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ORIGINAL ARTICLE – THORACIC ONCOLOGY

Utility of Radiation After Neoadjuvant Chemotherapy for Surgically Resectable Esophageal Cancer

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ABSTRACT

Introduction. Neoadjuvant chemotherapy (NAC) ± radiation (NRT) is the "gold standard" approach for locally advanced esophageal cancer (EC). However, the benefits of RT on overall survival (OS) in patients with resectable EC undergoing neoadjuvant therapy followed by esophagectomy remain controversial.

Methods. The National Cancer Data Base was queried for patients with nonmetastatic EC between 2004 and 2014. Kaplan–Meier, log-rank, and Cox multivariable regression analysis were performed to analyze OS. Logistic regression analyzed factors associated with 90-day mortality, lymph node involvement, and complete pathological response (pCR).

Results. A total of 12,238 EC patients who underwent neoadjuvant therapy [neoadjuvant chemoradiation (NACR), 92.1% and NAC, 7.9%] followed by esophagectomy were included. OS was similar in patients undergoing NAC ± RT (35.9 vs. 37.6 mo, respectively, $p = 0.393$). pCR rate was 18.1% (19.2%, NACR vs. 6.3%, NAC, $p < 0.001$). NRT was an independent predictor for increased pCR (HR 2.593, $p < 0.001$). Patients with pCR had increased survival compared with those without pCR (62.3 vs. 34.4 mo, $p < 0.001$); however, no difference was found between NACR and NAC (61.7 mo vs. median not reached, $p = 0.745$) in pCR patients. In non-pCR patients, NAC had improved OS compared with NACR (37.3 vs. 30.8 mo, $p = 0.002$). NRT was associated with worse 90-day mortality (8.2% vs. 7.7%, HR1.872, $p = 0.036$) In Cox regression, NRT was an independent predictor of worse OS (HR 1.561, $p < 0.001$).

Conclusions. Neoadjuvant RT is associated with improved pCR rates; however, it had deleterious effects in short- and long-term survival. Also, patients who did not achieve pCR had worse OS after neoadjuvant RT.

Esophageal cancer (EC) is rapidly rising in several developed countries.1 The incidence of EC, especially adenocarcinoma (AC), in the United States is predicted to increase by 36% in 2030.[1,2] It is a highly lethal disease with 5-year overall survival (OS) rates rarely exceeding 40%.[3] Due to early local and metastatic spread, recent interest have focused on the benefits of neoadjuvant chemotherapy (NAC) with or without radiation (RT).[4] Several randomized trials provided robust evidence that neoadjuvant therapy led to better oncological outcomes, including significant pathologic tumor response, higher rates of R0 resection, and improved OS.[3,5–7]

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The MAGIC and the MRC OEO2 trials demonstrated that NAC prolonged OS without increasing surgical complications for gastroesophageal AC.[6,8] The CROSS trial showed that neoadjuvant chemoradiation (NACR) prolonged OS compared with surgery alone.[3] Furthermore, NACR yielded a R0 resection rate of 92%, a marked improvement from less than 70% reported after NAC.[6] NACR became the preferred neoadjuvant option for EC in several centers worldwide.[9]

The benefit of NACR is well established for patients with squamous cell carcinoma (SCC), and the addition of RT is associated with improved survival and increased complete pathological response (pCR) rates.[3,10] However, the role of RT for the overall cohort of EC patients, especially those with AC, is still not clear.[11] While data from the POET trial demonstrated a trend toward increased OS in the NACR group, a recent, single-institutional retrospective series, and the NeoRes I—a phase II trial—showed that RT did not improve survival despite higher pCR rates.[11–13] These studies are limited to small sample size and may be underpowered. Herein, we sought to assess the role of neoadjuvant RT in patients with resectable EC undergoing neoadjuvant therapy followed by esophagectomy using a large nationwide cohort database.

METHODS

Data were obtained from the National Cancer Data Base (NCDB) for esophageal tumors from 2004 to 2014. Details regarding NCDB and patient selection are included in "online Appendix A".[14]

Potentially relevant patient, tumor, and treatment characteristics were included. Clinical and pathological T-stage, N-stage, and overall stage were based on the American Joint Committee on Cancer (AJCC) staging guidelines 7th edition.[15] pCR (ypT0/N0) was defined as no evidence of primary tumor or any lymph node (LN) involvement in the surgical specimen. R0 resection was defined as no microscopic tumor visualized at any margins in the surgical specimen. Variables included were age, gender, race/ethnicity, T category, nodal status, Charlson–Deyo comorbidity score (CDCC), facility type, and tumor characteristics, such as grade, histological type, surgical margins, and tumor location.

This study was reviewed as exempt by Institutional Review Board at the University of Miami School of Medicine.

The primary endpoint was OS, measured from the date of diagnosis until death. Secondary endpoints were LN metastasis, pCR, and 90-day mortality. Univariate and multivariable logistic regression models were used to examine the predictors associated with secondary endpoints. The multivariate model was created accounting for clinical and demographical data, including T and N stage, histologic subtype, anatomical location, presence of lymphovascular invasion, and use of radiation (Table 1). Statistical analysis is described in detail in "online Appendix B".

RESULTS

Patient Demographics

A total of 12,238 EC patients who underwent neoadjuvant therapy followed by curative-intent esophagectomy were included. The flow chart of the study inclusion criteria is listed in Fig. S1. Baseline characteristics are described in Table 2. The majority of patients underwent NACR (92.1%). Patients undergoing NACR were younger (62 vs. 64 year, $p < 0.001$) and more likely white non-Hispanic (91.4% vs. 88.9%; Hispanic 2.5% vs. 4.8%, $p < 0.001$) than NAC patients.

Clinical and Tumor Characteristics

Most tumors were located in the distal third of the esophagus (85.1%). A trend was observed toward increased NACR in the middle third (12.5 vs. 9.5%) and NAC in distal third tumors (86.9% vs. 85%, $p = 0.063$). Patients with cT3 (69.9% vs. 61.6%, $p < 0.001$), cN1 (54.5% vs. 47.5%, $p < 0.001$), cN2 (7% vs. 4.5%, $p < 0.001$) were more likely to undergo NACR. NAC group had smaller tumors compared with NACR (4.0 vs 3.5 mm; $p = 0.470$) after surgical resection. There was no difference in comorbidity score or tumor grading between the two groups.

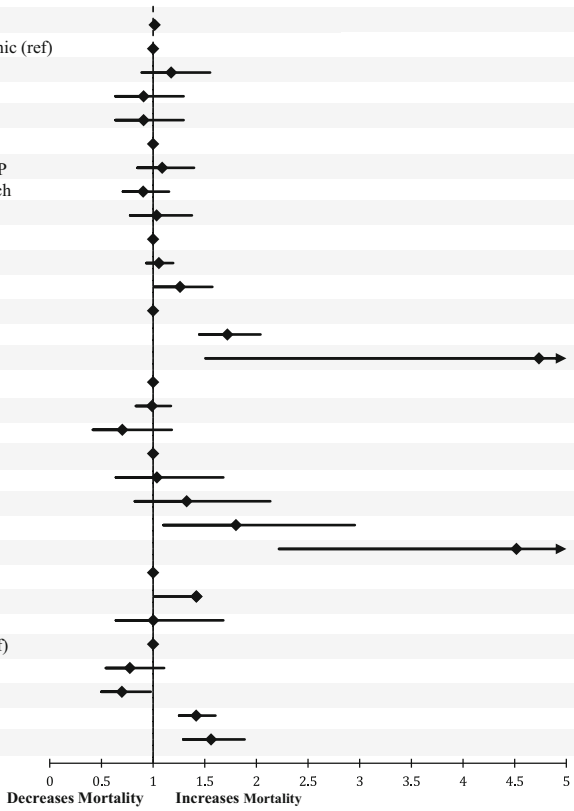
Table S1 summarizes surgical and pathological data. There was no difference in hospital stay, 30-day readmission, or 30-day mortality between NACR and NAC (Table S1). The rate of margin positivity (R1) was significantly increased in NAC compared with NACR (10.6% vs. 5.4%, $p < 0.001$; Table S1). Lymphovascular invasion was more prevalent in NAC group (35.9% vs. 16.9%, $p < 0.001$). Median number of LNs examined was significantly decreased after NACR (15 vs. 11, $p = 0.006$). pN1 was more likely observed after NAC compared with NACR (37.9% vs. 28.6%, $p < 0.001$; Table S1).

When adjusted for other confounders, multivariable logistic regression showed that cN1, lymphovascular invasion, and AC were independent predictors of LN involvement. Neoadjuvant RT was not an independent predictor of nodal involvement (Table S2).

The proportion of patients undergoing NAC was very heterogeneous among the different institutions, ranging

TABLE 1 Cox proportional hazards model predicting all-cause mortality

		HR	95%CI	p–value
Age		1.015	1.009–1.021	<0.001*
Race	White Non-Hispanic (ref)			
	African American	1.175	0.890–1.552	0.255
	Hispanic	0.908	0.636–1.296	0.596
	Other	1.039	0.717–1.506	0.838
Facility type	CCP (ref)			
	Comprehensive CP	1.088	0.848–1.396	0.509
	Academic/Research	0.904	0.708–1.154	0.419
	INCP	1.034	0.778–1.376	0.816
Comorbidity Score	CDCC 0 (ref)			
	CDCC 1	1.056	0.934–1.195	0.381
	CDCC 2	1.261	1.011–1.574	0.040*
Margins	R0 (ref)			
	R1	1.719	1.448–2.040	<0.001*
	R2	4.735	1.508–14.873	0.008*
Histology	Adenocarcinoma			
	SCC	0.989	0.834–1.173	0.898
pCR		0.702	0.417–1.181	0.182
pT Stage	T0 (ref)			
	T1	1.037	0.640–1.680	0.882
	T2	1.325	0.823–2.134	0.247
	T3	1.802	1.100–2.953	0.019*
	T4	4.517	2.219–9.194	<0.001*
pN Stage	N0 (ref)			
	N1	1.417	1.014–1.420	0.034*
Number of Positive LNs		1.002	0.640–1.680	0.882
Site	Proximal third (ref)			
	Middle third	0.775	0.543–1.107	0.161
	Distal third	0.698	0.499–0.977	0.036*
Lymphovascular Invasion		1.417	1.252–1.604	<0.001*
Neoadjuvant Radiation		1.561	1.292–1.886	<0.001*



CDCC score Charlson–Deyo score, *CCP* Community Cancer Program, *INCP* Integrated Network Cancer Program, *R0* complete microscopic resection, *SCC* squamous cell carcinoma

*Statistically significant

from 0 to 75.3% in the facilities performing more than five esophagectomies per year. Only few hospitals (3.7%) were responsible for more than 50% of the patients in the NAC group among the 1057 different institutions.

Tumor Histology

Most tumors were AC (81.1%). Patients with SCC were more likely to undergo NACR (19.2% vs. 15.9%) and AC patients to undergo NAC (84.2% vs. 80.8%, $p = 0.009$; Table 2). Patients with AC were more likely male (89.2% vs. 63.9%, $p < 0.001$), white non-Hispanic (95.4% vs. 74.4%, $p < 0.001$), whereas African-American and Hispanics had more commonly SCC than AC (16.4% vs. 1.5% and 4.3% vs. 2.1%, $p < 0.001$; Table S3) The rate of lymphovascular invasion was increased in AC compared with SCC (18% vs. 2.2%, $p < 0.001$); however, no statistical difference in surgical margins between the two histological types was found. There was increased proportion of pT1-3 and pN1-3 in AC, whereas pT0 and pN0 was more prevalent in SCC (Table S3).

pCR

pCR was observed in 1752 patients (18.1%) in this cohort (Table S3). pCR was more commonly observed in SCC compared with AC (31.4% vs. 16.5%, $p < 0.001$, respectively). NACR was associated with a higher rate of pCR than NAC (19.2% vs. 6.3%, $p < 0.001$).

When adjusted for other confounders, multivariable logistic regression showed that treatment at academic/research program or Integrated Network Cancer Program, SCC subtype and neoadjuvant RT were independent predictors of increased pCR. Lymphovascular invasion was associated with decreased rates of pCR (Table 2).

TABLE 2 Patient and tumor characteristics

	Total n = 12,238	Neoadjuvant chemoradiation n = 11,269	Neoadjuvant chemotherapy n = 969	p
Age, year (median, SD)	62 ± 9.3	62 ± 9.3	64 ± 9.9	< 0.001*
Male sex, no (%)	10,298 (84.1%)	9499 (84.3%)	799 (82.5%)	0.141
Race/ethnicity (n = 12,133)				
White non-Hispanic	11,062 (%)	10,214 (91.4%)	848 (88.9%)	
African American	520 (%)	487 (4.4%)	33 (3.5%)	<0.001*
Hispanic	330 (%)	284 (2.5%)	46 (4.8%)	
Other	221 (%)	194 (1.7%)	27 (2.8%)	
Facility type (n = 12,065)				
Community Cancer Program	707 (%)	668 (6%)	39 (4.1%)	
Comprehensive Community Cancer Program	3846 (%)	3543 (31.9%)	303 (31.7%)	<0.001*
Academic/research Program	6228 (%)	5750 (51.8%)	478 (50%)	
Integrated network Cancer Program	1284 (%)	1148 (10.3%)	136 (14.2%)	
Comorbidity score (CDCC)				
0	9212 (75.3%)	8474 (75.2%)	738 (76.2%)	
1	2465 (20.1%)	2281 (20.2%)	184 (19%)	0.616
2	561 (4.6%)	514 (4.6%)	47 (4.9%)	
Tumor type				
Adenocarcinoma	9916 (81.1%)	9100 (80.8%)	816 (84.2%)	0.009*
Squamous-cell carcinoma	2322 (18.9%)	2169 (19.2%)	153 (15.8%)	
Tumor location (n = 6.364)				
Proximal third	165 (2.6%)	148 (2.5%)	17 (3.7%)	
Middle third	780 (12.3%)	736 (12.5%)	44 (9.5%)	0.063
Distal third	5419 (85.1%)	5016 (85%)	403 (86.9%)	
Clinical T stage (n = 10,711)				
cT1	716 (6.7%)	623 (6.3%)	93 (12.1%)	
cT2	2224 (20.7%)	2046 (20.6%)	178 (23.2%)	<0.001*
cT3	7419 (69.3%)	6947 (69.9%)	472 (61.6%)	
cT4	352 (3.3%)	329 (3.3%)	23 (3%)	
Clinical N stage (n = 11,148)				
cN0	4242 (38.1%)	3856 (37.4%)	386 (46.8%)	
cN1	6020 (54%)	5628 (54.5%)	392 (47.5%)	<0.001*
cN2	760 (6.8%)	723 (7%)	37 (4.5%)	
cN3	126 (1.1%)	116 (1.1%)	10 (1.1%)	
Grade (n = 10,321)				
Well differentiated	515 (4.9%)	485 (5.1%)	30 (3.6%)	
Moderately differentiated	4641 (45.1%)	4252 (44.9%)	389 (46%)	0.191
Poorly differentiated	5016 (48.6%)	4605 (48.6%)	411 (48.6%)	
Undifferentiated	149 (1.4%)	134 (1.4%)	15 (1.8%)	

SD standard deviation, *CDCC* Charlson–Deyo score

Survival Analysis

The overall 90-day mortality rate was 8.2% (NACR 8.2% vs. NAC, 7.7%, p = 0.574). After controlling for patient and tumor variables, multivariate logistic regression demonstrated that high comorbidity score (CDCC ≥ 2: HR 1.812, 95% CI 1.107–2.965, p = 0.018), lymphovascular invasion (HR 1.431, 95% CI 1.038–1.974, p = 0.029), and neoadjuvant RT (HR 1.872, 95% CI 1.041–3.368, p = 0.036) were independent predictors for increased 90-day mortality (Table S4).

Median OS was 35.9 (95% CI 34.7–37.2) months. Patients in the NACR group had OS of 35.9 (95% CI 34.6–37.1) months and OS in the NAC group was 37.6 (95% CI 32.1–43.1) months ($p = 0.393$; Fig. 1). Three-year OS reached 34.8% in the NACR group and 39.4% in the NAC group ($p = 0.012$). In patients with pT2, median OS was statistically superior in patients undergoing NAC compared with NACR (60.9 vs. 35.9 months, $p = 0.002$; Fig. S2). For all remaining pathological T stages, there was similar OS between NAC and NACR (Fig. S2).

Median OS in patients with AC was 35.6 months (95% CI 34.2–36.9 months) and 40.2 months (95% CI 36.5–43.9 months) in patients with SCC ($p = 0.163$). There was no difference between NAC and NACR with either AC (37.6 [95% CI 31.5–43.7] months) vs. 35.5 [95% CI 34.1–36.8] months, $p = 0.203$, respectively) or SCC (32.9 [95% CI 18.5–47.2] months vs. 40.7 [95% CI 36.9–44.5] months, $p = 0.503$, respectively; Fig. S3).

In patients with pCR, 3-year OS rate was 38.4% compared with 31.6% in those who did not achieve pCR ($p < 0.001$). Median OS was similar between NAC and NACR in patients who achieved pCR (not reached vs. 61.7 [95% CI 52.9–70.5] months, $p = 0.745$; Fig. 2). In patients who did not achieve pCR, NAC had superior median OS compared with NACR (37.3 [95% CI 32–42.6] months vs. 30.8 [95% CI 29.7–31.9] months, $p = 0.002$; Fig. 2).

Of patients who underwent RT (7551 patients), 45.6% received high-dose RT (50–50.4 Gy), 41.3% received lower dose (40–45 Gy), and 11.1% had incomplete treatment with doses lower than 40 Gy. The exclusion of patients who received suboptimal doses of RT did not change survival between groups (NACR 37.0 vs. NAC 37.6; $p = 0.753$).

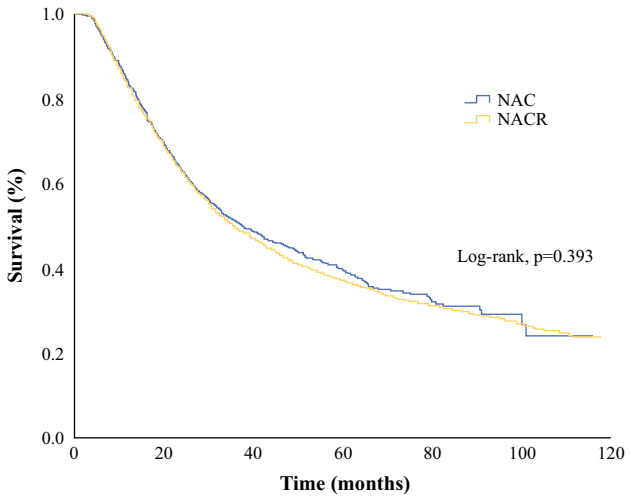


FIG. 1 Kaplan–Meier curves depicting similar overall survival in patients undergoing NAC or NACR. Median OS was 35.9 months (NACR: 35.9 months vs. NAC 37.6 months, $p = 0.393$)

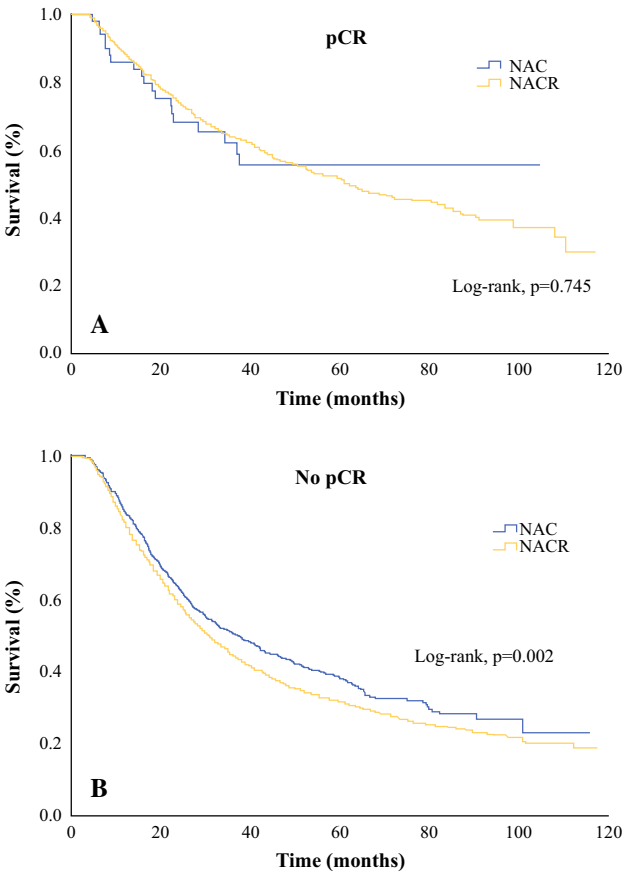


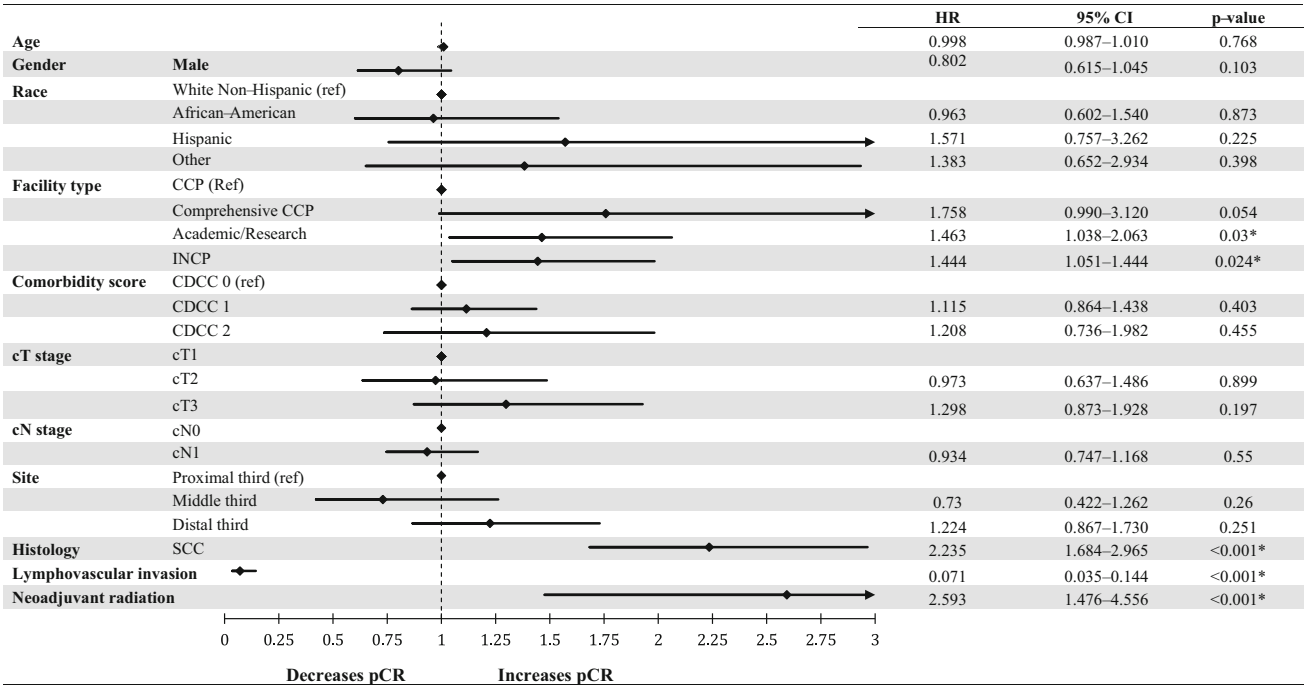
FIG. 2 Kaplan–Meier curves demonstrating overall survival in patients with complete pathological response who underwent NAC or NACR. **a** Median OS was similar between NAC and NACR in patients who achieved pCR (not reached vs. 61.7 months, $p = 0.745$). **b** In non-pCR patients, NAC had superior median OS compared with NACR (37.3 vs. 30.8 months, $p = 0.002$)

In Cox regression, controlling for patient and disease-related factors, negative prognostic factors included: advanced age, positive surgical margins, advanced tumor stage, nodal metastasis, lymphovascular invasion, and neoadjuvant RT (Table 3). Histological type was not an independent predictor, whereas distal esophageal tumor location was associated with improved OS (Table S4).

DISCUSSION

The management of EC has drastically changed over the past two decades after the introduction of NAC with or without RT. The MRC OEO2 was the first large, multicenter study to evaluate the benefit of NAC in EC patients.[8] It showed that NAC with cisplatin plus fluorouracil significantly increased the R0 resection (60% vs. 53%) and survival rates compared with surgery alone. The MAGIC trial showed that perioperative chem/otherapy improved outcomes with increased 5-year OS compared with surgery alone.[6] Although the trial was designed to include

TABLE 3 Multivariate logistic regression of predictors associated with pCR



LN lymph node, *CDCC* Charlson–Deyo score, *CCP* Community Cancer Program, INCP Integrated Network Cancer Program, *SCC* squamous cell carcinoma

*Statistically significant results

primarily gastric cancer, 26% of the cases were described as distal esophageal tumors. These results were corroborated by the FNCLCC/FFCD trial, which randomized patients to perioperative chemotherapy with cisplatin/fluorouracil versus surgery alone.[7] The 5-year OS rate was 38% for the NAC versus 24% in the surgery-only group. R0 resection rates also were higher in the NAC group (84% vs. 74%).

The rationale of adding concurrent RT in EC seems appealing and NACR has been widely used, especially after the initial findings of the Walsh trial.[16] The Walsh trial randomized only 58 patients into surgery alone versus NACR with 5-FU and cisplatin plus RT. The median survival of patients assigned to NAC was significantly superior to those undergoing surgery alone (16 vs. 11 months).[16] Subsequently, the CROSS trial reported a median OS of 49.4 months in the NACR group versus 24 months in the surgery alone group.[5] They also reported a pCR of 29% and increased R0 resection rates (92% vs. 69%) after NACR without significant increase in complications. After CROSS trial, NACR gained wide acceptance in several cancer centers worldwide. The NCCN guidelines now recommend NACR as the preferred treatment for cT1b-T4a or N + lesions.[9] However, the CROSS trial has been criticized as its findings have not been reproduced by other studies.[17,18] This trial excluded patients with more than 10% weight loss, which represents about one-quarter of all EC patients in the "real world" clinical practice.[19,20] Furthermore, the CROSS study is a comparison of NACR followed by surgery versus surgery alone. Therefore, the CROSS trial cannot be used to suggest that NACR is superior to NAC alone followed by surgery.

Recently, the NeoRes I trial compared NACR with NAC in 181 patients with resectable EC or GEJ cancer. Patients were randomized to receive three cycles of cisplatin and fluorouracil with or without RT followed by esophagectomy. Not surprisingly, NACR patients had increased pCR (28%) and rate of negative LNs (65%). This compared favorably with the 9% pCR rate and a 38% rate of negative nodes following NAC. However, there was no survival advantage between NACR and NAC (5-year OS, 42.2% vs. 39.6%, respectively).[13] In addition, NACR had statistically significant higher morbidity and long-term mortality secondary to postoperative complications.[21] The 90-day mortality also was higher after NACR, although it did not reach statistical difference (6% vs 3%). In a phase II randomized trial, Burmeister et al.[18] reported similar results,

showing that NACR increased pCR (31% vs. 8%; $p = 0.04$), R0 resection rate (100% vs. 89%; $p = 0.04$) without changes in OS.

Our results are congruent with these findings. In our study, we did not observe any survival benefit in patients undergoing NAC with or without RT, regardless of clinical stage or histological type (AC or SCC). In fact, after controlling for patient and tumor variables, we demonstrated that neoadjuvant RT was an independent predictor for worse long-term OS. Also, neoadjuvant RT together with lymphovascular invasion and high comorbidity score were independent predictors for early mortality. This is another compelling argument in favor of NAC alone. Avoiding neoadjuvant RT would spare its potential postoperative complications in this often debilitated patient population. Trial data and a large meta-analysis have suggested an increase in postoperative complications following NACR compared with NAC.[22–25] This was translated into slight worse 90-day mortality in NACR arm compared with NAC (8.2% vs. 7.7%) and confirmed on multivariate analysis (OR 1.87; $p = 0.033$). The clinical significance of this subtle difference is yet to be determined, although we believe that these findings should be considered and disclosed to patients before initiation of the neoadjuvant treatment.

We demonstrated that NACR was associated with higher rates of pCR (18.1% vs. 6.3%), and patients with SCC were more likely to have pCR. Neoadjuvant RT was a predictor of increased pCR rates, especially in SCC. However, no survival difference was found between NACR and NAC in pCR patients. RT is expected to lead to greater local tissue response compared with NAC, and in some patients the systemic effects will be minimal, which could potentially lead to late distant recurrence despite the initial encouraging local effects. This can explain at least in part the dichotomy between the demonstrated improved local effect and the lack of survival advantage, which also can be observed on the AC subgroup.

This discrepancy between pCR and OS confirmed previous observations from our group.[26] Tiesi et al.[26] reported that OS was similar between pCR in both NAC and NACR (median not reached and 121.1 months, respectively). However, partial responders in the NAC group had improved OS than those in the NACR group (147.2 vs. 83.7 months). This suggests that pCR is increased by neoadjuvant RT and may overcome its potential morbidity. However, patients who do not achieve pCR are more subjected to the deleterious effects of RT on short- and long-term outcomes.

Undoubtedly, the better local tissue response with RT led to rapid adoption of NACR as the preferred approach for EC in the United States. Our data confirmed an increase in R0 resection rates and pCR for both AC and SCC compared with NAC. However, patients who achieve pCR likely have a distinct tumor biology. Despite much lower rates of pCR, survival in the NAC group was non-inferior than in the NACR group. Notwithstanding the enthusiasm and emphasis on pCR, our data show that its use as an indicator of treatment efficacy and surrogate of survival benefit is debatable and should be analyzed cautiously.

For AC patients, preliminary results of the German FLOT4-AIO (5-fluorouracil, leucovorin, oxaliplatin, and docetaxel) study demonstrated 3-year survival of 57%, a significantly better survival than ECX (epirubicin, cisplatin, and capecitabine) and superior to the 3-year survival of 45% reported for patients with AC in the CROSS trial.[27] Caution is needed until full publication of the FLOT4 trial, but FLOT will probably become the first-line regimen for patients with esophageal and gastric AC. The German ESOPEC study, a multicenter, randomized controlled trial, is currently recruiting patients for randomization in two groups: NACR (CROSS protocol) followed by surgery versus perioperative chemotherapy and surgery (FLOT protocol).[28] This trial will shed light into a superior neoadjuvant protocol with regard to patient survival, treatment morbidity, and quality of life.

Despite the debatable benefits of the NACR over NAC, our data confirmed that the former is the preferred approach in most US centers. Based on the finding that the NAC group were smaller postoperatively, it is reasonable to assume that NAC was reserved for smaller tumors at the beginning the treatment. Moreover, only few centers accounted for most of the patients in the NAC group, which suggests that the adoption of a regimen over the other also is highly dependent on the institutional protocol and expertise with each approach. Other factors may have influenced the selection of the neoadjuvant regimen, such as the presence of dysphagia, the proportion of weight loss, or previous use of radiation therapy. These details are not captured by the NCDB database and at some extent may have influenced the selection process and outcome.

We acknowledge that our study has several important limitations. First, this was a population-based retrospective series, which may include potential for selection bias. The NCDB does not detail the indication for neoadjuvant or adjuvant treatment. Due to heterogeneity between each study and its therapeutic protocols, primary endpoints, and criteria used to define resectability, the interpretation of data should be taken carefully. Second, the NCDB does not include details or complications of each chemotherapy regimen. Third, the NCDB also does not contain information regarding surgical approach, either transhiatal or transthoracic esophagectomy. RT may indeed improve local control and survival in patients undergoing transhiatal approach with limited mediastinal lymphadenectomy. This has not yet been proven by previous studies. Despite the

limitations, this is the largest series comparing the results of NACR versus NAC for EC. We do not believe these drawbacks weaken our results, because our data may represent the pooled external validity of several prospective trials published to date.

CONCLUSIONS

Our data suggest that the addition of RT to NAC is associated with increased pCR rate; however, no survival difference was found in this subgroup between NAC or NACR. Neoadjuvant RT was an independent predictor of early mortality and negatively impacted long-term OS. These findings suggest that NAC without RT may be the optimal neoadjuvant therapy in resectable EC, especially AC. The role of RT in esophageal SCC continues to evolve as modern RT delivery techniques with less toxicity profiles are developed and rates of pCR seems to be superior in this subtype. These findings should encourage further evidence with well-designed, randomized, clinical trials in the pursuit of an optimal neoadjuvant strategy for this lethal disease.

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