AN ALGORITHMIC APPROACH TO OROPHARYNGEAL SQUAMOUS CELL CARCINOMA SURGERY

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Introduction

- HPV-positive status is a favorable prognostic factor for overall survival (OS) of patients with HNSCC and there is a growing body of literature that supports the deintensification of adjuvant treatment in HPV-positive OPSCC, specifically turning towards more surgical approaches.

- There exists a paucity in the literature with regards to what extent of surgical procedures (primary resection, neck dissection levels, +/- reconstruction) are associated with increased OS and disease-free survival (DFS) as well as quality of life and function of the upper aerodigestive tract.

- The purpose of this study is to quantify, for specific primary subsites, what combination of treatment modalities and procedures promote OS and DFS in patients with newly diagnosed primary OPSCC while maintaining appropriate speech and swallowing function.

- The secondary objective of the study was to gather data to inform the development of a surgical and reconstruction algorithm for the treatment of OPSCC based on the subsite and pathological staging of the primary tumor.

Methodology

- A retrospective analysis of patients who were newly diagnosed with OPSCC and treated initially with primary surgical resection at a tertiary academic referral center was performed. 206 patients between the ages of 36 and 89 were identified as having received a new histological diagnosis of OPSCC between January 1, 2010 and September 1, 2020.

- Tumor subsite was binned into one of three categories to facilitate analysis: (1) base of the tongue; (2) tonsil and pillar; (3) uvula, soft palate, lateral and posterior pharyngeal wall. Study inclusion criteria were (1) age >18 years; (2) new histologic diagnosis of primary OPSCC; (3) initial treatment via primary surgical resection at the primary site +/- neck dissection.

- Patients were excluded if they received no treatment or if they had a pre-existing diagnosis. Types of reconstruction (none, locoregional flap, or free flap) were recorded. Adjuvant treatment was defined as having completed the recommended course of radiation or chemotherapy. Right-censorship at last follow up was assumed. Survival analysis with endpoints of OS and DFS was completed.

- Non-parametric Kaplan Meier log rank tests were performed after patients were binned by subsite.

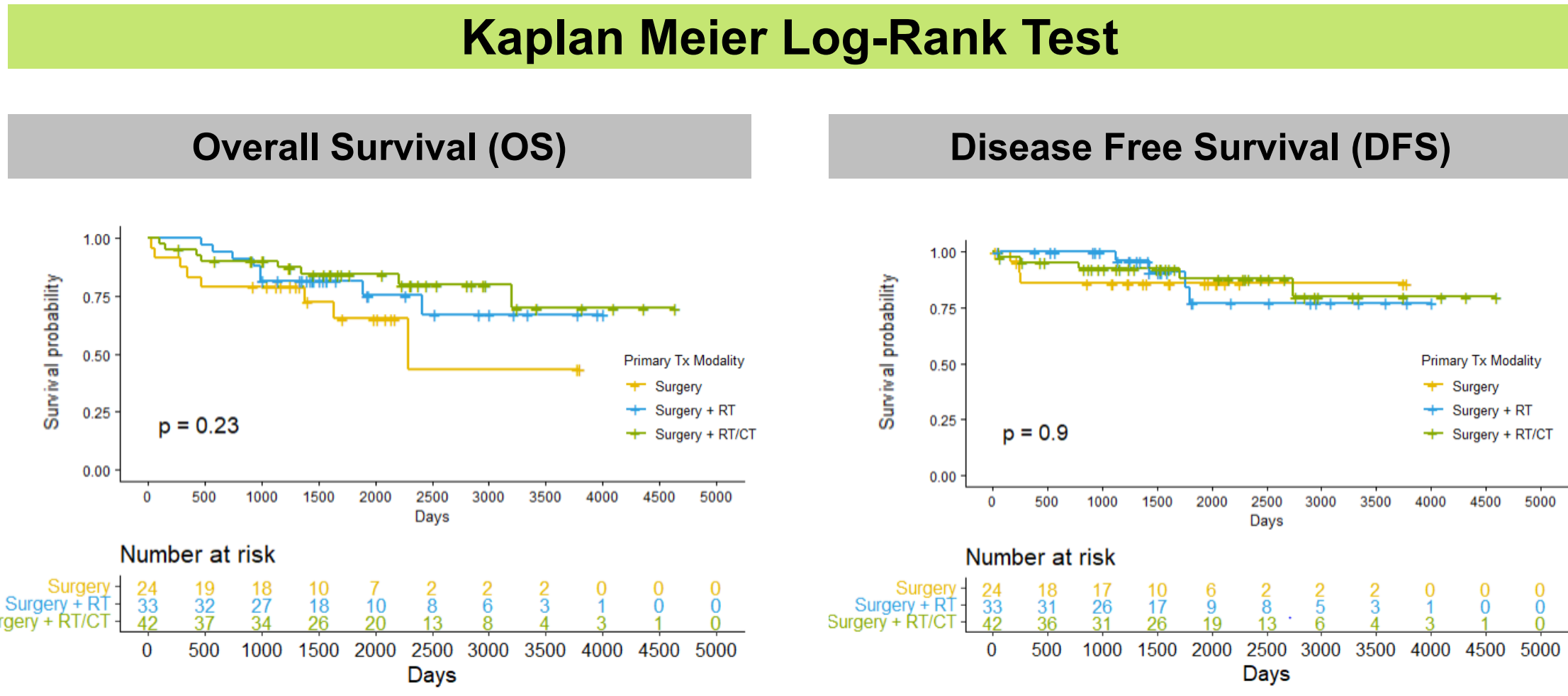$$\widehat{S}(t) = \prod_{i:\, t_i \leq t} \left(1 - \frac{d_i}{n_i}\right)$$

- Traditional CPH models were fit and found to not abide by the proportional hazards assumption as evidenced by Global and Individual Schoenfeld Tests. The models were stratified upon attributes with non-proportional hazards (treatment regimen and TNM staging), as these variables are a predictor of severity and higher hazard in any case.

$$h_t(t,\mathbf{X}) = h_{0t}(t)\exp[\beta_1 X_1 + \beta_2 X_2 + \cdots + \beta_p X_p]$$

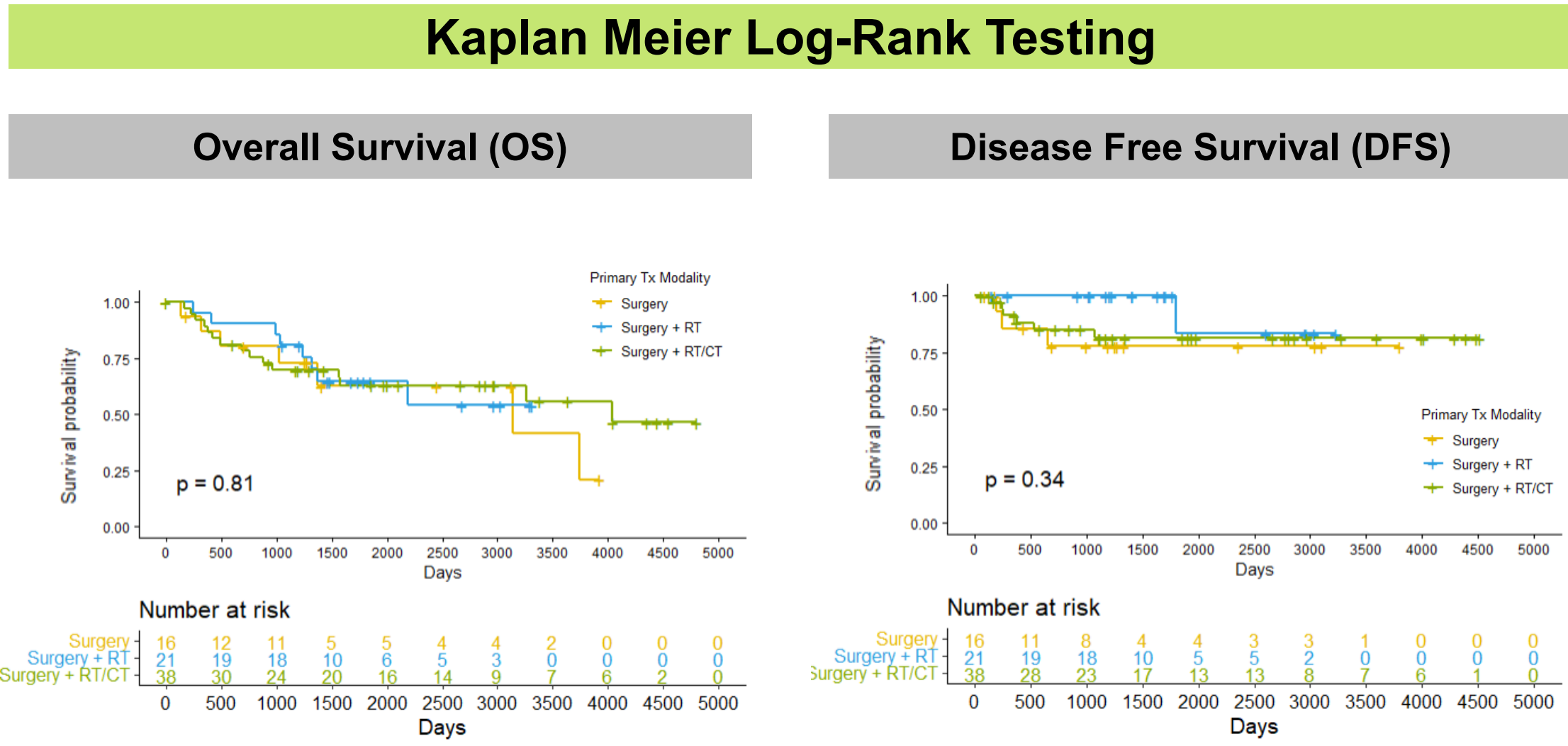β coefficients do not vary over strata (no-interaction assumption)

Results

Subsite: Tonsil & Pillars (n = 99)

Kaplan Meier Log-Rank Test — Overall Survival (OS); Disease Free Survival (DFS)

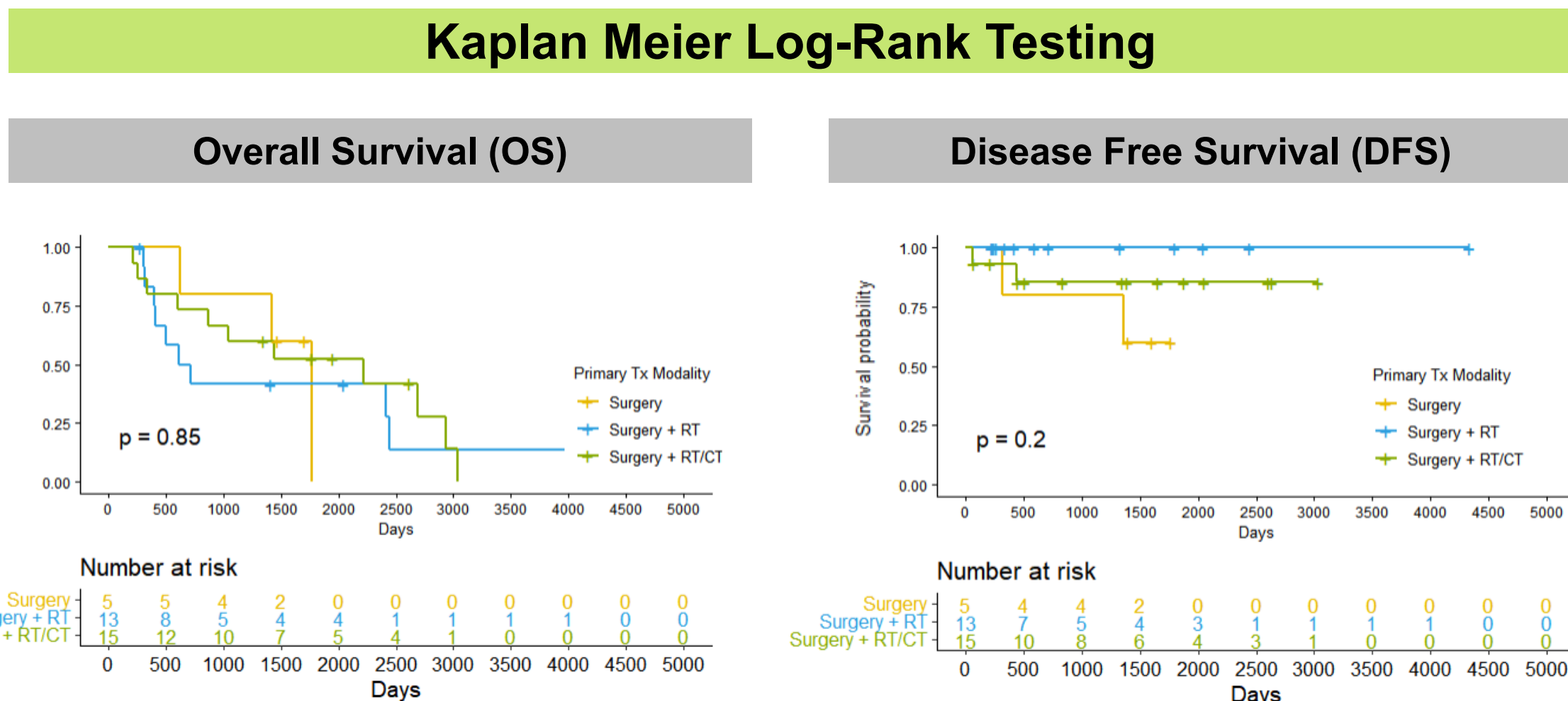Multi-Stratified Multivariate CPH — Overall Survival (OS); Disease Free Survival (DFS)

- There is weak but existent support for the use of adjuvant RT and CT in the setting of oral SCC with a primary site of tonsil and pillars. As evidenced by the above Kaplan Meier Curves and log rank tests (null hypothesis of HR=1), there is weak evidence (p=0.23) when evaluating the end-point of OS and little evidence when evaluating the end-point DFS (p=0.9) for the use of adjuvant RT and CT.

- Stratification by T, N, and M stages as well as treatment regimen were implemented. There is evidence that bilateral ND (HR 0.16 [0.02, 1.08]; p = 0.069) as well as radial forearm free flap (HR 0.38 [0.004, 1.6]; p = 0.217) procedures are associated with OS. Bilateral ND (HR 0.54 [0.12, 0.88]; p = 0.046) was also associated with lower rate of recurrence in the case of DFS.

Subsite: Base of Tongue (n = 75)

Kaplan Meier Log-Rank Testing — Overall Survival (OS); Disease Free Survival (DFS)

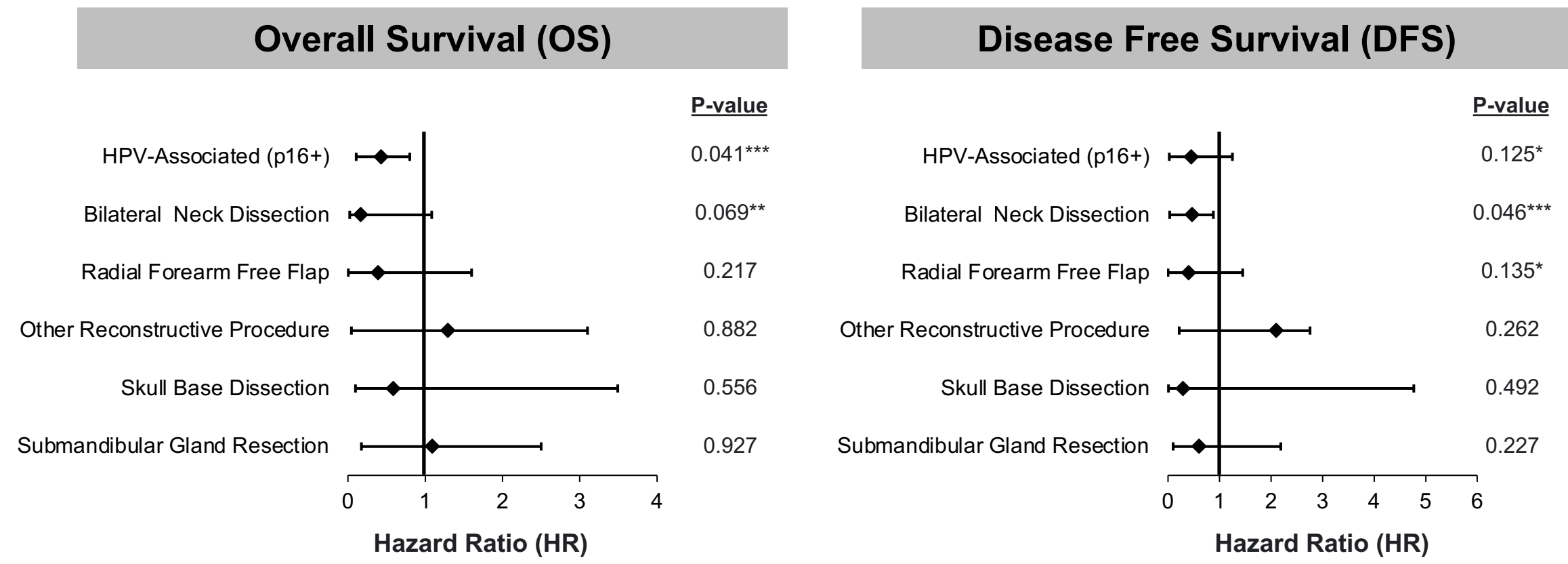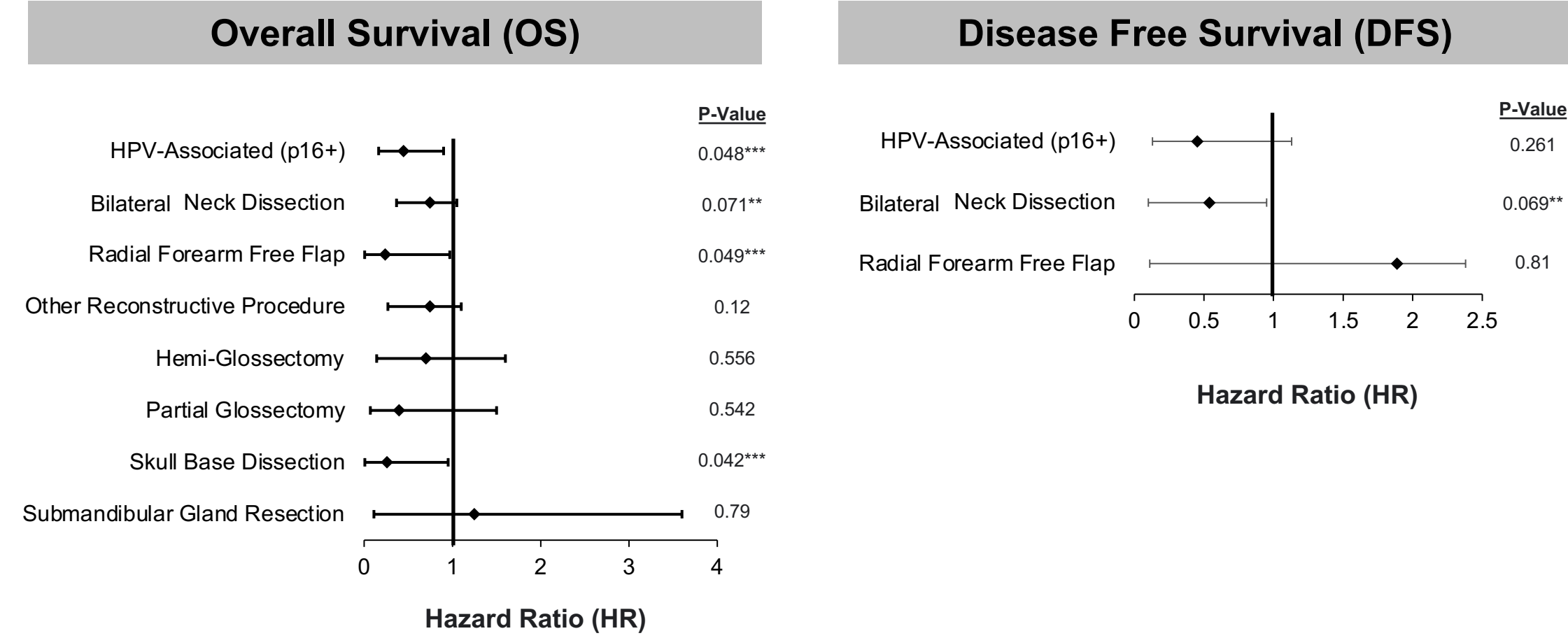Multi-Stratified Multivariate CPH — Overall Survival (OS); Disease Free Survival (DFS)

- There is limited support for the use of adjuvant RT and CT in the setting of oral SCC with a primary site of the tongue base (p=0.81 when evaluating the end-point of OS and p=0.34 when evaluating the end-point DFS). Given heavy right censoring within the dataset, the assumption of proportional hazards is not adequately met.

- Strong support for bilateral ND (HR 0.71 [0.21, 1.04]; p = 0.071), radial forearm free flap (HR 0.23 [0.04, 0.97]; p = 0.049) , and skull base dissection (HR 0.28 [0.05, 0.96]; p = 0.042). There is limited support for submandibular gland resection (HR 1.2 [0.11, 3.61]; p = 0.79). The DFS model is limited because there were few recurrence events at tongue base site and the multi-stratified model struggled to converge.

Subsite: Uvula, Soft Palate, Lateral and Posterior Pharyngeal Wall (n = 32)

Kaplan Meier Log-Rank Testing — Overall Survival (OS); Disease Free Survival (DFS)

- Heavy right censoring and small sample size for soft palate, lateral and posterior pharyngeal wall primary subsite (n=32) prevented the multi-stratified multivariate model from converging to a meaningful result.

- When an aggregated multi-stratified multivariate model was run with all subjects (n=206) and not binned by primary subsite. Bilateral ND (HR 0.69 [0.22, 1.04]; p = 0.068) and radial forearm free flap procedures (HR 0.44 [0.14, 0.94]; p = 0.049) were showed to improve OS and DFS.

- There was limited support for submandibular gland resection in the aggregated model (HR 2.2 [0.18, 2.8]; p = 0.74).

Limitations

- 206 patients between the ages of 36 and 89 who met inclusion and exclusion criteria were treated at only one tertiary academic referral center by four individuals and thus there was significant homogeneity in surgical treatment approaches. A bilateral neck dissection was performed in 81% of cases and thus statistically it was challenging to assess whether unilateral neck dissections were equally as effective when assessing endpoints of OS and DFS.

- There is significant variability in treatment protocols across subsites and therefore variability in the number of reconstructive procedures which were performed for each subsite, Most reconstructive hemi-mandibulectomy and tibular/fibular free flap procedures were performed for posterior pharyngeal wall and late-stage base of tongue primary sites. This prevented an aggregated analysis from being statistically meaningful and thus low-volume reconstructive procedures were removed as explanatory variables from the aggregated model

- Heavy right censorship created statistical limitations in this study as data analysis was performed retrospectively

Conclusion

- Analysis of treatment selection, extent of surgery, and survival shows that primary aggressive surgery including bilateral neck dissection does convey a survival advantage.

- Primary aggressive surgery does show strong utility in maintaining survival outcomes for both p16 + and – OPSCC.

- Current data collection on long term speech and swallowing outcomes on patients treated with different surgical resection and reconstruction approaches will help elucidate an informed surgical treatment algorithm in this complex patient population.

- Supplementing the current data set with data from other tertiary academic referral centres who frequently utilize different surgical approaches (unilateral neck dissection) will allow for more insights to be drawn regarding benefits of aggressive surgery, particular in early stage oral SCC.

Acknowledgements