Loco-regional control (LRC) of hypopharyngeal cancer following RT.

Table 2. Univariate Analysis of Patients with Hypopharyngeal Cancer

Variable	Overall Survival (OS)		Loco-Regional Control (LRC)		Progression-Free Survival (PFS)	
	Hazard Ratio (95% CI)	P Value [†]	Hazard Ratio (95% CI)	P Value [†]	Hazard Ratio (95% CI)	P Value [†]
Age, years						
Per year increase	0.99 (0.96 – 1.03)	0.629	0.99 (0.95 – 1.04)	0.775	1.00 (0.96 – 1.04)	0.915
Gender						
Male	2.35 (0.71 – 7.83)		0.62 (0.21 – 1.82)		0.88 (0.31 – 2.53)	
Female	1	0.163	1	0.387	1	0.818
Chemotherapy						
Yes	0.82 (0.44 – 1.53)		0.75 (0.36 – 1.57)		0.87 (0.45 – 1.66)	
No	1	0.530	1	0.443	1	0.669
Subsite						
Pyriiform fossa	1.09 (0.59 – 2.00)		0.75 (0.35 – 1.58)		0.87 (0.45 – 1.67)	
Others	1	0.793	1	0.448	1	0.677
RT technique						
IMRT	0.52 (0.20 – 1.35)		0.59 (0.18 – 1.97)		0.57 (0.20 – 1.63)	
2D	1	0.18	1	0.391	1	0.297
Smoking status [‡]						
Yes	0.86 (0.33 – 2.24)		0.59 (0.20 – 1.75)		0.61 (0.23 – 1.59)	
No	1	0.764	1	0.343	1	0.313
T stage						
T1 – T2	0.46 (0.22 – 0.96)		0.40 (0.16 – 0.99)		0.28 (0.12 – 0.69)	
T3 – T4	1	0.040*	1	0.049*	1	0.005*
N stage						
N0 – N1	0.66 (0.35 – 1.28)		0.57 (0.25 – 1.27)		0.56 (0.28 – 1.13)	
N2 – N3	1	0.220	1	0.166	1	0.104
Group stage						
IVA – IVB	2.36 (0.92 – 6.05)		2.73 (0.81 – 9.14)		3.69 (1.12 – 12.10)	
II – III	1	0.075	1	0.104	1	0.032*
Surgery						
No	1.09 (0.53 – 2.23)		3.24 (0.97 – 10.79)		1.41 (0.64 – 3.09)	
Yes	1	0.818	1	0.055	1	0.396

IMRT: Intensity modulated radiotherapy; RT: Radiotherapy; 2D: 2-dimensional

*P value <0.05 is statistically significant.

[†]P value is based on Cox-proportional hazard.

[‡]Patients with unknown smoking status were excluded from the analysis.

6.6 to 81.1 months). The median LRC was 26 months with a 3-year LRC rate of 45% (95% CI, 29.6% to 59.2%) (Fig. 1). Local recurrence was observed in 12 patients, whereas 2 patients developed regional recurrence and 14 patients had both local and regional recurrence. The overall incidence of distant metastasis was 36.2% (n = 21). The lung was the most frequent site of distant metastasis (76.2%). The 3-year distant recurrence-free survival rate was 58.2% (95% CI, 41% to 72%). In univariate analysis, T stage was the only significant predictor found for LRC ($P = 0.049$) with a hazard ratio (HR) of 0.40 (95% CI, 0.16 to 0.99) of T1/T2 against T3/T4 as reference (Table 2).

Survival

Forty-three patients died over the study period and the cause of death was cancer-related in most of the patients (35/43). Of the others who died, 6 patients died from pneumonia, 1 patient died from a second esophageal primary, 1 patient died from a second lung primary. At the time of analysis, 15 patients were alive and 14 of them were disease-free at the last follow-up. The median OS was 21.0 months with a 3-year OS rate of 33.5% (95% CI, 20.8% to 46.7%) (Fig. 2). The median PFS was 12.8 months with a 3-year PFS rate of 34.9% (95% CI, 22% to 48.2%) (Fig. 3). Univariate analysis showed that T stage was the only significant prognostic factor for OS. Group stage and T stage were respectively significant univariate prognostic factors for PFS. In a multivariate analysis, only T stage was significant with T1/T2 showing a HR of 0.28 (95% CI, 0.12 to 0.69, $P = 0.005$) vs T3/T4 (Table 2).

Discussion

Our study results demonstrated the poor outcome expected in hypopharyngeal carcinoma with 3-year OS of 33.5% and LRC of 45%. The majority of patients (83%) in our cohort presented with very advanced stage (stages IVA

& IVB). Although 88% of patients managed to achieve complete response 3 months after completion of treatment, loco-regional recurrence remained the major cause of failure following curative intent RT. Most deaths occurred in patients who succumbed to loco-regional rather than systemic failure.

Our centre has increasingly employed IMRT in the last decade for the definitive treatment of head and neck cancer. The use of IMRT has allowed the delivery of high dose conformal RT whilst achieving normal tissue tolerances. The earlier group of patients in our study was treated with 2D RT and the latter half received IMRT. On univariate analysis, the use of IMRT was not found to be a statistically significant prognostic factor affecting OS, PFS and LRC compared to conventional RT. However, the small number of patients and significant shorter follow-up period of IMRT patients (median follow-up: 12.0 months in IMRT group vs 22.4 months in 2D group) may have accounted for this finding.

Few studies have reported the outcomes of IMRT due to the relative rarity of hypopharyngeal cancer. Mok et al⁸ compared 3-dimensional (3D) RT and IMRT in 181 patients with hypopharyngeal squamous cell carcinoma (SCC), 40% of which had T1/T2 stage. The IMRT group had a higher 3-year LRC (75% vs 58%) compared with the 3D RT group, but both groups had similar OS (50% vs 52%) and distant relapse rate. Huang et al⁹ reported the results of 47 hypopharyngeal patients treated with concomitant IMRT-chemotherapy, although 30% of these patients were treated in the adjuvant setting. After a relatively short median follow-up of 18.8 months, the 5-year OS for all patients was 37% and the 5-year LRC in the concomitant CRT group was 53%. Longer follow-up and bigger cohort of patients are needed to validate these IMRT findings with regard to control rates and toxicities.

These results provide a clear rationale for efforts aimed at improving LRC and OS. Strategies that are being explored include altered fractionation, use of conformal RT

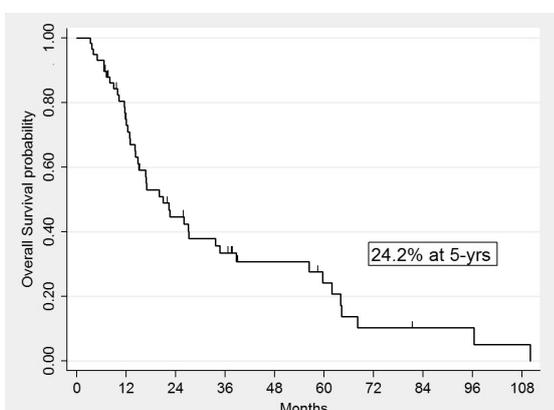


Fig. 2. Overall survival (OS) of hypopharyngeal cancer patients following RT.

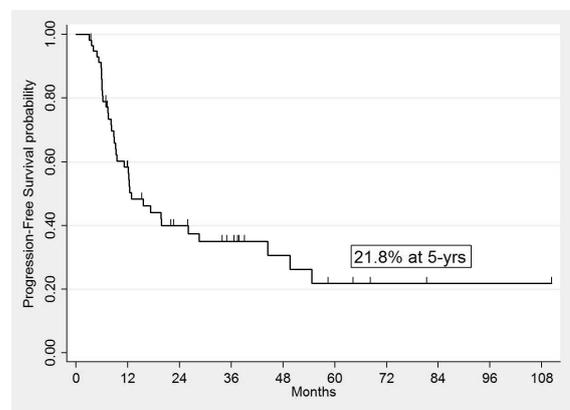


Fig. 3. Progression-free survival (PFS) of hypopharyngeal cancer following RT.

such as IMRT, and intensification of concurrent systemic chemotherapy. Several reports have shown improvement in LRC and a small benefit of OS with altered fractionation, often at the price of significant morbidities.^{10,11} Gujraj et al reported the long-term outcome of a phase I/II accelerated RT study of dose-escalated IMRT for locally advanced laryngo-hypopharyngeal cancers.^{12,13} This study demonstrated that dose-escalated IMRT at 67.2 Gy in 28# (2.4 Gy per fraction) to PTV1 and 56 Gy in 28# (2 Gy per fraction) to PTV2 resulted in 5-year local control rate of 75% and 5-year OS of 67.6% with acceptable late toxicity. This dose level is currently being investigated in the context of a randomised controlled trial (ART-DECO) in the United Kingdom.

Significant advances have been made over the last 2 decades with the development of more complex RT delivery techniques such as IMRT, volumetric modulated arc therapy (VMAT), and proton therapy. The increasing incorporation of newer imaging modalities such as MRI and positron emission tomography (PET) also allows for more precise staging, tumour localisation and assessment of treatment response. There is also ongoing interest and research to investigate the role of imaging to improve target delineation and possibly identify areas of radio-resistance within the tumour for dose painting/escalation.¹⁴ Further clinical research is needed to assess the utilisation of newer highly conformal RT techniques combined with novel systemic agents in head and neck cancers.

Conclusion

Patients with hypopharyngeal cancers often presented with advanced stage with extensive nodal involvement and were at high risk of developing distant metastasis. Tumour load is the most important prognostic factor for outcome. Intensification of treatment is warranted to enhance local control and OS rates.

REFERENCES

1. Induction chemotherapy plus radiation compared with surgery plus radiation in patients with advanced laryngeal cancer. The Department of Veterans Affairs Laryngeal Cancer Study Group. *N Engl J Med* 1991;324:1685.
2. Lefebvre JL, Chevalier D, Lubinski B, Kirkpatrick A, Collette L, Sahnoud T. Larynx preservation in pyriform sinus cancer: preliminary results of a European Organization for Research and Treatment of Cancer phase III trial. EORTC Head and Neck Cancer Cooperative Group. *J Natl Cancer Inst* 1996;88:890.
3. Lefebvre JL, Andry G, Chevalier D, Lubinski 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.
4. 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* 2013;31:845-52.
5. Forastiere AA, Goepfert H, Maor M, Pajak TF, Weber R, Morrison W, et al. Concurrent chemotherapy and radiotherapy for organ preservation in advanced laryngeal cancer. *N Engl J Med* 2003;349:2091-8.
6. Pignon JP, le Maître A, Maillard E, Bourhis J; MACH-NC Collaborative Group. Metaanalysis of chemotherapy in head and neck cancer (MACH-NC): an update on 93 randomised trials and 17,346 patients. *Radiother Oncol* 2009;92:4-14.
7. Blanchard P, Baujat B, Holostenco V, Bourredjem A, Baey C, Bourhis J, et al. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): a comprehensive analysis by tumour site. *Radiother Oncol* 2011;100:33.
8. Mok G, Gauthier I, Jiang H, Huang SH, Chan K, Witterick IJ, et al. Outcomes of intensity-modulated radiotherapy versus conventional radiotherapy for hypopharyngeal cancer. *Head Neck* 2015;37:655-61.
9. Huang WY, Jen YM, Chen CM, Su YF, Lin CS, Lin YS, et al. Intensity modulated radiotherapy with concurrent chemotherapy for larynx preservation of advanced resectable hypopharyngeal cancer. *Radiat Oncol* 2010;5:37.
10. Beitler JJ, Zhang Q, Fu KK, Trotti A, Spencer SA, Jones CU, et al. Final results of local-regional control and late toxicity of RTOG 9003: a randomized trial of altered fractionation radiation for locally advanced head and neck cancer. *Int J Radiat Oncol Biol Phys* 2014;89:13-20.
11. Bernier J. Alteration of radiotherapy fractionation and concurrent chemotherapy: a new frontier in head and neck oncology? *Nat Clin Pract Oncol* 2005;2:305-14.
12. Gujral DM, Miah AB, Bodla S, Richards TM, Welsh L, Schick U, et al. Final long-term results of a phase I/II study of dose-escalated intensity-modulated radiotherapy for locally advanced laryngo-hypopharyngeal cancers. *Oral Oncol* 2014;50:1089-97.
13. Miah AB, Bhide SA, Guerrero-Urbano MT, Clark C, Bidmead AM, StRose S, et al. Dose-escalated intensity-modulated radiotherapy is feasible and may improve locoregional control and laryngeal preservation in laryngo-hypopharyngeal cancers. *Int J Radiat Oncol Biol Phys* 2012;82:539-47.
14. Grosu AL, Souvatzoglou M, Roper B, Dobritz M, Wiedenmann N, Jacob V, et al. Hypoxia imaging with FAZA-PET and theoretical considerations with regard to dose painting for individualization of radiotherapy in patients with head and neck cancer. *Int J Radiat Oncol Biol Phys* 2007;69:541-51.

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