



Disparities in Management and Survival for T4 Larynx Squamous Cell Carcinoma

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Introduction

- The T4 larynx cancer population is heterogeneous. There is significant variability within this group with respect to:
 - Larynx preservation
 - Regional/nodal disease distribution
 - Overall survival
- National guidelines and expert consensus support the management of resectable T4 larynx cancers with laryngectomy.
- The purpose of this study is to review T4 larynx cancer treatment pathways in the U.S. National Cancer Database, in order to identify factors that may be associated with deviation from practice guidelines
 - Patient-specific factors
 - Disease-specific factors

Methods

- Patients with T4 larynx squamous cell carcinoma were identified by site-specific, histologic and surgical codes.
- Patient demographics, treatment, and tumor characteristics were identified.
- Standard of care/intent to cure pathways were considered to be:
 - Surgery (total laryngectomy or TL) plus adjuvant radiation with (SRC) or without (SRT) chemotherapy
 - Non-surgical (chemoradiation or CRT)
- Adjuvant treatment after surgery was defined as radiation, at least 40 Gy, delivered within 90 days of surgery, with or without chemotherapy.
- CRT was limited to patients undergoing treatment within 90 days of diagnosis, who received at least 50 Gy of radiation.
- Chi-squares tests were used to compare descriptive and demographic data. Survival rates between clinical care pathways were compared. Survival was estimated by the Kaplan-Meier method and the significance of difference among the curves was calculated by the log-rank test.
- All analyses were performed using SAS 9.4 (SAS Institute Inc, Cary NC). Statistical significance was set at 0.05.

Results

Demographics:

- 11,556 patients ≥18 years between 2004 and 2016 had clinical T4 M0 larynx squamous cell carcinoma
- Groups had similar age, racial distribution, Charlson-Deyo comorbidity indices.
- Laryngectomy: more often male, at academic institutions, higher T4a and N0 rates, greater total tumor size ($p<0.0001$).
- Lower N3 rates, and less frequent poorly differentiated histology ($p<0.0001$).

Pathologic features of the resected tumors:

- 10.1% down T-staged to pT3 ($n=460$)
- Extranodal extension (ENE) was present in 970 patients.
- Positive margin rate after surgery 13.7% ($n=564$).
- T4b rate in chemoradiation (CRT) 23.9% ($n=752$).

Figure 1: CONSORT Diagram of NCDB Larynz Cancers

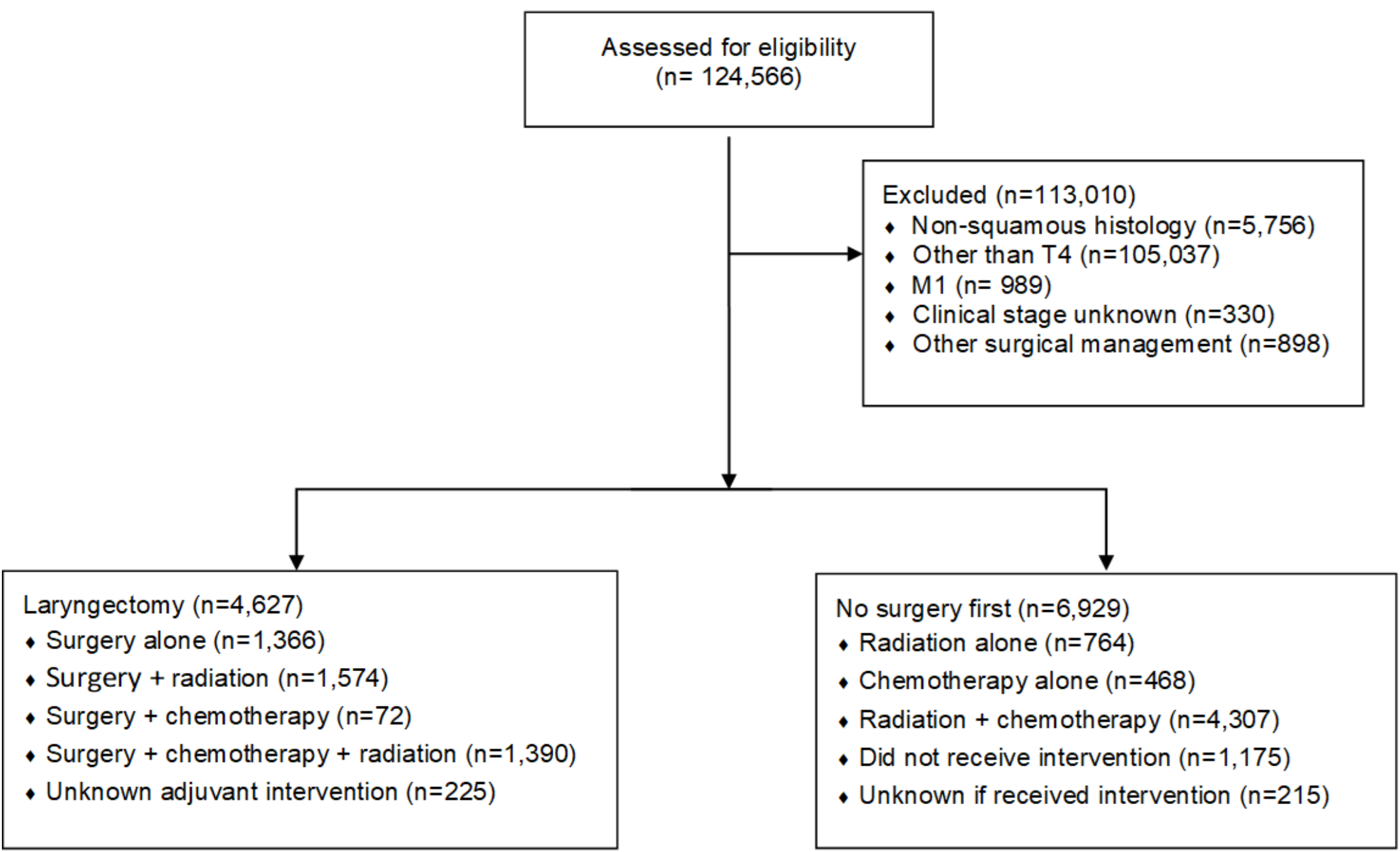
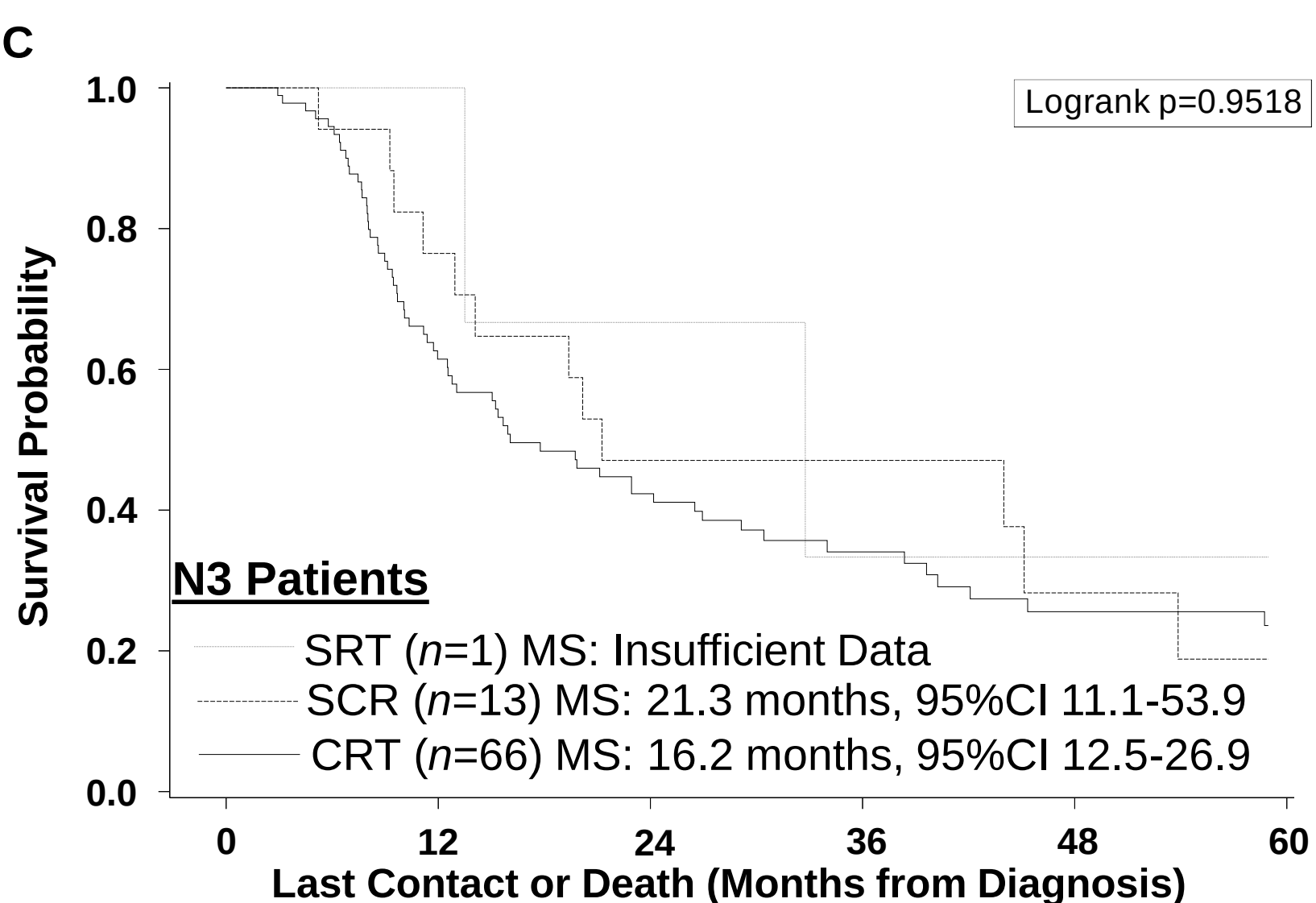
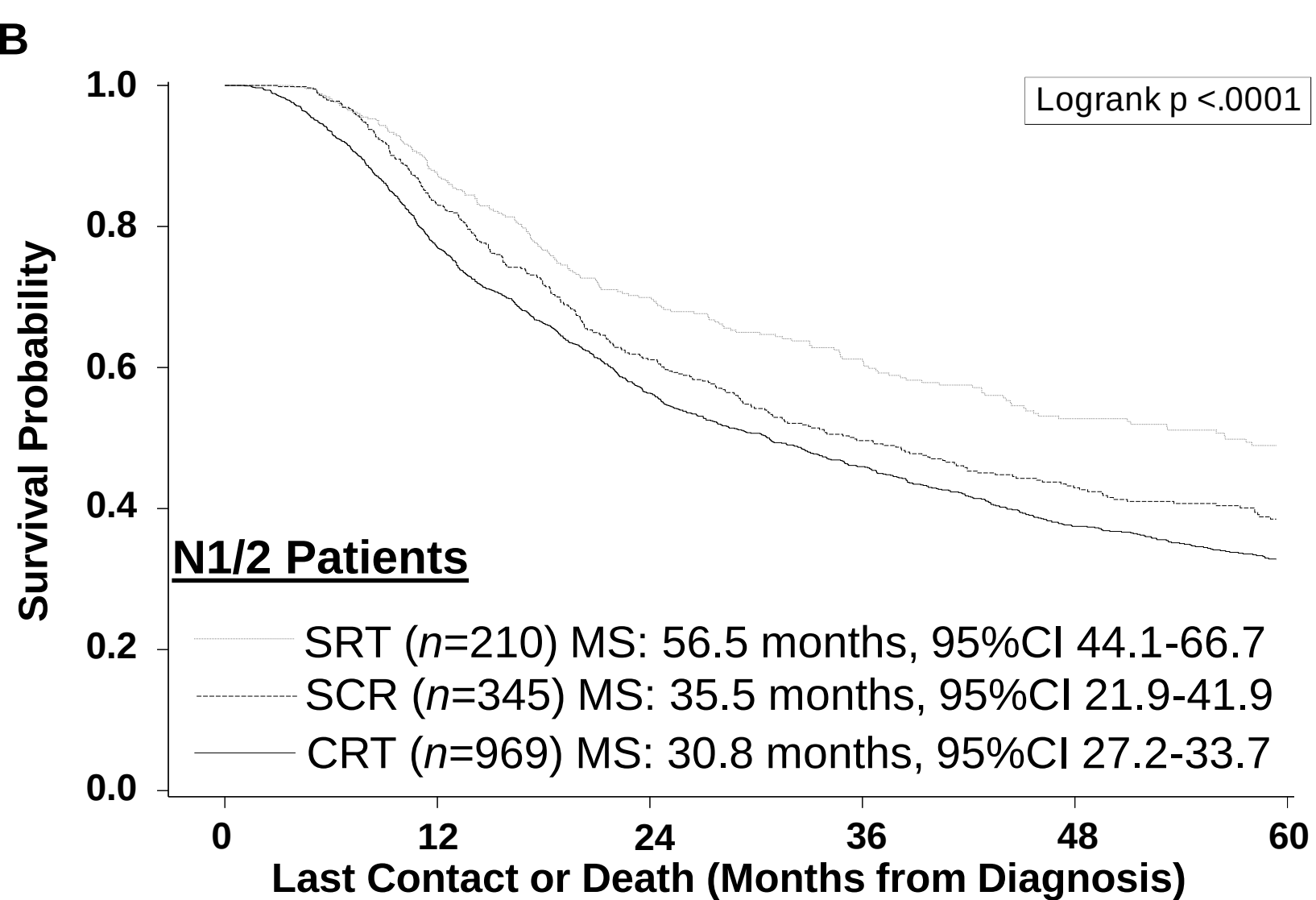
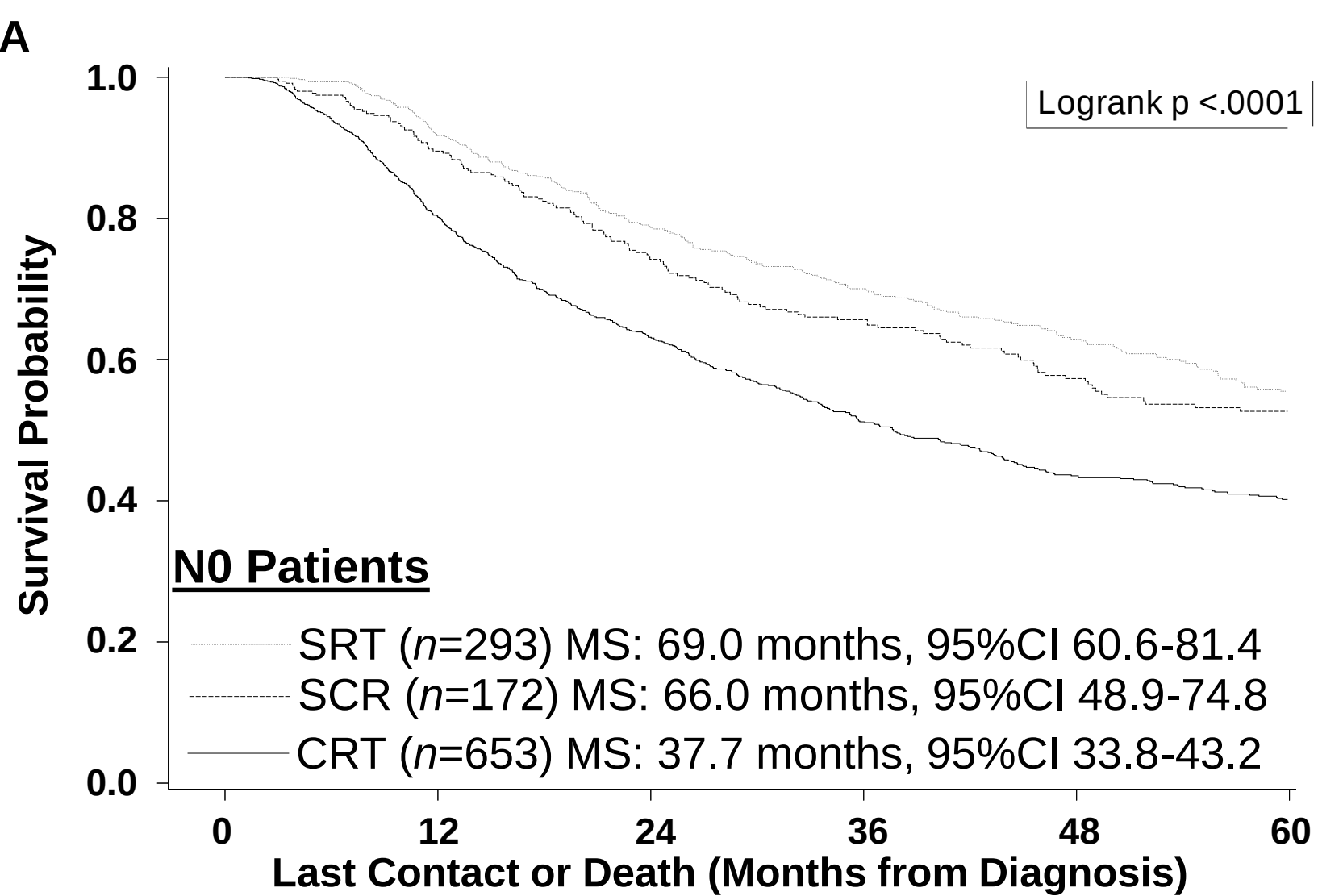


Figure 2: Kaplan-Meier Survival Based on Treatment Pathway and Nodal Status Kaplan-Meier survival curves for patients with (A) N0, (B) N1 and N2, or (C) N3 treated with chemoradiation therapy (CRT), surgery with chemoradiation (SCR), surgery with radiation therapy (SRT), or salvage. Median survival (MS) and p -values denoted on each graph. ($N=11,556$).

*Limiting the data set to T4a patients did not impact survival.



Discussion

- Limited randomized control data is available to guide clinical management:
 - VA Larynx trial and RTOG 91-11 of limited applicability to T4 patients.
- Management currently guided by historical standards of care, multivariable regression analyses of national data.
 - Multivariate analyses presume that treatment for T4 Larynx cancer should be indiscriminate of nodal status.
- This study suggests management algorithms should consider clinical nodal status:
 - N0 in a safe operative candidate: Laryngectomy should be recommended (best median survival, cure rate).
 - N1 or N2: Wide survival range between treatment pathways (SRT, SRC, CRT)
 - Narrow gap between SRC and CRT survival – balance of odds of chemotherapy/ENE with a non-functional larynx and salvage.
 - Failure of tri-modality therapy to overcome the negative prognostic value of ENE. (Al-Mamgani 2019, Harris 2016)
 - SRC subgroup, <10% of the laryngectomy population.
 - N3: Laryngectomy is generally part of a tri-modality therapy. No clear benefit in survival for N3 patients who receive SRC vs. CRT.
 - Poor compliance with CRT treatment impacts operative and non-operative arms equally. (Lin 2016)
 - Quality of life preferences should be prioritized in decision-making.
- Larynx preservation is more commonly practiced by non-academic institutions.
 - Impaired access to a qualified surgeon.
 - Patient survival for CRT at low-surgical volume facilities is significantly inferior. (Chen 2007)
 - Survival is not the only metric by which successful CRT is defined. (Wick 2017)
- Study Limitations: Administrative dataset (coding, data entry error, incomplete data). Disease-specific survival cannot be assessed. Retrospective. Selection bias —multidirectional (CRT: smaller primary tumors or non-resectable).

Conclusions

- cT4 patients have survival disparities associated with treatment pathway, tumor biology and nodal disease burden.
- These differences are challenging to adjust for in multivariable logistic regression analyses.
- Surgery for all T4 patients should be considered and individual treatment discussions should include a multidisciplinary team with a qualified surgeon.

Resources

- Al-Mamgani A et al. Organ-preservation (chemo)radiotherapy for T4 laryngeal and hypopharyngeal cancer: is the effort worth? Eur Arch Otorhinolaryngol. 2019;276(2):575-583.
- Harris BN et al. Primary surgery for advanced-stage laryngeal cancer: A stage and subsite-specific survival analysis. Head Neck. 2016;38(9):1380-1386.
- Lin CC et al. Comparative effectiveness of surgical and nonsurgical therapy for advanced laryngeal cancer. Cancer. 2016;122(18):2845-2856.
- Chen AY et al. Factors predictive of survival in advanced laryngeal cancer. Arch Otolaryngol Head Neck Surg. 2007;133(12):1270-1276.
- Wick CC et al. Use of concurrent chemoradiation in advanced staged (T4) laryngeal cancer. Am J Otolaryngol. 2017;38(1):72-76.

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