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ORIGINAL ARTICLE

Role of radiation therapy in node-negative esophageal cancer: A propensity-matched analysis

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

Keywords
Adjuvant radiotherapy; esophagectomy; esophageal cancer; neoadjuvant radiotherapy; survival.

Correspondence
Hui-Jiang Gao, Department of Thoracic Surgery, The Affiliated Hospital of Qingdao University, No.16 Jiangsu Road, Qingdao, China
Email: gaohuijiang2008@163.com; or 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, Tianjin, China
Email: yuzhtao@hotmail.com

†These authors contributed equally to this work.

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Abstract

Background: This study investigated the prognostic impact of (neo-)adjuvant radiation therapies in early stage esophageal cancer.

Methods: A retrospective analysis using the Surveillance, Epidemiology, and End Results (SEER) database was conducted from 2004 to 2016. Patients with pathologically staged T1-4N0M0 esophageal cancer were divided into two treatment groups: (i) neoadjuvant radiotherapy followed by surgery; and (ii) upfront esophagectomy followed by adjuvant radiotherapy. Propensity scored match and Cox proportional hazards model were used to identify covariates associated with overall survival and cancer-specific survival.

Results: There were 821 patients selected, of whom 588 (71.6%) received neoadjuvant radiotherapy and 233 (28.4%) received adjuvant radiotherapy. For the entire cohort, neoadjuvant radiotherapy was associated with a significantly benefit in five-year survival outcomes compared with adjuvant radiotherapy ($P < 0.01$). After matching, the survival outcomes were still better for neoadjuvant radiotherapy than that of adjuvant treatment. Stratifying based on pathologic tumor status, neoadjuvant radiation was associated with improved CSS (five-year survival 73.7% vs. 42.1%; $P = 0.014$) for localized (pT3-4N0) disease. The Cox multivariate regression analysis revealed that the addition of neoadjuvant radiation for pT3-4N0 diseases with tumor length ≥ 5 cm and squamous cell carcinoma, was a powerful prognostic factor for improved cancer-specific survival ($P < 0.01$).

Conclusions: Compared with adjuvant radiotherapy, the addition of neoadjuvant radiation for pT3-4N0 diseases has been associated with improved cancer-specific survival in high-risk patients. Studies on preoperative neoadjuvant therapies would be plausible in high-risk esophageal cancer patients.

Introduction

Esophageal cancer is the sixth most common cause of cancer-related death globally, and the incidence of esophageal cancer is increasing.[1,2] Patients with resectable esophageal cancer have been reported to have an overall five-year survival between 15% and 25%.[3,4] Although surgery is the mainstay of potentially curative treatment,[5] neoadjuvant or adjuvant therapies in selected patients have been shown to improve survival outcomes. However, the optimal timing, schedules, and chemotherapy (CT), radiotherapy (RT), or synchronous chemoradiotherapy (CRT) dose rates remain unclear.[6,7]

Randomized controlled trials and meta-analyses comparing the survival benefits of CT and RT in both the adjuvant and neoadjuvant settings have reported equivocal, even sometimes contrasting results.[5,8–10] A previous meta-analysis compared neoadjuvant CT and CRT with surgery alone, showing both significantly reduced the risk of death by 13% and 22%, respectively.[8] In the CROSS trial, multimodality treatment with neoadjuvant CRT followed

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by surgery was shown to improve the five-year survival by 14% compared to the surgery alone approach.[9,10] From the adjuvant perspective, CT and RT have been shown to improve local control and possibly survival in selected groups such as patients with lymph node positive disease.[5,11] However, even after investigation by several predominant trials, those studies focus on the locally advanced nonmetastatic esophageal cancer diseases, and controversy still exists regarding the optimal treatment strategy for patients with early stage esophageal cancer.

In this retrospective study, we analyzed the Surveillance, Epidemiology, and End Results (SEER) database to investigated the prognostic impact of (neo-)adjuvant radiation therapies in pathologic node-negative esophageal cancer.

Methods

In 1973, the National Cancer Institute established the SEER program, thereby creating a comprehensive dataset that holds information on cancer diagnosis, incidence, survival and treatment modalities. This data is collected from 18 population-based registries among 14 states across the US, representing nearly 30% of the US population.[12] This retrospective study tracked the data by SEER including patient demographics, disease characteristics, treatment, and outcome information. Data for all esophageal carcinoma patients from 2004 to 2016 (n = 50 743) were acquired in plain text format from SEER and imported into SPSS software using modified versions of SEER database provided scripts. The endpoints of this study included overall survival (OS) and cancer-specific survival (CSS), which were the interval between the initial diagnosis of esophageal cancer and the occurrence of all-cause or cancer-specific death.

We identified patients diagnosed with pathologic node-negative esophageal cancer within the SEER database. The inclusion and exclusion criteria are summarized in Fig 1. Patients were included for analysis if they were documented to receive a radiotherapy (neoadjuvant vs. adjuvant) related to esophagectomy, and recorded as having one or more examined lymph node (ELN). Patients who received chemotherapy and external beam radiotherapy before surgery were included for analysis and were designated as having received neoadjuvant CRT for their esophageal cancer.[13] The exclusion criteria for data extraction in this study were (i) patients confirmed to have positive lymph-nodes involvement at pathological diagnosis, unknown or positive metastatic status; and (ii) patients with missing or incomplete data such as survival status and time, race, T stage, N stage, primary tumor site,

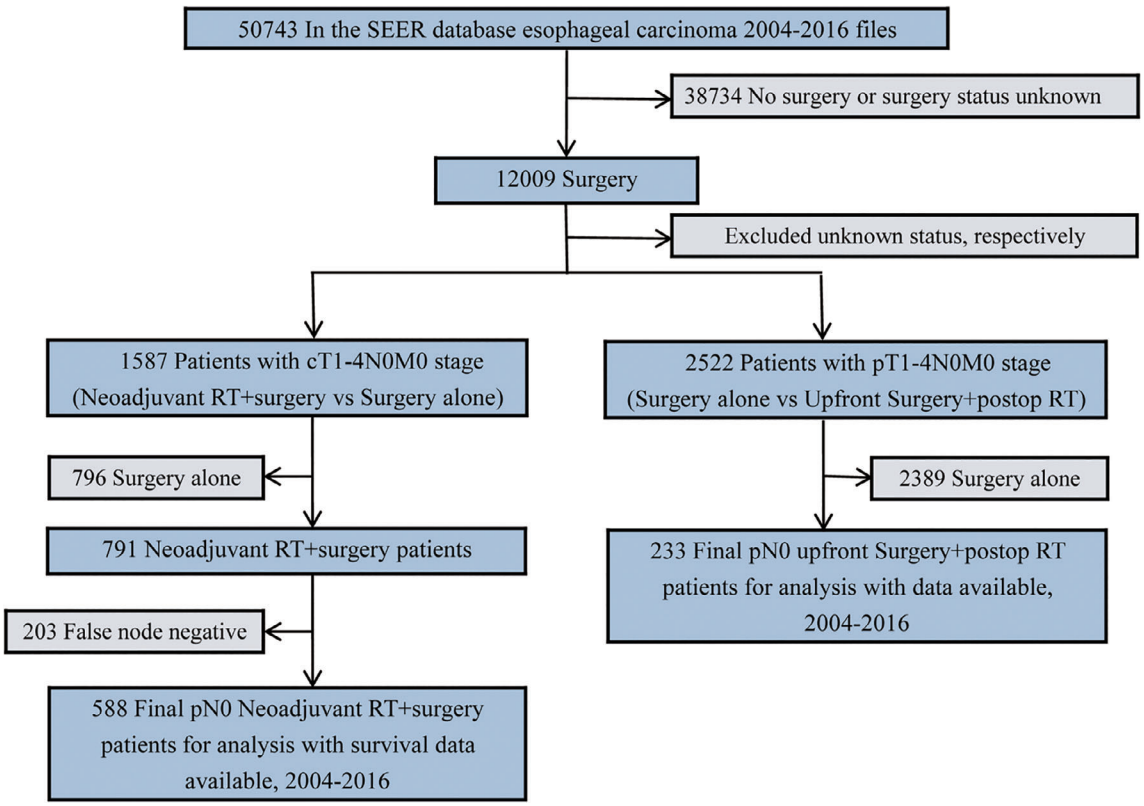

Figure 1 Flow chart for inclusion and exclusion of esophageal cancer patients in this study.

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Table 1 Comparison of patient demographics and tumor characteristics for the entire patient cohort

Characteristics	Neoadjuvant RT + surgery (*n* = 588)	Surgery + postop RT (*n* = 233)	Overall (*n* = 821)	*P*-value
Age, year, n (%)				<0.001
<60	179 (30.4)	64 (27.5)	243 (29.6)	
60–70	273 (46.4)	81 (34.8)	354 (43.1)	
≥70	136 (23.2)	88 (37.7)	224 (27.3)	
Male sex, n (%)	483 (82.1)	186 (79.8)	669 (81.5)	0.441
Race/ethnicity, n (%)				0.434
White	526 (89.5)	204 (87.6)	730 (88.9)	
Other	62 (10.5)	29 (12.4)	91 (11.1)	
Disease site, n (%)				0.053
Upper third	31 (5.3)	10 (4.3)	41 (5.0)	
Middle third	75 (12.8)	45 (19.3)	120 (14.6)	
Lower third	482 (81.9)	178 (76.4)	660 (80.4)	
Tumor length, cm, n (%)				<0.001
< 3	159 (27.0)	104 (44.6)	263 (32.0)	
3–5	198 (33.7)	63 (27.0)	261 (31.8)	
≥ 5	231 (39.3)	66 (28.4)	297 (36.2)	
Tumor histology, n (%)				0.498
Squamous cell carcinoma	148 (25.2)	64 (27.5)	212 (25.8)	
Adenocarcinoma	440 (74.8)	169 (72.5)	609 (74.2)	
Histologic grade, n (%)				0.507
Well + moderate	353 (60.0)	134 (57.5)	487 (59.3)	
Poor + undifferentiated	235 (40.0)	99 (42.5)	334 (40.7)	
Pathological T stage, n (%)				<0.001
T0	59 (10.1)		59 (7.2)	
T1–2	169 (28.7)	134 (57.5)	303 (36.9)	
T3–4	360 (61.2)	99 (42.5)	459 (55.9)	

RT, radiation therapy.

pathological type, local treatment, and radiotherapy, along with those who received surgery alone or unknown treatment sequence with respect to the operation.

In an effort to include patients who received different radiotherapy regimens, the total dose of radiation was not limited.[14] In addition, those who survived <four months were also excluded, to reduce a bias favoring the (neo-) adjuvant radiotherapy.[9] Since the data from SEER did not include any patient identifying information, Institutional Review Board approval was not required.

Statistical analysis

SPSS software version 24.0 (IBM, Armonk, NY, USA) was used to perform all analyses. 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.[15] Potential confounders included patients' age at diagnosis, sex, race, disease site, tumor length, tumor histology, histologic grade, pathological T stage and ELN. Neoadjuvant RT followed by surgery (NRT + S) or postop RT followed surgery (S + RT) 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 (Figs S1 and S2). Kaplan–Meier survival analysis and the log-rank test were used for the distributions of OS and CSS. Multivariable analysis was performed using the Cox's proportional hazards regression model. Statistically significant values were defined as those with a P-value < 0.05.

Results

There were 821 patients available for analysis after application of selection criteria, of whom 588 (71.6%) received NRT + S and 233 (28.4%) received S + RT. None of the patients received adjuvant radiotherapy after neoadjuvant treatment. The baseline unadjusted comparison of patient demographics by treatment groups (NRT + S vs. S + RT) is shown in Table 1. Patients who received NRT + S tended to have a significantly larger total tumor size, younger age and more localized disease. Conversely, patients in the S + RT group were older and had a smaller total tumor

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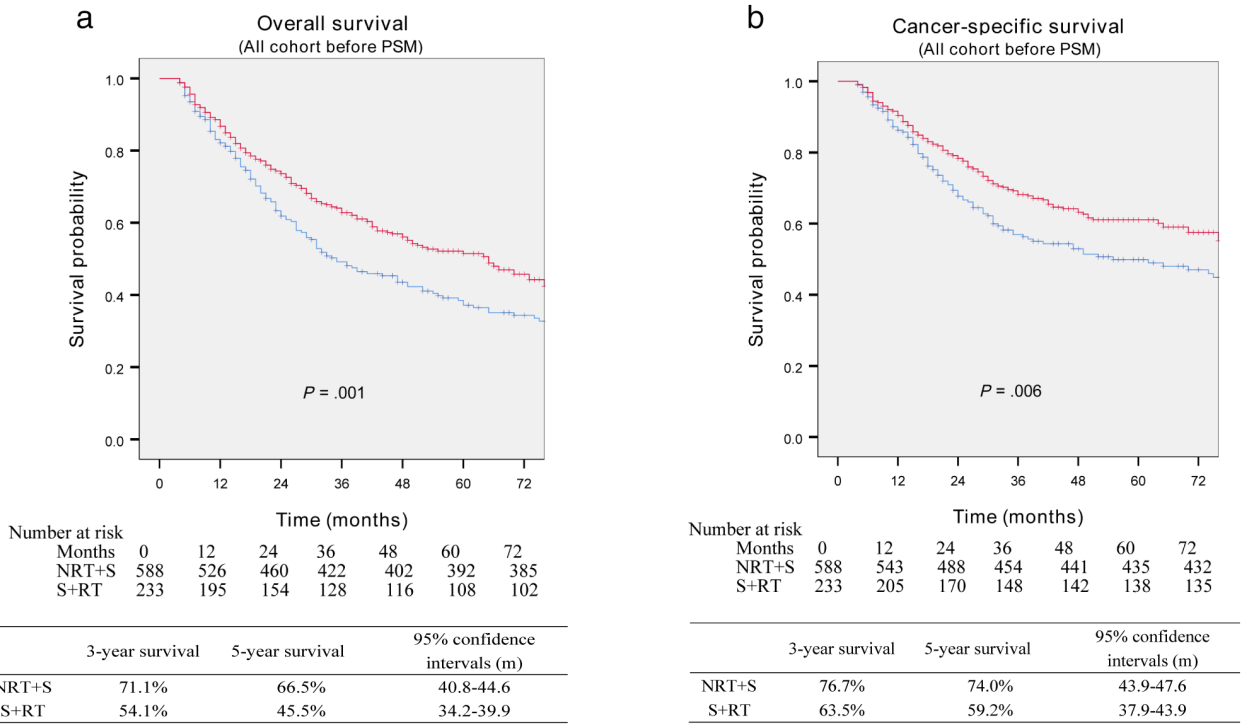

	3-year survival	5-year survival	95% confidence intervals (m)
NRT+S	71.1%	66.5%	40.8-44.6
S+RT	54.1%	45.5%	34.2-39.9

	3-year survival	5-year survival	95% confidence intervals (m)
NRT+S	76.7%	74.0%	43.9-47.6
S+RT	63.5%	59.2%	37.9-43.9

Figure 2 (**a**) Overall survival between neoadjuvant RT + surgery and surgery + postop RT groups before matching (P = 0.001) (┘┌) Surgery + postop RT, (┐└) Neoadjuvant RT + surgery, (┼) S + RT censored, (┼) NRT + S-censored. (**b**) Cancer-specific survival between neoadjuvant RT + surgery and surgery + postop RT groups before matching (P = 0.006) (┘┌) Surgery + postop RT, (┐└) Neoadjuvant RT + surgery, (┼) S + RT censored, (┼) NRT + S-censored.

Table 2 Comparison of patient demographics and tumor characteristics for the entire patient cohort after PSM

Characteristics	Neoadjuvant RT + surgery (n = 197)	Surgery + postop RT (n = 197)	Standardized difference Before	After
Age, year, n (%)			−0.242	0.019
<60	53 (26.9)	60 (30.5)		
60–70	88 (44.7)	73 (37.1)		
≥70	56 (28.4)	64 (32.5)		
Male sex, n (%)	161 (81.7)	163 (82.7)	0.060	0.059
Race/ethnicity, n (%)			−0.062	0.044
White	176 (89.3)	174 (88.3)		
Other	21 (10.7)	23 (11.7)		
Disease site, n (%)			0.086	0.017
Upper third	11 (5.6)	6 (3.1)		
Middle third	30 (15.2)	36 (18.3)		
Lower third	136 (69.2)	135 (68.6)		
Tumor length, cm, n (%)			0.354	0.006
<3	78 (39.6)	74 (37.6)		
3–5	53 (26.9)	62 (31.5)		
≥5	66 (33.5)	61 (30.9)		
Tumor histology, n (%)			0.053	0.031
Squamous cell carcinoma	52 (26.4)	50 (25.4)		
Adenocarcinoma	145 (73.6)	147 (74.6)		
Histologic grade, n (%)			−0.051	0.028
Well + moderate	113 (57.4)	112 (56.9)		
Poor + undifferentiated	84 (42.6)	85 (43.1)		
Pathological T stage, n (%)			−0.635	−0.000
T1-2	102 (51.8)	102 (51.8)		
T3-4	95 (48.2)	95 (48.2)		

PSM, propensity score matching; RT, radiotherapy.

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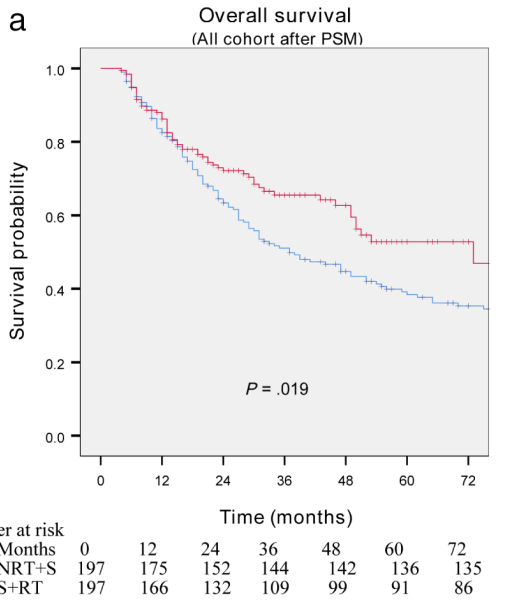
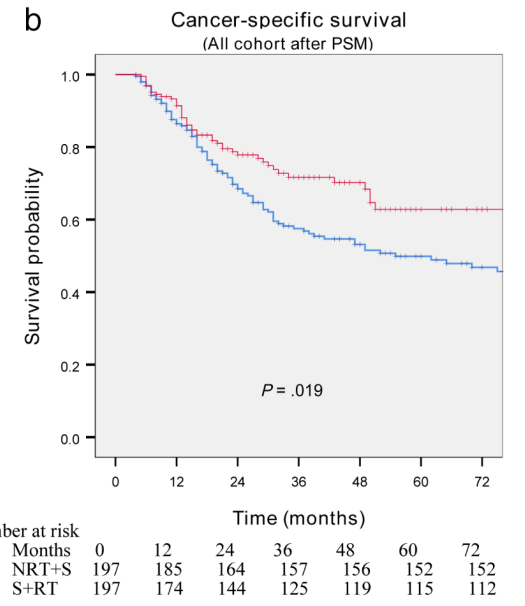


Number at risk

Months	0	12	24	36	48	60	72
NRT+S	197	175	152	144	142	136	135
S+RT	197	166	132	109	99	91	86

	3-year survival	5-year survival	95% confidence intervals (m)
NRT+S	73.1%	69.0%	40.0-46.8
S+RT	55.3%	45.7%	34.6-40.8



Number at risk

Months	0	12	24	36	48	60	72
NRT+S	197	185	164	157	156	152	152
S+RT	197	174	144	125	119	115	112

	3-year survival	5-year survival	95% confidence intervals (m)
NRT+S	79.7%	77.2%	43.7-50.2
S+RT	63.5%	58.4%	37.9-44.2

Figure 3 (**a**) Overall survival between neoadjuvant RT + surgery and surgery + postop RT groups after matching ($P = 0.019$) (┌┐) Surgery + postop RT, (┌┐) Neoadjuvant RT + surgery, (┼┼) S + RT censored, (┼┼) NRT + S-censored. (**b**) Cancer-specific survival between neoadjuvant RT + surgery and surgery+postop RT groups after matching ($P = 0.019$) (┌┐) Surgery + postop RT, (┌┐) Neoadjuvant RT + surgery, (┼┼) S + RT censored, (┼┼) NRT + S-censored.

size, earlier pT stage disease compared with patients in the NRT + S group. A pathological complete response was achieved in 59 of 588 patients (10.1%) who underwent resection after neoadjuvant RT, which likely reflected the better survival outcomes.

The median follow-up period after diagnosis was 32.5 months (interquartile range, 11–47 months). Among all patients, those who received NRT + S procedure showed significantly better OS (five-years OS 69.0% vs. 45.7%; $P = 0.001$) and CSS (five-year CSS 74.0% vs. 59.2%; $P = 0.006$) when compared to patients in the S + RT group (Fig 2). After propensity matching, 197 patients in the NRT + S group were matched and compared with 197 patients in the S + RT group. Variables were included, without significant differences in those mentioned demographics (Table 2). Taking into account for all matched patients, there were still survival benefits for neoadjuvant radiotherapy in OS (five-year survival 63.2% vs. 46.5%; $P = 0.019$) and CSS (five-year survival 77.2% vs. 58.4%; $P = 0.019$) than that of adjuvant treatment (Fig 3). The univariable analysis and Cox proportional hazards regression analysis for CSS of all cohort patients after PSM are described in Table 3. All significant factors in the univariable analysis were entered into the multivariable analysis based on the Cox's proportional hazards regression model. The multivariate regression analysis indicated that male ($P = 0.029$), worse histologically differentiated grade ($P = 0.007$) and pathological T stage ($P = 0.002$) were independent CSS prognostic factors for pathologically staged node-negative esophageal cancer. In addition, NRT + S was also an independent prognostic factor for CSS compared with adjuvant radiotherapy ($P = 0.041$).

On subgroup analysis, neoadjuvant radiation was not associated with improved overall survival (five-year survival 72.5% vs. 54.9%; $P = 0.181$) and cancer-specific survival (five-year survival 80.4% vs. 73.5%; $P = 0.619$) for pT1-2N0 (early-staged) disease, even for pT3-4N0 (localized) disease only with a modest but not statistically significant increase in overall survival (five-year survival 69.5% vs. 43.2%; $P = 0.060$). However, neoadjuvant radiation was associated with significantly improved CSS (five-year survival 73.7% vs. 42.1%; $P = 0.014$) for pT3-4N0 disease (Fig 4). The Cox multivariate regression analysis according to (neo-)adjuvant radiotherapy on pT3-4N0 disease revealed that the addition of neoadjuvant radiation for tumor length ≥5 cm ($P = 0.006$; 95% CI: 1.38–6.78) and squamous cell carcinoma ($P = 0.007$; 95% CI: 1.43–9.79) was a powerful prognostic factor for better CSS than adjuvant treatment (Table 4).

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Table 3 Univariable analysis and Cox proportional hazards regression analysis for all cohort cancer-specific survival after PSM

	Univariable analysis	Multivariable analysis		
Characteristics	*P*-value	HR	95% CI	*P*-value
Age, year, n (%)	0.357			
<60		1 (ref)		
60–70		0.99	0.63–1.54	0.957
≥70		1.31	0.83–2.06	0.249
Sex, n (%)	0.359			
Female		1 (ref)		
Male		1.78	1.06–2.99	0.029
Race/ethnicity, n (%)	0.313			
White		1 (ref)		
Other		0.96	0.54–1.72	0.897
Disease site, n (%)	< 0.001			
Upper third		1 (ref)		
Middle third		1.44	0.55–3.76	0.463
Lower third		0.68	0.25–1.85	0.452
Tumor length, cm, n (%)	0.843			
<3		1 (ref)		
3–5		0.78	0.48–1.26	0.308
≥5		1.06	0.65–1.71	0.829
Tumor histology, n (%)	0.011			
Squamous cell carcinoma		1 (ref)		
Adenocarcinoma		0.80	0.46–1.39	0.428
Histologic grade, n (%)	0.003			
Well + moderate		1 (ref)		
Poor + undifferentiated		1.64	1.14–2.36	0.007
Pathological T stage, n (%)	<0.001			
T1-2		1 (ref)		
T3-4		1.98	1.29–3.04	0.002
Treatment procedure	0.019			
Surgery + postop RT		1 (ref)		
Neoadjuvant RT + surgery		1.49	1.02–2.19	0.041

HR, hazard ratio; CI, confidence interval; HR, hazard ratio; ref, reference; RT, radiation therapy.

Discussion

This study for the first time compared neoadjuvant radiotherapy versus adjuvant radiotherapy focus on pathologically node-negative esophageal cancer. The results provided evidence of survival advantage of neoadjuvant RT followed by esophagectomy compared with adjuvant treatment. This finding was also driven by patients with pT3-4N0 disease on multivariable logistic regression analysis according to (neo-)adjuvant radiotherapy, and the addition of neoadjuvant radiotherapy for localized disease was a powerful prognostic factor for improved survival than adjuvant procedure in high-risk patients.

The impact of neoadjuvant and adjuvant RT in survival for esophageal carcinoma has been controversial for decades, making it difficult for practitioners to recommend the most optimal course of treatment. [5,6,9,10,16] The CROSS trial compared neoadjuvant CRT followed by surgery with surgery alone and demonstrated that neoadjuvant CRT improved both locoregional control and distant metastasis-free survival.[5,6] The FFCD-9901 phase III trial also compared neoadjuvant CRT along with surgery with surgery alone in patients with stage I–II esophageal cancer. Initially, the study recruitment was amended before being stopped early as an interim analysis demonstrated that the neoadjuvant CRT along with surgery arm was unlikely to show superiority (HR, 1.09; 95% CI: 0.75–1.59; $P = 0.66$).[16] Adjuvant therapies appeared less effective compared with neoadjuvant approaches, but may provide a survival benefit in lymph node-positive patients; however, this has not been investigated in a formal RCT.[9,10] Even most randomized controlled trials (RCT) focus on this field, and effectiveness of preoperative or postoperative RT was assessed using samples comprising solely of patients that underwent surgery alone. Pasquali *et al.*[17] conducted a network meta-analysis basing on 33 eligible randomized controlled trials, which revealed that neoadjuvant therapies along with surgery was superior

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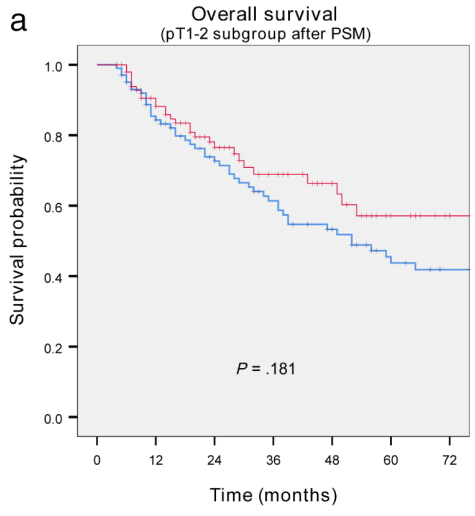
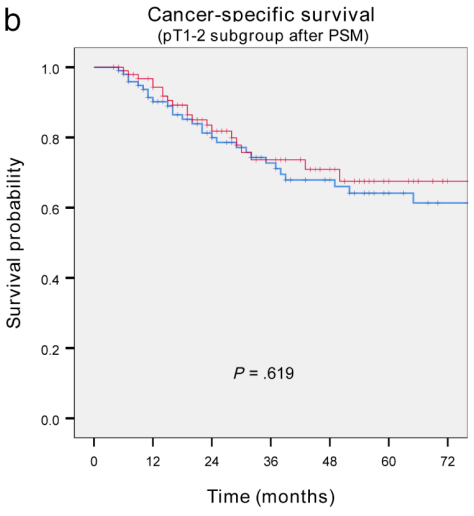


Number at risk

Months	0	12	24	36	48	60	72
NRT+S	102	93	83	78	77	74	74
S+RT	102	88	78	68	62	57	55

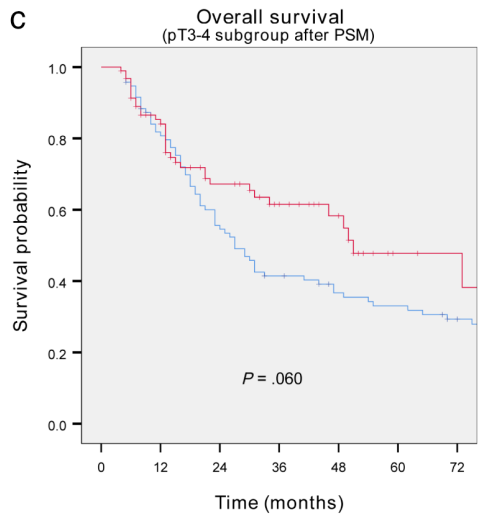
	3-year survival	5-year survival	95% confidence intervals (m)
NRT+S	76.5%	72.5%	40.9-49.9
S+RT	66.7%	54.9%	37.2-45.9



Number at risk

Months	0	12	24	36	48	60	72
NRT+S	102	99	89	84	83	82	82
S+RT	102	94	86	80	77	75	74

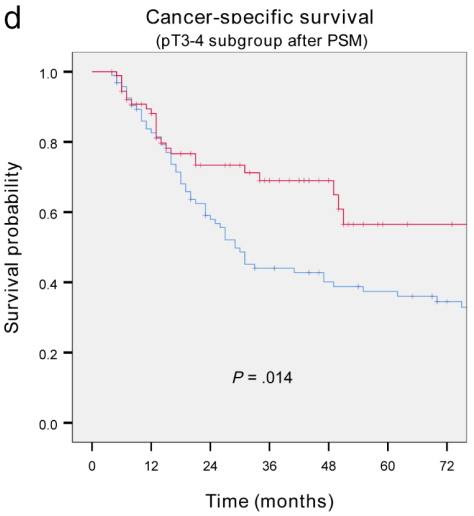
	3-year survival	5-year survival	95% confidence intervals (m)
NRT+S	82.4%	80.4%	44.4-52.9
S+RT	78.4%	73.5%	43.1-51.4



Number at risk

Months	0	12	24	36	48	60	72
NRT+S	95	82	69	66	65	62	61
S+RT	95	78	54	41	37	34	31

	3-year survival	5-year survival	95% confidence intervals (m)
NRT+S	69.5%	65.3%	35.9-46.0
S+RT	43.2%	35.8%	29.7-38.3



Number at risk

Months	0	12	24	36	48	60	72
NRT+S	95	86	75	73	73	70	70
S+RT	95	80	58	45	42	40	38

	3-year survival	5-year survival	95% confidence intervals (m)
NRT+S	76.8%	73.7%	39.8-49.7
S+RT	47.4%	42.1%	31.1-39.9

Figure 4 (**a**) Overall survival between neoadjuvant RT + surgery and surgery + postop RT groups with pT1-2 subgroup (P = 0.181) (⌐¬) Surgery + postop RT, (⌐¬) Neoadjuvant RT + surgery, (—|—) S + RT censored, (—|—) NRT + S-censored. (**b**) Cancer-specific survival between neoadjuvant RT + surgery and surgery + postop RT groups with pT1-2 subgroup (P = 0.619) (⌐¬) Surgery + postop RT, (⌐¬) Neoadjuvant RT + surgery, (—|—) S + RT censored, (—|—) NRT + S-censored. (**c**) Overall survival between neoadjuvant RT + surgery and surgery + postop RT groups with pT3-4 subgroup (P = 0.060) (⌐¬) Surgery + postop RT, (⌐¬) Neoadjuvant RT + surgery, (—|—) S + RT censored, (—|—) NRT + S-censored. (**d**) Cancer-specific survival between neoadjuvant RT + surgery and surgery + postop RT groups with pT3-4 subgroup (P = 0.014) (⌐¬) Surgery + postop RT, (⌐¬) Neoadjuvant RT + surgery, (—|—) S + RT censored, (—|—) NRT + S-censored.

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Table 4 Univariable and multivariable HRs for cancer-specific survival according to pT3-4 subgroup characteristics after PSM

			Univariable analysis		Multivariable analysis	
Cohort	Neoadjuvant RT + surgery (n = 95)	Surgery + postop RT (n = 95)	HR (95% CI)	P-value	HR (95% CI)	P-value
Sex, n (%)						
Male	76 (80.0)	77 (81.1)	1.62 (0.97–2.69)	0.066	1.67 (0.97–2.88)	0.062
Female	19 (20.0)	18 (18.9)	2.94 (0.81–10.6)	0.102	3.88 (0.75–20.2)	0.107
Race/ethnicity, n (%)						
White	82 (86.3)	81 (85.3)	1.88 (1.12–3.14)	0.017	1.92 (1.12–3.28)	0.017
Other	13 (13.7)	14 (14.7)	1.33 (0.39–4.44)	0.646	1.09 (0.25–4.74)	0.904
Disease site, n (%)						
Upper+Middle third	24 (25.3)	26 (27.4)	2.16 (0.94–4.97)	0.069	3.84 (1.37–10.8)	0.011
Lower third	71 (74.7)	69 (72.6)	1.65 (0.93–2.94)	0.082	1.49 (0.83–2.69)	0.184
Tumor length, n (%)						
< 5cm	51 (53.7)	52 (54.7)	1.16 (0.63–2.12)	0.630	1.17 (0.61–2.26)	0.639
≥ 5cm	44 (46.3)	43 (45.3)	3.13 (1.41–6.91)	0.005	3.06 (1.38–6.78)	0.006
Histology, n (%)						
SCC	31 (32.6)	31 (32.6)	2.97 (1.31–6.71)	0.009	3.74 (1.43–9.79)	0.007
Adenocarcinoma	64 (67.4)	64 (67.4)	1.38 (0.77–2.48)	0.278	1.16 (0.64–2.10)	0.620
Histologic grade, n (%)						
Well+Moderate	49 (51.6)	50 (52.6)	1.62 (0.81–3.26)	0.174	1.26 (0.59–2.67)	0.548
Poor+Undifferentiated	46 (48.4)	45 (47.4)	1.98 (1.03–3.79)	0.040	2.35 (1.12–4.94)	0.024

RT, radiation therapy; SCC, squamous cell carcinoma.

treatment followed by surgery along with adjuvant treatments than surgery alone (SUCRA values 0.82, 0.59, and 0.08, respectively). However, neoadjuvant versus adjuvant RT in patients with nodal-negative esophageal carcinoma have also not been compared to date.

The gold standard for definitively evaluating the optimal treatment for pN0 patients might be to conduct a randomized controlled trial. However, conducting such a large-scale trial in this limited subset of patients with esophageal cancer would be costly, accrue patients slowly, and require long-term follow-up, making a clinical trial a very difficult way to demonstrate the superiority of treatment procedures. In addition, with the more convincing benefit of neoadjuvant therapies described here and previously, it is unlikely that adjuvant therapies will be tested again. Therefore, we conducted this retrospective study based on the SEER database to address this problem. The use of the SEER database has a significant strength of being able to investigate uncommon tumor stages with enough power to even perform subgroup analysis, due to its population-based nature.[18] Furthermore, clinicians should strongly consider including patients with this stage of disease in multi-institutional registries to allow further evaluation of different treatment strategies and outcomes in a prospective fashion.

There has been an increasing interest in neoadjuvant therapy, which could potentially downstage cancer, eliminate micrometastasis and ergo increase resectability and curative resection.[9,10] However, utilization of neoadjuvant therapy, in particular combined CRT, is associated toxicity which may negatively affect quality of life, and can result in increased postoperative morbidity and mortality.[16,19–22] To solve this problem, Semenkovich *et al.* created a decision analysis mode for cT2N0 esophageal cancer, which estimated 6% patients in this model to represent the proportion of patients who underwent chemoradiation and were no longer operative candidates because of progression of disease, patient preference, toxicity of chemotherapy, or decline in health making them medically unfit for surgery.[19] Furthermore, many studies used second-best neoadjuvant therapies such as radiotherapy alone,[23] or nCRT including the chemotherapeutic component fluorouracil/cisplatin[16,24] which may be inferior with regard to safety and postoperative mortality in comparison with the chemotherapeutic regimen used in the current study (paclitaxel/carboplatin according to the CROSS-trial).[9,10] Therefore, the identification of higher-risk pN0 esophageal cancer patients for neoadjuvant therapy would be expected to yield better results than taking a uniform approach to this group.

The prognosis for patients with pN0 esophageal cancer is modulated by T status and histologic grade.[25–27] Currently, the benefit of induction therapy in patients with preoperative node-negative status is likely to be minimal given their better prognosis, and induction treatment indeed may be harmful. However, in case of upstaging in the pathologic report to node-positive disease, multimodality therapy could still be implemented using adjuvant radiotherapy and chemotherapy.[28,29] Modalities generally used to establish clinical esophageal cancer stage before treatment include

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computed tomography scanning, positron emission tomography scanning, endoscopic ultrasound with fine-needle aspiration, and laparoscopy. It is likely that variability in staging modalities over the course of the study period may have led to different rates of stage migration over time, particularly as positron emission tomography has become more accessible in recent years. Endoscopic ultrasound has also gained popularity and is a valuable tool in clinical staging, but is known to be less accurate for early-stage lesions such as T1 or T2 compared with more advanced tumors.[19,30] Furthermore, most incidences of understaging are because of missed nodal disease.[31] There are conflicting data from retrospective studies on the benefit of neoadjuvant chemoradiation for clinical T2N0 disease, and this observed variability in results may be due to inaccuracies in clinical staging.[19] To address the tumor downstaging effect of neoadjuvant therapy, as well as the potential misclassification of clinical nodal categories, we matched the clinical node-negative stage to pathologic stage and performed the analysis on patients who received neoadjuvant RT. Although this predetermined subset analysis resulted in decreased numbers for comparison, this allowed for a more robust statistical analysis. In this study, neoadjuvant radiotherapy along with esophagectomy did not improve survival for pT1-2N0 esophageal cancer in pathologically node-negative disease compared with the adjuvant approach. However, neoadjuvant radiation was associated with significantly improved CSS for pT3-4N0. disease. 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 clinical node negative stage group.

There are several well-characterized advantages of using the SEER database. Its large size allows for a rigorous statistical comparison. As more current survival data are verified and subsequently released, there will be opportunities to perform updated analysis of many studies, including this one. Meanwhile, important limitations of this study that should be acknowledged are its retrospective character and lack of randomization, potentially resulting in a confounding selection bias. In order to minimize the effects of this limitation, propensity matching using known confounders was performed to improve the comparability between the two groups. However, due to the inclusion of two groups receiving treatment partly in different time periods, it is possible that variables are difficult to measure with equivalent, which may explain the differences between the study groups to some extent. In addition, this study may overestimate the benefits of neoadjuvant therapy, because the initial treatment intended for the patients who were treated with RT and did not receive surgery is unknown. Some of those patients might have been started on RT with the plan to ultimately undergo esophagectomy, but never made it to surgery. We are unable to identify instances of patient death after induction therapy but before definitive resection. In addition, eligibility for adjuvant therapies is, however, limited by patient fitness, especially in those who have prolonged postoperative recovery. Therefore, not all of these patients may have the physiologic reserve to receive timely adjuvant therapy after esophagectomy. In our study, those patients who survived <four months were excluded to reduce the bias favoring the (neo-)adjuvant radiotherapy. Finally, limitation inherent to the database does not provide data on other factors that may influence survival, including surgical margin status, patient comorbidities, performance status, lymphovascular invasion, type of lymphadenectomy and gene mutations, which may contribute to a list of unknown confounders affecting outcomes.

In conclusion, although this study had its limitations, it indicated that the addition of neoadjuvant RT for pT3-4N0 diseases followed by esophagectomy was associated with improved cancer-specific survival in patients with tumor length ≥5 cm and squamous cell carcinoma. The identification of higher-risk patients for neoadjuvant therapy would be expected to yield better results than taking a uniform approach to this population, to avoid unnecessary and possibly harmful treatment in node-negative diseases.

Disclosure

The authors confirm that there are no conflicts of interest.

References

1 Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. *CA Cancer J Clin* 2018; **68** (1): 7–30.
2 Rustgi AK, El-Serag HB. Esophageal carcinoma. *N Engl J Med* 2014; **371**: 2499–509.
3 Allum WH, Stenning SP, Bancewicz J, Clark PI, Langley RE. Long-term results of a randomized trial of surgery with or without preoperative chemotherapy in esophageal cancer. *J Clin Oncol* 2009; **27**: 5062–7.
4 Cen P, Banki F, Cheng L *et al.* Changes in age, stage distribution, and survival of patients with esophageal adenocarcinoma over three decades in the United States. *Ann Surg Oncol* 2012; **19**: 1685–91.
5 Mariette C, Piessen G, Triboulet JP. Therapeutic strategies in oesophageal carcinoma: Role of surgery and other modalities. *Lancet Oncol* 2007; **8**: 545–53.
6 Cohen DJ, Leichman L. Controversies in the treatment of local and locally advanced gastric and esophageal cancers. *J Clin Oncol* 2015; **33**: 1754–9.
7 Gwynne S, Falk S, Gollins S *et al.* Oesophageal chemoradiotherapy in the UK-current practice and future directions. *Clin Oncol* 2013; **25**: 368–77.
8 Sjoquist KM, Burmeister BH, Smithers BM *et al.* Survival after neoadjuvant chemotherapy or chemoradiotherapy for resectable oesophageal carcinoma: An updated meta-analysis. *Lancet Oncol* 2011; **12**: 681–92.

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9 van Hagen P, Hulshof M, van Lanschot JJB *et al.* Preoperative chemoradiotherapy for esophageal or junctional cancer. *N Engl J Med* 2012; **366**: 2074–84.
10 Shapiro J, Van Lanschot JJ, Hulshof MC *et al.* Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS): Long-term results of a randomised controlled trial. *Lancet Oncol* 2015; **16**: 1090–8.
11 Pennathur A, Gibson MK, Jobe BA, Luketich JD. Oesophageal carcinoma. *Lancet* 2013; **381**: 400–12.
12 Cronin KA, Ries LA, Edwards BK. The surveillance, epidemiology, and end results (SEER) program of the National Cancer Institute. *Cancer* 2014; **120** (Suppl 23): 3755–7.
13 Eil R, Diggs BS, Wang SJ, Dolan JP, Hunter JG, Thomas CR. Nomogram for predicting the benefit of neoadjuvant chemoradiotherapy for patients with esophageal cancer: A SEER-Medicare analysis. *Cancer* 2014; **120** (4): 492–8.
14 Franko J, Voynov G, Goldman CD. Esophagectomy timing after neoadjuvant therapy for distal esophageal adenocarcinoma. *Ann Thorac Surg* 2016; **101**: 1123–30.
15 Winger DG, Nason KS. Propensity-score analysis in thoracic surgery: When, why, and an introduction to how. *J Thorac Cardiovasc Surg* 2016; **151** (6): 1484–7.
16 Mariette C, Dahan L, Mornex F *et al.* Surgery alone versus chemoradiotherapy followed by surgery for stage I and II esophageal cancer: Final analysis of randomized controlled phase III trial FFCD9901. *J Clin Oncol* 2014; **32**: 2416–22.
17 Pasquali S, Yim G, Vohra RS *et al.* Survival after neoadjuvant and adjuvant treatments compared to surgery alone for resectable esophageal carcinoma: A network meta-analysis. *Ann Surg* 2017; **265** (3): 481–91.
18 Zeng C, Wen W, Morgans AK, Pao W, Shu XO, Zheng W. Disparities by race, age, and sex in the improvement of survival for major cancers results from the National Cancer Institute surveillance, epidemiology, and end results (SEER) program in the United States, 1990 to 2010. *JAMA Oncol* 2015; **1** (1): 88–96.
19 Semenkovich TR, Panni RZ, Hudson JL *et al.* Comparative effectiveness of upfront esophagectomy versus induction chemoradiation in clinical stage T2N0 esophageal cancer: A decision analysis. *J Thorac Cardiovasc Surg* 2018; **155**: 2221–30.
20 Zhang JQ, Hooker CM, Brock MV *et al.* Neoadjuvant chemoradiation therapy is beneficial for clinical stage T2 N0 esophageal cancer patients due to inaccurate preoperative staging. *Ann Thorac Surg* 2012; **93** (429): 436–7.
21 Robb WB, Messager M, Goere D *et al.* Predictive factors of postoperative mortality after junctional and gastric adenocarcinoma resection. *JAMA Surg* 2013; **148**: 624–31.
22 Safieddine N, Xu W, Quadri SM *et al.* Health related quality of life in esophageal cancer: Effect of neoadjuvant chemoradiotherapy followed by surgical intervention. *J Thorac Cardiovasc Surg* 2009; **137**: 36–42.
23 Martin JT, Worni M, Zwischenberger JB *et al.* The role of radiation therapy in resected T2 N0 esophageal cancer: A population-based analysis. *Ann Thorac Surg* 2013; **95**: 453–8.
24 Markar SR, Gronnier C, Pasquer A *et al.* Role of neoadjuvant treatment in clinical T2N0M0 oesophageal cancer: Results from a retrospective multi-center European study. *Eur J Cancer* 2016; **56**: 59–68.
25 Gilbert S, Gresham GK, Jonker DJ *et al.* Impact of patient selection, disease progression, and adverse events on esophageal cancer outcomes after trimodality therapy. *Ann Thorac Surg* 2012; **94**: 1659–66.
26 Rizk NP, Ishwaran H, Rice TW *et al.* Optimum lymphadenectomy for esophageal cancer. *Ann Surg* 2010; **251**: 46–50.
27 Rice TW, Rusch VW, Ishwaran H, Blackstone EH. Cancer of the esophagus and esophagogastric junction: Data-driven staging for the seventh edition of the American joint committee on cancer/International Union against cancer staging manuals. *Cancer* 2010; **116**: 3763–73.
28 Kountourakis P, Correa AM, Hofstetter WL *et al.* Combined modality therapy of cT2N0M0 esophageal cancer: The university of Texas M. D. Anderson cancer center experience. *Cancer* 2011; **117**: 925–30.
29 Kofoed SC, Muhic A, Baeksgaard L *et al.* Survival after adjuvant chemoradiotherapy or surgery alone in resectable adenocarcinoma at the gastro-esophageal junction. *Scand J Surg* 2012; **101**: 26–31.
30 Pech O, Günter E, Dusemund F, Origer J, Lorenz D, Ell C. Accuracy of endoscopic ultrasound in preoperative staging of esophageal cancer: Results from a referral center for early esophageal cancer. *Endoscopy* 2010; **42**: 456–61.
31 Crabtree TD, Yacoub WN, Puri V *et al.* Endoscopic ultrasound for early stage esophageal adenocarcinoma: Implications for staging and survival. *Ann Thorac Surg* 2011; **91**: 1509–15.

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 neoadjuvant RT + surgery and surgery + postop RT groups.

Figure S2. Standardized differences of variables between patients who received neoadjuvant RT + surgery and those who received surgery + postop RT. Hollow diamond symbolized differences before propensity matching and black diamond symbolized differences after propensity matching. Propensity matching effectively reduced heterogeneity among variables between the two treatment approaches in comparison.

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