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ORIGINAL ARTICLE

Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for clinical node-negative esophageal carcinoma

Hui-Jiang Gao[1†], Yu-Cheng Wei[1†], Lei Gong[2], Nan Ge[1], Bin Han[1], Guo-Dong Shi[1] & Zhen-Tao Yu[2]

1 Department of Thoracic Surgery, The Affiliated Hospital of Qingdao University, Qingdao, China
2 Department of Esophageal Cancer, Tianjin's Clinical Research Center for Cancer and Key Laboratory of Cancer Prevention and Therapy, Tianjin Medical University Cancer Institute and Hospital, Tianjin, China

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Esophageal carcinoma; esophagectomy; neoadjuvant chemoradiotherapy; survival.

Correspondence
Hui-Jiang Gao, Department of Thoracic Surgery, The Affiliated Hospital of Qingdao University, 266003 Qingdao, China.
Tel: +86 186 6180 9060; Fax: +86 532 8291 9900; Email: gaohuijiang2008@163.com

Zhen-Tao Yu, Department of Esophageal Cancer, Tianjin's Clinical Research Center for Cancer and Key Laboratory of Cancer Prevention and Therapy, Tianjin Medical University Cancer Institute and Hospital, 300060 Tianjin, China.
Tel: +86 138 2098 9000; Fax: +86 22 2334 0123; Email: yuzhtao@hotmail.com

[†]These authors contributed equally to this work

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Abstract

Background: The impact of neoadjuvant chemoradiotherapy (nCRT) on early stage esophageal cancer is unknown. Here, we compared the outcomes after esophagectomy alone or nCRT plus surgery for clinically staged node-negative esophageal cancer.

Methods: We searched the Surveillance, Epidemiology, and End Results database for patients with clinically node-negative (cN0) esophageal cancer from 2004 to 2016 who underwent surgery alone or nCRT plus surgery. Propensity score matching and Cox regression analysis were used to identify covariates associated with overall survival and cancer-specific survival.

Results: A total of 1587 patients were retrospectively identified, of whom 49.8% (n = 791) received nCRT and 80.2% (n = 1273) were truly node-negative diseases. For the entire cohort, surgery alone was associated with a statistically significant but modest absolute increase in survival outcomes ($P < 0.01$). After matching, nCRT was associated with improved five-year overall survival for pT3-4N0 (localized) disease (59.6% vs. 37.7%; $P < 0.001$) and pathological node-positive disease (60.5% vs. 40.7%; $P = 0.002$). Cox multivariate regression analysis revealed that the addition of nCRT for truly node-negative patients with tumor length ≥ 3 cm, pT1-2N0 (early-staged) and localized disease were independent risk factors for survival than surgery alone ($P < 0.01$).

Conclusions: Compared with surgery alone, patients with cN0 esophageal cancer with pathological node-positive or localized true node-negative disease gain a significant survival benefit from nCRT. However, nCRT plus surgery was associated with decreased survival for early-staged true node-negative patients. This finding may have significant implications on the use of neoadjuvant chemoradiation in patients with cN0 disease.

Introduction

Treatment options for esophageal cancer varies according to stage. Neoadjuvant chemoradiotherapy (nCRT) followed by surgery has become the preferred approach for locally advanced and/or node-positive esophageal carcinoma (EC).[1] Although patients with early stage localized cancer may be candidates for surgical resection alone,[2, 3] there have been several randomized clinical trials that support neoadjuvant therapy for esophageal carcinoma prior to esophagectomy.[4–6] However, given the frequent presentation of locally advanced diseases in those trials, no conclusions regarding survival benefit of nCRT can be drawn for earlier stage EC.

Utilization of neoadjuvant therapy is associated with significant tumor downstaging as reflected by increases in no residual disease, and the effect is further enhanced by nCRT. The publication of the Chemoradiotherapy for

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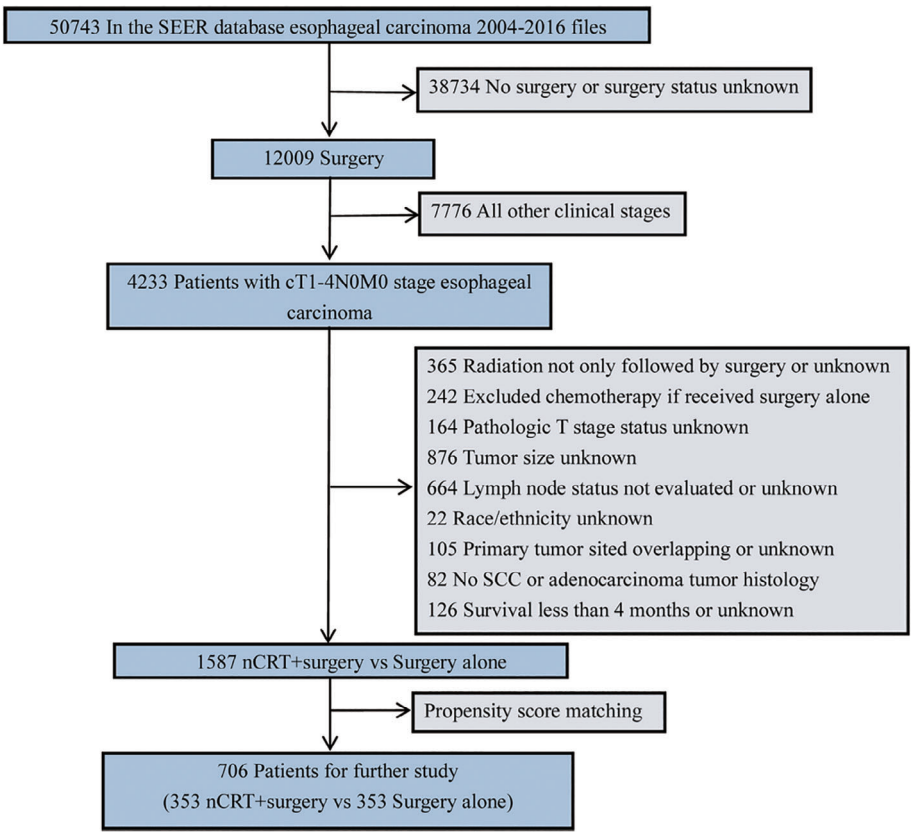

Figure 1 Flow chart for inclusion and exclusion of esophageal carcinoma patients in this study.

Esophageal Cancer followed by Surgery Study (CROSS) trial provides evidence for the benefit of nCRT in potentially curable disease, where its downsizing and downstaging effects are remarkable.[4] However, synchronously, there is the potential for misclassification as a result of neoadjuvant therapy, leading to analysis by consistent clinical to pathologic tumor stage not being easily available. Currently, there is a paucity of data regarding which population among clinically staged node-negative EC may derive more benefit from neoadjuvant therapy.

The aim of this study was to compare the survival outcomes in patients with clinically node-negative (cN0) esophageal carcinoma treated with esophagectomy alone or nCRT plus surgery using a large population-based database allowing for propensity score matching analysis.

Methods

The Surveillance, Epidemiology, and End Results database (SEER) limited access database is a population-based cancer registry system collecting data from 18 registries among 14 states across the US, representing nearly 30% of the US population.[7] This retrospective study tracked the data by SEER including patient demographics, disease characteristics, treatment, and survival information. Data for all EC patients from 2004 to 2016 were acquired in plain text format from SEER and imported into SPSS software using modified versions of SEER database provided scripts. Since the data from SEER did not include any patient identifying information, Institutional Review Board approval was not required. The endpoints included overall survival (OS) and cancer-specific survival (CSS), which were the interval between the initial diagnosis of EC and the occurrence of all-cause or cancer-specific death.

We identified patients diagnosed with cN0 esophageal carcinoma from 2004 to 2016 within the SEER database. To restrict the cohort to patients with cN0 diseases, the tumor, node, and metastasis stage was directly extracted from the SEER database or was manually recoded using available SEER variables. The inclusion and exclusion criteria are shown in Fig 1. Patients who received chemotherapy within six months of diagnosis and external beam radiotherapy before surgery were included for analysis and designated as having received neoadjuvant CRT for their EC. [8, 9] The exclusion criteria for data extraction in this study were as follows: (i) patients confirmed to have chemotherapy if received surgery alone; and (ii) patients with missing or incomplete data such as survival status and time, race, T stage, primary tumor site, pathological type,

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Table 1 Comparison of patient demographics and tumor characteristics for the clinical node-negative patients

Characteristics	Neoadjuvant CRT + surgery (*n* = 791)	Surgery alone (*n* = 796)	Overall (*n* = 1587)	*P*-value
Age, years, n (%)				<0.001
< 60	261 (33.0)	179 (22.5)	440 (27.7)	
60–70	349 (44.1)	301 (37.8)	650 (41.0)	
≥ 70	181 (22.9)	316 (39.7)	497 (31.3)	
Male sex, n (%)	660 (83.4)	620 (77.9)	1280 (80.7)	0.005
Race/ethnicity, n (%)				0.344
White	715 (90.4)	708 (88.9)	1423 (89.7)	
Other	76 (9.6)	88 (11.1)	164 (10.3)	
Disease site, n (%)				0.002
Upper third	37 (4.7)	70 (8.8)	107 (6.7)	
Middle third	93 (11.8)	106 (13.3)	199 (12.5)	
Lower third	661 (83.5)	620 (77.9)	1281 (80.8)	
Tumor length, cm, n (%)				<0.001
< 3	209 (26.4)	538 (67.6)	747 (47.1)	
3–5	266 (33.6)	175 (22.0)	441 (27.8)	
≥ 5	316 (40.0)	83 (10.4)	399 (25.1)	
Tumor histology, n (%)				0.162
Squamous cell carcinoma	178 (25.5)	203 (25.5)	381 (24.0)	
Adenocarcinoma	613 (77.5)	593 (74.5)	1206 (76.0)	
Histologic grade, n (%)				<0.001
Well + moderate	450 (56.9)	558 (70.1)	1008 (63.5)	
Poor + undifferentiated	341 (43.1)	238 (29.9)	579 (36.5)	
Pathological T stage, n (%)				<0.001
T0	67 (8.5)		67 (4.2)	
T1-2	208 (26.3)	615 (77.3)	823 (51.9)	
T3-4	516 (65.2)	181 (22.7)	697 (43.9)	
Pathological N stage, n (%)				<0.001
N0	588 (74.3)	685 (86.1)	1273 (80.2)	
N1	203 (25.7)	111 (13.9)	314 (19.8)	
ELN count, n (%)				0.361
< 12	287 (36.2)	307 (38.6)	594 (37.4)	
12–16	131 (16.6)	142 (17.8)	273 (17.2)	
≥ 16	373 (47.2)	347 (43.6)	720 (45.4)	

CRT, chemoradiotherapy; ELN, examined lymph node.

local treatment, and radiotherapy, together with those who received adjuvant therapy or unknown treatment sequence with respect to the surgery.

In an effort not to exclude patients who received different radiotherapy regimens, the total dose of radiation was not limited.[10] In addition, given the limitation of the database capturing only surgical patients, there may be a subset whose disease progressed during the administration of induction therapy or who failed to receive resection because of treatment-related morbidity. Therefore, those who survived <4 months were also excluded to reduce a bias favoring the neoadjuvant therapy, considering that patients might receive surgery four to six weeks after the neoadjuvant therapy.[6] Furthermore, to account for potential confounding effects of tumor downstaging and clinical misclassification, the clinical node status was matched to pathologic outcomes to define truly node-negative (both clinically and pathologically node negative, cN0/pN0) and falsely node-negative (clinically negative but pathologically node positive, cN0/pN+) patients.

Statistical analysis

Statistical analysis was performed using SPSS version 23.0 (IBM, Armonk, NY). Mean and standard deviations were used for continuous variables, whereas percentages were used for discrete characteristics. Propensity score matching (PSM) was used to eliminate baseline demographic differences and to achieve better patient group homogeneity by logistic regression model.[11] Neoadjuvant chemoradiotherapy plus surgery (CRT + S) or surgery alone (SA) pairs were matched 1-to-1with the nearest propensity score with a caliper width 0.1-fold of the standard deviation, and an algorithm was used to sequentially match the next best pair (Figures S1 and S2). Kaplan-Meier survival analysis and the log-rank test were used for the distributions of OS

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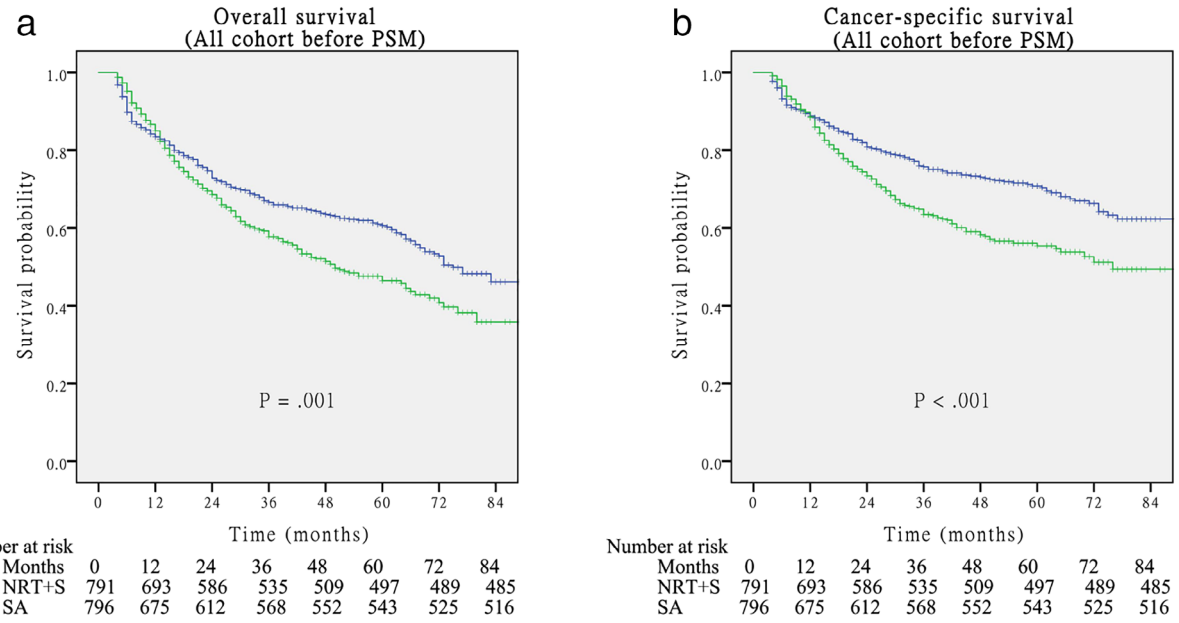

All Cohort OS before PSM

	3-year survival	5-year survival	95% confidence intervals (m)
NRT+S	66.9%	62.6%	38.8-42.2
SA	71.1%	68.2%	42.7-45.9

All Cohort CSS before PSM

	3-year survival	5-year survival	95% confidence intervals (m)
NRT+S	72.9%	70.2%	41.8-45.2
SA	80.4%	78.1%	47.2-50.2

Figure 2 (**a**) Overall survival (——) Surgery alone, (——) Neoadjuvant CRT + surgery, (—|—) SA-censored, and (—|—) CRT + S-censored and (**b**) cancer-specific survival (——) Surgery alone, (——) Neoadjuvant CRT + surgery, (—|—) SA-censored; and (—|—) CRT + S-censored between surgery alone and nCRT + surgery groups before matching ($P < 0.001$).

and CSS. Multivariable analysis was performed using the Cox's proportional hazards regression model. *P*-values were derived from two-tailed tests and significant values were defined as those with a $P < 0.05$.

Results

A total of 1587 patients were retrospectively identified, of whom 49.8% (n = 791) received nCRT plus surgery and 80.2% (n = 1273) were truly node-negative disease. The baseline unadjusted comparison of patient demographics and oncologic outcomes by treatment groups (CRT + S vs. SA) are shown in Table 1. As expected, patients in the SA group tended to be older, and had smaller total tumor sizes, earlier pT and pN stage and better differentiated histologic grade disease compared with patients in the CRT + S group, which probably reflected the better survival outcomes. The median follow-up period after diagnosis was 31.6 months (interquartile range, 11.0–49.0 months).

Compared to CRT + S group, those patients who received SA treatment showed significantly better OS (five-year OS 68.2% vs. 62.6%; $P = 0.001$) and CSS (five-year CSS 78.1% vs. 70.2%; $P < 0.001$) (Fig 2). After PSM, 353 patients in the CRT + S group were matched and compared with 353 patients in the SA group. Patients and tumor characteristics were well balanced between the two treatment groups (Table 2). Taking into account the matched cohorts, there was a significant survival benefit associated with nCRT (five-year OS 67.8% vs. 62.5%; $P = 0.007$), but without statistical difference in CSS (five-year CSS 75.3% vs. 72.7%; $P = 0.059$) between those treatment groups (Fig 3).

The univariable and Cox proportional hazards regression analysis of OS for matched cohorts are described in Table 3. All significant factors in the univariable analysis were entered into the multivariable analysis basing on the Cox's proportional hazards regression model. The multivariate regression analysis indicated that lower third disease ($P = 0.03$), pathological T stage ($P < 0.001$), pathological N stage ($P = 0.003$) and ELN count ($P < 0.001$) were independent risk factors for cN0 esophageal carcinoma. Furthermore, nCRT was also an independent prognostic factor for improved OS compared with surgery alone patients ($P = 0.002$).

For cN0/pN0 esophageal carcinoma patients, the five-year OS (67.8% vs. 62.5%; $P = 0.175$) and CSS (75.3% vs.

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Table 2 Comparison of patient demographics and tumor characteristics for the clinical node-negative patients after PSM

Characteristics	Neoadjuvant CRT + surgery (*n* = 353)	Surgery alone (*n* = 353)	Standardized difference	
			Before	After
Age, years, n (%)			0.127	−0.006
< 60	114 (32.3)	116 (32.9)		
60–70	154 (43.6)	163 (46.1)		
≥ 70	85 (24.1)	74 (21.0)		
Male sex, n (%)	292 (82.7)	269 (76.2)	0.149	0.023
Race/ethnicity, n (%)			0.049	−0.009
White	312 (88.4)	307 (87.0)		
Other	41 (11.6)	46 (13.0)		
Disease site, n (%)			−0.048	−0.035
Upper third	24 (6.8)	23 (6.6)		
Middle third	50 (14.2)	51 (14.4)		
Lower third	279 (79.0)	279 (79.0)		
Tumor length, cm, n (%)			0.246	−0.024
< 3	146 (41.4)	145 (41.1)		
3–5	126 (35.7)	130 (36.8)		
≥ 5	81 (22.9)	78 (22.1)		
Tumor histology, n (%)			0.072	0.047
Squamous cell carcinoma	97 (27.5)	100 (28.3)		
Adenocarcinoma	256 (72.5)	253 (71.7)		
Histologic grade, n (%)			0.267	0.039
Well + moderate	215 (60.9)	215 (60.9)		
Poor + undifferentiated	138 (39.1)	138 (39.1)		
Pathological T stage, n (%)			0.892	0.018
T1-2	180 (51.0)	181 (51.3)		
T3-4	173 (49.0)	172 (48.7)		
Pathological N stage, n (%)			0.268	0.019
N0	267 (75.6)	267 (75.6)		
N1	86 (24.4)	86 (24.4)		
ELN count, n ± SD			−0.034	0.008
< 12	122 (34.6)	137 (38.8)		
12–16	67 (19.0)	58 (16.4)		
≥ 16	164 (46.4)	158 (44.8)		

ELN, examined lymph node; RT, radiotherapy.

72.7%; $P = 0.37$) were identical in the CRT + S and SA groups. However, for cN0/pN+ patients, the five-year OS and CSS were significantly better for the CRT + S group (60.5% vs. 40.7%; $P = 0.002$ and 65.1% vs. 53.5%; $P = 0.024$, respectively) (Fig 4). On pathologic T stage subgroup analysis, nCRT was associated with significantly improved OS (five-year survival 59.6% vs. 37.7%; $P < 0.001$) and CSS (five-year survival 66.7% vs. 53.5%; $P < 0.001$) for pT3-4N0 (localized) disease, but with a modest absolute disadvantage in survival outcomes for pT1-2N0 (early-staged) disease ($P < 0.05$) (Fig 5). Cox multivariate regression analysis according to truly node-negative disease revealed that the addition of nCRT for patients with tumor length ≥3 cm ($P = 0.004$; 95% CI: 0.36–0.83), early-staged disease ($P = 0.007$; 95% CI: 1.20–3.27) and localized disease ($P < 0.001$; 95% CI: 0.26–0.58) were powerful independent risk factors for survival than surgery alone (Table 4).

Discussion

In this large population-based study, the use of chemoradiotherapy before esophagectomy was associated with a 5.3% absolute five-year OS benefit compared with esophagectomy alone for cN0 patients after PSM. On subgroup analysis, this finding was driven by patients with cN0/pN+ and cN0/pT3-4N0 status. There were 19.8% absolute improvement in five-year survival with the addition of nCRT in cN0/pN+ disease and up to 21.9% absolute improvement in cN0/pN0 patients with localized disease.

Increasingly, nCRT is becoming the preferred induction treatment for patients with resectable EC. Although investigated by several studies, the benefit of nCRT in cN0 esophageal carcinoma is still unknown, owing to infrequent presentation and absence of dedicated randomized trials.[12] The CROSS phase III multicenter trial show

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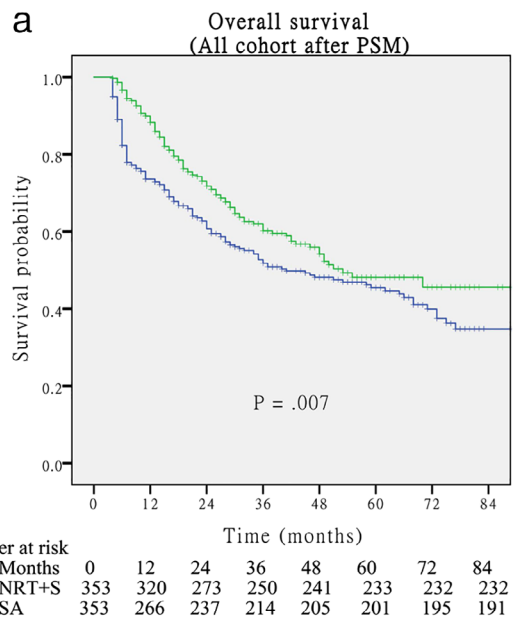
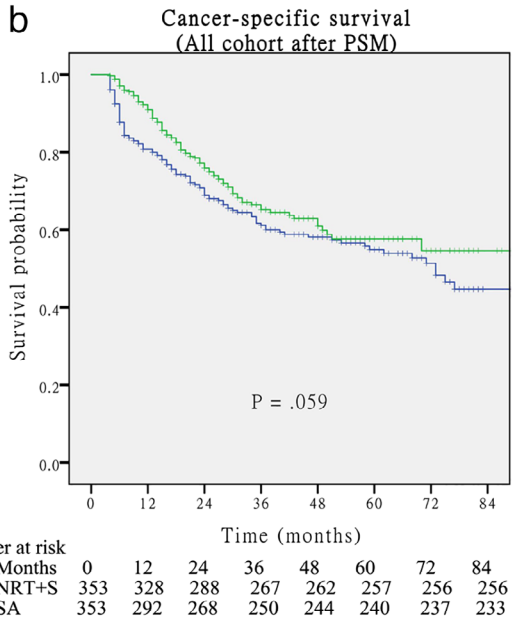


All Cohort OS after PSM

	3-year survival	5-year survival	95% confidence intervals (m)
NRT+S	70.0%	66.0%	39.5-44.4
SA	60.1%	57.2%	34.5-39.9



All Cohort CSS after PSM

	3-year survival	5-year survival	95% confidence intervals (m)
NRT+S	75.1%	72.8%	42.3-47.2
SA	70.5%	68.0%	39.1-44.5

Figure 3 (**a**) Overall survival between surgery alone and nCRT + surgery groups after matching (P = 0.007) (——) Surgery alone, (——) Neoadjuvant CRT + surgery, (—|—) SA-censored, and (—|—) CRT + S-censored. (**b**) Cancer-specific survival between surgery alone and nCRT + surgery groups after matching (P = 0.059) (——) Surgery alone, (——) Neoadjuvant CRT + surgery, (—|—) SA-censored, and (—|—) CRT + S-censored.

improved long-term oncologic benefits for patients treated with preoperative weekly paclitaxel and carboplatin five weeks with 41.4 Gy radiotherapy compared with surgery alone (HR 0.67; P = 0.011) without any increase in postoperative mortality.[4, 6] However, the majority of patients had clinically staged node-positive tumors (236/366), and the R0 resection rate was relatively low in the surgery-alone arm (111/161).

There are two previous trials which have attempted to investigate nCRT compared with surgery alone in purportedly early-stage EC.[13, 14] However, those trials had important limitations with inaccurate staging procedures, nonstandardized surgical approaches and outdated neoadjuvant treatment regimens approximately 30 years ago. Finally, neither trial showed a significantly treatment benefit of nCRT compared with surgery alone. The recently published FFCD 9901 phase III trial, which focused on stage I or II EC, also failed to influence survival or recurrence in comparison to surgery alone in all cohort and propensity score matched analysis.[15] In this randomized study, 98 patients (50.3%) received nCRT followed by surgery, with a three-year overall survival rate of 47.5% versus 53.0% (P = 0.94) and postoperative mortality rate of 11.1% versus 3.4% (P = 0.049), which recommended surgery alone as the primary treatment approach for patients with earlier EC stages, as well as cN0 patients. However, to date, there has been no study which has aimed to investigate the effect of nCRT on clinically node-negative disease. Although randomized trials would be ideal to definitively evaluate treatment strategies, such trials are unlikely to ever be performed considering the relative uncommon nature of this subset. Even if such a trial was instigated, it is extremely unlikely that any clinical trial would be able to assemble the number of patients that were included in this study. The use of the SEER database has a significant strength of being able to investigate uncommon tumor stages with enough power, due to its population-based nature.[16]

Treatment decisions for EC must be made according to clinical staging. Nowadays, clinical staging is systematically performed by thoracoabdominal CT scan and endoscopic ultrasound examination. Positron tomography scan and radionucleotide bone scan are optional, but limitations in these techniques mean lymph node metastases often go undetected preoperatively. Previous institutional studies have shown rates of occult nodal metastases can range from 16% to 39%, even in clinical early stage disease.[17, 18]

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Table 3 Univariable analysis and Cox proportional hazards regression analysis for the entire cohort overall survival after PSM

Characteristics	Univariable analysis *P*-value	Multivariable analysis		
		HR	95% CI	*P*-value
Age, years, n (%)	0.011			
< 60			1 (reference)	
60–70		0.99	0.72–1.36	0.948
≥ 70		1.25	0.91–1.72	0.162
Male sex, n (%)	0.632	1.11	0.80–1.52	0.538
Race/ethnicity, n (%)	0.068			
White			1 (reference)	
Other		1.13	0.78–1.62	0.524
Disease site, n (%)	0.001			
Upper third			1 (reference)	
Middle third		0.69	0.42–1.12	0.135
Lower third		0.63	0.41–0.96	0.030
Tumor length, cm, n (%)	0.667			
< 3			1 (reference)	
3–5		0.85	0.64–1.12	0.245
≥ 5		0.94	0.68–1.31	0.722
Tumor histology, n (%)	<0.001			
Squamous cell carcinoma			1 (reference)	
Adenocarcinoma		0.81	0.59–1.11	0.184
Histologic grade, n (%)	0.097			
Well + moderate			1 (reference)	
Poor + undifferentiated		1.09	0.85–1.39	0.517
Pathological T stage, n (%)	<0.001			
T1-2			1 (reference)	
T3-4		2.70	2.05–3.57	<0.001
Pathological N stage, n (%)	<0.001			
N0			1 (reference)	
N1		1.51	1.15–1.98	0.003
ELN count, n ± SD	<0.001			
< 12			1 (reference)	
12–16		0.79	0.56–1.12	0.185
≥ 16		0.54	0.41–0.70	<0.001
Treatment procedure	<0.001			
SA			1 (reference)	
Neoadjuvant CRT + surgery		0.67	0.52–0.87	0.002

CI, confidence interval; CRT, chemoradiotherapy; ELN, examined lymph node; HR, hazard ratio; SA, surgery alone.

In addition, the utilization of neoadjuvant therapy has also been demonstrated to be associated with significant tumor downstaging as reflected by increases in pathological no residual disease.[19, 20] Currently, several studies do not support the use of neoadjuvant chemoradiation in the subset of node-negative patients;[15, 21] however, other studies have definitively shown an improved outcome.[22, 23] Perhaps, owing to staging migration, the clinical staging inaccuracies have resulted in a relatively high incidence of patients actually having nodal disease at the time of surgical resection. This indicates that current clinical staging practices alone may not be adequate for appropriately risk stratifying patients preoperatively.

Nonetheless, in order to reduce the tumor downstaging effect of neoadjuvant therapy, as well as the potential misclassification of clinical nodal status, we matched the clinical node-negative stage to pathologic stage and performed analysis on patients who were in cN0/pN0 and cN0/pN+ status. Although this predetermined subset analysis resulted in decreased numbers for comparison, it allowed for a more robust analysis. This study showed that patients with EC who were cN0/pN+ or pT3-4N0 derived a significant survival benefit from nCRT, even after propensity score-adjusted for other demographic and pathological data. In contrast, decreased survival benefit of neoadjuvant chemoradiation was observed among patients with early-stage cN0/pN0 disease when compared with surgery alone.

The patterns and types of esophageal cancer histology are different between Asian and western populations. Esophageal squamous cell carcinoma is a common

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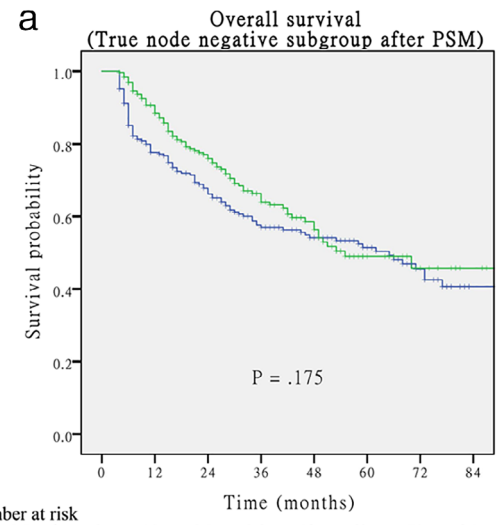
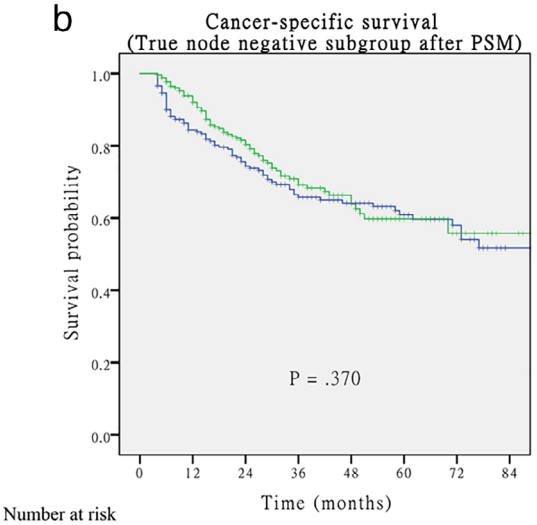


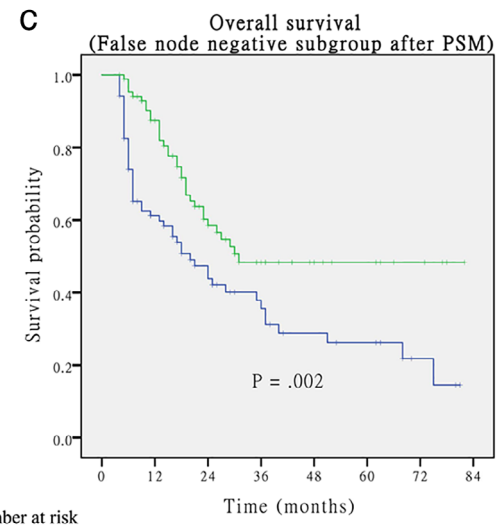
True node negative subgroup OS after PSM

	3-year survival	5-year survival	95% confidence intervals (m)
NRT+S	73.0%	67.8%	40.5-46.1
SA	64.8%	62.5%	37.2-43.2



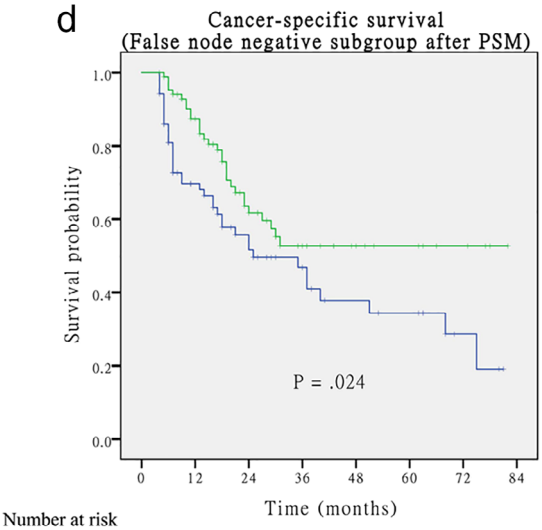
True node negative subgroup CSS after PSM

	3-year survival	5-year survival	95% confidence intervals (m)
NRT+S	78.3%	75.3%	43.6-49.1
SA	74.5%	72.7%	41.7-47.7



False node negative subgroup OS after PSM

	3-year survival	5-year survival	95% confidence intervals (m)
NRT+S	60.5%	60.5%	32.8-43.4
SA	45.3%	40.7%	22.5-30.0



False node negative subgroup CSS after PSM

	3-year survival	5-year survival	95% confidence intervals (m)
NRT+S	65.1%	65.1%	34.6-45.4
SA	58.1%	53.5%	26.7-38.1

Figure 4 (**a**) Overall survival between surgery alone and nCRT + surgery groups with pN-subgroup (P = 0.175) (——) Surgery alone, (——) Neoadjuvant CRT + surgery, (—|—) SA-censored, and (—|—) CRT + S-censored. (**b**) Cancer-specific survival between surgery alone and nCRT+surgery groups with pN0 subgroup (P = 0.370) (——) Surgery alone, (——) Neoadjuvant CRT + surgery, (—|—) SA-censored, and (—|—) CRT + S-censored. (**c**) Overall survival between surgery alone and nCRT+surgery groups with pN+ subgroup (P = 0.002) (——) Surgery alone, (——) Neoadjuvant CRT + surgery, (—|—) SA-censored, and (—|—) CRT + S-censored. (**d**) Cancer-specific survival between surgery alone and nCRT + surgery groups with pN+ subgroup (P = 0.024) (——) Surgery alone, (——) Neoadjuvant CRT + surgery, (—|—) SA-censored, and (—|—) CRT + S-censored.

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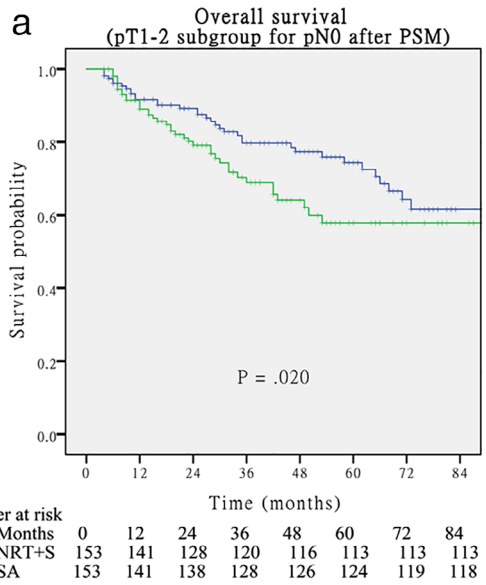
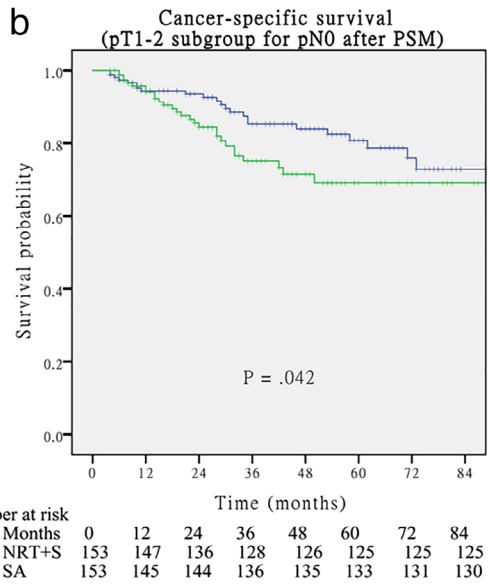


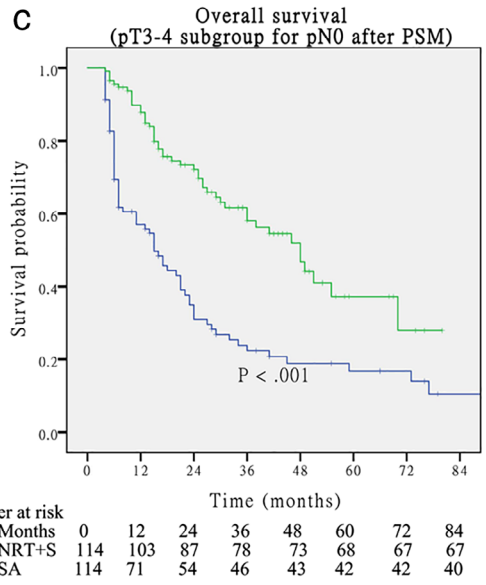
pT1-2 for true node negative subgroup OS after PSM

	3-year survival	5-year survival	95% confidence intervals (m)
NRT+S	77.8%	73.9%	42.2-49.5
SA	83.7%	81.0%	48.3-54.2



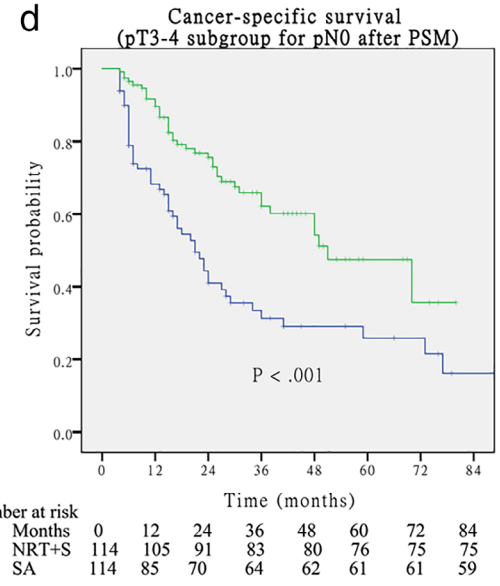
pT1-2 for true node negative subgroup CSS after PSM

	3-year survival	5-year survival	95% confidence intervals (m)
NRT+S	83.7%	81.7%	45.9-52.8
SA	88.9%	86.9%	51.4-56.5



pT3-4 for false node negative subgroup OS after PSM

	3-year survival	5-year survival	95% confidence intervals (m)
NRT+S	66.7%	59.6%	35.9-44.3
SA	39.5%	37.7%	18.9-27.5



pT3-4 for false node negative subgroup CSS after PSM

	3-year survival	5-year survival	95% confidence intervals (m)
NRT+S	71.1%	66.7%	38.3-46.9
SA	55.3%	53.5%	23.4-33.6

Figure 5 (**a**) Overall survival between surgery alone and nCRT + surgery groups with pT1-2N0 subgroup ($P = 0.02$) (——) Surgery alone, (——) Neoadjuvant CRT + surgery, (—|—) SA-censored, and (—|—) CRT + S-censored. (**b**) Cancer-specific survival between surgery alone and nCRT+surgery groups with pT1-2N0 subgroup ($P = 0.042$) (——) Surgery alone, (——) Neoadjuvant CRT+Surgery, (—|—) SA-censored, and (—|—) CRT + S-censored. (**c**) Overall survival between surgery alone and nCRT+surgery groups with pT3-4N0 subgroup ($P < 0.001$) (——) Surgery alone, (——) Neoadjuvant CRT + surgery, (—|—) SA-censored, and (—|—) CRT + S-censored. (**d**) Cancer-specific survival between surgery alone and nCRT + surgery groups with pT3-4N0 subgroup ($P < 0.001$) (——) Surgery alone, (——) Neoadjuvant CRT + surgery, (—|—) SA-censored, and (—|—) CRT + S-censored.

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Table 4 Univariable and multivariable HRs for overall survival, according to the pathological node-negative patients after PSM

Cohort	Neoadjuvant CRT + surgery (*n* = 267)	Surgery alone (*n* = 267)	Univariable analysis		Multivariable analysis	
			HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Age, years, n (%)						
< 60	80 (30.0)	62 (23.2)	1.62 (0.86–3.06)	0.135	1.41 (0.71–2.79)	0.323
60–70	118 (44.2)	92 (34.5)	0.89 (0.55–1.46)	0.661	0.63 (0.37–1.06)	0.083
≥ 70	69 (25.8)	113 (42.3)	0.57 (0.34–0.94)	0.027	0.53 (0.32–0.88)	0.014
Sex, n (%)						
Male	222 (83.1)	200 (74.9)	0.89 (0.65–1.22)	0.470	0.82 (0.58–1.15)	0.252
Female	45 (16.9)	67 (25.1)	0.58 (0.29–1.17)	0.128	0.46 (0.22–1.00)	0.049
Race/ethnicity, n (%)						
White	230 (86.1)	237 (88.8)	0.78 (0.57–1.07)	0.117	0.62 (0.44–0.86)	0.040
Other	37 (13.9)	30 (11.2)	1.06 (0.49–2.24)	0.890	1.39 (0.56–3.44)	0.480
Disease site, n (%)						
Upper third	21 (7.9)	18 (6.7)	0.83 (0.37–1.89)	0.661	0.66 (0.21–2.14)	0.491
Middle third	39 (14.6)	42 (15.7)	0.67 (0.34–1.29)	0.230	0.62 (0.29–1.34)	0.224
Lower third	207 (77.5)	207 (77.6)	0.86 (0.61–1.22)	0.408	0.72 (0.49–1.04)	0.081
Tumor length, n (%)						
< 3 cm	117 (43.8)	117 (43.8)	1.16 (0.75–1.79)	0.504	0.98 (0.61–1.59)	0.945
≥ 3 cm	150 (56.2)	150 (56.2)	0.62 (0.42–0.92)	0.017	0.55 (0.36–0.83)	0.004
Tumor histology, n (%)						
SCC	76 (28.5)	80 (30.0)	0.71 (0.45–1.12)	0.140	0.75 (0.47–1.20)	0.229
Adenocarcinoma	191 (71.5)	187 (70.0)	0.91 (0.62–1.32)	0.609	0.75 (0.49–1.15)	0.186
Histologic grade, n (%)						
Well + moderate	170 (63.7)	170 (63.7)	0.76 (0.52–1.11)	0.150	0.68 (0.46–1.00)	0.051
Poor + undifferentiated	97 (36.3)	97 (36.3)	0.90 (0.57–1.43)	0.663	0.78 (0.48–1.27)	0.315
pT stage, n (%)						
T1-2	153 (57.3)	153 (57.3)	1.78 (1.09–2.84)	0.022	1.98 (1.20–3.27)	0.007
T3-4	114 (42.7)	114 (42.7)	0.38 (0.26–0.56)	<0.001	0.39 (0.26–0.58)	<0.001
ELN count, n (%)						
< 12	106 (71.1)	103 (56.7)	0.85 (0.57–1.27)	0.417	0.85 (0.56–1.29)	0.451
12–16	49 (11.9)	46 (14.0)	1.07 (0.52–2.18)	0.450	0.60 (0.24–1.52)	0.280
≥ 16	112 (17.0)	118 (29.3)	0.63 (0.38–1.07)	0.086	0.54 (0.30–0.97)	0.040

CRT, chemoradiotherapy; ELN, examined lymph node; SCC, squamous cell carcinoma.

malignant tumor occurring in Asian individuals, while most esophageal adenocarcinomas are found in patients in western countries. Although recommended by NCCN guidelines, many of the nCRT-related studies include patients with both squamous cell carcinoma and adenocarcinoma. For example, one of the trials performed by the CROSS group showed improved long-term oncologic benefits for patients treated with nCRT compared with surgery alone.[6] However, when survival outcomes were analyzed by histology, neoadjuvant chemoradiation appeared to benefit adenocarcinoma to a significantly lesser degree than squamous cell carcinoma. In our study, the multivariate regression analysis revealed that the addition of nCRT for truly node-negative patients with squamous cell carcinoma and adenocarcinoma disease were not independent risk factors for survival than surgery alone.

Although there has been advancement in radiation techniques and chemotherapy regimens,[24, 25] utilization of neoadjuvant therapy, in particular combined chemoradiotherapy, may be associated with grade III–IV toxicity with an adverse impact upon quality of life and an increase in postoperative mortality. [26–28] In the CROSS trial, it was estimated that 6% of patients who underwent chemoradiation were no longer operative candidates because of progression of disease, toxicity, or decline in health and preference, which made them medically unfit for surgery.[4, 6] In our study, survival of patients with pT1-2N0 disease was better with upfront surgery due to the avoidance of unnecessary and possibly harmful treatment in this population that could cause deconditioning, chemoradiation-related morbidity or mortality, treatment delay, and potentially increase surgical complications and mortality. This result demonstrates that identification of higher-risk patients for induction therapy would be expected to yield better results than taking a uniform approach to this cN0 group.

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To our knowledge, this is the largest study to date to specifically examine the role of nCRT plus esophagectomy in cN0 esophageal carcinoma patients. There are several well-characterized advantages of using the SEER database. As more current survival data are verified and subsequently released, there will be opportunities to perform updated analysis of many studies. However, we recognize that there are also several limitations of the SEER database. First, our results were yielded by a retrospective analysis. The patients were grouped based on treatment mode and were thus not randomized, potentially resulting in a selection bias. In addition, owing to the retrospective nature of this report, no information was recorded on radiation dose and field design in the SEER database. In addition, we were also unable to provide an explanation as to why there was a wide variation in chemotherapy usage and radiation timing. This aspect requires further investigation, given that the radiation and chemotherapy regimens have rapidly evolved during the past few decades and survival rates are dependent on the chemoradiotherapy technologies used. Finally, limitation inherent to the database did not provide data on other factors that may influence survival, including surgical margin status, patient comorbidities, performance status, lymphovascular invasion, type of lymphadenectomy and toxicity data, which may contribute to a list of unknown confounders affecting outcomes.

In conclusion, this study provides further evidence that cN0 patients who are in cN0/pN+ or localized cN0/pN0 status gain a significant survival benefit from neoadjuvant chemoradiation plus surgery compared with surgery alone. However, nCRT was associated with decreased survival for early-stage cN0/pN0 patients. This finding may demonstrate that the identification of higher-risk patients for neoadjuvant therapy would be expected to yield better results than taking a uniform approach to cN0 disease. Methods to accurately diagnosis or even predict truly positive nodal disease warrant clinical application and further study.

Disclosure

The authors confirm that there are no conflicts of interest.

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Supporting Information

Additional Supporting Informationmay be found in the online version of this article at the publisher's website:

Figure S1. Histogram of propensity scores for patients between the surgery alone group and neoadjuvant chemoradiotherapy plus surgery group. (a) Unmatched patients who received surgery alone. (b) Matched patients who received surgery alone. (c) Unmatched patients who received neoadjuvant chemoradiotherapy plus surgery. (d) Matched patients who received neoadjuvant chemoradiotherapy plus surgery. Matched groups have similar propensity score distributions.

Figure S2. Standardized differences of variables between patients who received surgery alone and those who received neoadjuvant chemoradiotherapy plus surgery. Hollow diamond symbolized differences before propensity matching and black diamond symbolized differences after propensity matching. Propensity score matching effectively reduced heterogeneity among variables between the two surgical approaches in comparison.

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