# Transoral Robotic Surgery Versus Chemoradiation Treatment in Oropharyngeal Cancer: Case-matched Comparison of Survival and Swallowing Outcomes

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**Research article**

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# Abstract

Background As the incidence of HPV/p16-positve oropharyngeal squamous cell carcinoma (OPSCC) continues to rise, a large population of survivors with treatment related morbidity is emerging. Transoral robotic surgery (TORS) is an excellent surgical option for p16-positive OPSCC but data comparing both survival and swallowing outcomes of this treatment versus radiotherapy/chemoradiotherapy (RT/CRT) remains limited. Methods Data was prospectively collected (05/2014 - 02/2019) in a tertiary care referral center from OPSCC patients treated with curative intent by TORS (+/-post-operative RT/CRT) or RT/CRT. Surgical and non-surgical treatment groups were case-matched for smoking status, T-stage, and N-stage based on AJCC 8th edition staging. Patients who were treated with curative intent by TORS (+/-post-operative RT/CRT) or RT/CRT for OPSCC were included. Overall survival, recurrence free survival, aspiration free survival and gastrostomy tube outcomes were compared using univariate and multivariate statistical analyses. Results A total of 82 patients treated with TORS were case-matched with 61 patients who received RT/CRT. TORS patients demonstrated a significantly (p=0.02) higher overall survival (OS) at 3 years (OS=93.2%) compared to RT/CRT patients (OS=78.9%). No statistically significant difference was seen in recurrence free survival when comparing the two groups. TORS patients demonstrated an aspiration free survival (AFS) of 64.7% compared to 26.1% in RT/CRT patients (p=0.02 Log-Rank, 0.018 Breslow). TORS patients also had significantly ($p < 0.01$) lower gastrostomy tube placement (13.4%) compared to RT/CRT (22.9%) at any point during treatment. Conclusion Patients undergoing treatment by TORS may have comparable survival and improved swallowing outcomes when compared to those undergoing RT/CRT for HPV-OPSCC.


# Background

The incidence of HPV/p16-positive oropharyngeal carcinoma (HPV-OPSCC) has been steadily rising in North America for decades(1,2). Given that HPV-OPSCC carries a favorable treatment response with high cure rates compared to its HPV-negative counterpart, a large population of survivors with treatment-related morbidity is emerging(3).

Transoral robotic surgery (TORS) is an excellent surgical option(4) for p16-positive OPSCC but data comparing functional outcomes versus chemoradiotherapy (CRT) remains limited(5). Recent studies have suggested that there may be improved outcomes with primary surgery versus primary chemoradiotherapy particularly in a cohort of patients with a significant smoking history(6). TORS has demonstrated encouraging oncologic, functional, and quality of life outcomes(7).

Health-related quality of life measures in survivors of head and neck cancer patients often include dysphagia with up to 50% of patients identifying swallowing difficulties as their primary concern post-treatment(8). Dysphagia and aspiration are under-reported and underappreciated consequences of head

and neck cancer and its treatment(9). There is also an association between the intensity of CRT treatment regimens and the rates of acute and long-term dysphagia(9).

HPV-OPSCC is often seen in younger, otherwise healthy patients in which excellent survival rates can be achieved but this outcome measure is inadequate. Patient-centered treatments must be tailored to minimize swallowing impairment and its impact on a patient's quality of life(10). When considering both survival and function, a lack of comparative studies has left equipoise regarding the optimal treatment for OPSCC(11–13). This study aims to compare survival and swallowing outcomes of transoral robotic surgery versus chemoradiation in patients with OPSCC.

# Methods

*Patients*

Patients included in this study were prospectively identified through the Northern Alberta Head and Neck Tumor Board. Patients who were p16+ and treated with curative intent by TORS (+/- post-operative RT/CRT) or RT/CRT were included. Data collection occurred from 05/2014 - 02/2019 at a tertiary head and neck cancer referral center at the University of Alberta Hospital. p16 status was obtained from clinical pathology as standard of care for patients with OPSCC with an accepted cutoff of >70% nuclear and cytoplasmic staining(11).

Patients were treated with TORS using the DaVinci SI system and a planned tracheostomy prior to tumor resection, as per our institutional surgical practice protocol. Free flap reconstruction of the oropharynx was performed in cases where the resection caused a significant surgical oro-cervical fistula, carotid artery was exposure or a $\geq$50% of BOT defect. Patients with tonsillar or lateral posterior pharyngeal wall tumors received an ipsilateral selective neck dissection +/- contralateral submandibular gland transfer(14,15). Bilateral selective neck dissection was performed in patients with BOT tumors or bilateral nodal disease based on pre-operative PET-CT imaging.

Those patients who were included in the study were compared using videofluoroscopic swallow studies, gastrostomy tube dependence, and survival outcomes. The videofluoroscopic swallow studies were then scored using the Penetration-Aspiration Scale (PAS) originally created by Rosenbek(12) and categorized into a 4-level PAS scale as per Steele and Grace-Martin(13). Chart reviews were completed to construct a database used for further analysis including the following variables: gender, age, date of diagnosis, recurrent disease, date of surgery, date of death, cause of death, date of recurrence, date last

known alive, treatment type, TNM staging (8th edition AJCC(16)), p16 status, smoking status (defined as those patients with >10 pack year smoking history as per Ang K et al.(17)), smoking pack years, gastrostomy tube placement, gastrostomy tube placement date, gastrostomy tube removal date, radiotherapy dosing (Gy), PAS, VFSS. If patients did not receive the full radiation and/or chemotherapy intended due to toxicity, they remained included in their respective treatment group.

p16 positive patients were categorized into two comparative treatment cohorts: A) primary surgery through a TORS approach with or without post-operative RT or CRT and B) RT +/- chemotherapy. Groups were case-matched for smoking status, T-stage and N-stage based on AJCC 8th edition staging.

*Statistical Analysis*

Survival time was calculated in years from time of pathologic diagnosis to date last known alive by electronic medical records or date of death using a right censoring method. Aspiration free survival (AFS) was defined as the time of pathologic diagnosis up to last documented aspiration (as previously reported(10)) on VFSS as measured by a certified speech and language pathologist or radiologist.

Univariate and multivariate statistical analyses were performed utilizing SPSS version 25.0 software (SPSS Inc., Chicago, IL, USA). Comparison of mean outcome measure between groups was performed using parametric statistics. Non-parametric tests were used to compare outcomes between smaller groups. The Kaplan-Meier algorithm was used to estimate overall (OS) and recurrence free survival (RFS), employing the Log-rank and Breslow tests to compare survival between strata. A Cox proportional hazards model was used to perform multivariate analysis of factors and covariates including age, sex, T-stage, N-stage, overall stage, treatment type, and smoking status. For PAS scoring, an ordinal scale was utilized. Statistical significance was defined as $p < 0.05$.

# Results

*Patient Characteristics*

A total of 191 patients with OPSCC treated with primary TORS or RT/CRT at the University of Alberta were identified for inclusion in this study (Figure 1.) Of these, 37 were p16-negative and one was converted to a lip-split mandibulotomy and were thus excluded. Following case-matching, 61 patients

were included in the RT/CRT group and 82 patients were included in the TORS group. There were 11 patients who remained unmatched (supplementary Table 1).

A cohort of 143 patients was included for comparative analyses in this study. In comparing characteristics between the TORS and RT/CRT groups for age, sex, T-stage, N-stage, smoking status (>10 years(17)), and mean pack years, no statistically significant differences were identified (Table 1.)

*Survival Analysis*

Stratification of OPSCC patients according to treatment type as well as smoking status showed significant differences in 3-year overall survival (Figure 2). TORS patients demonstrated a significantly ($p=0.02$) higher overall survival (93.2%) when compared to primary RT/CRT patients (78.9%). No statistically significant difference was seen in recurrence free survival when comparing the two groups.

With stratification based on smoking status, no statistically significant difference between groups was seen in overall survival or recurrence free survival (Figure 3.) A trend was observed ($p=0.08$) towards higher overall survival in smokers who underwent primary TORS (93.8%) versus smokers who underwent RT/CRT (75.2%).

Multivariate Cox regression analysis of survival outcomes was performed to include age, gender, stage, smoking status, and treatment type (Table 2.) Overall TNM stage was found to be a statistically significant covariate, predicting lower overall survival ($HR = 2.31$, $p = 0.03$) and recurrence free survival ($HR = 4.00$, $p < 0.01$) with increasing stage.

*Dysphagia Analysis*

As a measure of dysphagia, aspiration free survival (AFS) was estimated using a Kaplan-Meier analysis of patients treated with a primary TORS or primary RT/CRT approach, estimating a 3-year aspiration free

survival (Figure 4.) In this comparison, the TORS group demonstrated an AFS of 64.7% versus 26.1% in patients treated by RT/CRT (p=0.02 Log-Rank, 0.018 Breslow).

A multivariate Cox regression analysis of AFS was performed to include age, gender, 8$^{th}$ AJCC overall stage, smoking status, and treatment type. Covariates of smoking status and TORS vs. RT/CRT were statistically significant predictors of aspiration free survival. Smokers demonstrated a higher risk of death (HR = 2.56, p = 0.02.) Those patients undergoing RT/CRT had a significantly higher risk of death compared to those patients undergoing TORS (HR = 2.22, p = 0.05) (Table 3.)

In comparing gastrostomy tube dependence between TORS and RT/CRT groups, a statistically significant difference was observed. Patients who had a gastrostomy tube placed at any point during treatment made up 13.4% of TORS patients whereas RT/CRT patients had a gastrostomy tube placed 22.9% of the time (p < 0.01.) RT/CRT patients were less likely to have a gastrostomy tube placed <1-month post-treatment (1.6%) versus TORS patients (6.1%) (p = 0.02) (Table 4.)

# Discussion

As the population of HPV-OPSCC survivors increases, it will become important to better understand survival and swallowing outcomes in different treatment modalities in order to appropriately address patients' needs. Patients with HPV-OPSCC are younger, less likely to smoke or drink, and tend to have better survival outcomes (18). Comparison of TORS to RT/CRT has been made previously in a retrospective manner (19) or through prospective study without case-matching (20). Even fewer studies have included advanced stages of disease(21). This study is unique in comparing survival and swallowing outcomes for TORS versus RT/CRT patients in a prospective case-matched design.

Gastrostomy tube dependence is commonly reported as a marker of dysphagia related morbidity from OPSCC treatment. Treatment with TORS has shown lower rates of swallow dysfunction with a <10% gastrostomy tube dependence rate (21–23). Gastrostomy tube dependence in OPSCC patients treated with RT/CRT can be as high as 23% at 6 months post-treatment(21). In a retrospective analysis, non-surgically treated patients were 10.6 times more likely to require a g-tube compared to those who received TORS (24). Other studies have demonstrated significant dysphagia post-chemoradiotherapy with 40% dysphagia at 3 years post-treatment(25) and gastrostomy tube dependence of 46% at 3 months and 3% at 2 years(26).

A prospective study by Dziegielewski et al.(22) suggested that TORS for OPSCC results in excellent swallowing function with low g-tube dependence and minimal reduction in quality of life. Post-operative g-tube was not required in patients who received TORS alone but was 9% at 1 year in patients treated with adjuvant RT/CRT. Consistent with their study, our results showed no g-tube dependence one-year post-TORS treatment, significantly lower than patients who received RT/CRT. A limitation of their study however was the lack of a comparative cohort (22). Our results address this limitation using a case-matched comparison group and are consistent with the study by Dziegielewski et al(22). Higher stage disease with a larger TORS resection also predicted gastrostomy tube dependence and was accompanied with higher rates of dysphagia. Free flap reconstruction was guided by institutional protocol and occurred if resection caused: a significant oro-cervical fistula, carotid artery exposure, or if there was a >50% base of tongue defect.

The treatment of OPSCC with a primary TORS approach offers a number of advantages. TORS provides excellent access and visibility to for oropharyngeal resection while preserving neuromuscular structures important for swallowing(4,21). Despite the use of conformal techniques, xerostomia and dysphagia remain common morbidities with significant impacts on quality of life(11,27). Our patients treated primary TORS received radiotherapy doses of 60-66 Gy but also underwent a submandibular gland transfer, which likely decreased RT-related xerostomia(14,15). As with other primary surgical approaches, TORS can also offer the opportunity for de-escalation of treatment by reducing or avoiding post-operative RT/CRT(21).

Current studies examining survival in OPSCC have been largely limited to retrospective review. Consistent with previous reports, our prospectively-collected study showed 3-year overall survival for patients undergoing TORS at 93.2% (p=0.02)(28,29). Recent AJCC staging recommendations suggest 3-year survival being an adequate measure of cure in this disease(16). For patients undergoing primary chemoradiation, overall survival estimates are also in-keeping with recent studies with our study showing an overall survival of 78.9% (p=0.02.) Univariate survival analysis suggests TORS is associated with improved survival outcomes compared to RT/CRT. Our multivariate analysis suggests however that treatment with TORS vs RT/CRT is not an independent predictor of survival.

Swallowing outcomes research to date is largely found in nonsurgical literature. It is often difficult to compare treatment modalities as the number of modern-day approaches increases to include radiation therapy, chemoradiation, transoral laser microsurgery, lip-split mandibulotomy, and transoral robotic surgery. Our study examines the differences attributable to primary treatment modality in either transoral robotic surgery or chemoradiation in order to optimize therapy. AFS was significantly improved (p=0.02) with primary transoral robotic surgery (64.7%) versus primary chemoradiation (26.1%) 3 years following

treatment. As well, our multivariate Cox regression displayed a hazard ratio of 2.22 (p=0.05) for RT/CRT versus TORS patients. This suggests that AFS attributable solely to treatment modality favors those patients undergoing TORS in that they are more likely to survive without an aspiration event.

A study by El-Deiry et al identified that the presence of a gastrostomy tube strongly influences quality of life(27). Gastrostomy tube placement rates and dependence were examined in our study. Here, patients treated with transoral robotic surgery were less likely to have a gastrostomy tube placed at any time post-treatment (13.4% vs. 22.9% p<0.01.) However, this may reflect the use of prophylactic placement of gastrostomy tubes commonly performed by Radiation Oncology. This finding is similar to that seen in a recent study by Sharma et al(5) and may represent an advantage of TORS by avoiding prophylactic placement.

Stratification based on smoking status did not show a statistically significant difference between TORS and RT/CRT patients. This held true in both our overall survival and recurrence free survival estimates. A trend (p=0.08) was demonstrated towards higher overall survival in smokers who underwent primary TORS (93.8% vs. 75.2% 3-year OS.) Further study with a larger cohort may be required to better elucidate this relationship.

This study provides important data that can be used to better counsel patients with p16+ OPSCC regarding their treatment choice. Survival outcomes appear to be comparable with higher rates of aspiration and gastrostomy tube dependence in those treated with RT/CRT. Treatment with TORS alone has been seen to result in superior outcomes by avoiding the toxic effects of RT/CRT(10,22,26,30,31).

A number of limitations in this study should be considered when interpreting our results. Our data was obtained from a single tertiary care referral center which may not directly translate to other centers. In addition, our analysis of dysphagia did not include patient-reported outcomes or quality-of-life questionnaires, but this would be important for future studies.

# Conclusions

Patients undergoing treatment by TORS may have comparable survival and improved swallowing outcomes when compared to those undergoing RT/CRT for HPV-OPSCC.

# Abbreviations

| | |
|---|---|
| AFS | aspiration free survival |
| CRT | chemoradiotherapy |
| Gy | Gray |
| HPV | human papillomavirus |
| HR | hazard ratio |
| OPSCC | oropharyngeal squamous cell carcinoma |
| OS | overall survival |
| PAS | penetration aspiration scale |
| PET-CT | positron emission tomography-computed tomography |
| QOL | quality of life |
| RFS | recurrence free survival |
| RT | radiotherapy |
| TNM | tumor, node metastasis |
| TORS | transoral robotic surgery |
| VFSS | videofluoroscopic swallowing study |

# Declarations

*Consent for Publication*

Not applicable.

*Ethics Approval and Consent to Participate*

The need for consent was waived by an institutional review board and deemed unnecessary with no patient identifiable information released. Institutional health research ethics (protocols Pro00062302 and Pro16426) was obtained from the University of Alberta.

*Availability of Data and Material*

Demographic, pathologic and survival data that support the findings of this study are available from the Alberta Cancer Registry but restrictions apply to the availability of these data including health ethics approval obtained for the current study.

*Competing Interests*

Dr. Vincent Biron is a member of the BMC Cancer Editorial Board.

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*Authors' Contributions*

CS: experimental design, data collection, data analysis and primary contributor in manuscript preparation

CJ: experimental design and data analysis

JC: data collection

DO: data collection

JH: data collection

HS: experimental design, data collection, and data analysis

VB: experimental design, data collection, data analysis, and manuscript preparation

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# Tables

Table 1. Characteristics of matched patient cohorts in this study

| Characteristic | TORS (N=82) | RT/CRT (N=61) | P-value |
|---|---|---|---|
| Age (mean) | 57.9 | 59.4 | 0.37 |
| Sex, % male | 78.0 | 88.5 | 0.12 |
| T-stage (%)<br>T1<br>T2<br>T3<br>T4 | <br>37.8<br>46.3<br>9.8<br>6.1 | <br>24.5<br>50.8<br>19.7<br>4.9 | 0.20 |
| N-stage (%)<br>N0<br>N1<br>N2 | <br>7.3<br>65.9<br>26.8 | <br>11.5<br>55.7<br>32.8 | 0.86 |
| Smokers (%) | 52.4 | 60.6 | 0.39 |
| Mean pack years | 16.1 | 18.9 | 0.62 |

Table 2. Multivariate Cox Regression Analysis of Survival Outcomes

| Variable | Overall Survival | | Recurrence Free Survival | |
|---|---|---|---|---|
| | Hazard Ratio | p-value (95 % CI) | Hazard Ratio | p-value (95 % CI) |
| **Age (>60)** | 2.21 | 0.12 (0.80-6.08) | 1.57 | 0.40 (0.55-4.46) |
| **Sex (Male)** | 1.01 | 0.98 (0.22-4.74) | 2.74 | 0.36 (0.33-21.22) |
| **Stage (I, II, III)** | **2.31** | 0.03 (1.11-4.82) | **4.00** | <0.01 (1.89-8.47) |
| **smoking** | 1.36 | 0.57 (0.47-3.96) | 2.29 | 0.17 (0.71-7.45) |
| **RT/CRT vs TORS** | 2.79 | 0.09 (0.86-9.05) | 0.61 | 0.39 (0.20-1.89) |

Table 3. Multivariate Cox Regression analysis of aspiration free survival

| Variable | Aspiration Free Survival | |
|---|---|---|
| | Hazard Ratio | p-value (95 % CI) |
| **Age (>60)** | 1.98 | 0.74 (0.94-4.18) |
| **Sex (Male)** | 1.11 | 0.86 (0.36-3.44) |
| **Stage (I, II, III)** | 1.13 | 0.69 (0.63-2.00) |
| **smoking** | **2.56** | 0.02 (1.20-5.46) |
| **RT/CRT vs TORS** | **2.22** | 0.05 (1.00—4.97) |

Table 4. Comparison of gastrostomy tube dependence between treatment groups

| G-tube dependent | TORS (%) | RT/CRT (%) | P-value |
|---|---|---|---|
| Any g-tube | 13.4 | 22.9 | <0.01 |
| <1 month | 6.1 | 1.6 | 0.02 |
| 1-6 months | 4.9 | 11.4 | |
| 6 months-1 year | 2.4 | 1.6 | |
| >1 year | 0 | 8.2 | |

## Figures

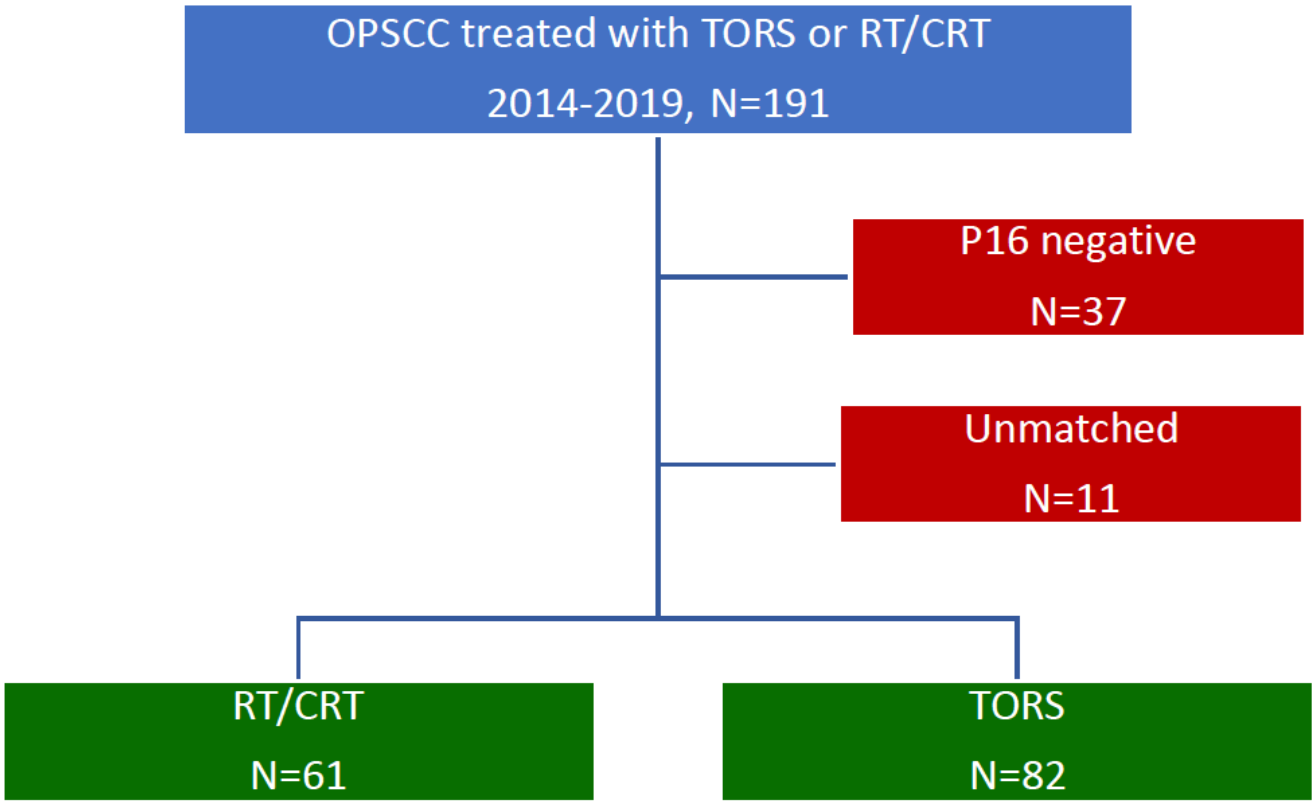



**Figure 1**

Flow chart of matched patients included in this study.

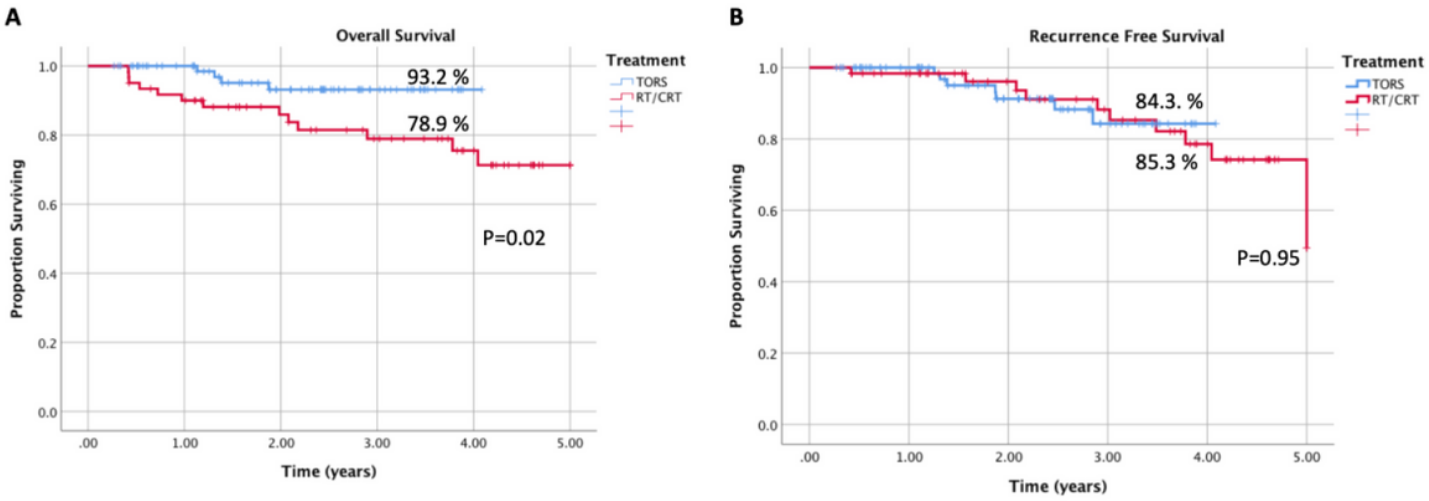
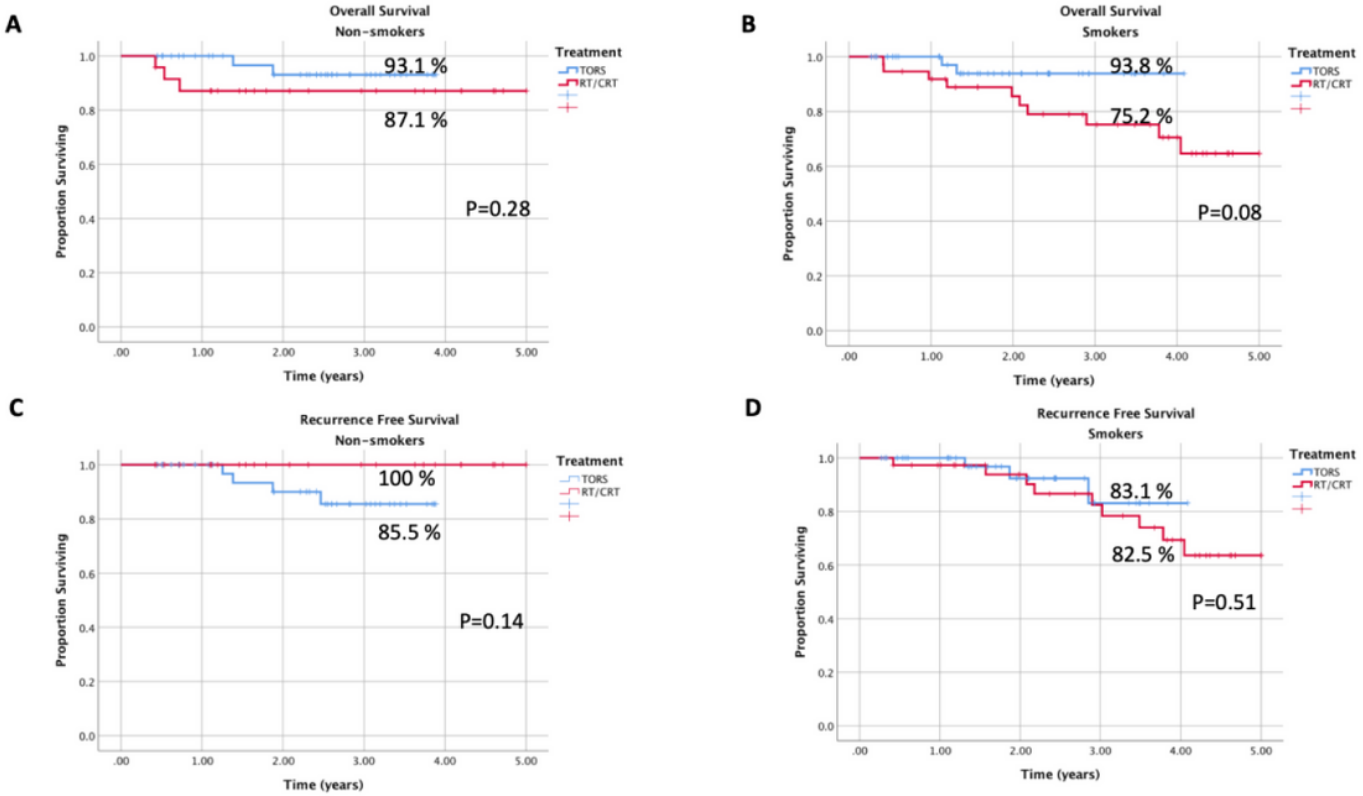



**Figure 2**

Survival outcomes of oropharyngeal cancer patients stratified by treatment. Kaplan-Meier analysis ofpatients treated with a primary TORS or RT/CRT approach, showing estimates of A) overall survival

and B) recurrence free survival. Survival estimates are shown at 3 years. P-value is shown using the Log-Rank method.




## Figure 3

Survival outcomes of oropharyngeal cancer patients stratified by treatment and smoking status. Kaplan-Meier analysis of patients treated with a primary TORS or RT/CRT approach, showing estimates of overall survival A) non-smokers and B) smokers, and recurrence free survival in C) non-smoker and D) smokers. Survival estimates are shown at 3 years. P-value is shown using the Log-Rank method.

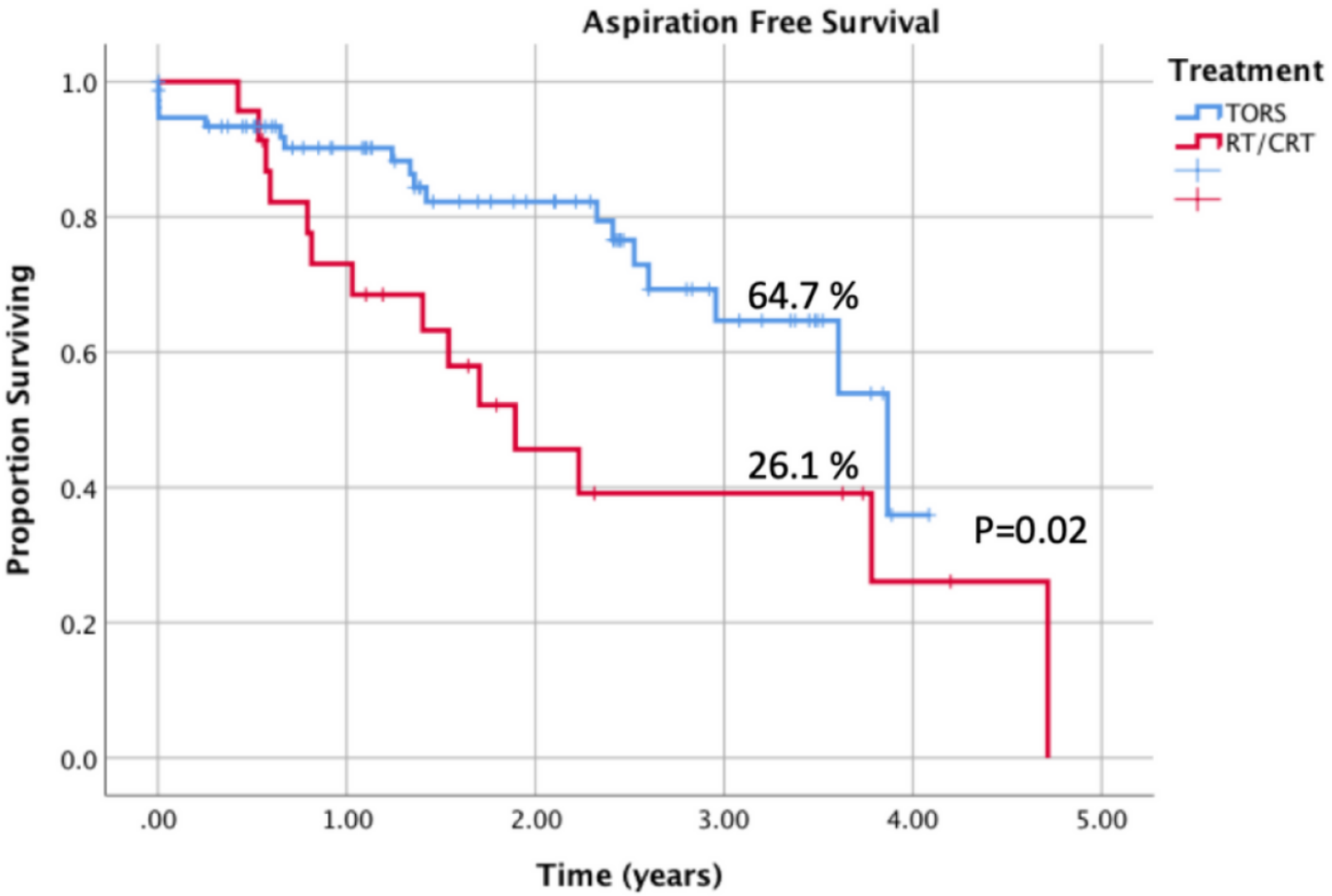



**Figure 4**

Dysphagia related survival outcomes of oropharyngeal cancer patients. Kaplan-Meier analysis of patients treated with a primary TORS or RT/CRT approach, estimating 3-year aspiration free survival. P-value is shown using the Log-Rank method. P-value using the Breslow method is also statistically significant at 0.018.

# Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryTable1.png