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Benefit of adjuvant chemotherapy based on lymph node involvement for oesophageal cancer following trimodality therapy

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ABSTRACT

Background Oesophageal cancer (OC) survival rates have improved since the widespread adoption of neoadjuvant chemoradiation therapy (NACRT) followed by oesophagectomy (trimodality therapy). Unfortunately, the overall prognosis for patients with locally advanced disease remains poor. In this study, we sought to assess the effect of adjuvant chemotherapy (AC) in patients treated with trimodality therapy.

Methods Using the National Cancer Database we retrospectively identified 6785 patients with locally advanced (cT1b-T4a, N0-N+, M0) OC who were treated with trimodality therapy from 2006 to 2014. Patients were separated based on receipt of AC (n=463), as well as clinical and pathological lymph node involvement. Overall survival (OS) between groups was compared using the Kaplan-Meier method and Cox proportional hazard modelling.

Results Based on multivariate analysis, AC was associated with a statistically significantly reduced risk of death (HR 0.77, p<0.001). Subgroup analysis revealed that AC was associated with reduced risk of death compared with NACRT alone in the cN+/pN0 (median OS 64 vs 43 months; p=0.019) and the cN+/pN+ (median OS 27 vs 22 months; p=0.010) groups, but not in the cN0/pN0 (median OS 48 vs 49 months; p=0.253) or cN0/pN+ (median OS 31 vs 24 months; p=0.077) groups.

Conclusion AC following trimodality therapy may improve survival in patients with locally advanced OC. Patients who undergo lymph node downstaging may be the most likely to benefit from AC. Prospective studies are needed to confirm this finding.

INTRODUCTION

In 2018, there will be an estimated 17 290 new cases of oesophageal cancer (OC) diagnosed in the USA. While this number represents only 1% of all newly diagnosed cancers in the USA, OC will account for >2.5% of all cancer-related deaths, with 5-year overall survival (OS) <20%.[1] The poor OS is partially attributed to a large proportion of patients who have either locally advanced or metastatic disease at the time of diagnosis.

Key questions

What is already known about this subject?

► Retrospective analyses have suggested that adjuvant chemotherapy may improve survival in locally advanced oesophageal cancer following trimodality therapy.

► Currently, published data are inconsistent with regard to which patients may be most likely to benefit from adjuvant chemotherapy, specifically patients with node-negative disease following oesophagectomy.

What does this study add?

► Our retrospective analysis of the National Cancer Database suggests that patients with clinically positive nodes who are pathologically node-negative following surgery may be the most likely to benefit from adjuvant chemotherapy.

How might this impact on clinical practice?

► An assessment of both clinical and pathological lymph node status may help determine the likelihood that a patient will benefit from adjuvant chemotherapy in locally advanced oesophageal cancer and should be considered in future clinical trials.

With regard to those who present with locally advanced disease, numerous trials have compared various combinations of surgical resection, radiation therapy and chemotherapy.[2 3] While the conclusions of these studies are not all in agreement, neoadjuvant chemoradiotherapy (NACRT) followed by oesophagectomy (trimodality therapy), as validated in the 2012 phase III ChemoRadiotherapy for Oesophageal cancer followed by Surgery Study (CROSS) trial,[4 5] has been widely adopted as the standard of care in Western countries.[6]

The adoption of trimodality therapy has appeared to improve survival rates over the past decade.[7] However, the overall prognosis

for patients with locally advanced OC remains poor. Disease recurrence is common in patients with positive lymph nodes at the time of resection and is possible even in the setting of a pathological complete response to chemoradiation therapy.[8 9] This has led to increased interest in the role of postoperative therapies.

In this study, we used a large multicentre database to evaluate the effect of adjuvant chemotherapy (AC) on survival in patients with locally advanced OC who are initially treated with trimodality therapy. We also performed a subgroup analysis based on a patient's nodal response to NACRT in an attempt to further identify which patient populations may benefit most from AC. We hypothesised that patients who are downstaged by nodal status after NACRT may have more chemotherapy-sensitive disease and thus may be more likely to benefit from AC.

METHODS

Data source

Data were obtained by retrospectively reviewing the 2014 OC participant user file provided by the National Cancer Database (NCDB). The NCDB is a joint project of the American Cancer Society and the Commission on Cancer of the American College of Surgeons. Over 1500 Commission-accredited cancer programmes submit reports to the NCDB, which include data on approximately 70% of all new cases of cancer diagnosed in the USA each year.

Study cohort

Using the NCDB, we identified all patients diagnosed with locally advanced (cT1b-T4a, N0-N+, M0) OC who underwent NACRT followed by oesophagectomy from 2006 to 2014. Patients diagnosed before 2006 were excluded as this was the first year that the NCDB included data on the sequence of systemic therapy, thus allowing identification of patients who received both neoadjuvant and adjuvant therapy. Only patients with adenocarcinoma or squamous cell carcinoma histology were included. In an attempt to exclude patients who received non-curative intent therapy, we included patients who received multiagent chemotherapy and neoadjuvant radiation therapy between 40 and 60 Gray (Gy) given in 1.8 or 2.0 Gy fractions delivered to the neck, chest, oesophagus, stomach, abdomen, lymph nodes or unknown site. Patients with incomplete follow-up data or who died within 90 days of diagnosis were excluded. The study CONSORT (Consolidated Standards of Reporting Trials) diagram with the inclusion criteria is shown in figure 1.

Statistical analysis

χ^2 analysis was used to compare categorical demographic and tumour characteristics between the NACRT and the neoadjuvant plus adjuvant therapy (NACRT+AC) groups. Student's t-test was used to compare continuous variables between groups. The primary outcome of interest for all comparisons was OS. Univariable and multivariable (MVA) Cox proportional hazard modelling was used
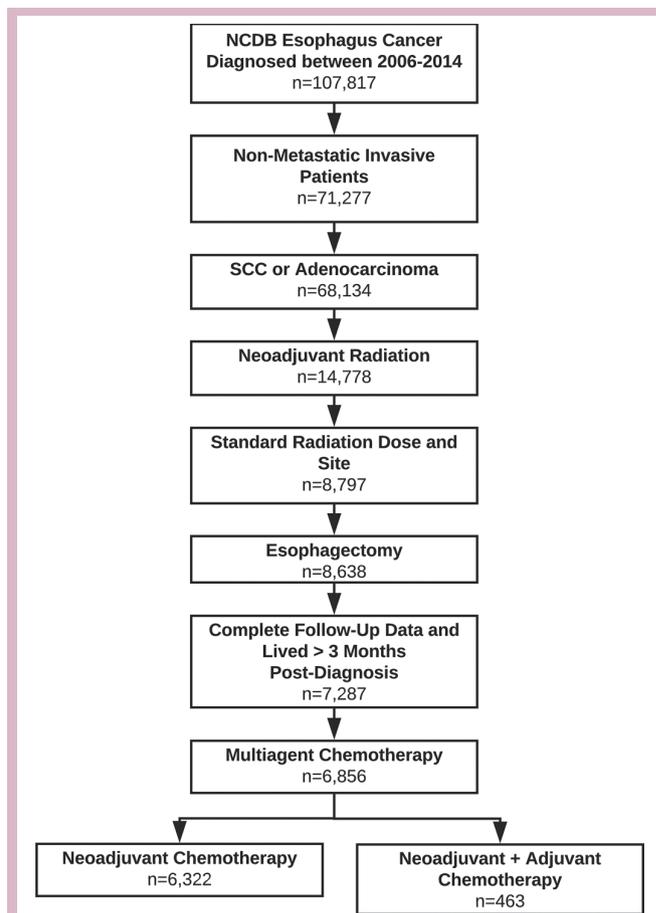

Figure 1 CONSORT diagram. CONSORT, Consolidated Standards of Reporting Trials; NCDB, National Cancer Database; SCC, squamous cell carcinoma.

to identify factors associated with OS, reported as HRs. Multivariate models were created using a reverse stepwise approach by initially including all covariates and then removing each covariate with a p value >0.2, starting with the covariate with the largest p value. Kaplan-Meier survival analysis with log-rank testing was also employed. Statistical analysis was carried out using STATA V.14.2.

RESULTS

Study cohort characteristics

A total of 107817 patients diagnosed with OC were identified from 2006 to 2014. Based on our inclusion criteria, 6785 patients were included for analysis. Of these, 463 patients received NACRT+AC (figure 1). The characteristics of the patients are shown in table 1.

There was no difference in clinical T-stage between those who received NACRT or NACRT+AC. However, a larger percentage of pT0-2 tumours were identified at the time of resection in the NACRT-only group (60%) compared with the NACRT+AC group (47%). Additionally, 69% of those who received NACRT+AC had clinically positive nodes compared with 62% of those who received NACRT alone (p=0.017). Following resection, 71% of the NACRT+AC group and 35% of the NACRT-alone group

Table 1 Baseline patient demographics

	NACRT		NACRT + AC		Total		
	N	**(%)**	**N**	**(%)**	**N**	**(%)**	**P-value**
Age, years							
Mean (SD)	61.9 (9.3)		58.5 (9.0)		61.7 (9.3)		0.000
Sex							0.001
Male	5311	(84)	416	(90)	5727	(84)	
Female	1011	(16)	47	(10)	1058	(16)	
Total	6322	(100)	463	(100)	6785	(100)	
Charlson Comorbidity Score							0.407
0	4690	(74)	353	(76)	5043	(74)	
1	1336	(21)	94	(20)	1430	(21)	
≥ 2	296	(5)	16	(3)	312	(5)	
Total	6322	(100)	463	(100)	6785	(100)	
Histology							0.000
Adenocarcinoma	5184	(83)	421	(91)	5605	(83)	
SCC	1068	(17)	40	(9)	1108	(17)	
Total	6252	(100)	461	(100)	6713	(100)	
Grade							0.010
Well-Differentiated	289	(5)	14	(3)	303	(5)	
Moderately-Differentiated	2376	(44)	159	(38)	2535	(43)	
Poorly-Differentiated	2695	(49)	238	(57)	2933	(50)	
Undifferentiated	94	(2)	4	(1)	98	(2)	
Total	5454	(100)	415	(100)	5869	(100)	
LVSI							0.038
Negative	2051	(32)	133	(29)	2184	(32)	
Positive	406	(6)	42	(9)	448	(7)	
Unknown	3865	(61)	288	(62)	4153	(61)	
Total	6322	(100)	463	(100)	6785	(100)	
Clinical T-Stage							0.531
T0	5	(0)	0	(0)	5	(0)	
T1	331	(6)	19	(5)	350	(6)	
T2	1168	(20)	80	(19)	1248	(20)	
T3	4077	(71)	311	(74)	4388	(71)	
T4	170	(3)	9	(2)	179	(3)	
Total	5751	(100)	419	(100)	6170	(100)	
Clinical N-Stage							0.017
N0	2264	(38)	138	(31)	2402	(38)	
N1	3174	(53)	265	(60)	3439	(54)	
N2	450	(8)	30	(7)	480	(8)	
N3	59	(1)	7	(2)	66	(1)	
Total	5947	(100)	440	(100)	6387	(100)	
Pathologic T-Stage							0.000
ypT0	1021	(21)	49	(12)	1070	(20)	
ypT1	924	(19)	51	(13)	975	(19)	
ypT2	962	(20)	89	(22)	1051	(20)	
ypT3	1897	(39)	212	(53)	2109	(40)	

Table 1 Continued

	NACRT		NACRT + AC		Total		
	N	**(%)**	**N**	**(%)**	**N**	**(%)**	**P-value**
ypT4	57	(1)	1	(0)	58	(1)	
Total	4861	(100)	402	(100)	5263	(100)	
Pathologic N-Stage							0.000
ypN0	3309	(65)	123	(30)	3432	(63)	
ypN1	1345	(27)	205	(50)	1550	(28)	
ypN2	316	(6)	54	(13)	370	(7)	
ypN3	94	(2)	31	(8)	125	(2)	
Total	5064	(100)	413	(100)	5477	(100)	
Surgery Type							0.032
Partial Esophagectomy	949	(15)	57	(12)	1006	(15)	
Total Esophagectomy	646	(10)	48	(10)	694	(10)	
Esophagectomy & Laryngectomy or Gastrectomy	4294	(68)	339	(73)	4633	(68)	
Esophagectomy, NOS	433	(7)	19	(4)	452	(7)	
Total	6322	(100)	463	(100)	6785	(100)	
Margin Status							0.001
Negative Margins	5765	(97)	411	(94)	6176	(97)	
Positive Margins	186	(3)	27	(6)	213	(3)	
Total	5951	(100)	438	(100)	6389	(100)	
Radiation Dose, Gy							0.012
Median (IQR)	50.40 (46.80 – 50.40)		50.40 (45.00 – 50.40)		50.40 (46.00 – 50.40)		

AC, adjuvant chemotherapy; Gy, Gray; IQR, interquartile range; LVSI, lymphovascular space invasion; NACRT, neoadjuvant chemoradiotherapy; No., number; NOS, not otherwise specified; SCC, squamous cell carcinoma; SD, standard deviation.

were pN+ (p<0.001). Overall, this suggests that lymph node downstaging after NACRT was more frequently found in the subset of patients who received NACRT alone.

Survival analyses

With a median follow-up of 25.7 months, patients in the NACRT group had a median OS of 36.5 months (95% CI 35.3 to 38.3 months), compared with the NACRT+AC group, which had a median follow-up of 28.7 months and a median OS of 35.5 months (95% CI 31.1 to 43.0 months; p=0.38) (figure 2). The 5-year OS of the NACRT group was 37.8% and for the NACRT+AC group was 36.3%. However, after accounting for the fact that the NACRT+AC group included more adenocarcinoma histology patients, more patients with a poorly differentiated grade of tumour, more patients with evidence of lymphovascular space invasion, and more advanced clinical N-stage as well as pathology T-stage and N-stage, our MVA revealed a significant association between receiving AC and reduced risk of death (HR 0.77, p<0.001) (online supplementary table 1).

On subgroup analysis based on pathological nodal status following surgery, MVA showed a significantly

Table 2 Median overall survival separated based on receipt of adjuvant chemotherapy. Hazard ratios showing risk of death with receipt of adjuvant chemotherapy compared to postoperative observation

	Median Overall Survival (Months)			Multivariate analysis	
Group	**NACRT**	**NACRT + AC**	**P**	**Hazard Ratio**	**P**
Overall Cohort	36.5 (35.3 - 38.3)	35.5 (31.1 - 43.0)	0.380	0.77 (0.66 – 0.89)	<0.001
cN+/pN+	22.7 (20.9 - 24.6)	27.8 (24.2 - 32.6)	0.010	0.82 (0.67 - 1.00)	0.048
cN+/pN0	43.7 (40.5 - 50.7)	64.4 (41.9 - NR)	0.019	0.59 (0.39 - 0.88)	0.009
cN0/pN+	24.9 (21.7 - 27.3)	31.4 (24.5 - 43.5)	0.077	0.76 (0.54 - 1.06)	0.105
cN0/pN0	49.1 (43.6 - 55.4)	48.3 (35.7 - NR)	0.253	0.73 (0.41-1.30)	0.253

AC, adjuvant chemotherapy; HR, hazard ratio; NACRT, neoadjuvant chemoradiotherapy; NR, not reached.
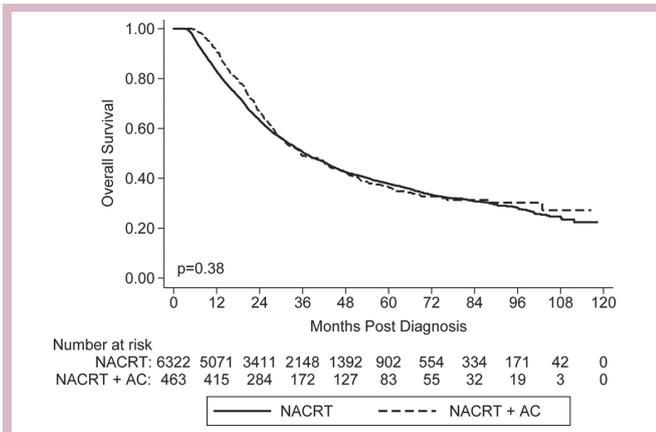
Figure 2 Kaplan-Meier survival curve for the overall cohort. AC, adjuvant chemotherapy; NACRT, neoadjuvant chemoradiotherapy.

reduced risk of death with NACRT+AC compared with NACRT alone for both the pN0 group (HR 0.65, p=0.007) and the pN+ group (HR 0.80, p=0.008) (online supplementary table 2). Additional subgroup analysis considering both clinical and pathological nodal status revealed that NACRT+AC was associated with a significantly

reduced risk of death compared with NACRT alone for the cN+/pN0 group (median OS 64 vs 43 months; p=0.019) and the cN+/pN+ group (median OS 27 vs 22 months; p=0.010), but not in the cN0/pN0 group (median OS 48 vs 49 months; p=0.253) or cN0/pN+ group (median OS 31 vs 24 months; p=0.077) (figure 3). These findings were confirmed on MVA (online supplementary tables 3 and 4). The key results are summarised in table 2.

DISCUSSION

The standard of care for locally advanced OC in patients with surgically resectable disease is an area of active debate. In the USA, standard treatment often includes NACRT followed by oesophagectomy (trimodality therapy).[4 10 11] Alternatively, at some institutions, patients with gastro-oesophageal junction cancers are now offered treatment with perioperative chemotherapy based on the fluorouracil, leucovorin, oxaliplatin and docetaxel (FLOT) trial data.[12] Importantly, this trial has also shown that the administration of postoperative chemotherapy remains a challenge in many patients as only 50% of patients were able to complete postoperative FLOT per protocol. With regard to radiation
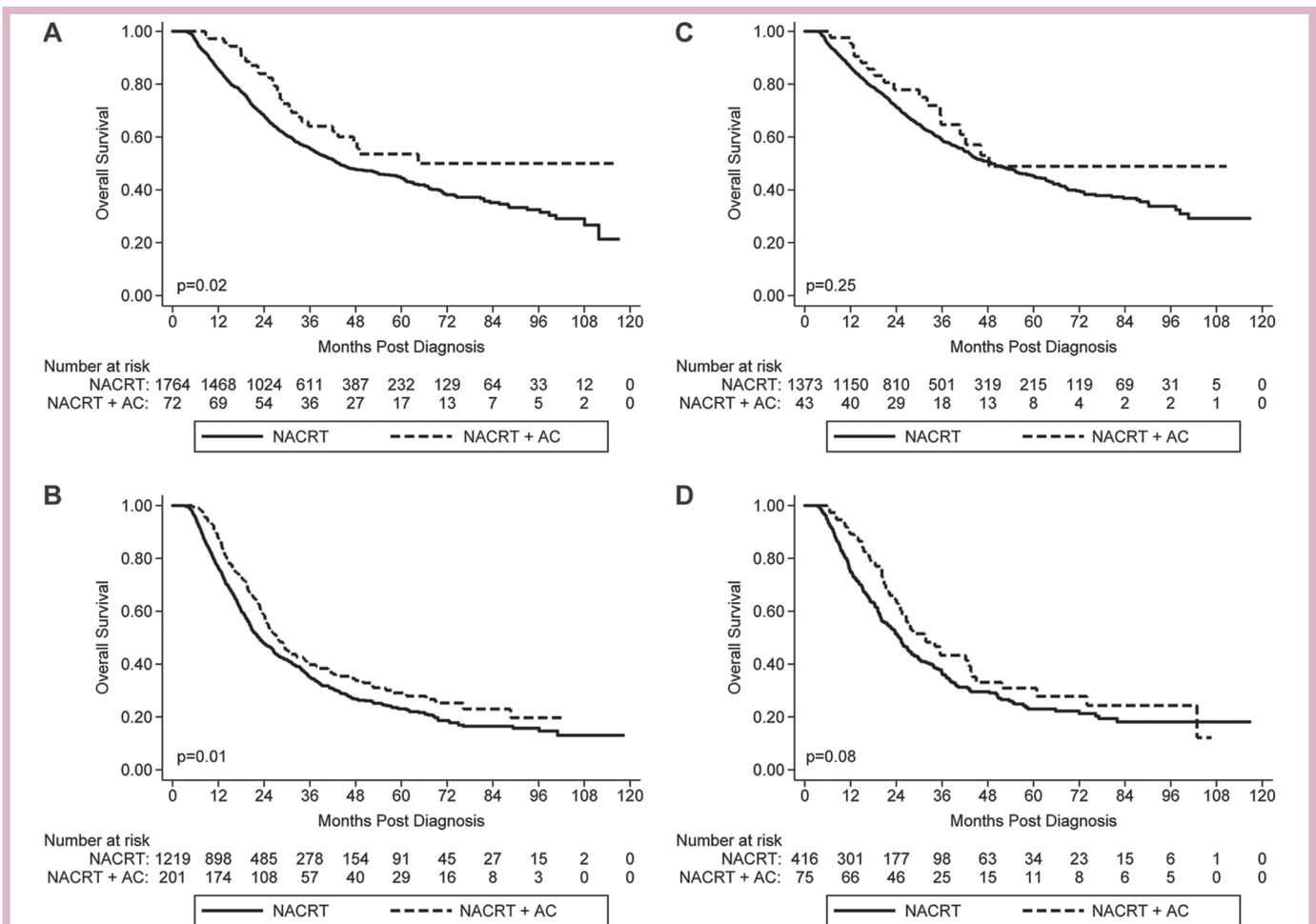

Figure 3 Kaplan-Meier survival curves for the (A) cN+/pN0, (B) cN+/pN+, (C) cN0/pN0 and (D) cN0pN+ groups. AC, adjuvant chemotherapy; NACRT, neoadjuvant chemoradiotherapy.

therapy, the pathological complete response rates seem to be higher in neoadjuvant studies including chemoradiation when compared with chemotherapy alone.[13–16] The ongoing perioperative chemotherapy compared to neoadjuvant chemoradiation in patients with adenocarcinoma of the esophagus (ESOPEC) trial comparing perioperative FLOT versus NACRT per the CROSS schedule will help to further elucidate the best treatment strategy in these patients.[17] At present, the optimal postoperative management strategy remains unknown.

In this study, we found that the patients with locally advanced OC who are treated with NACRT+AC often have worse tumour characteristics when compared with patients who do not receive AC. After adjusting for this imbalance, we found that the addition of AC was associated with improved OS. The use of AC following trimodality therapy was investigated in two recently published retrospective analyses of the NCDB by Burt *et al* and Mokdad *et al*.[18 19] Both studies concluded that AC appears to improve OS in patients who are found to have positive nodes following oesophagectomy. However, these studies provide conflicting evidence when the subgroup of patients with negative lymph nodes at the time of resection was analysed. In the study by Burt *et al*,[18] a benefit from AC was not seen in patients with pathological complete response or residual non-nodal disease (pN0). In contrast, Mokdad *et al*[19] showed that AC improved survival regardless of lymph node status at the time of resection, with a 32% decrease in the risk of death i patients with negative lymph nodes and a 16% decrease in those who had positive lymph nodes.

Our multivariate analysis is in agreement with the conclusions by Mokdad *et al*[19] in that AC appears to be associated with a survival benefit regardless of a patient's pathological node status. We also went a step further with our analysis to identify a subset of patients without residual nodal disease that may benefit from AC. Thus, in an analysis not previously reported, we performed a subgroup analysis which incorporated both clinical and pathological node status. We found that patients who underwent nodal downstaging (cN+/pN0) received the greatest survival benefit with the addition of AC (median OS 64 vs 43 months; p=0.019). Patients who were node-positive at the time of diagnosis and following surgery (cN+/pN+) had a smaller, yet still significant, improvement in survival with the addition of AC (median OS 27 vs 22 months; p=0.010). Interestingly, we found that AC was not associated with a significant increase in OS in patients who were clinically node-negative at the time of diagnosis, regardless of whether or not they had positive lymph nodes following surgery (cN0/pN0 and cN0/pN+).

It is believed that patients who have clinically positive nodes at the time of diagnosis are more likely to have widespread, yet clinically undetectable, micrometastases. These micrometastases are likely responsible for the predominantly distant disease recurrence pattern observed in patients following trimodality therapy.[20 21] At least some of the survival benefit of AC we observed in the cN+ groups may be attributed to preventing progression of these distant micrometastases. We hypothesise that patients who underwent nodal downstaging (cN+/pN0) likely had a more favourable disease biology (ie, more chemosensitive malignancy), and the effect of AC on distant micrometastases in these patients was accentuated.

cN0/pN0 patients are unlikely to have distant micrometastases. Thus our finding that AC in these patients was not associated with a significant survival benefit was not unexpected. In fact, in this population, AC may be harmful as evidenced by a slightly, although statistically insignificant, decreased median OS in the AC group. Also, taking into account the effect of chemotherapy toxicities on the overall quality of life, a fairly strong case could be made against using AC in these patients.

Finally, patients who have nodal progression of the disease despite trimodality therapy (cN0/pN+) likely have unfavourable disease biology. Thus, while these patients likely have distant micrometastatic disease following surgery, the fact that they responded poorly to initial chemotherapy may make it less likely that they will respond to AC. However, given a slight trend towards a survival benefit in this group, it is possible that there may still be some individuals who could benefit from additional therapy. While the NCDB data do not record the specific chemotherapy used, oncologists who choose to treat individuals in this group may find benefit in using agents that were not used in the initial chemoradiotherapy regimen.

Of course, it should be noted that our conclusions are subject to the limitations inherent to any retrospective database study. Our analysis included a large number of patients; however, only a small fraction received AC, creating the possibility for selection bias. While we attempted to control for overall health by excluding patients who died within 90 days of diagnosis and included comorbidities based on the Charlson/Deyo Scores in our analyses, it is possible that some of the benefits we observed with AC could be attributed to a preference for healthier patients to be selected for adjuvant treatment. However, patients in the NACRT-alone group were more likely to undergo nodal downstaging than the NACRT+AC group. Thus there may have been bias towards more favourable disease biology in the NACRT-alone group. Lastly, while we included only patients who received multiagent chemotherapy (excluding those who received non-curative intent single-agent chemotherapy), the exact chemotherapy agents and dosing regimen are not available in the NCDB data.

CONCLUSION

AC following trimodality therapy is associated with improved survival in patients with locally advanced OC. Patients who undergo downstaging with regard to nodal status following NACRT may be the most likely to benefit from AC. Prospective trials are needed to verify these findings.

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