First-Line surgery is Associated with Longer Overall Survival Among Patients with Locoregionally Advanced Hypopharyngeal Cancer: A National Cancer Database Study.

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Background

Management of locoregionally advanced hypopharyngeal squamous cell carcinoma (SCC) is an area of controversy in the field of head and neck oncology[1-2]. Prior reviews of large cancer databases such as the National Cancer Database (NCDB) and the Surveillance, Epidemiology and End Results (SEER) database have demonstrated a trend towards increased use of primary chemoradiation (CRT) in the management of hypopharyngeal cancer[3-6].

Objectives

The objective of this study was to use the American College of Surgeons' National Cancer Database (NCDB) to examine the association between primary treatment and overall survival (OS) among patients with locoregionally advanced hypopharyngeal cancer.

Methods and Materials

- Subjects with hypopharyngeal squamous cell carcinoma as their first malignancy were identified within the NCDB between 2004-2015 (**Figure 1**).
- Patients who received primary chemoradiation (CRT) were compared to those that received surgery with either adjuvant radiation or chemoradiation (S+Adj). Treatment groups were defined using similar to previously published methods[6]. OS was compared between treatment groups using Kaplan-Meier analyses, propensity score adjustment, and Cox regression analyses. All statistical analysis was done using STATA, version 15.1.

Propensity Score:

- A propensity score (PS) was built to adjust for potential sources of selection bias in observational studies. The PS was built using a multivariable logistic model of the probability of receiving curative-intent surgery as compared to CRT. Variables were included for their ability to reduce standardized differences between the treatment groups. The final PS included variables for facility type, geographic region, treatment at multiple locations, histology, and T stage.

Primary Analyses:

- Overall survival (OS) were defined as date of diagnosis until death or subject was lost to follow-up. OS was assessed using Kaplan-Meier (KM) survival curves, and log rank tests.

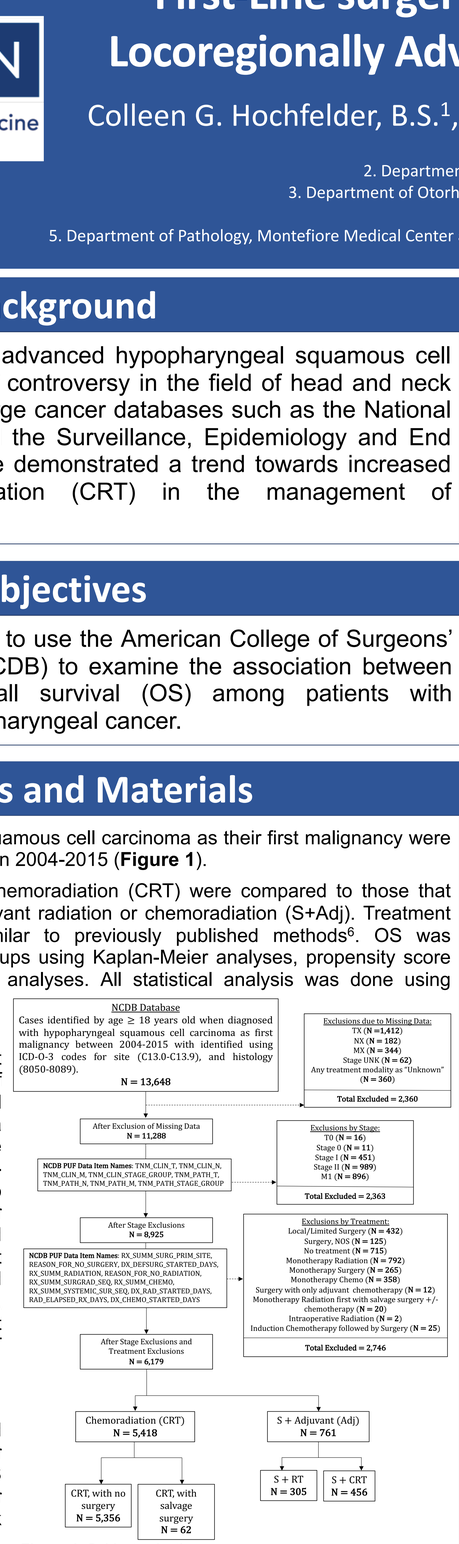

Figure 1. Subject selection.

- Multivariable Cox regression models of OS were built using variables with significant univariate Cox regression results.
- Sensitivity analyses for survival outcomes were conducted after stratifying subjects by T stage, including subjects that received only surgery following an intention-to-treat analysis, inclusion of partial pharyngectomy subjects, and assessing using survival time beginning at the end of radiation treatment.

Results

Study Population

- The final cohort was made up of 6,179 subjects. The mean age was 61.1 years (SD ± 10.0 years), predominantly male (81.7%) and non-Hispanic white (76.0%) with cancers of the pyriform sinus (52.4%). Most subjects were insured through Medicare (37.2%) followed by private insurance (35.9%) and Medicaid (16.8%).
- The median overall survival was 22.7 months (IQR: 11.1-48.9).
- The S+Adj subjects lived further from the hospital, had a higher Charlson-Deyo Comorbidity score, and had a higher proportion with high-grade tumors compared to the CRT group ($p < 0.05$ for all).
- The S+Adj group contained a higher proportion of patients with T4 disease (54.0%) compared to the CRT group (27.1%) and had a higher proportion of patients with N2 disease (63.9% vs 57.2%), while the CRT group carried a higher percentage with N3 disease (8.4% vs. 4.6%).
- The CRT group had a significantly higher percentage of patients with stage IVA disease as compared to the S+Adj group (56.6% vs 7.2%), and the S+Adj group had a higher proportion with stage IVB (71.4% vs 15.4%) and IVC disease (7.2% vs 1.3%).

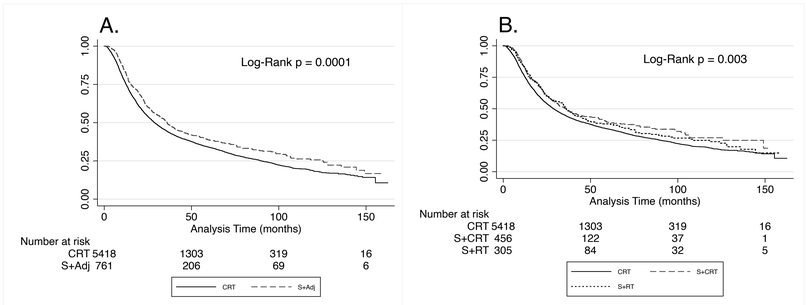

Figure 2. Kaplan-Meier survival estimates of subjects managed with chemoradiation (CRT) compared to surgery with adjuvant CRT or radiation (S+Adj). **A.** S+Adj grouped and **B.** shows S+Adj split into surgery with adjuvant radiation therapy (S+RT) and surgery with adjuvant CRT (S+CRT).

Primary Results: Multivariable Analysis Adjusting for Competing Factors

- S+Adj was associated with a 26% reduction in hazard of all-cause mortality as compared to CRT after adjustments for age, sex, race and ethnicity, insurance through Medicaid, comorbidity score, year of diagnosis, N stage and the propensity score (HR: 0.74; 95% CI: 0.65-0.83; p<0.001).
- When the model was redeveloped with S+Adj stratified into S+RT and S+CRT, both S+RT and S+CRT were associated with significantly longer OS after adjustments for other model components (S+RT HR: 0.71; 95% CI: 0.58-0.87; p=0.001; S+CRT HR: 0.75; 95% CI: 0.65-0.87; p<0.001).

Sensitivity Analyses

- After stratification by T stage, OS was longer with S+Adj among those with T2 disease (HR: 0.65; 95% CI: 0.46-0.92; p=0.0016), T3 disease (HR: 0.76; 95% CI: 0.46-0.97; p=0.025), and T4 disease (HR: 0.77; 95% CI: 0.66-0.91; p=0.002).
- When surgery-only subjects were included in the S+Adj group, S+Adj remained significantly associated with longer survival (HR: 0.74; 95% CI: 0.65-0.83; p<0.001).
- When partial laryngectomy/pharyngectomy subjects were. included, S+Adj was associated with an independent 26% reduction in hazard of all-cause mortality as compared to CRT after adjustments for other model components (HR: 0.74; 95% CI: 0.66-0.87; p<0.001).
- When Kaplan-Meier curves were re-assessed using survival time (from end of radiation therapy until last follow-up or death), S+Adj remained associated with a longer survival as compared to CRT (p=0.0065).

Results, continued

Table I. Results of multivariable cox regression analysis for overall survival in selected cohort of patients with stage III or IV (M0) hypopharyngeal squamous cell carcinoma in the NCDB.

	Overall Survival		
	HR	95% CI	P-Value
Age	1.02	1.02 to 1.03	<0.001
Gender			0.5419
Female	1	(Reference)	
Male	0.97	0.88 to 1.07	0.542
Race*			0.0899
NHW	1	(Reference)	
NHB	1.10	1.01 to 1.24	0.060
NHO	0.83	0.66 to 1.05	0.121
H	1.00	0.84 to 1.20	0.958
Insurance			<0.0001
Private Insurance/Medicare	1	(Reference)	
Uninsured	1.33	1.15 to 1.55	<0.001
Medicaid	1.45	1.31 to 1.61	<0.001
Comorbidity			0.0007
0	1	(Reference)	
1	1.15	1.05 to 1.26	0.003
2	1.18	0.99 to 1.41	0.061
>3	1.45	1.12 to 1.93	0.006
Year of Diagnosis			0.0069
2006	1	(Reference)	
2007	0.99	0.84 to 1.15	0.862
2008	1.02	0.87 to 1.19	0.844
2009	0.95	0.82 to 1.11	0.533
2010	1.03	0.88 to 1.21	0.697
2011	0.89	0.76 to 1.04	0.151
2012	0.88	0.75 to 1.03	0.107
2013	0.80	0.67 to 0.94	0.007
2014	0.85	0.72 to 1.02	0.080
2015	0.78	0.65 to 0.94	0.010
Treatment Delay†	1.10	1.00 to 1.21	0.056
N Stage			<0.0001
N0	1	(Reference)	
N1	1.01	0.88 to 1.15	0.919
N2	1.17	1.04 to 1.31	0.007
N3	1.77	1.50 to 2.08	<0.001
Propensity Score‡	6.22	3.96 to 9.77	<0.001
Treatment§			
CRT	1	(Reference)	
S+Adj	0.74	0.65 to 0.83	<0.001

* Race Abbreviations: NHW - Non-Hispanic White, NHB - Non-Hispanic Black, NHO - Non-Hispanic, Other Race, H - Hispanic
† Delay in treatment was defined as 60 days or longer from diagnosis to treatment based on the results published by Liao *et al.* 2019[7].
‡ Propensity score included adjustments for facility type, geographic region, treatment at multiple locations, histology, and T stage.
§ Subjects were included in the chemotherapy and radiation group (CRT) if they had received primary radiation and chemotherapy. Subjects were included in the surgery with adjuvant therapy group (S+Adj) if they received primary surgery with either adjuvant radiation or adjuvant radiation and chemotherapy.

Conclusion

- The majority of patients with locoregionally advanced hypopharynx cancer received primary radiation and chemotherapy (CRT) (87.7%) compared to S+Adj (12.3%).
- Despite primary surgery being used for more advanced disease, there was an independently longer overall survival associated with primary surgery followed by adjuvant treatment when compared to CRT. This trend was consistent throughout sensitivity analyses.
- Prospective studies would be required to determine a true survival benefit with up-front surgery.
- Further studies are necessary to optimize the application of standard treatment modalities to balance quality of life and function with survival.

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Acknowledgements

This research was supported by NIH/National Center for Advancing Translational Science (NCATS) Einstein-Montefiore CTSA Grant Number KL2TR001071. Thomas J. Ow's contribution was supported by NIH-NIDCR K23 grant 1 K23 DE027425-01. The authors have no other funding, financial relationships, or conflicts of interest to disclose.

References

1. Garneau JC, Bakst RL, Miles BA. Hypopharyngeal cancer : A state of the art review. Oral Oncol 2018;86:244–50. doi:10.1016/j.oraloncology.2018.09.025.
2. Tassler AB, Gooding WE, Ferris RL. Hypopharyngeal cancer treatment: Does initial surgery confer survival benefit? *Head Neck.* 2019;41(7):2167-2173. doi:10.1002/hed.25687
3. Kuo P, Chen MM, Decker RH, Yarbrough WG, Judson BL. Hypopharyngeal cancer incidence, treatment, and survival: Temporal trends in the United States. *Laryngoscope.* 2014;124(9):2064-2069. doi:10.1002/lary.24651
4. Kuo P, Sosa JA, Burtness BA, et al. Treatment trends and survival effects of chemotherapy for hypopharyngeal cancer: Analysis of the National Cancer Data Base. *Cancer.* 2016;122(12):1853-1860. doi:10.1002/cncr.29962
5. Newman JR, Connolly TM, Illing EA, Kilgore ML, Locher JL, Carroll WR. Survival trends in hypopharyngeal cancer: A population-based review. *Laryngoscope.* 2015;125(3):624-629. doi:10.1002/lary.24915
6. Hochfelder CG, McGinn AP, Mehta V, Castellucci E, Kabarriti R, Ow TJ. Treatment sequence and survival in locoregionally advanced hypopharyngeal cancer: A surveillance, epidemiology, and end results-based study. *Laryngoscope.* 2019:1-11. doi:10.1002/lary.28452
7. Liao DZ, Schlecht NF, Rosenblatt G, et al. Association of Delayed Time to Treatment Initiation with Overall Survival and Recurrence among Patients with Head and Neck Squamous Cell Carcinoma in an Underserved Urban Population. *JAMA Otolaryngol - Head Neck Surg.* 2019;145(11):1001-1009. doi:10.1001/jamaoto.2019.2414