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ORIGINAL ARTICLE

Stage selection for neoadjuvant radiotherapy in non-cervical esophageal cancer: A propensity score-matched study based on the SEER database

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Abstract

Background: The effect of neoadjuvant radiotherapy (NRT) was controversial in non-cervical esophageal cancer. The aim of this study was to identify which stage of non-cervical esophageal cancer would get benefit from NRT using propensity score matching (PSM) and survival analysis based on the Surveillance Epidemiology, and End Results (SEER) database.

Methods: A selection process was used for case screening from the SEER database. Seven baseline variables were included in PSM. The survival analysis were based on T stage (T_2 and T_3) and status of lymph node involvement (N_0 and N_+) using Kaplan-Meier method and log-rank test for comparing the overall survival of patient with NRT plus surgery *versus* those who with surgery alone (SA).

Results: A total of 1631 cases were included in this study. After PSM, 225 cases of esophageal squamous cell carcinoma (ESCC) and 606 cases of esophageal adenocarcinoma (EAC) were enrolled in survival analysis. We found that only T_3N_+ stage of EAC would got survival benefit from NRT ($P = 0.0052$), while NRT showed no significant benefit in overall survival in other stages of EAC and ESCC.

Conclusions: NRT followed by resection had a significant survival benefit in non-cervical EAC patients with T_3N_+ stage. For patients with ESCC and other EAC stages, NRT *versus* SA did not demonstrate a statistical significant survival difference.

Introduction

In the past decade, esophageal carcinoma, which involves a poor prognosis, has become the sixth most common cancer.[1] The main histological types of esophageal cancer include squamous cell carcinoma and adenocarcinoma, and > 95% esophageal cancers are located in the non-cervical esophagus.[2] Treatment strategies are similar for both types of esophageal cancer, and include surgery, chemotherapy, and radiotherapy. For early stage and thoracic or abdominal esophageal cancer, surgical resection is the primary option, while definitive chemoradiotherapy is utilized more often in advanced or cervical esophageal cancer. Currently, neoadjuvant chemoradiotherapy (NCRT) has gradually gained clinical acceptance, but has the potential for degrading the staging of primary tumors, and is thus controversial, especially neoadjuvant radiotherapy (NRT).[3] Though NRT can reduce the size of a local tumor and make it possible to perform surgery, NRT might also

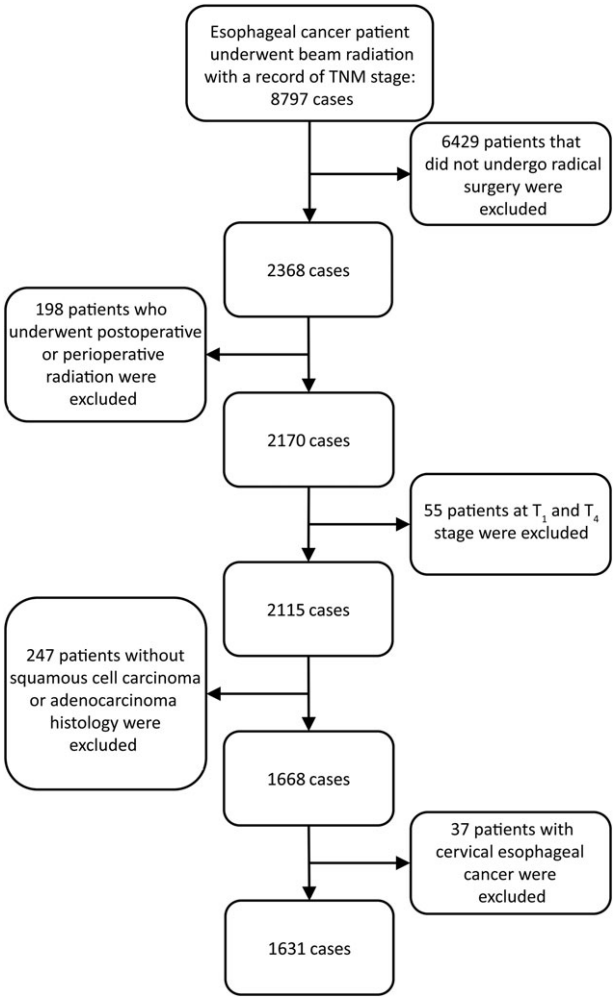

Figure 1 The flow diagram of the selection process for the study.

increase the risk of postoperative complications, which are associated with a poor prognosis.[4] Furthermore, the stage of non-cervical esophageal cancer that would result in a greater benefit from NRT has not been established, and no research based on a large population has determined the correlation between NRT and prognosis in patients with esophageal cancer. All these factors limit the application of NRT in the treatment of non-cervical esophageal cancer, and additional evidence is needed to demonstrate its effects.

Propensity score-matched (PSM) analysis, which was defined by Rosenbaum and Robin[5] and has been increasingly applied to medical research, is a method for reducing treatment selection bias by adjusting for variables related to exposure and pretreatment confounding, which might affect outcomes in non-randomized studies. In the current study we compared the overall survival of patients with thoracic or abdominal esophageal squamous cell carcinoma (ESCC)/ esophageal adenocarcinoma (EAC) who underwent surgery with or without NRT based on the data from the Surveillance Epidemiology, and End Results [SEER (http://seer.cancer.gov/)] database after applying the PSM method to provide evidence for NRT in the treatment of esophageal cancer.

Patients and Methods

Study population

The data used in the current study was selected from the SEER database, which is freely available to the public (https://seer.cancer.gov/). The SEER program of the National Cancer Institute is an authoritative source of information on the incidence and prevalence of cancer, mortality rates, population-based variables, primary tumor characteristics, and treatment, and covers approximately 28% of the US population.

SEER*Stat software was used to screen the population for the current study. The patients with T_2 and T_3 stage non-cervical esophageal cancer who had accurate TNM records and underwent surgical resection between 2004 and 2014 were enrolled in the study. We did not include T_1 and T_4 stages that lacked adequate statistics in this research. Patients who did not undergo radical surgery or did not have ESCC nor EAC histological types were excluded from the study. Patients with M_1 stage or patients who underwent peri- or postoperative radiotherapy were

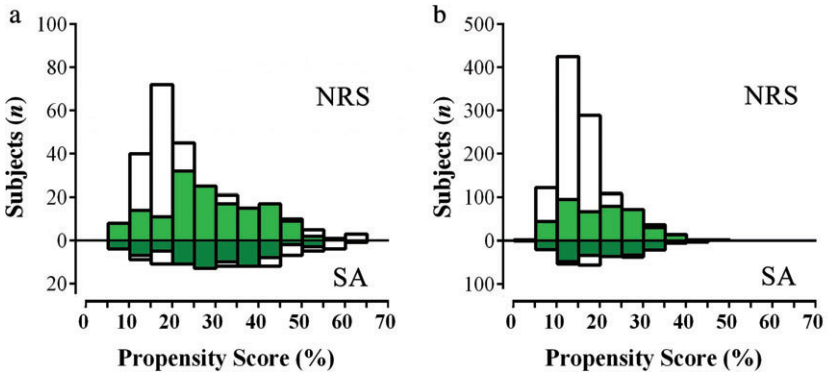

Figure 2 The mirror histograms of propensity scores for cases with NRS (above the horizontal line at zero) and SA (below the horizontal line at zero) in group of ESCC (**a**) and EAC (**b**). Matched cases are a subset of original data and their volumes are highlighted. NRS, neoadjuvant radiotherapy plus surgery; SA, surgery alone.

Table 1 Comparison of baseline variables between NRS and SA groups in the original and matched data sets in cases of ESCC

	Original Data Set				Matched Data Set			
Characteristics	NRS (%)	SA (%)	Sdiff	*P** Value	NRS (%)	SA (%)	Sdiff	*P** Value
Total	252	93			150	75		
Age(year)				0.163				0.108
<60	102 (40.5)	30(32.3)	0.172		44(29.3)	30(40.0)	0.186	
≥60	150 (59.5)	63(67.7)	0.172		106(70.7)	45(60.0)	0.186	
Gender				0.334				0.848
Male	158 (62.7)	53 (57.0)	0.096		90 (60.0)	44 (58.7)	0.022	
Female	94 (37.3)	40 (43.0)	0.096		60 (40.0)	31 (41.3)	0.022	
Race				0.625				0.749
White	187 (74.2)	63 (67.7)	0.118		111 (74.0)	54 (72.0)	0.036	
Others	65 (25.8)	30 (32.3)	0.118		39 (26.0)	21 (28.0)	0.036	
Insurance status				0.043				1.000
Insured	178 (70.7)	55 (59.1)	0.201		102 (68.0)	51 (68.0)	0.000	
Others	74 (29.4)	38 (40.9)	0.201		48 (32.0)	24 (32.0)	0.000	
Marital status				0.514				0.924
Married	140 (55.6)	48 (51.6)	0.065		85 (56.7)	42 (56.0)		
Others	112 (44.4)	45 (48.4)	0.065		65 (43.3)	33 (44.0)		
Primary site				0.712				0.777
Thoracic	133 (52.8)	47 (50.5)	0.036		77 (51.3)	40 (53.3)	0.032	
Abdominal	119 (47.2)	46 (49.5)	0.036		73 (48.7)	35 (46.7)	0.032	
Pathologic grade				0.633				0.785
I	16 (6.4)	9 (9.7)	0.123		8 (5.3)	5 (6.7)	0.056	
II	141 (56.0)	49 (52.7)	0.066		91 (60.7)	42 (56.0)	0.049	
III	94 (37.3)	34 (36.6)	0.015		50 (33.3)	28 (37.3)	0.008	
IV	1 (0.4)	1 (1.1)	0.078		1 (0.7)	0 (0)	0.015	
T stage				0.008				0.478
T2	59 (23.4)	35 (37.6)	0.126		45 (30.0)	26 (34.7)	0.082	
T3	193 (76.6)	58 (62.4)	0.126		105 (70.0)	49 (65.3)	0.082	
Involvement of lymph node				<0.001				0.396
Negative	96 (38.1)	58 (62.4)	0.408		71 (47.3)	40 (53.3)	0.098	
Positive	156 (61.9)	35 (37.6)	0.408		79 (52.7)	35 (46.7)	0.098	

**P* value for chi-square test. NRS, Neoadjuvant radiotherapy plus surgery; SA, Surgery alone; Sdiff, Standardized differences.

also excluded. Information on age, sex, race, marital status, insurance status, primary site of tumor, pathological grade, histological type, TNM stage, radiotherapy status, and survival were collected for each case from the SEER database. The 7th edition of the TNM staging system for esophageal cancer was used as a reference in the study.[6]

Statistical analysis

All cases were divided into two groups on the basis of histological types (ESCC and EAC), and split into two subgroups by the presence or absence of NRT. Each pair of subgroups was matched for other baseline variables, which would confound comparisons by PSM. These variables included age, sex, race, marital status, insurance status, primary site of tumor, pathologic grade, T stage and lymph node involvement status. All cases in both groups with NRT plus surgery (NRS) were matched at a 2:1 ratio to cases with surgery alone (SA) using the nearest neighbor match method with a 0.1 standard deviation caliper width.[7]

Survival curves of the presence or absence of NRT for T_2 and T_3 stages in the ESCC and EAC groups were evaluated using the Kaplan-Meier method. Furthermore, according to positive or negative pathological involvement of lymph nodes in T_2 and T_3 stages, we drew another two pairs of survival curves. Each pair of curves were compared using the stratified log-rank test and a *P*-value <0.05 was considered to represent statistical significance. PSM analysis was performed using the MatchIt package (https://cran.r-project.org/web/packages/MatchIt/index), while the Kaplan-Meier method and log-rank test were performed using the survival package in R project 3.4.2 (http://www.r-project.org). SPSS 24.0 software (IBM Corporation, Armonk, NY, USA) was used for the remaining statistical analyses.

Results

A group of 8797 patients with esophageal cancer and TNM stage records who underwent beam radiation between 2004–2014 were identified by SEER*Stat. A total of 1631

Table 2 Comparison of baseline variables between NRS and SA groups in the original and matched data sets in cases of EAC

	Original Data Set				Matched Data Set			
Characteristics	NRS (%)	SA (%)	Sdiff	*P** Value	NRS (%)	SA (%)	Sdiff	*P** Value
Total	1070	216			404	202		
Age (year)				0.006				0.896
<60	366 (34.2)	53 (24.5)	0.171		104 (25.7)	53 (26.2)	0.009	
≥60	704 (65.8)	163 (75.5)	0.171		300 (74.3)	149 (73.8)	0.009	
Gender				0.225				0.649
Male	970 (90.7)	190 (88.0)	0.072		357 (88.4)	181 (89.6)	0.032	
Female	100 (9.3)	26 (12.0)	0.072		47 (11.6)	21 (10.4)	0.032	
Race				0.165				0.065
White	1028 (96.1)	203 (94.0)	0.081		391 (96.8)	189 (93.6)	0.036	
Others	42 (3.9)	13 (6.0)	0.081		13 (3.2)	13 (6.4)	0.036	
Insurance status				0.019				0.419
Insured	828 (77.4)	151 (69.9)	0.141		275 (68.1)	144 (71.3)	0.056	
Others	242 (22.6)	65 (30.1)	0.141		129 (31.9)	58 (28.7)	0.056	
Marital status				0.032				0.681
Married	725 (67.8)	130 (60.2)	0.130		241 (59.7)	124 (61.4)	0.028	
Others	345 (32.2)	86 (39.8)	0.130		163 (40.3)	78 (38.6)	0.028	
Primary site				0.978				0.248
Thoracic	54 (5.1)	11 (5.1)	0.268		14 (3.5)	11 (5.4)	0.081	
Abdominal	1016 (94.9)	205 (94.9)	0.268		390 (96.5)	191 (94.6)	0.081	
Pathologic grade				<0.001				0.887
I	61 (5.7)	14 (6.5)	0.030		21 (5.2)	13 (6.4)	0.025	
II	468 (43.7)	88 (40.7)	0.069		174 (43.1)	84 (41.6)	0.030	
III	530 (49.5)	109 (50.5)	0.028		203 (50.3)	101 (50.0)	0.005	
IV	11 (1.0)	5 (2.3)	0.100		6 (1.5)	4 (2.0)	0.037	
T stage				<0.001				0.534
T2	212 (19.8)	70 (32.4)	0.243		128 (31.7)	59 (29.2)	0.044	
T3	858 (80.2)	146 (67.6)	0.243		276 (68.3)	143 (70.8)	0.044	
Involvement of lymph node				0.002				0.719
Negative	314 (29.4)	87 (40.3)	0.191		142 (35.2)	74 (36.6)	0.025	
Positive	756 (70.6)	129 (59.7)	0.191		262 (64.8)	128 (63.4)	0.025	

**P* value for chi-square test. NRS, neoadjuvant radiotherapy plus surgery; SA, surgery alone; Sdiff, standardized differences.

patients, which included 345 patients with ESCC and 1286 patients with EAC were enrolled in the study after selection. The selection process is shown in Fig 1.

Propensity score-matching

Based on the original data, 252 patients (73.0%) with ESCC and 1070 patients (83.2%) with EAC underwent NRT. Among the ESCC patients, the distribution of NRS and SA showed a statistical significance in T and N stage and insurance status. A similar difference in distribution was detected with respect to age, T and N stage, insurance status, and marital status in patients with EAC. In both the ESCC and EAC groups, all characteristics not included in the Kaplan-Meier survival analysis were matched by PSM between the NRS and SA subgroups at a 2:1 ratio. The mirror histograms of propensity scores for patients stratified by therapy status were shown in Fig 2. The distribution of these baseline variables was appropriately balanced in the matched data set, which was detected by chi-square testing for both the ESCC (Table 1) and EAC groups (Table 2). All of the significant differences in the aforementioned distribution were decreased after matching, and chi-square testing in each line list of baseline characteristics showed a *P*-value >0.05. Additionally, the balance in the baseline variables in both original data set and matched data set were validated by limited standardized difference.[8] Finally, 225 patients with ESCC and 606 patients with EAC were enrolled in survival analysis.

Survival analysis

The overall survival curves of NRS *versus* SA before and after matching are shown in Fig 2. No significant differences were detected in each pair of curves in the ESCC (Fig 3a,b) and EAC groups (Fig 3c,d). The overall survival curve of NRS was nearly in agreement with SA in the ESCC group. In the EAC group, the 1 and 2 year survivals of NRS were better than SA, but the two subgroups had a similar survival rate > 3 years postoperatively.

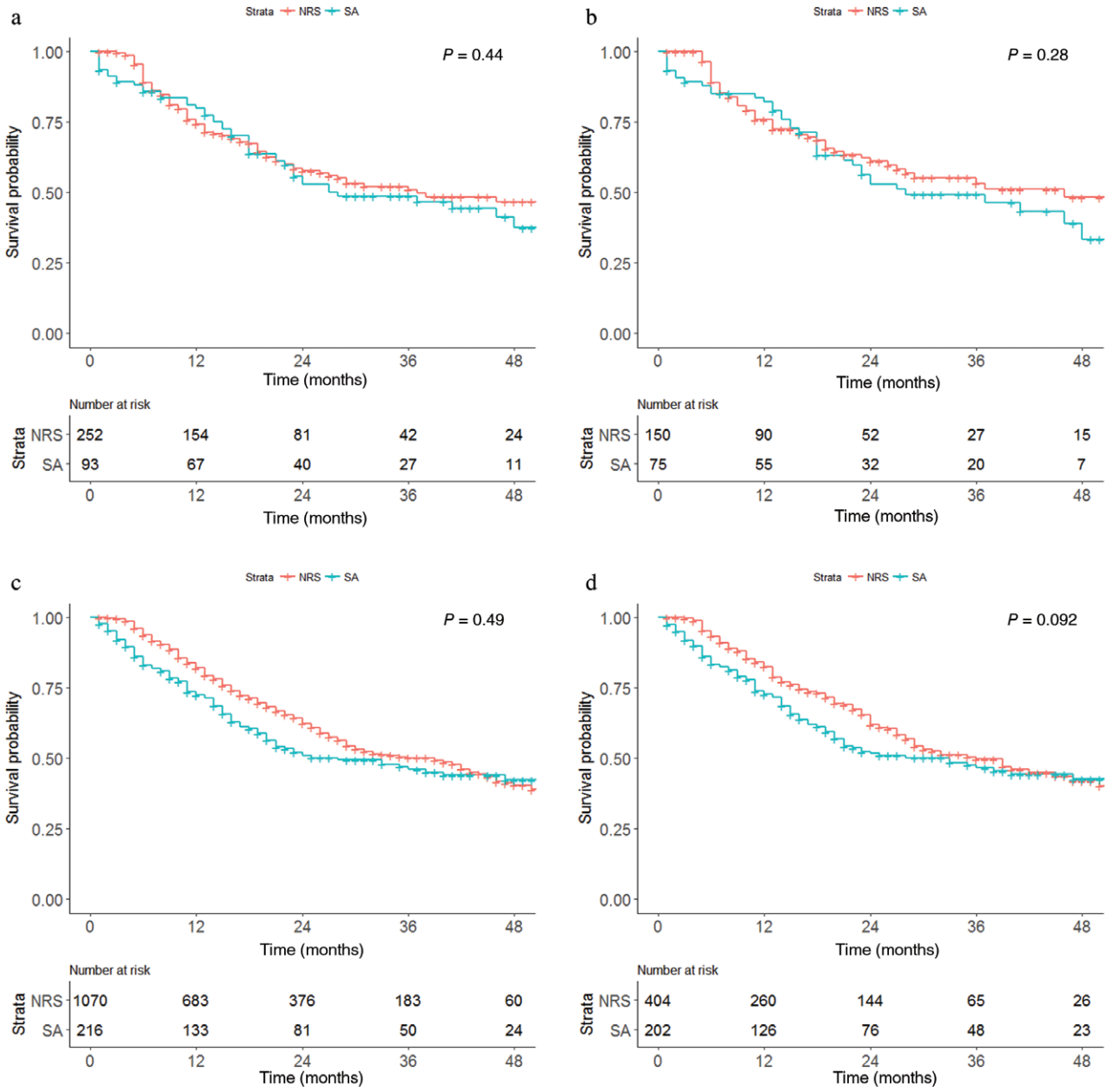

Figure 3 Overall Kaplan-Meier survival curve according to (**a**) ESCC without PSM, (**b**) ESCC with PSM, (**c**) EAC without PSM and (**d**) EAC with PSM. NRS, neoadjuvant radiotherapy plus surgery; SA, surgery alone.

To explore the relationship between NRS and stage of esophageal cancer, further survival analysis was carried out based on T_2 and T_3 stages. The Kaplan-Meier curves and log-rank test showed no statistical significance between the prognoses of ESCC patients with T_2 and T_3 stages who underwent NRS or SA (Fig 4a,b). In the EAC group, there was no significant difference in the T_2 stage (Fig 4c); however, the T_3 stage EAC patients would benefit from NRS ($P = 0.011$, Fig 4d).

In consideration of the fact that it is difficult to examine positive lymph nodes without a pathological diagnosis of surgical specimens preoperatively, which leads to N stage confusion; the T stage was the only basis for primary grouping in the current study. It is easy to confirm positive involvement of lymph nodes by preoperative imaging, thus the status of lymph node involvement based on each T stage was divided into two parts (N_0 and N_+). A comparison of survival curves in each subgroup is shown in Fig 5, 6. NRS improves the prognosis of T_3N_+ stage of EAC ($P = 0.0052$. Fig 6d), while NRS showed no significant benefit in overall survival for the other subgroups (Fig 5a–d, 6a–c).

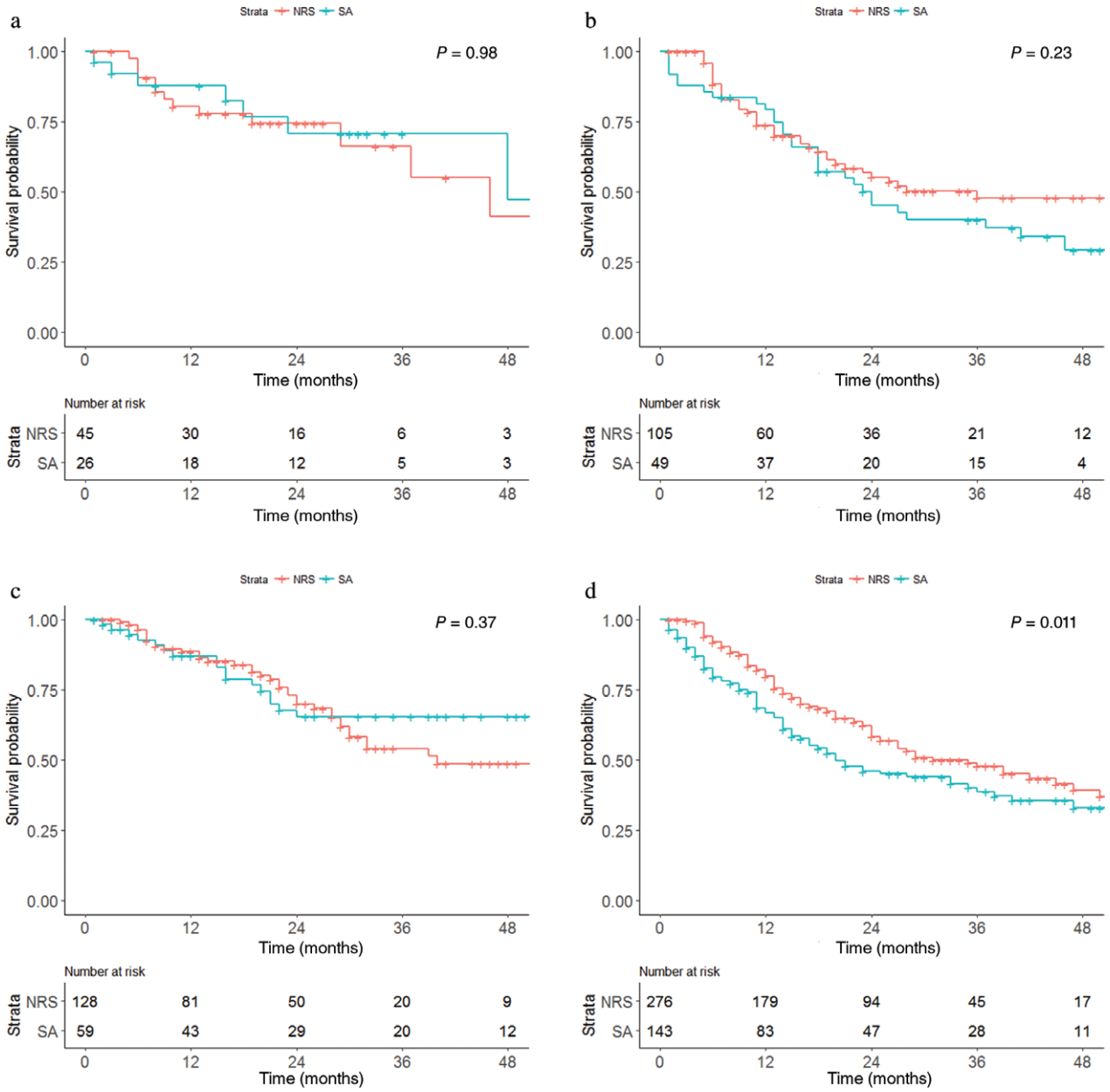

Figure 4 Overall Kaplan-Meier survival curve according to different histological type and stage including (**a**) ESCC T_2, (**b**) ESCC T_3, (**c**) EAC T_2 and (**d**) EAC T_3. NRS, neoadjuvant radiotherapy plus surgery; SA, surgery alone.

Discussion

This study focused on comparing the prognosis of patients who had undergone esophagectomy alone *versus* surgery with NRT in patients with non-cervical ESCC and EAC T_2 and T_3 stages based on a large sample size and the PSM method. Finally, we found that NRT was only associated with a better prognoses in patients with EAC T_3N_+ stage. Compared with surgical resection alone, another analysis showed that the overall survival in ESCC and other stages of EAC did not benefit from NRT.

However, there is several major limitations in this manuscript that should be noted. Since the preoperative chemotherapy details were not recorded in SEER database, some of the patients analyzed in our manuscript might also have received neoadjuvant chemotherapy. NRT strategy was not recommended by North American, Europe, or Japanese guidelines, therefore it is likely that the NRT patients might have some unmeasured confounders, just like comorbidity or body weight loss, which made their treatment physicians chose the non-recommended NRT instead

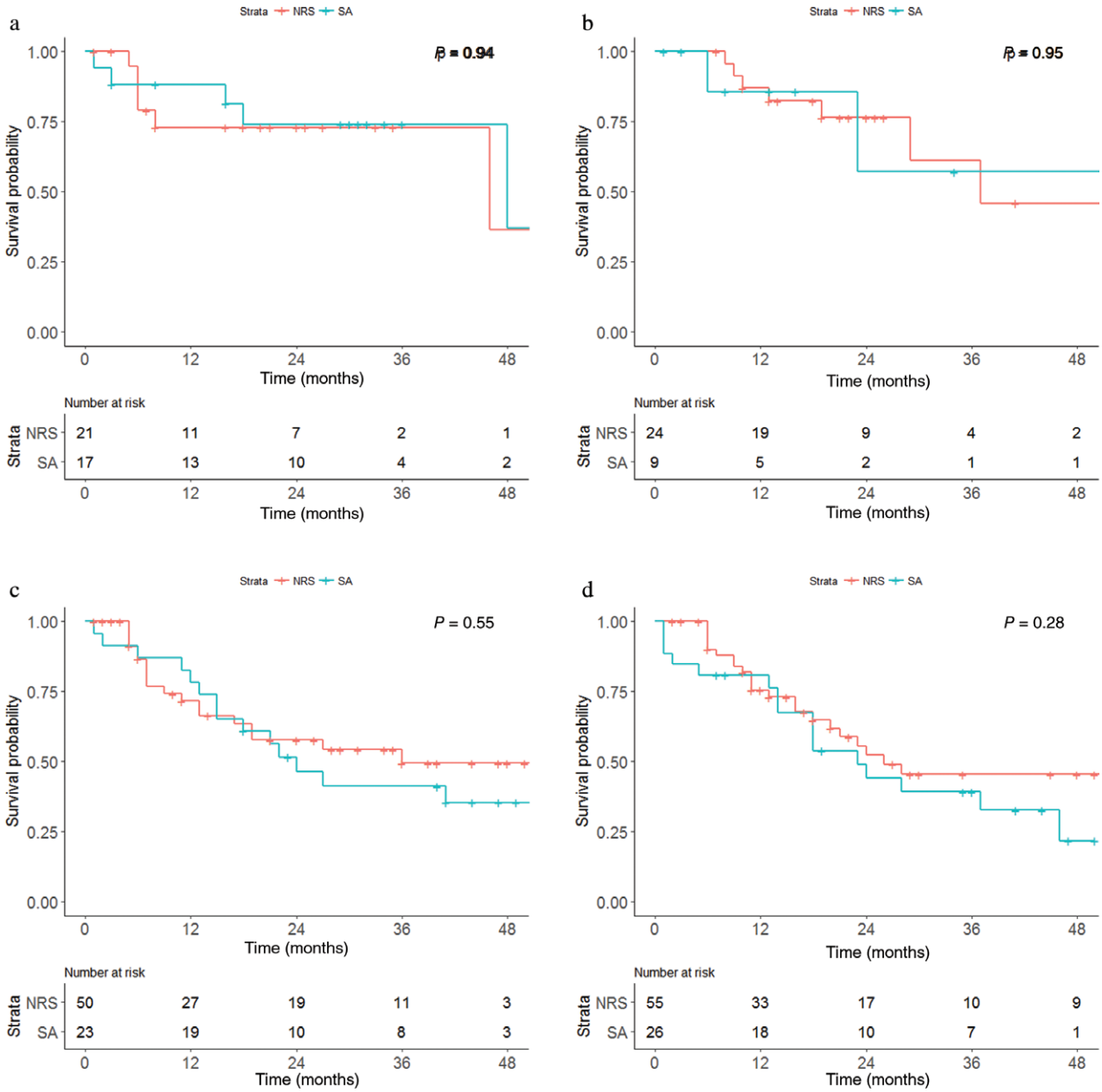

Figure 5 Overall Kaplan-Meier survival curve according to status of lymph node involvement in T_2 and T_3 stage of ESCC including (**a**) T_2N_0, (**b**) T_2N_+, (**c**) T_3N_0 and (**d**) T_3N_+. NRS, neoadjuvant radiotherapy plus surgery; SA, surgery alone.

of recommended NCRT. These unmeasured confounders made the analyses in the current manuscript biased and the results must be further validated.

In recent decades, a small number of studies have focused on the effect of NRT in patients with esophageal cancer. In a randomized clinical trial based on 206 thoracic ESCC patients, there was no advantage in 3 and 5 year survival compared to surgery alone.[9] A clinical trial by Arnott *et al.*,[10] including 56 patients with ESCC and 114 patients with EAC, also reported similar overall survival in patients who received NRT and those managed by SA. The result of two phase III trials also showed that NRT along with surgery had no value in improving resectability and overall survival in patients with esophageal cancer.[11,12] However, few studies have investigated the relationship between stage of esophageal cancer and NRT.

Currently, the majority of studies have compared the prognosis of NCRT with surgical resection *versus* SA. In combination with chemotherapy, NCRT has shown a potential survival benefit in a series of studies, but these

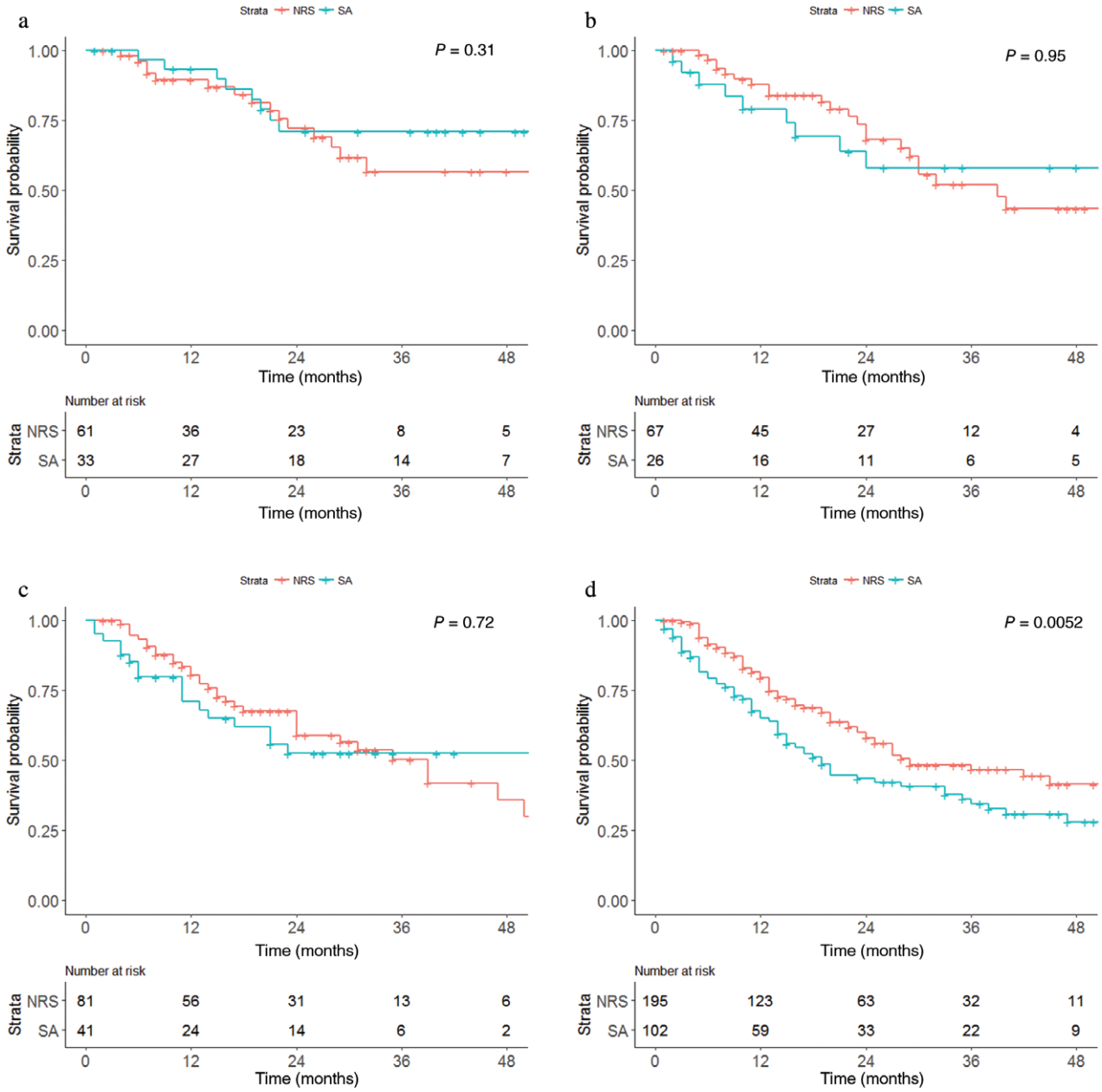

Figure 6 Overall Kaplan-Meier survival curve according to status of lymph node involvement in T_2 and T_3 stage of EAC including (**a**) T_2N_0, (**b**) T_2N_+, (**c**) T_3N_0 and (**d**) T_3N_+.

studies were heterogenous in terms of histological type, tumor stage, and therapeutic regimens. In a phase III trial by Tepper *et al.*,[13] cisplatin and fluorouracil concurrently with radiotherapy before resection reflected survival advantages in both ESCC and EAC patients. Another study by Walsh *et al.*[14] reported that NCRT was superior to resection alone with a similar regimen. A generic regimen of neoadjuvant therapy for both ESCC and EAC was proposed by van Hagen *et al.* that included cisplatin and paclitaxel (six cycles) and concurrent radiotherapy (41.4 Gy) based on a trial with 368 patients.[15] However, there are also several studies or clinical trials that have failed to demonstrate the statistical significance between NCRT and SA.[16–18]

Only a few studies have focused on the correlation between NRT or NCRT and stage of esophageal cancer. For early stage esophageal cancer, a trial by Nygaad *et al.*[19] involving 108 stage T_1 and T_2 ESCC patients did not show overall survival after NRT. A phase III trial based on 195 patients revealed that NCRT did not improve the R0

resection rate or survival, but increased the postoperative mortality in stage I and II esophageal cancer.[20] Different results were obtained following NCRT in patients with advanced esophageal cancer. A study involving 193 patients with ESCC concluded that a pathological complete response to NCRT was critical for improving survival in T3 stage, while another study based on 214 patients with T_3N_1 EAC suggested that NCRT was not a significant determinant of overall survival or disease-free survival.[21,22] Due to a lack of evidence, there was no consensus on which stage of esophageal cancer should be appropriate for neoadjuvant therapy.

Recently, the National Comprehensive Cancer Network (NCCN) guidelines for esophageal and esophagogastric junction cancer suggested that ESCC and EAC patients with T_{1b}-T_{4a}, N_0 to N_+, and M_0 stages receive preoperative chemoradiation, while the European Society for Medical Oncology (ESMO) guidelines showed that ESCC and EAC patients with T_3 to T_4 or N_1 to N_3 with M_0 stages should undergo NCRT.[23,24] In the clinical guidelines edited by the Japan Esophageal Society, NCRT was not recommended as preoperative therapy for any histological type.[25] In the current study, evidence of NRT for specific stages of esophageal cancer was provided. Unlike any guidelines mentioned, the results of this research suggested a limited benefit of NRT in EAC patients with esophageal cancer T3N+ stage, and NRT did not show an advantage in prognosis in any other stages. An accurate assessment for staging should be evaluated before neoadjuvant therapy.

Compared with SA, neoadjuvant therapy may add to the risk of toxicity. The potential complications, which included pneumonia, acute respiratory distress syndrome, anastomotic leakage, and cardiac complications, were mainly caused by radiotherapy.[26] In a study of Bosch *et al.*,[27] a significant increase in cardiopulmonary complications was observed in the neoadjuvant therapy group. Moreover, in a phase III trial, more postoperative deaths were demonstrated in patients treated by chemoradiotherapy preoperatively.[28] Although postoperative radiation-related complications would be reduced with the development of radiotherapy, such as application of stereotactic body radiation, it was also necessary to evaluate the cardiopulmonary function of patients for the design and modification of radiation dosage.[29]

There are several other limitations in this study. Because preoperative radiation dose and postoperative complication data were not available in the SEER database, even though it was a population-based database, we could not explore the relationship between dose and stage and compare the risk of complications in the PRS and SA groups. In addition, the current study was a retrospective study. What's more, we only focused on treatment mortality but not life quality in this analysis as the data of life quality were not provided by SEER.

Conclusions

Compared with SA, NRT followed by resection had a significant survival benefit in non-cervical EAC patients with T_3N_+ stage. For patients with ESCC and other EAC stages, NRT *versus* SA did not demonstrate a statistical significant survival difference.

Acknowledgments

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Disclosure

The authors have no conflicts of interest to declare.

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