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ORIGINAL ARTICLE – THORACIC ONCOLOGY

Impact of Chemoradiation-to-Surgery Interval on Pathological Complete Response and Short- and Long-Term Overall Survival in Esophageal Cancer Patients

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ABSTRACT

Background. The impact of the neoadjuvant chemoradiation-to-surgery (CRT-S) interval in patients with esophageal cancer is not clear. We aimed to determine the relationship between CRT-S interval and pathological complete response rate (pCR) and overall survival (OS).

Methods. National Cancer Data Base patients with CRT followed by surgery were studied. CRT-S interval was studied as a continuous (weeks) and categorical variable (quintiles: 15–37, 38–45, 46–53, 54–64, and 65–90 days, with $n = 1016$, 1063, 1081, 1083, and 938 patients, respectively).

Results. A total of 5181 patients were included; 81% had adenocarcinoma. There was a significant increase of pCR rate across quintiles (18%, 21%, 24%, 25%, and 29%, $p < 0.001$) and per week increase of CRT-S interval [odds ratio (OR) 1.11, $p < 0.001$]. The 90-day mortality increased as CRT-S increased across quintiles (5.7%, 6.2%, 6.8%, 8.5%, and 8.2%, $p = 0.02$) and through weeks (OR 1.05, $p = 0.03$). Mean OS across CRT-S quintiles was 36.4, 35.1, 33.9, 33.2, and 30.7 months, respectively. Multivariate Cox regression showed significantly worse OS per week increase in CRT-S interval [hazard ratio (HR) 1.02, $p = 0.02$], especially among the last quintile (CRT-S = 65–90 days: HR 1.2, $p = 0.009$). The squamous cell carcinoma (SCC) and pCR groups had similar OS across CTR-S intervals.

Conclusions. Despite the higher pCR rate with longer CRT-S interval, surgery is optimal less than 65 days after CRT to avoid worse 90-day mortality and achieve better OS. In patients with SCC and those with pCR, prolonged CRT-S interval had no impact on OS. Further studies are needed to consolidate our findings.

Keywords Esophageal cancer · Neoadjuvant chemoradiation · Interval to surgery · pCR · Survival

Esophageal cancer (EC) is the sixth most common cause of cancer death worldwide.[1] While the incidence of esophageal squamous cell carcinoma (SCC) is unchanged, the incidence of esophageal adenocarcinoma is rising rapidly.[2] Neoadjuvant chemoradiotherapy (CRT) followed by esophagectomy has emerged as a promising approach to downstage and possibly eliminate local disease [i.e., achieve pathological complete response (pCR)] as well as having a survival benefit.[3–6]

Although pCR is considered as a surrogate marker of successful CRT, its survival benefit sometimes comes at the cost of a rise in postoperative adverse events.[7–9] Studies have reported mixed results regarding the appropriate timing between CRT and surgery, known as CRT-S interval. While earlier trials suggested an optimum 2–8 week CRT-S interval,[3–6,9] some authors demonstrated an increased rate of pCR with a prolonged CRT-S interval, without a negative impact on survival or surgical morbidity.[10,11] Conversely, other studies observed higher

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postoperative morbidity and worse survival among those with CRT-S > 64 days compared with those with shorter CRT-S.[12,13]

None of the published studies evaluated the impact of CRT-S interval in large samples of esophageal cancer patients, addressing confounding variables such as histology [adenocarcinoma versus squamous cell carcinoma (SCC)], treatment pathological response (pCR), and comorbidities (Charlson–Deyo comorbidity index score) variables. Therefore, the aim of this study is to elucidate the impact of CRT-S interval on pCR rate, postoperative mortality, and long-term overall survival using the National Cancer Data Base (NCDB).

PATIENTS AND METHODS

The study was performed using NCDB EC patients (diagnosed between 2004 and 2014), who had CRT prior to definitive surgical treatment. The NCDB is a joint project of the Commission on Cancer of the American College of Surgeons and the American Cancer Society, encompassing over 70% of all cancer cases in the USA.[14] Patients were included only if they had confirmed pathology prior to treatment and were M0. We excluded those with intraoperative and adjuvant radiotherapy. We excluded those with CRT-S interval of less than 2 weeks or more than 3 months, to avoid confounding our analysis with those with interrupted neoadjuvant treatment and those who had definitive CRT followed by salvage esophagectomy. Nonetheless, a separate supplementary analysis, using those who had surgery between 90 and 270 days after CRT, was performed to address the cutoff interval point used in previous papers.[10]

Using International Classification of Disease for Oncology ICD-O-3 codes, we included adenocarcinoma (8140–8145, 8480), SCC (8070/3, 8071/3), and adenosquamous (8560/3) histology types. For Kaplan–Meier survival analysis, we used only adenocarcinoma and SCC and excluded adenosquamous type. The NCDB has no specific date for last chemotherapy session; however, the CRT–surgery sequence of treatment is available. As most CRT protocols have concurrent chemoradiotherapy, the CRT completion date was chosen to be the last date of radiation. All included patients had their chemotherapy completed before their definitive surgery. Definitive surgery (esophagectomy) was defined as those patients with site-specific surgery codes 30–80, to avoid palliative and local tumor resection procedures (e.g., gastrostomy, laser ablation). CRT-S interval was calculated using the NCDB as follows: CRT-S interval = (S) − (RT + E) [diagnosis to start radiotherapy (RT), elapsed days in radiotherapy (E), and diagnosis to definitive surgery (S)]. The baseline characteristics included demographic variables and a Charlson–Deyo comorbidity index score (0 = no comorbidity, 1 = one comorbidity, 2 = two or more comorbidities).[15] We extracted the cancer variables including the clinical and pathological cancer stages with the definition of pCR as pT0 and pN0.

Patients were categorized into quintiles according to their CRT-S interval (Q1 CRT-S: 15–37; Q2: 38–45; Q3: 46–53; Q4: 54–64; Q5: 65–90 days with n = 1016, 1063, 1081, 1083, and 938 patients, respectively). We chose these intervals to provide groups with almost equal numbers of patients for best mathematical comparability but that would be similar to prior reported intervals (e.g., > 64 days). More frequent intervals (i.e., deciles) showed a similar trend but would have been cumbersome to tabulate, with less statistical power and without significant clinical relevance. We also evaluated CRT-S interval as a continuous variable (i.e., per week increase). Our primary outcome was OS, while secondary outcomes included 90-day postoperative mortality and pCR.

Statistical analysis was performed using SPSS (version 16.0, SPSS Inc., Chicago, IL, USA). Continuous variables are presented as mean ± standard error (SE), and categorical variables as frequency and percentage. For group comparisons, Chi square and Fisher's exact tests were used for categorical variables; analysis of variance (ANOVA) test was used for continuous variables. A logistic regression model was used to examine the association of CRT-S interval with pCR and 90-day mortality as well as to calculate odds ratios (OR). Kaplan–Meier curve (KMC) survival estimates and log-rank test were used to examine differences in OS among CRT-S quintiles. Univariate screening individual Cox regression analyses were used to examine the association between each variable (including CRT-S interval) and survival. Cox regression multivariate analysis was used to identify independent factors associated with OS. We used cT and cN stages rather than pT and pN to avoid overlap when pCR was added to the simultaneous model. For continuous variables, the hazard ratio gives the increase in risk for each unit increase in value, while for categorical variables the hazard ratio gives the increased risk relative to the reference category. All probabilities are two-sided, and p values < 0.05 were considered statistically significant.

RESULTS

Baseline Characteristics

A total of 5181 EC patients were included with mean age of 62 years, 84% male, 94% White, and 76% with Charlson score 0. Adenocarcinoma and SCC represented 81% and 18% of the total study group, respectively. Most patients presented with T3 lesions (73%). The fifth CRT-S quintile group (65–90 days) was significantly older, had

TABLE 1 Baseline characteristics of esophageal cancer patients according to their chemoradiotherapy-to-surgery (CRT-S) interval

	Total	CRT-S interval quintiles					*p* value
	n = 5181	15–37 day *n* = 1016	38–45 day *n* = 1063	46–53 day *n* = 1081	54–64 day *n* = 1083	65–90 day *n* = 938	
Demographic characteristics							
Age (years, mean ± SE)	62 ± 0.4	61 ± 0.3	62 ± 0.3	62 ± 0.3	62 ± 0.3	64 ± 0.4	< **0.001**
Gender (males, *n*, %)	4356 (84)	867 (85)	907 (85)	925 (86)	889 (82)	768 (82)	**0.029**
Race (White, *n*, %)	4860 (94)	963 (96)	980 (93)	1012 (94)	1036 (96)	869 (93)	**0.006**
Charlson comorbidity index score = 0 (*n*, %)	3915 (76)	792 (78)	823 (77)	823 (76)	789 (73)	688 (73)	**0.018**
Cancer characteristics (*n*, %)							
Histology							0.071
Adenocarcinoma	4198 (81)	822 (81)	893 (84)	870 (81)	890 (82)	723 (77)	
Squamous cell carcinoma	924 (18)	178 (18)	159 (15)	201 (19)	182 (17)	204 (22)	
Tumor grade (low)	217 (5)	48 (6)	40 (4)	53 (6)	41 (4)	35 (4)	**0.001**
Lymphovascular invasion	380 (20)	66 (20)	73 (19)	76 (19)	91 (20)	74 (20)	0.9
cT stage							**0.024**
cT1	264 (5)	57 (6)	56 (5)	55 (5)	51 (5)	45 (5)	
cT2	976 (19)	186 (18)	222 (21)	216 (20)	192 (18)	160 (17)	
cT3	3772 (73)	739 (73)	769 (72)	776 (72)	798 (74)	690 (74)	
cT4	169 (3)	34 (3)	16 (2)	34 (3)	42 (4)	43 (5)	
cN0 stage	1794 (35)	344 (35)	370 (35)	394 (37)	351 (33)	335 (36)	**0.043**
AJCC stage							**0.039**
AJCC 1	280 (6)	62 (6)	56 (5)	61 (6)	55 (5)	46 (6)	
AJCC 2	2076 (41)	381 (39)	460 (44)	450 (43)	398 (37)	387 (42)	
AJCC 3	2739 (54)	545 (55)	532 (51)	548 (52)	619 (58)	495 (53)	
Treatment characteristics and outcomes							
Radiation dose (cGray, mean ± SE)	4659 ± 19	4700 ± 63	4638 ± 65	4642 ± 22	4651 ± 23	4668 ± 24	0.8
Diagnosis to surgery (days, mean ± SE)	153 ± 0.4	115 ± 0.4	124 ± 0.7	133 ± 0.7	143 ± 0.7	162 ± 0.8	**0.001**
Single-agent chemotherapy	256 (5%)	65 (7%)	48 (5%)	49 (5%)	50 (5%)	44 (5%)	0.2
Multiagent chemotherapy	4690 (95%)	899 (93%)	966 (95%)	985 (95%)	984 (95%)	856 (95%)	0.2
pT stage							**0.001**
pT0	1386 (27)	223 (22)	260 (25)	299 (28)	291 (27)	313 (33)	
pT1	452 (9)	114 (11)	90 (9)	96 (9)	90 (8)	62 (7)	
pT2	1120 (22)	230 (23)	229 (22)	216 (20)	246 (23)	199 (21)	
pT3	2167 (42)	433 (43)	474 (45)	458 (42)	450 (42)	352 (38)	
pT4	56 (1)	16 (2)	10 (1)	12 (1)	6 (1)	12 (1)	
pN stage							**0.001**
pN0	3219 (62)	570 (56)	638 (60)	678 (63)	719 (66)	614 (66)	
pN1	1534 (30)	355 (35)	331 (31)	323 (30)	275 (25)	250 (27)	
pN2	315 (6)	65 (6)	68 (6)	61 (6)	67 (6)	65 (6)	
pN3	113 (2)	26 (3)	26 (2)	19 (2)	22 (2)	20 (2)	
Positive margin	280 (6)	49 (5)	68 (7)	50 (5)	63 (6)	50 (5)	0.36
Positive lymph node (mean ± SE)	8.7 ± 0.4	9.1 ± 1.0	7.8 ± 0.9	7.5 ± 0.49	8.8 ± 0.9	10.5 ± 1.1	0.2

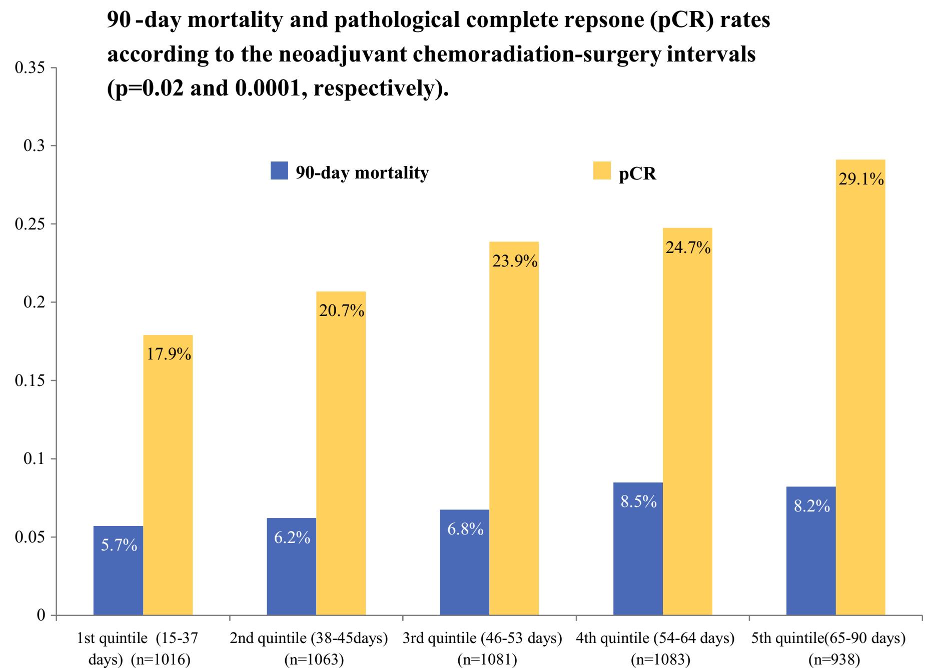
Statistically significant values ($p < 0.05$) are given in bold

more females, and more non-White EC patients. The last quintile also had higher Charlson–Deyo morbidity score, higher rate of SCC, and more advanced cancer stages (Table 1).

Pathological Complete Response (pCR)

The rate of pCR for the whole study population was 1210/5181 (23%). There was a significant gradual increase in pCR rate from the first to fifth CRT-S quintile (Q1: 18%,

FIG. 1 Histogram of 90-day mortality and pCR according to CRT-S interval in EC patients



Q2: 21%, Q3: 24%, Q4: 25%, and Q5: 29%, $p < 0.001$) (Fig. 1 and Table S1). This advantage persisted when CRT-S was measured as a continuous variable in weeks (OR 1.11, 95% CI 1.078–1.143, $p < 0.001$) (Table S2). Similarly, multivariate logistic regression analysis demonstrated that prolonged CRT-S interval and SCC histology were independent predictors of higher rate of pCR (fifth CRT-S quintile OR 1.8, 95% CI 1.4–2.3 and $p = 0.001$, per 1 week increase in CRT-S OR 1.1, 95% CI 1.07–1.14 and $p = 0.001$) (Table S2).

30- and 90-Day Postoperative Mortality

The 30- and 90-day postoperative mortality rates for the whole study group were 163/5155 (3.2%) and 366/5106 (7.2%). There was a trend of higher 30-day mortality as the CRT-S intervals increased (2.1%, 2.6%, 4%, 3.3%, and 3.8%, $p = 0.075$) and a statistically significant increase in 90-day mortality as CRT-S increased across quintiles (5.7%, 6.2%, 6.8%, 8.5%, and 8.2%, $p = 0.02$) (Fig. 1) and with each additional week of CRT-S (OR 1.05, 95% CI 1.005–1.106, $p = 0.03$) (Table S2). Multivariate logistic regression analysis, controlling for cancer stage, age, gender, race, and Charlson–Deyo comorbidity score, showed the highest 90-day mortality among the fourth quintile group (OR 1.5, 95% CI 1.03–2.07, $p = 0.035$) and a trend of higher mortality among the fifth quintile (OR 1.4, 95% CI 0.96–2.00, $p = 0.079$) compared with the first CRT-S quintile (Table S2). When CRT-S interval was evaluated as a continuous variable, there was no significant difference in 90-day mortality per unit increase in CRT-S interval (Table S2).

Overall Survival

Mean and median follow-up were 47 and 39 months with 2978 deaths (57%). Mean and median OS were 33.9 and 25.8 months. Mean OS across CRT-S quintiles was 36.4, 35.1, 33.9, 33.2, and 30.7 months, respectively ($p = 0.03$). Kaplan–Meier analysis showed poor survival among the fifth CRT-S quintile compared with the other four quintiles (log-rank, $p = 0.008$) (Fig. 2). Univariate Cox regression analyses showed that age, male gender, Charlson–Deyo comorbidity score, high tumor grade, advanced T stage, positive nodal stage, and prolonged CRT-S interval were associated with higher risk of mortality (fifth quintile > 65 days: HR 1.14, 95% CI 1.02–1.28, $p = 0.026$) (Table 2). Univariate analysis showed a trend of higher mortality with each week increase of CRT-S interval (HR 1.01, 95% CI 1.00–1.03, $p = 0.069$). However, pCR was associated with lower mortality rate (HR 0.6, 95% CI 0.5–0.6, $p = 0.001$). The variables that showed association with CRT-S interval and survival status were included in multivariate models. Two separate Cox proportional hazard multivariate models were run to include CRT-S as quintiles and as a continuous variable. After adjusting for confounding variables (age, gender, race, Charlson score, histology type, and pathological T and N stages) in both models, prolonged CRT-S interval was a predictor of mortality (fifth CRT-S quintile and 1 week increase of CRT-S HR = 1.2 and 1.02 with

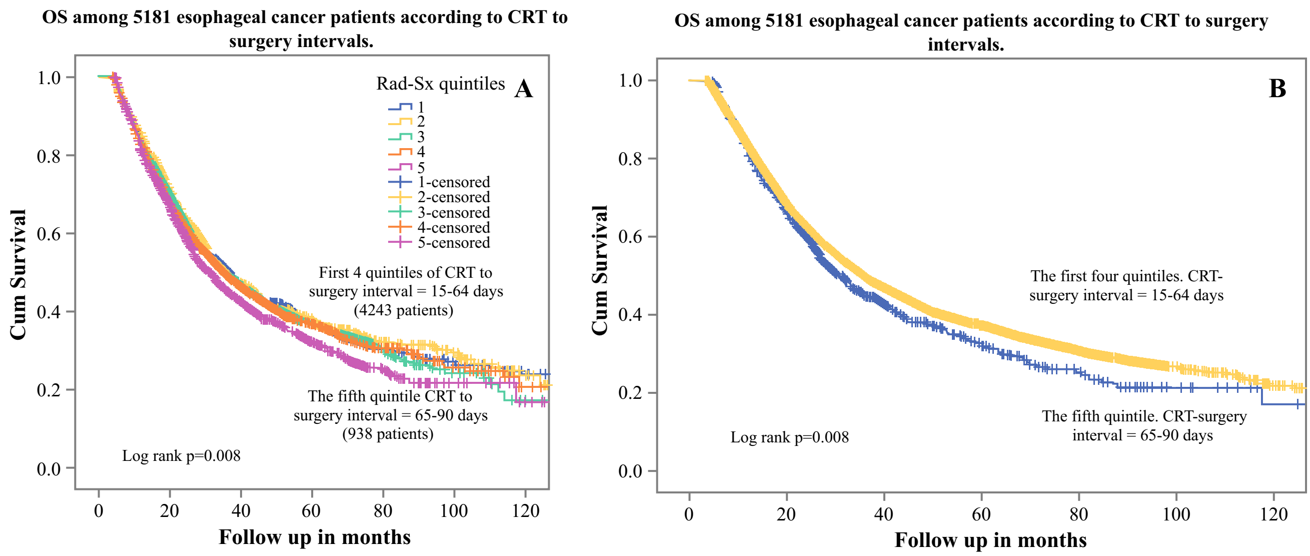


FIG. 2 Overall survival among EC patients according to their CRT-S interval quintiles: **a** across five quintiles, and **b** combined first four quintiles versus the fifth quintile

TABLE 2 Hazard ratios of baseline characteristics for 5-year overall survival among esophageal cancer patients (univariate and multivariate analyses)

Variable	Univariate analysis		Multivariate analysis (A)		Multivariate analysis (B)	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Age (per year)	1.02 (1.01–1.02)	0.001	1.02 (1.01–1.02)	0.001	1.02 (1.01–1.02)	0.001
Gender (male)	1.15 (1.03–1.27)	0.009	1.12 (0.99–1.25)	0.06	1.11 (0.99–1.25)	0.07
Race (Caucasian)	0.96 (0.82–1.13)	0.6	0.98 (0.81–1.18)	0.8	0.98 (0.82–1.18)	0.98
Charlson score (Ref: 0)						
Charlson score 1	1.14 (1.04–1.25)	0.004	1.14 (1.03–1.25)	0.01	1.14 (1.03–1.25)	0.01
Charlson score ≥2	1.28 (1.09–1.52)	0.003	1.23 (1.02–1.47)	0.026	1.22 (1.02–1.46)	0.03
Adenocarcinoma versus SCC	0.91 (0.83–1.00)	0.059	0.85 (0.45–1.59)	0.6	0.87 (0.45–1.60)	0.6
High tumor grade	1.30 (1.21–1.41)	0.001	1.30 (1.20–1.40)	0.001	1.29 (1.20–1.40)	0.001
T stage (ref: T1)						
T2	0.82 (0.64–1.06)	0.13				
T3&4	1.19 (1.09–1.30)	0.001	1.09 (0.99–1.20)	0.089	1.09 (0.99–1.20)	0.076
N stage (Ref: N0)						
cN positive	1.22 (1.13–1.32)	0.001	1.28 (1.18–1.39)	0.001	1.28 (1.17–1.39)	0.001
PCR	0.58 (0.53–0.64)	0.001	0.57 (0.51–0.64)	0.001	0.57 (0.51–0.64)	0.001
pT 3 and 4 versus 0–2	1.64 (1.52–1.76)	0.001				
pN positive	1.75 (1.62–1.88)	0.001				
CRT-S quintiles (Ref: 1st)						
CRT-S 2nd quintile	0.98 (0.87–1.09)	0.69				
CRT-S 3rd quintile	1.02 (0.91–1.14)	0.7				
CRT-S 4th quintile	1.03 (0.92–1.15)	0.6				
CRT-S 5th quintile*	1.14 (1.02–1.28)	0.026	1.16 (1.02–1.31)	0.027		
CRT-S interval (per week)**	1.01 (1.00–1.03)	0.069			1.02 (1.002–1.04)	0.029

*Model A: multivariate model including CRT-S interval as quintile

**Model B: multivariate model including CRT-S as continuous variable (per week)

$p = 0.03$, respectively). Along with prolonged CRT-S interval, multivariate models showed that greater age, Charlson–Deyo comorbidity score ≥ 2, high tumor grade, positive cN stage, and absence of pCR were associated with poor overall survival. After excluding those who died during the 90-day postoperative period, CRT-S fifth quintile remained associated with poor OS ($p = 0.005$) (Fig. S1).

Further patient categorization according to pCR and histology demonstrated that prolonged CRT-S was associated with poor survival among those without pCR ($p < 0.001$) and those with esophageal adenocarcinoma ($p < 0.001$). Patients with pCR ($p = 0.9$) as well as those with SCC histology ($p = 0.8$) had no difference of survival across the CRT-S quintiles (Fig. 3).

Additional Kaplan–Meier analysis, to evaluate the impact of patient comorbidity on overall survival according to CRT-S interval, was performed using only esophageal adenocarcinoma patients with Charlson–Deyo score 0. Among patients without pCR, the prolonged CRT-S group (65–90 days) had poor survival compared with the short CRT-S interval group (log-rank, $p = 0.003$). However, patients with pCR and Charlson–Deyo score 0 had similar survival regardless of their CRT-S interval (log-rank, $p = 0.8$) (Fig. S2).

For comparison with other papers that evaluated patients with CRT-S > 90 days, supplementary Kaplan–Meier analysis was performed using the NCDB of 438 patients with CRT-S more than 90 days (91–270 days). Among the patients with CRT-S interval 91–270 days, we found results similar to our main analysis; prolonged CRT-S interval was associated with poor survival (log-rank, $p = 0.003$) (Fig. S3).

DISCUSSION

The results of this study demonstrate that prolonged CRT-S interval is a significant independent predictor for high pCR rate; however, prolonged CRT-S is also associated with worse postoperative mortality and OS. All

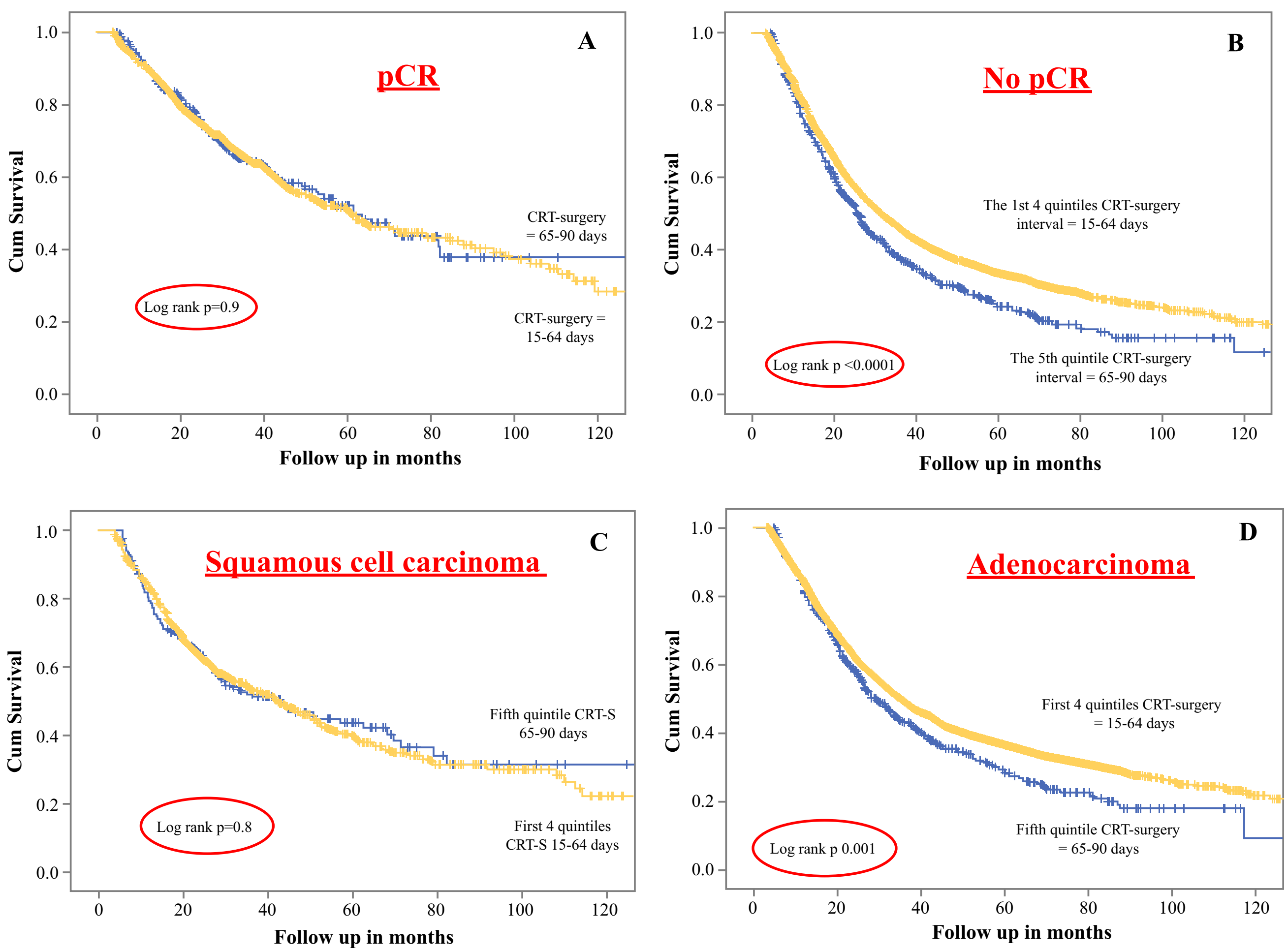


FIG. 3 Overall survival among EC patients according to their CRT-S interval quintiles (first four quintiles versus fifth quintile): **a** patients with pCR, **b** patients without pCR, **c** patients with SCC, and **d** patients with adenocarcinoma

patients with pCR had comparable OS survival, regardless of CRT-S interval. Patients with SCC showed no negative impact of longer CRT-S interval in either the pCR or non-pCR subgroup.

As shown in Table S3, our results demonstrating increased pCR with prolonged CRT-S are concordant with several prior studies[10,11,16] but contrast with several others with smaller sample size and varying CRT-S interval cutoffs[12,17–19] (Table S3). Two of the discordant studies evaluated SCC patients only,[12,17] and one included > 60% SCC patients,[18] which we believe may have impacted the time needed to achieve pCR. Our study evaluated CRT-S as both a categorical and continuous variable to predict the pCR rate and minimize categorization biases. Per each week increase in CRT-S timing, the pCR rate increased by 10–20% of the average rate of pCR, similar to results found by Shaikh et al.[11] Haisley et al.[10] showed increasing pCR, up to 42%, with prolonged CRT-S interval up to 90 days. With CRT-S > 90 days, Haisley et al. reported a slight decline of pCR to 33%.[11] Likewise, our study showed a nonlinear rise of pCR and a decline to 23.5% in the separate supplementary analysis of patients with CRT-S > 90 days. Increased pCR with prolonged CRT-S interval was suggested to be a translation of uninterrupted antitumor immunity during the post-neoadjuvant period.[10] Interruption of this post-neoadjuvant period with major surgery may produce an immune-suppressed status that negates the effects of antitumor immunity. Several studies[20–22] suggest the presence of post-neoadjuvant immunogenic tumor necrosis and induced tumor-specific immunity; on the other hand, tolerogenic tumor necrosis plays an immunosuppressive effect and is pro-tumor.[23] The nonlinear rise of pCR, and its decline after 90 days of cessation of CRT, may suggest repopulation of chemoresistant cancer cells.[24]

With regards to postoperative mortality, our study showed a trend towards higher 30-day postoperative mortality and significantly higher 90-day mortality with delayed surgery, similar to prior studies.[13,25] We attribute the lack of significant difference in postoperative mortality in some of the multivariate models to the small number of these outcomes. We also believe 90-day mortality is a better tool than 30-day mortality given our current advanced critical care.

Regarding overall survival, similar large-sample-size NCDB studies[13,26] have shown similar poor OS with delayed surgery. In contrast, ten studies showed no statistically significant difference in OS among different CRT-S intervals.[10–12,16–19,25,27,28] Among these ten studies, seven demonstrated poor survival among the prolonged CRT-S interval group but were not statistically significant.[12,17–19,25,28] We believe that these negative studies' results can be attributed to lack of power.

According to our results, the patients with prolonged CRT-S interval were older and had higher Charlson comorbidity index and advanced cancer stages. These high risk factors may have forced patients to have a longer recovery after neoadjuvant therapy. Thus, an assumption could be made that prolonged CRT-S interval was associated with these high-risk mortality factors rather than being a sole predictor of survival. However, the multivariate models controlled for these variables, and prolonged CRT-S remained a predictor of OS. Moreover, when we excluded those with Charlson index > 0, we found similar results with negative impact of prolonged CRT-S > 65 days. Interestingly, our additional analysis, which included only those who had survived beyond 90 days post-neoadjuvant therapy, still demonstrated poor OS in the prolonged CRT-S group.

Our findings affirm the value of predicting pCR, which may tailor the timing of surgery. Prior studies have shown a correlation between clinical complete remission (cCR) and pCR based on imaging and endoscopic findings.[29,30] Moreover, the comparable OS among delayed and early surgery in the pCR group may justify initiation of trials for EC similar to the proposed watch and wait protocol trials in rectal cancer.[31]

Limitations of this study include the retrospective nature of the NCDB. However, this large sample study provides significant insight into the impact of CRT-S interval on pCR, postoperative mortality, and long-term survival in adjusted multivariate models.

In conclusion, among esophageal cancer patients, despite higher pCR rate as CRT-S interval increases, definitive surgery is optimally performed less than 65 days after CRT to avoid worse 90-day mortality and achieve better OS. However, among esophageal cancer patients with either pCR or SCC, prolonged CRT-S interval had no negative impact on long-term OS. Further randomized studies are needed to consolidate our findings.

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