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Outcomes of Neoadjuvant Chemoradiation in Clinical Stage I-II Esophageal Cancers with Signet Ring Histology

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- **Shortened Title:** NCRT in Esophageal Signet Ring Cancer
- **Key Words:** Signet ring, adenocarcinoma, esophagus, outcomes, neoadjuvant
- **Synopsis:** In a national cohort of patients with clinical stage I-II esophageal signet ring cell carcinoma undergoing esophagectomy, neoadjuvant chemoradiation was independently associated with worse overall survival compared with upfront surgery, highlighting uncertainty regarding optimal multimodality treatment for this histologic subtype.

ABSTRACT

Purpose: Esophageal signet ring cell carcinoma (SRC) is a rare subtype of esophageal adenocarcinoma associated with aggressive biology and poor outcomes. The role of neoadjuvant chemoradiation (NCRT) in clinical stage I-II esophageal SRC remains poorly defined.

Methods: Patients with clinical stage I-II (cT1-2N0, cT1N1) esophageal SRC who underwent esophagectomy between 2004 and 2017 were identified from the National Cancer Database. Patients were stratified by receipt of NCRT followed by esophagectomy versus upfront surgery. Overall survival was evaluated using Kaplan–Meier analysis and the log-rank test. Multivariable Cox proportional hazards regression assessed the association between NCRT and survival after covariate adjustment.

Results: Of 198 patients, 88 (44.4%) received NCRT and 110 (55.6%) underwent upfront surgery. Patients receiving NCRT presented with more advanced disease preoperatively. Postoperative T stage differed between groups, with higher rates of residual pT3 disease following NCRT. Median overall survival was significantly shorter among patients receiving NCRT compared with upfront surgery (36.1 vs. 68.2 months; p=0.038). In subgroup analysis, upfront surgery was associated with improved survival in cT1 disease (97.5 vs. 26.9 months; p=0.008), with no difference observed in cT2 disease (36.1 vs. 33.4 months; p=0.790). On multivariable analysis, NCRT remained independently associated with worse overall survival (HR 1.62, 95% CI 1.05–2.50, p=0.030).

Conclusion: In this national cohort of patients with clinical stage I-II esophageal SRC, NCRT was associated with inferior overall survival compared with upfront surgery. These findings suggest standard neoadjuvant approaches may not benefit this aggressive subtype and highlight the need for histology-specific treatment strategies.

INTRODUCTION

Signet ring cell carcinoma (SRC) of the esophagus represents a distinct histopathologic subtype of esophageal adenocarcinoma associated with a more aggressive phenotype and poorer outcomes compared to conventional esophageal adenocarcinoma.[1] Occurring in approximately 5% of esophageal cancer cases, SRC contain high levels of intracellular mucin, causing displacement of the nucleus and the classic "signet ring" shape.[1,2] In medically fit patients with esophageal adenocarcinoma, current treatment guidelines recommend stage-specific, multimodality management, including endoscopic therapy or esophagectomy alone for select early lesions and systemic therapy with or without radiotherapy in combination with esophagectomy for more advanced disease.[3]

Multimodality treatment strategies for esophageal adenocarcinoma have historically centered on neoadjuvant chemoradiation using the CROSS regimen (carboplatin and paclitaxel with concurrent radiotherapy) followed by esophagectomy.[4] Perioperative chemotherapy with FLOT (fluorouracil, leucovorin, oxaliplatin, and docetaxel) has more recently emerged as an alternative and often preferred approach.[5] Esophageal SRC poses a particular clinical challenge, as large institutional cohorts demonstrate inferior overall survival and diminished response to traditional multimodality therapy.[6–9] Amidst treatment paradigm shifts, the optimal multimodal strategy for esophageal SRC remains uncertain.

Given the rarity of esophageal SRC, population-level datasets provide a promising approach to evaluating treatment outcomes compared to institutional cohorts. The National Cancer Database (NCDB) provides extensive case volume and detailed treatment data for rare cancers.[10,11] Population-level studies of esophageal adenocarcinoma evaluating solely SRC cohorts or SRC subgroups suggest heterogeneous and sometimes conflicting associations between multimodality treatment and survival. Across NCDB and Surveillance, Epidemiology, and End Results (SEER) studies, surgical resection consistently emerges as a key determinant of improved survival in SRC, while the survival benefit of

chemotherapy and radiation remains inconsistent and highly dependent on analytic approach, patient selection, and lack of treatment-sequence specification.[12–16] Importantly, some registry-based studies generally evaluate systemic therapy and radiation as binary exposures and do not account for the timing or sequencing of neoadjuvant treatment relative to esophagectomy.[15,16] Consequently, the optimal role of neoadjuvant chemoradiation in surgically resected esophageal SRC remains poorly defined. The present study addresses this gap by specifically evaluating outcomes following curative-intent esophagectomy stratified by receipt of neoadjuvant chemoradiation versus upfront surgery.

METHODS

Patients with clinical stage I-II (cT1-2N0, cT1N1) esophageal signet ring cell carcinoma (ICD-O-3 histology code 8490) who underwent curative-intent esophagectomy between 2004 and 2017 were identified from the NCDB using American Joint Committee on Cancer (AJCC) staging. This analysis of deidentified NCDB data did not constitute human subject research; institutional review board approval and informed consent were not required. The study period was limited to 2004-2017 because esophageal signet ring cell carcinoma was not consistently identifiable as a distinct histologic entity in later NCDB data. After changes in staging and pathology reporting, such tumors may be grouped under broader poorly differentiated adenocarcinoma categories, which cannot reliably distinguish true signet ring cell morphology. M1 disease was excluded. Patients were stratified by receipt of neoadjuvant chemoradiation followed by esophagectomy versus receipt of upfront surgery.

Tumor and nodal staging were reported according to the AJCC edition at diagnosis, which corresponds predominately to the AJCC 7th edition for this study period.[17] Disease stage was defined using the NCDB Analytic Stage Group, which is predominately reflective of the pathologic stage and defaults to clinical stage when pathologic stage is unavailable. Surgical procedures were reported using

the SEER Program Coding Staging Manual definitions for the esophagus disease site (C150-C159). Thirty-day re-admission was defined as any readmission to the same hospital as index procedure within 30 days of surgical discharge. Overall survival was defined as time from esophagectomy to death from any cause or last follow-up.

Categorical variables were compared using the Chi-square test or Fisher's exact test, as appropriate. Continuous variables were compared between groups using the Mann-Whitney U test and are reported as medians with interquartile ranges. Survival distributions were estimated using the Kaplan–Meier method and compared between treatment groups using the log-rank test. Multivariable survival analysis was performed using Cox proportional hazards regression to evaluate the association between neoadjuvant chemoradiation and overall survival. Covariates were selected based on clinical relevance and included age at diagnosis, Charlson–Deyo comorbidity score, clinical T staging, surgical margin status, and receipt of adjuvant chemotherapy. Hazard ratios (HRs) with 95% confidence intervals (CIs) were reported. All statistical analyses were performed using SPSS (IBM Corp., Armonk, NY), and a two-sided p value < 0.05 was considered statistically significant.

RESULTS

Study Population

A total of 198 patients with clinical stage I-II esophageal SRC who underwent curative-intent esophagectomy between 2004 and 2017 were identified. Of these, 88 patients (44.4%) received neoadjuvant chemoradiation followed by esophagectomy, while 110 patients (55.6%) underwent upfront surgery.

Baseline Clinicopathologic Characteristics

Baseline demographic and clinical characteristics are summarized in **Table 1**. The median age at diagnosis was 62 years in the neoadjuvant chemoradiation group and 65 years in the upfront surgery group, a non-significant difference (p=0.092). The distribution of sex, race, Hispanic ethnicity, Charlson–Deyo comorbidity score, insurance status, and treatment facility type was similar between groups (**Table 1**). Clinical stage at diagnosis differed between treatment cohorts (p=<0.001, **Table 2**), with a higher proportion of patients receiving neoadjuvant chemoradiation presenting with more advanced clinical stage I-II disease, driven in part by a higher frequency of cT2 disease in the neoadjuvant chemoradiation group (65.9%) compared to the upfront surgery group (36.4%, **Table 2**). Clinical nodal staging did not significantly differ between groups (p = 0.095, **Table 2**). Only 10 patients (5.1%) had clinically node-positive disease; 7 received neoadjuvant chemoradiation and 3 underwent upfront surgery.

Treatment Characteristics

Treatment characteristics are summarized in **Table 3**. Of the patients receiving neoadjuvant chemoradiation, 4 (4.5%) received additional chemotherapy. In contrast, patients in the upfront surgery cohort more commonly received adjuvant chemotherapy (28.2%) and/or adjuvant radiation (19.1%) (both $p < 0.001$). The median time from diagnosis to surgery was significantly longer among patients receiving neoadjuvant chemoradiation (4.4 months [IQR, 3.9-5.2]) compared with upfront surgery (1.8 months [IQR, 1.2-2.6], p <0.001). Most patients underwent esophagectomy within 6 months of diagnosis in both cohorts: 79 of 88 patients receiving neoadjuvant chemoradiation (89.9%) and 106 of 110 undergoing upfront surgery (96.4%). Notably, all cT1 patients in the preoperative chemoradiation group underwent surgery within 6 months (30/30, 100%). The distribution of surgical procedures performed did not differ significantly between groups (p = 0.594), with esophagectomy and partial gastrectomy representing the most common operation in both cohorts (**Table 3**).

Pathologic Outcomes

Pathologic staging and margin status are summarized in **Table 2** and **Table 3**, respectively. Pathologic T stage differed between cohorts ($p < 0.001$, **Table 2**). The neoadjuvant chemoradiation cohort demonstrated a higher frequency of pT0 tumors (14.8% vs. 0.9%), while pT1–2 tumors were less common and pT3 tumors were more common compared with upfront surgery (27.3% vs. 20.0%, **Table 2**). Pathologic nodal status did not significantly differ between groups ($p = 0.159$, **Table 2**). NCDB Analytic Stage Group significantly differed between groups, with a higher frequency of stage II disease in the NCRT group (45.5%) compared to upfront surgery (30.9%) ($p=0.021$, **Table 2**). Rates of negative surgical margins weren't significantly different: 86.4% in the neoadjuvant chemoradiation group and 87.3% in the upfront surgery group ($p=0.30$, **Table 3**).

Short Term Surgical Outcomes and Overall Survival

Short-term postoperative outcomes are shown in **Table 3**. There were no significant differences between groups in 30-day readmission rates (6.8% vs 6.4%, $p = 0.949$) or 90-day mortality (5.7% vs 3.6%, $p = 0.359$) between the neoadjuvant chemoradiation and upfront surgery cohorts, respectively. Median follow-up was 45.2 months. Median overall survival was 36.1 months (95% CI, 15.7–56.5) among patients receiving neoadjuvant chemoradiation compared with 68.2 months (95% CI, 29.9–106.4) in patients undergoing upfront surgery (log-rank $p = 0.038$) (**Figure 1**).

Subgroup Analysis by Clinical T Stage

Given baseline differences in clinical T stage between treatment cohorts, we performed subgroup analyses stratified by clinical T stage (**Figure 2**). Among patients with cT1 disease, upfront surgery was associated with significantly improved overall survival compared with neoadjuvant chemoradiation. Median overall survival was 26.9 months in the neoadjuvant chemoradiation group versus 97.5 months in the upfront surgery group (log-rank $p = 0.008$). In contrast, among patients with cT2 disease, no significant

difference in overall survival was observed between treatment strategies. Median overall survival was 36.1 months in the neoadjuvant chemoradiation group and 33.4 months in the upfront surgery group (log-rank p = 0.790).

Multivariable Survival Analysis

Results of the multivariable Cox proportional hazards regression analysis are shown in **Table 4**. After adjustment for age at diagnosis, Charlson–Deyo comorbidity score, clinical tumor staging, surgical margin status, and receipt of adjuvant chemotherapy, receipt of neoadjuvant chemoradiation remained independently associated with worse overall survival (HR 1.62, 95% CI 1.05–2.50, p = 0.030). Age at diagnosis ≥65 (p = 0.012), and surgical margin status (p = 0.011) were independently associated with overall survival, while Charlson–Deyo comorbidity score (p = 0.425), clinical tumor stage cT2 vs. cT1 (p = 0.213) and receipt of adjuvant chemotherapy (p = 0.865) were not.

DISCUSSION

In this national cohort of patients with clinical stage I-II esophageal signet ring cell carcinoma undergoing curative-intent esophagectomy, receipt of neoadjuvant chemoradiation was independently associated with worse overall survival compared with upfront surgery. Collectively, these findings suggest that neoadjuvant chemoradiation may confer no survival advantage—and may in fact be detrimental—in patients with SRC histology, a subgroup known to exhibit distinct and aggressive tumor biology.

Interpretation of these findings requires careful consideration of baseline differences between treatment cohorts. Patients receiving neoadjuvant chemoradiation presented with more advanced clinical stage I-II disease, driven in part by a higher frequency of cT2 tumors at diagnosis. This pattern is consistent with contemporary clinical practice, in which patients perceived to have higher-risk disease are preferentially selected for multimodality therapy. In subgroup analyses by clinical T stage, among patients

with cT1 SRC, neoadjuvant chemoradiation was associated with markedly worse survival compared with upfront surgery, with a nearly 4-fold difference in median overall survival. In contrast, among patients with cT2 disease, no significant survival difference was observed between treatment approaches. These findings suggest that the detrimental association of neoadjuvant chemoradiation is most pronounced in patients with the earliest clinical T stage and may reflect overtreatment of biologically aggressive but potentially resectable tumors.

Pathologic findings further highlight the heterogeneous response of SRC tumors to neoadjuvant therapy. As expected, the neoadjuvant cohort demonstrated a higher rate of complete pathologic response at the primary tumor site (pT0), reflecting some degree of treatment sensitivity in a subset of patients. However, this was accompanied by a relative depletion of intermediate residual stages (pT1–2) and a higher proportion of residual pT3 tumors at resection compared with upfront surgery. This pattern suggests that while some SRC tumors can achieve complete response, others exhibit marked resistance to therapy and perhaps progress to locally advanced disease despite treatment. Similar heterogeneous responses to neoadjuvant therapy in SRC histology have been described in institutional series,[7–9] supporting the concept that SRC represents a biologically diverse but overall treatment-resistant phenotype.

Notably, pathologic nodal status and rates of negative surgical margins did not differ significantly between groups. Additionally, there were no differences in 30-day readmission or 90-day mortality, suggesting that receipt of neoadjuvant chemoradiation did not increase short-term operative risk. These findings argue against perioperative morbidity as a primary explanation for the observed survival differences and instead point toward tumor biology and treatment–tumor interactions as more likely drivers.

Several biologically plausible mechanisms may explain why neoadjuvant chemoradiation appears detrimental in SRC. Delayed definitive local control of aggressive cancers has been associated with worse

survival outcomes, suggesting that prolonged intervals to surgery or completion of therapy may permit tumor progression and dissemination.[18,19] Multiple institutional series have demonstrated that esophageal adenocarcinoma with signet ring cell features is associated with reduced pathologic response to neoadjuvant chemoradiation and inferior outcomes compared with conventional adenocarcinoma, suggesting an SRC phenotype that may be relatively treatment-resistant.[7,8] A suboptimal response to chemotherapy could further exacerbate oncologic outcomes by selecting for minor drug resistant clones, allowing more aggressive subpopulations to dominate and drive treatment failure.[20] Additionally, prolonged exposure of biologically aggressive tumors to ineffective systemic therapy prior to resection may permit ongoing micro-metastatic dissemination, a process that upfront surgery could theoretically interrupt. While these mechanisms remain speculative, they are biologically plausible and warrant further investigation in translational and prospective studies.

Our findings should be interpreted in the context of existing population-level data. Sathe et al. (2020) examined NCDB patients with stage I–III SRC or conventional adenocarcinoma and demonstrated improved survival with chemoradiation followed by esophagectomy compared with chemoradiation alone,[12] underscoring the importance of surgery in SRC. Tang et al. (2021), in a large NCDB analysis of esophageal adenocarcinoma, showed that SRC histology was associated with worse survival and higher rates of positive margins compared with other subtypes, even after stage matching.[13] Wan et al. (2017), using SEER data, reported no survival benefit to preoperative radiation compared with surgery alone in SRC, while receipt of chemotherapy at any point was associated with improved outcomes.[14] Taken together, these studies highlight both the aggressive nature of SRC and the uncertainty surrounding optimal sequencing of multimodality therapy. Our study builds on this literature by focusing specifically on clinical stage I-II SRC and directly comparing neoadjuvant chemoradiation with upfront surgery in an esophagectomy-only cohort.

This study has several important limitations. First, definitions of SRC vary across institutions, and outcomes may differ based on the proportion of signet ring cells within the tumor. NCDB histology coding is assigned by the reporting institution and is subject to misclassification. Prior institutional studies suggest that tumors labeled as SRC typically contain a predominant (>50%) signet ring component, whereas tumors with minor SRC features are more often coded as adenocarcinoma not otherwise specified.[8,9] As such, our cohort is likely enriched for biologically aggressive SRC and has less clinical applicability for low-percentage SRC, though this cannot be confirmed. Second, there are inherent limitations in the accuracy of recording clinical staging for clinical stage I-II esophageal tumors. Third, the NCDB does not capture patterns of recurrence or failure, precluding assessment of whether survival differences were driven by local or distant disease progression. Fourth, detailed chemotherapy regimen data are unavailable. During the study period, the predominant neoadjuvant approach was the CROSS regimen; therefore, these findings may be less directly applicable in the current era, in which perioperative FLOT chemotherapy has become increasingly adopted.[5] Finally, treatment intent is not captured in the NCDB, limiting our ability to distinguish planned neoadjuvant chemoradiation followed by definitive esophagectomy from definitive chemoradiation followed by salvage esophagectomy.

In conclusion, in this national cohort of patients with clinical stage I-II esophageal SRC undergoing curative-intent esophagectomy, neoadjuvant chemoradiation was independently associated with worse overall survival compared with upfront surgery. These findings suggest that SRC histology may represent a subgroup in which standard neoadjuvant chemoradiation strategies confer limited benefit and may be detrimental. Prospective studies are needed to define optimal treatment strategies for patients with esophageal SRC.

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Author contributions: Study conception and design: BM, AK, SAG, MDM. Data acquisition: BM, AK, HP, KF, IAZ, SAG, ALG. Data analysis and interpretation: BM, AK, SAG, SAM, HP, KF, IAZ, AHM, MDM. Drafting of the manuscript: BM, SAM, AK, SAG, AHM. Critical revision of the manuscript: BM, SAM, AK, SAG, HP, KF, IAZ, AHM, EAD, AC, RAM, JM, ALG, MDM. All authors read and approved the final manuscript.

Data availability: The data analyzed in this study were obtained from the National Cancer Database Participant User File and are subject to its data use agreement. Access is available to eligible investigators through the NCDB application process.

Ethics approval: Consistent with Colorado Multiple Institutional Review Board (COMIRB) policies, this secondary analysis of deidentified National Cancer Database data did not constitute human subjects research because investigators could not readily ascertain participants' identities; therefore, institutional review board approval and informed consent were not required.

Consent to participate: Not applicable.

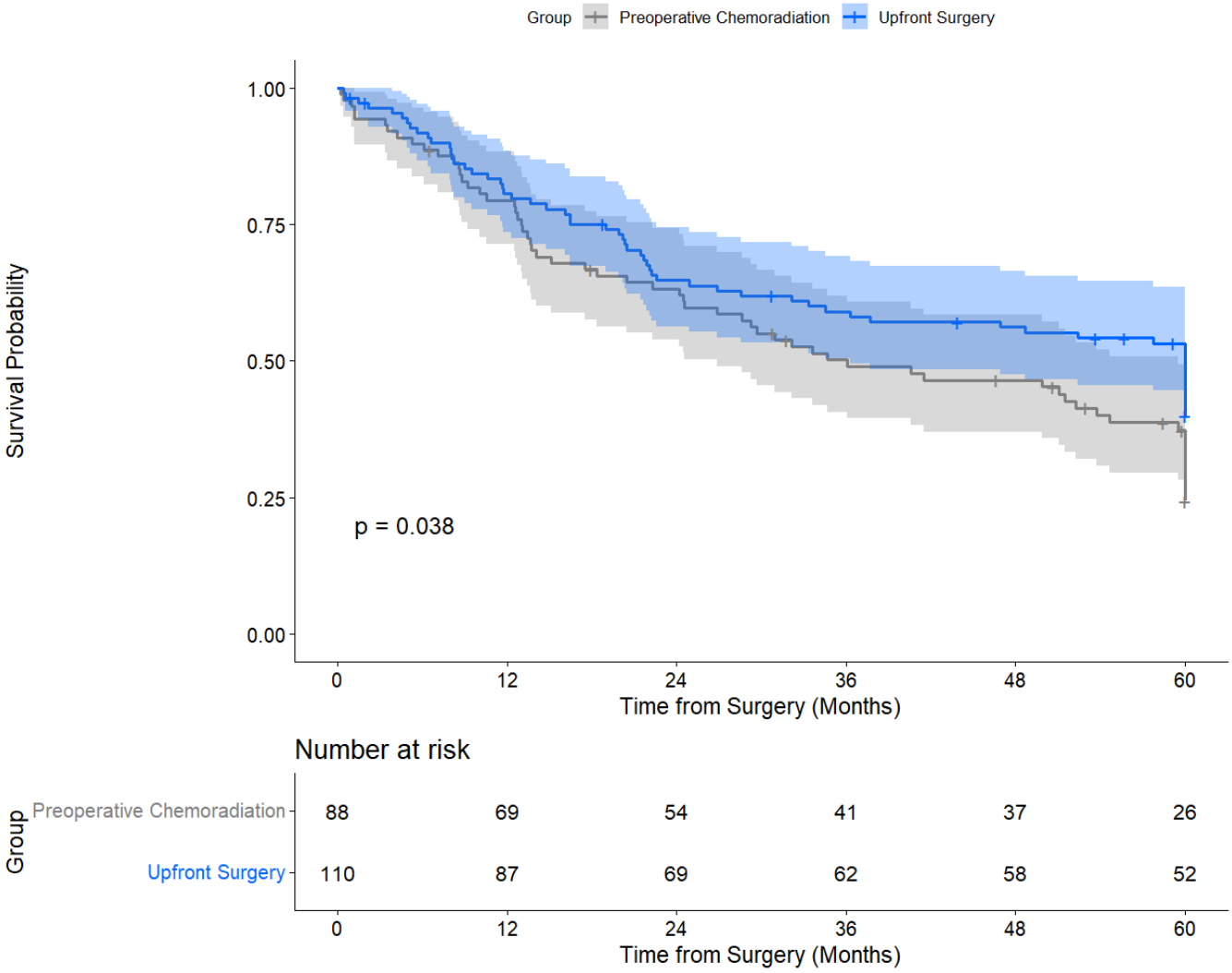


Fig. 1 *Kaplan Meier Survival Analysis for Patients Undergoing Preoperative Chemoradiation vs Upfront Surgery*

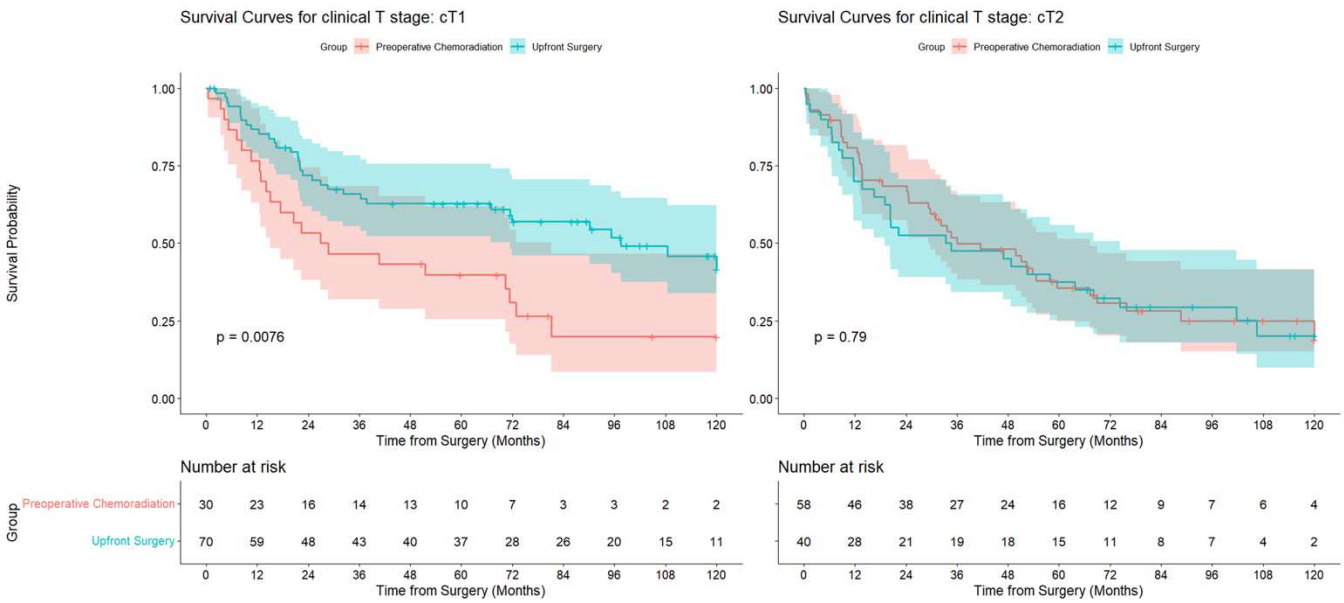


Fig. 2 *Kaplan Meier Survival Analysis for Patients Undergoing Preoperative Chemoradiation vs Upfront Surgery, Subgroup Analyses by cT stage*

		NCRT = 88 (44.4%)		Upfront surgery = 110 (55.6%)		Overall = 198 (100%)		
		N	%	N	%	N	%	p-value
Median age at diagnosis in years (IQR)		62 (57-68)		65 (57-72)		64 (57-71)		0.092
Sex	Male	77	87.5%	98	89.1%	175	88.4%	
	Female	11	12.5%	12	10.9%	23	11.6%	0.728
Race	White	87	98.9%	107	97.3%	194	98.0%	
	Non-white	1	1.1%	3	2.7%	4	2.0%	0.429
Ethnicity	Hispanic	81	92.0%	100	90.9%	181	91.4%	
	Non-Hispanic	5	5.7%	3	2.7%	8	4.1%	
	Unknown	2	2.3%	7	6.4%	9	4.5%	0.467
Charlson-Deyo Score	0	60	68.2%	81	73.6%	141	71.2%	
	≥ 1	28	31.8%	29	26.3%	57	28.8%	0.494
Primary payor at diagnosis	Not insured	2	2.3%	2	1.8%	4	2.0%	
	Private insurance	44	50.0%	40	36.4%	84	42.4%	
	Medicaid	6	6.8%	3	2.7%	9	4.5%	
	Medicare	35	39.8%	60	54.5%	95	48.0%	
	Other government	1	1.1%	2	1.8%	3	1.5%	
	Unknown	0	0.0%	3	2.7%	3	1.5%	0.119
Facility type	Community Cancer Program	6	6.8%	2	1.9%	8	4.1%	
	Comprehensive Community Cancer Program	22	25.0%	20	18.5%	42	21.4%	
	Academic/Research Program	40	45.5%	66	61.1%	106	54.1%	
	Integrated Network Cancer Program	20	22.7%	20	18.5%	40	20.4%	0.090
Great circle distance in miles (IQR)		17 (6-39)		19 (8-48)		18 (7-46)		0.339

Table 1. Cohort baseline and treatment facility characteristics for patients with esophageal SRC undergoing NCRT followed by surgery versus upfront surgery. **Abbreviations:** SRC = signet ring carcinoma; NCRT = neoadjuvant chemoradiation; IQR = interquartile range.

		NCRT = 88 (44.4%)		**Upfront Surgery = 110 (55.6%)**		**Overall = 198 (100%)**		
		N	%	N	%	N	%	p-value
Clinical stage group	cT1N0	23	26.1%	67	60.9%	90	45.5%	
	cT1N1	7	8.0%	3	2.7%	10	5.0%	
	cT2N0	58	65.9%	40	36.4%	98	49.5%	**<0.001**
Clinical N	cN0	81	92.0%	107	97.3%	188	94.9%	
	cN1	7	8.0%	3	2.7%	10	5.1%	0.095
Postoperative T[a]	pT0	13	14.8%	1	0.9%	14	7.1%	
	pTis	2	2.3%	0	0.0%	2	1.0%	
	pT1	9	10.2%	20	18.2%	29	14.6%	
	pT1a	4	4.5%	14	12.7%	18	9.1%	
	pT1b	10	11.4%	22	20.0%	32	16.2%	
	pT2	11	12.5%	17	15.5%	28	14.1%	
	pT3	24	27.3%	22	20.0%	46	23.2%	
	pT4	0	0.0%	1	0.9%	1	0.5%	
	pTX	9	10.2%	10	9.1%	19	9.6%	
	Unknown	6	6.8%	3	2.7%	9	4.5%	**0.001**
Postoperative N[a]	pN0	53	60.2%	60	54.5%	113	57.1%	
	pN1	13	14.8%	32	29.1%	45	22.7%	
	pN2	4	4.5%	4	3.6%	8	4.0%	
	pN3	2	2.3%	2	1.8%	4	2.0%	
	pNX	10	11.4%	10	9.1%	20	10.1%	
	Unknown	6	6.8%	2	1.8%	8	4.0%	0.159
NCDB Analytic Stage Group	I	32	36.4%	58	52.7%	90	45.5%	
	II	40	45.5%	34	30.9%	74	37.4%	
	III	12	13.6%	17	15.5%	29	14.6%	
	IV	0	0.0%	0	0.0%	0	0.0%	
	Unknown	0	0.0%	1	0.9%	1	0.5%	**0.021**
Tumor Grade	Well differentiated	0	0.0%	1	0.9%	1	0.5%	
	Moderately differentiated	5	5.7%	8	7.3%	13	6.6%	
	Poorly differentiated	69	78.4%	91	82.7%	160	80.8%	
	Anaplastic	1	1.1%	7	6.4%	8	4.0%	
	Not applicable	13	14.8%	3	2.7%	16	8.1%	**0.010**

Table 2. Pre-treatment clinical staging and postoperative pathologic staging for patients with esophageal SRC undergoing neoadjuvant chemoradiation versus upfront surgery. [a]For patients who received neoadjuvant chemoradiation, postoperative T and N categories represent ypT and ypN stage respectively; for patients who underwent upfront surgery, they represent pT and pN stage. **Abbreviations**: NCRT = neoadjuvant chemoradiation; NCDB = National Cancer Database.

		NCRT = 88 (44.4%)		Upfront Surgery = 110 (55.6%)		Overall = 198 (100%)		
		N	%	N	%	N	%	p-value
Surgery-chemotherapy sequence	No chemotherapy	0	0.0%	79	71.8%	79	39.9%	
	Neoadjuvant chemotherapy	84	95.5%	0	0.0%	84	42.4%	
	Adjuvant chemotherapy	0	0.0%	31	28.2%	31	15.7%	
	Neoadjuvant + adjuvant	4	4.5%	0	0.0%	4	2.0%	**<0.001†**
Radiation-surgery sequence	No radiation	0	0.0%	84	76.4%	84	42.4%	
	Neoadjuvant radiation	88	100%	0	0.0%	88	44.4%	
	Adjuvant radiation	0	0.0%	21	19.1%	21	10.6%	
	Sequence unknown	0	0.0%	5	4.5%	5	2.5%	**<0.001†**
Median time from diagnosis to surgery in months (IQR)		4.4 (3.9-5.1)		1.8 (1.2-2.6)		3.5 (1.6-4.3)		**<0.001†**
Extent of resection	Partial esophagectomy	9	10.2%	23	20.9%	32	16.2%	
	Esophagectomy with gastric resection	61	69.3%	64	58.2%	125	63.1%	
	Esophagectomy (other/unspecified)	18	20.5%	23	20.9%	41	20.7%	0.594
Surgical margins	Negative	76	86.4%	96	87.3%	172	86.9%	0.304
	Positive	6	6.8%	11	10.0%	17	8.6%	
	Unknown	6	6.8%	3	2.7%	9	4.5%	
30-day readmission	No readmission	79	89.8%	100	90.9%	179	90.4%	
	Any readmission	6	6.8%	7	6.4%	13	6.6%	
	Unknown	3	3.4%	3	2.7%	6	3.0%	0.949
90-day mortality	No 90-day mortality	83	94.3%	104	94.5%	187	94.4%	
	90-day mortality	5	5.7%	4	3.6%	9	4.5%	
	Unknown	0	0.0%	2	1.8%	2	1.0%	0.359

Table 3. Treatment variables and surgical outcomes for patients with esophageal SRC undergoing NCRT versus upfront surgery. "Other" esophagectomy included SEER surgery codes 40, 50, and 51 for esophagus disease site and collapsed due to rarity and table presentation. **Abbreviations:** SRC = signet ring carcinoma; NCRT = neoadjuvant chemoradiation; IQR = interquartile range; NOS = not otherwise specified. † = expected statistical difference by cohort definition.

Variable	Hazard Ratio (HR)	95% CI	p-value
Neoadjuvant chemoradiation (vs. upfront surgery)	1.62	1.05 - 2.50	**0.030**
Age at diagnosis (≥65 vs. <65)	1.62	1.11 - 2.35	**0.012**
Charlson-Deyo score (≥1 vs. 0)	0.85	0.57 - 1.27	0.425
Clinical T Stage (cT2 vs. cT1)	1.30	0.86 - 1.97	0.213
Surgical margin status (positive vs. negative)	2.19	1.20 - 4.00	**0.011**
Adjuvant chemotherapy (no vs. yes)	0.96	0.57 - 1.61	0.865

Table 4. Multivariable Cox proportional hazards analysis of overall survival after esophagectomy.
Abbreviations: HR = hazard ratio; CI = confidence interval; NCDB = National Cancer Database.