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Development and validation of specific Nomograms for individualized Treatment options in Gastrointestinal Cancers

Dissertation

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1.1 Effect of neoadjuvant radiotherapy on survival of non-metastatic pancreatic ductal adenocarcinoma: a SEER database analysis

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Effect of neoadjuvant radiotherapy on survival of non-metastatic pancreatic ductal adenocarcinoma: a SEER database analysis

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Abstract

Background: Neoadjuvant radiotherapy has been shown to improve marginal negative resection and local control of Pancreatic Ductal Adenocarcinoma (PDAC). However, whether it improves overall survival (OS) in patients with non-metastatic PDAC remains controversial. Therefore, the purpose of this study was to analyze the benefits of only surgery, neoadjuvant radiotherapy, adjuvant radiotherapy, and surgery plus chemotherapy for OS in patients with non-metastatic PDAC.

Methods: PDAC diagnosed by surgical histopathology in the Surveillance, Epidemiology, and End Results (SEER) database between 2004 and 2016 was selected. Kaplan-Meier analysis was used to compare the prognosis of patients with different treatments. Cox proportional risk model was used to analyze independent predictors of OS. Propensity score matching (PSM) was used to analyze the tumor prognosis of different treatment methods.

Results: Before PSM analysis, the OS of surgery plus chemotherapy (HRs = 0.896, 95%CIs, 0.827–0.970; $P = 0.007$) were significantly better than the other three treatments for stage T1-3N0M0 PDAC patients. For stage T1-3N + M0 patients, adjuvant radiotherapy (HRs = 0.613, 95% CIs, 0.579–0.649; $P < 0.001$) had significantly better OS than surgery plus chemotherapy and neoadjuvant radiotherapy. For stage T4N0M0 patients, neoadjuvant radiotherapy (HRs = 0.482, 95% CIs, 0.347–0.670; $P < 0.001$) had significantly better OS than surgery plus chemotherapy and adjuvant radiotherapy. For stage T4N + M0 patients, neoadjuvant radiotherapy (HRs = 0.338, 95% CIs, 0.215–0.532; $P < 0.001$) had significantly longer OS than adjuvant radiotherapy and surgery plus chemotherapy. Even after PSM, Chemotherapy plus surgery was still the best treatment for T1-3N0M0 patients. Postoperative adjuvant radiotherapy had the best prognosis among T1-3N + M0 patients, and neoadjuvant radiotherapy was the best treatment for T4 patients.

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Conclusions: For patients with non-metastatic PDAC, neoadjuvant radiotherapy, adjuvant radiotherapy and surgery plus chemotherapy were superior to only surgery in OS. For patients with stage T4 non-metastatic PDAC, neoadjuvant radiotherapy had the potential to be strongly recommended over adjuvant radiotherapy and surgery plus chemotherapy. However, neoadjuvant radiotherapy failed to benefit the survival of T1-3N0M0 stage patients, and surgery plus chemotherapy was preferred. For T1-3N + M0, neoadjuvant radiotherapy had no obvious advantage over adjuvant radiotherapy or surgery plus chemotherapy in OS, and adjuvant radiotherapy was more recommended.

Keywords: Neoadjuvant radiotherapy, Pancreatic ductal adenocarcinoma, Overall survival, SEER, Propensity score matching

Background

Pancreatic Ductal Adenocarcinoma (PDAC) is a highly malignant tumor with a 5-year survival of about 7% and is on pace to become the second leading cause of cancer-related death in the United States by 2030 [1, 2].The main reasons for this frustrating survival are the lack of specific diagnostic methods in early PDAC, the high aggressiveness of the tumor, and the early metastasis [3, 4]. More than 80% of PDAC patients already have locally advanced unresectable or metastatic disease at the time of diagnosis [5]. Moreover, only about 20% of PDAC patients who underwent surgical resection achieve long-term remission, which may be related to the high rate of recurrence after surgery [6].

Neoadjuvant therapy is gaining more and more attention from physicians and scholars due to the dismal survival. Based on a retrospective analysis of significant adjuvant chemotherapy studies in the 1970s, Frei firstly proposed the concept of neoadjuvant therapy (chemotherapy before surgery), which extended disease-free survival in 1982 [7]. Then, the further study of neoadjuvant therapy included preoperative radiotherapy and chemoradiotherapy. In 1990, the term of neoadjuvant therapy was first used in PDAC. Fox Chase cancer center reported that neoadjuvant chemotherapy and radiotherapy improved the resectability of locally advanced PDAC [8]. Moreover, the treatment model for PDAC was changed from “surgical-first” to “multi-disciplinary team” (MDT) with advances in medical technology and treatment concepts in the past decades [9]. It is widely recognized regarding the application of neoadjuvant chemotherapy for patients with PDAC today [10, 11]. However, the role of neoadjuvant radiotherapy in PDAC is still under debate due to the lack of relatively reliable data. Currently, neoadjuvant radiotherapy is mainly used for borderline resectable PDAC and locally advanced PDAC since which may improve the marginal negative resection rate and local control rate [12, 13]. However, it is unclear whether neoadjuvant radiotherapy improves survival of patients with PDAC. In addition, it is still highly controversial and requires further discussion about whether patients with initially resectable PDAC can get benefit from neoadjuvant radiotherapy.

The Surveillance, Epidemiology, and End Results (SEER) Program collects data on cancer diagnosis, treatment, and survival for approximately 30% of the U.S. population. We attempted to use the SEER database to analyze the effects of different treatment methods including surgery-limited, neoadjuvant radiotherapy, adjuvant radiotherapy and surgery plus chemotherapy on overall survival (OS) in patients with non-metastatic PDAC.

Materials and methods

Data source

The cohort used in this study was created from custom data (additional treatment fields) from SEER 18 Registries, and a report was submitted in November 2018 (varied from 1973 to 2016). PDAC diagnosed by surgical histopathology between 2004 and 2016 was selected. In addition, we included basic patient information, detailed clinical staging data, as well as follow-up information, tumor size, and treatment options. Combined with tumor size, T and N staging were recorded on the basis of the 8th edition of TNM staging system. The study was limited to patients with non-metastatic PDAC (any T with any N and M0). After excluding patients who had not undergone surgery and classifying radiotherapy as “no radiation”, “radiation after surgery”, “radiation prior to surgery” and “no/unknown”, 21,030 patients were contained in the study (Fig. 1). The patients were divided into the following four groups according to the treatment methods: 1. Only surgery group (No radiation or chemotherapy); 2. Surgery + chemotherapy group (without radiation); 3. Neoadjuvant radiotherapy group (Neoadjuvant radiotherapy + surgery with or without chemotherapy); 4. Adjuvant radiotherapy group (surgery + adjuvant radiotherapy with or without chemotherapy). The International Study Group on Pancreatic Surgery (ISGPS) consensus recommended that the number of lymph nodes examined should be at least > 15.

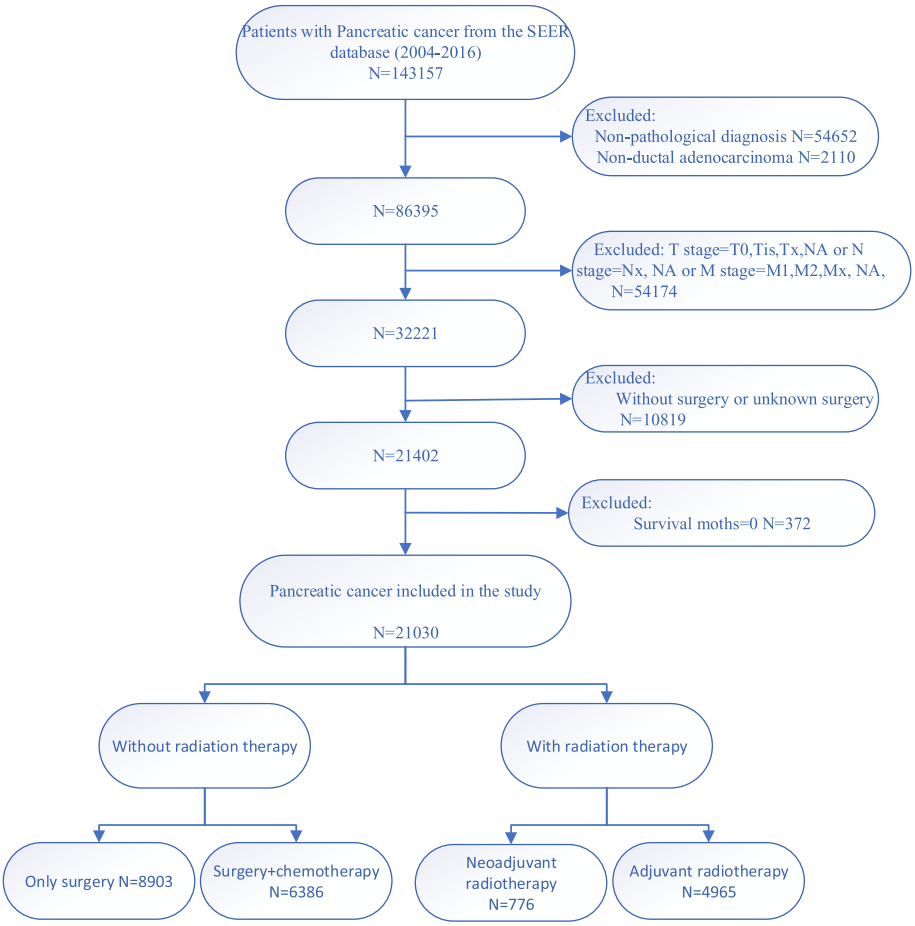


Fig. 1 Procedures for inclusion and exclusion of PDAC patients

Therefore, the number of regional nodes examined was divided into three groups: < 15, ≥15 and unknown.

Statistical analyses

Chi-square test was utilized to compare the classification data. Kaplan-Meier method was used to estimate the survival probability and log-rank test was applied to evaluate the significance difference of OS. Only variables significantly associated with survival in univariate Cox analysis were contained in multivariate Cox analysis. Cox proportional risk model was used to analyze the relationship between patients' clinical characteristics and treatment methods and their survival. Univariate and multivariate models were used to assess the Hazard ratios (HRs) and 95% confidence interval (CIs). The oncological outcomes of different treatments were analyzed by propensity score matching (PSM) analysis. SPSS 25.0 (IBM, Armonk, NY, USA) was used for statistical analysis in this study, and all p values less than 0.05 were statistically significant.

Results

Basic characteristics of the patients

The basic demographic characteristics of all the patients in this study were shown in Table 1. The majority of the patients were married and Caucasians. 55.17% of the target population were over 65 years old and about 50.68% were males. Most of the patients (64.56%) had tumor lesions in the head of the pancreas. Moderately differentiated tumors (41.26%) constituted the majority of the population. Among the 21,030 patients, most of them were stage T2, accounting for 50.87% (10,699 patients), and about 4.60% (968 patients) were stage T4. In terms of the treatment regimen, about 42.33% of patients only were managed with surgical treatment, about 30.37% received surgery plus chemotherapy, about 23.61% received postoperative adjuvant radiotherapy, and only about 3.69% underwent neoadjuvant radiotherapy.

Survival analysis before propensity score matching

Using univariate and multivariate Cox proportional risk analysis for the total population (Table 2), uninsured

Table 1 The basic and clinical features of non-metastatic PDAC

Characteristics	Level	Number (%)
Insurance Recode	Insured	17,218(81.87%)
	No/unknown	3812(18.13%)
Marital status	Married	13,291(63.20%)
	Single	6984(33.21%)
	Unknown	755(3.59%)
Age, years	< 65	9427(44.83%)
	≥65	11,603(55.17%)
Race recode	White	17,170(81.65%)
	Other	3860(18.35%)
Sex	Male	10,657(50.68%)
	Female	10,373(49.32%)
Tumor site	Pancreas Head	13,576(64.56%)
	Pancreas Body Tail	5175(24.61%)
	Pancreas Other	2279(10.83%)
Grade	I	4147(19.72%)
	II	8677(41.26%)
	III/IV	6075(28.89%)
	Unknown	2131(10.13%)
T stage	T1	4242(20.17%)
	T2	10,699(50.87%)
	T3	5121(24.36%)
	T4	968(4.60%)
N stage	N0	9467(45.02%)
	N1	7400(35.19%)
	N2	4163(19.79%)
Treatment methods	Only surgery	8903(42.33%)
	Surgery + chemotherapy	6386(30.37%)
	Neoadjuvant radiotherapy	776(3.69%)
	Adjuvant radiotherapy	4965(23.61%)
Regional nodes examined	< 15	11,410(54.26%)
	≥15	9437(44.87%)
	Unknown	183(0.87%)

PDAC Pancreatic Ductal Adenocarcinoma

status, single status, advanced age (≥65 years old), pancreatic head tumor, high tumor grade, tumor T, N stage, therapy methods and regional nodes examined < 15 were all relevant to poor prognosis (all $P < 0.001$). The Kaplan Meier curve of overall survival in PDAC patients were shown in Fig. 2. For patients with non-metastatic PDAC, neoadjuvant radiotherapy, adjuvant radiotherapy and surgery plus chemotherapy had significantly better OS than surgery alone ($P < 0.001$). After adjusting for insurance status, marital status, age, race, gender, tumor site, tumor grade, T stage, N stage and regional nodes examined, multivariate Cox analysis of different treatment methods was performed, and the influence of each group on OS was shown in Table 3. The mean 1-, 3-year survival rates for PDAC patients were shown in Table 4.

The OS of surgery plus chemotherapy (HRs =0.896, 95%CIs, 0.827–0.970; $P = 0.007$) were significantly better than the other three treatments in stage T1-3N0M0 PDAC patients. Adjuvant radiotherapy (HRs = 0.950; 95% CIs, 0.874–1.032; $P = 0.223$), and only surgery had similar OS results. However, neoadjuvant radiotherapy (HRs = 1.171;95% CIs, 1.019–1.347; $P = 0.027$) seems to be a risk factor for OS. The median survival for only surgery, surgery plus chemotherapy, neoadjuvant radiotherapy and adjuvant radiotherapy was 21months, 25months, 19months, 24months, respectively. Adjuvant radiotherapy (HRs = 0.613, 95% CIs, 0.579–0.649; $P < 0.001$) had significantly better OS results than surgery plus chemotherapy (HRs = 0.686; 95% CIs, 0.649–0.726; $P < 0.001$) and neoadjuvant radiotherapy (HRs = 0.751; 95% CIs, 0.635–0.887; $P = 0.001$) in stage T1-3N + M0 patients, with median survival of 19 months, 15 months, and 16 months, respectively. Specially, for stage T4N0M0 patients, neoadjuvant radiotherapy (HRs = 0.482, 95% CIs, 0.347–0.670; $P < 0.001$) had significantly better OS outcomes than surgery plus chemotherapy (HRs = 0.588; 95% CIs, 0.424–0.814; P = 0.001) and adjuvant radiotherapy (HRs = 0.858; 95% CIs, 0.621–1.185; $P = 0.353$), with median survival of 20 months, 17 months, and 14 months, respectively. Similarly, for stage T4N + M0 patients, neoadjuvant radiotherapy (HRs = 0.338, 95% CIs, 0.215–0.532; $P < 0.001$) had significantly longer OS outcomes than adjuvant radiotherapy (HRs = 0.430; 95% CIs, 0.334–0.554; $P < 0.001$) and surgery plus chemotherapy (HRs = 0.530; 95% CIs, 0.411–0.683; $P < 0.001$), with median survival of 17 months, 16 months, and 10 months, respectively.

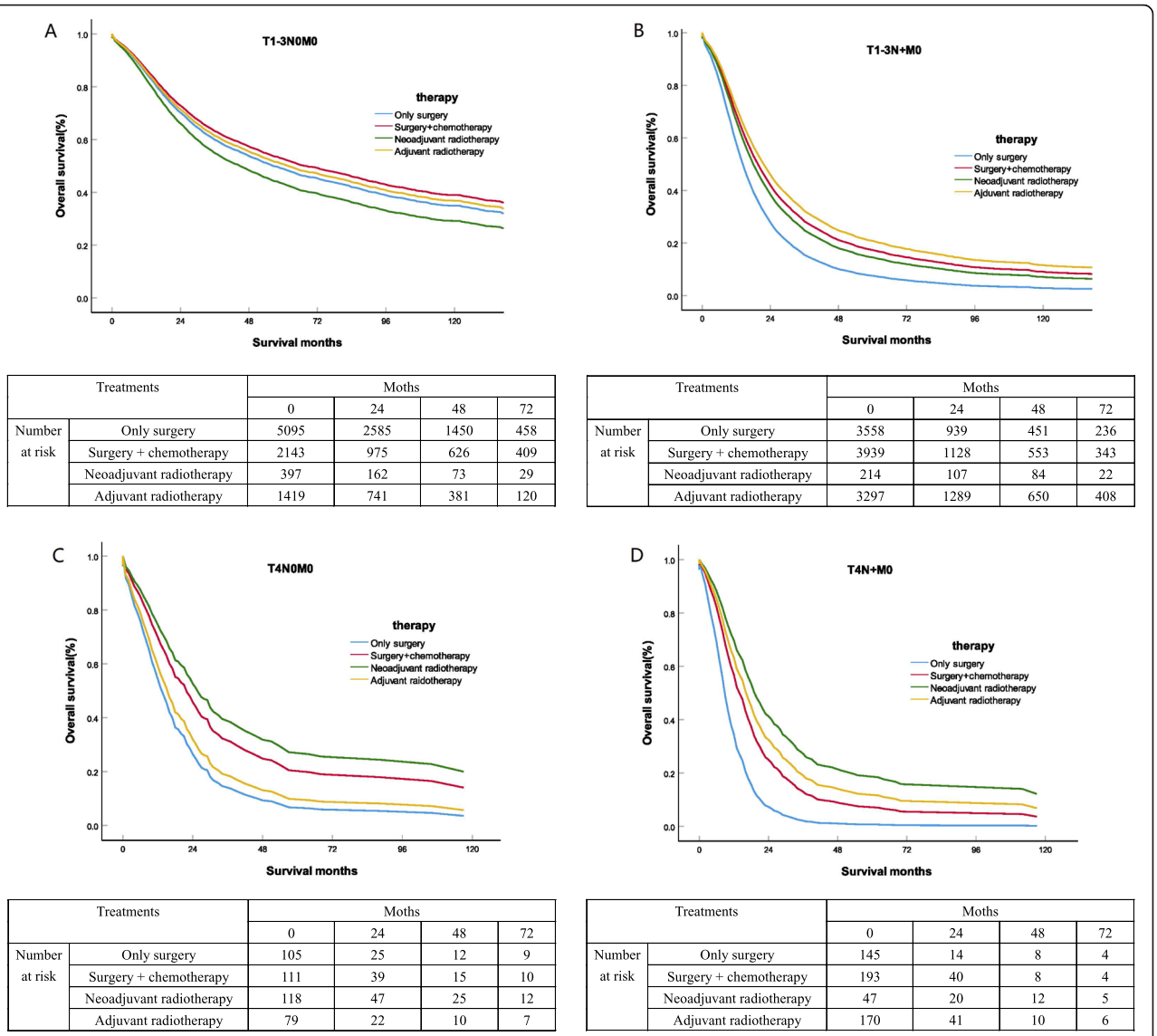
Survival analysis after propensity score matching

The balanced population of the neoadjuvant radiotherapy group and the only surgery group($n = 296$), the neoadjuvant radiotherapy group and the adjuvant radiotherapy group($n = 208$), the neoadjuvant radiotherapy group and the surgery plus chemotherapy group ($n = 288$) were obtained by multiple 1:1 propensity score matching for stage T1-3N0M0 PDAC patients. Before and after the PSM, the results of univariate and multivariate analyses of OS in different groups were shown in Table 5. The OS of the neoadjuvant radiotherapy group was no better than that of the adjuvant radiotherapy group (HRs = 0.807; 95% CIs, 0.649–1.035; $P = 0.125$) and the only surgery group (HRs = 1.164; 95% CIs, 0.934–1.449; $P = 0.176$), while the OS of the surgery plus chemotherapy group was better than that of the neoadjuvant radiotherapy group (HRs = 1.280; 95% CIs, 1.045–1.574; $P = 0.025$) in stage T1-3N0M0 PDAC patients.

Table 2 Univariate and multivariate analysis for OS of all patients($n = 21,030$)

Characteristics	Level	Univariate analysis	Multivariate analysis		
		P	HR	95%CI	*P*
Insurance Recode		< 0.001			< 0.001
	Insured		Reference	Reference	Reference
	No/unknown		1.201	1.152–1.253	< 0.001
Marital status		< 0.001			< 0.001
	Married		Reference	Reference	Reference
	Single		1.140	1.098–1.184	< 0.001
	Unknown		0.985	0.891–1.088	0.760
Age, years		< 0.001			< 0.001
	< 65		Reference	Reference	Reference
	≥65		1.436	1.384–1.489	< 0.001
Race recode		< 0.001			0.508
	White		Reference	Reference	Reference
	Other		1.016	0.970–1.065	0.508
Sex		< 0.001			< 0.001
	Female		Reference	Reference	Reference
	Male		1.106	1.068–1.147	< 0.001
Tumor site		< 0.001			< 0.001
	Pancreas Head		Reference	Reference	Reference
	Pancreas Body Tail		0.704	0.670–0.739	< 0.001
	Pancreas Other		0.844	0.795–0.897	< 0.001
Grade		< 0.001			< 0.001
	I		Reference	Reference	Reference
	II		2.409	2.260–2.567	< 0.001
	III/IV		3.274	3.064–3.498	< 0.001
	Unknown		1.578	1.449–1.719	< 0.001
T stage		< 0.001			< 0.001
	T1		Reference	Reference	Reference
	T2		1.407	1.335–1.483	< 0.001
	T3		1.595	1.503–1.692	< 0.001
	T4		2.396	2.192–2.620	< 0.001
N stage		< 0.001			< 0.001
	N0		Reference	Reference	Reference
	N1		1.617	1.550–1.688	< 0.001
	N2		2.078	1.975–2.186	< 0.001
Treatment methods		< 0.001			< 0.001
	Only surgery		Reference	Reference	Reference
	Surgery + chemotherapy		0.773	0.739–0.809	< 0.001
	Neoadjuvant radiotherapy		0.855	0.776–0.943	0.002
	Adjuvant radiotherapy		0.719	0.686–0.752	< 0.001
Regional nodes examined		< 0.001			< 0.001
	< 15		Reference	Reference	Reference
	≥15		0.828	0.797–0.859	< 0.001
	Unknown		1.133	0.954–1.346	0.156

OS Overall Survival, *CI* Confidence intervals, *HR* Hazard ratios



Treatments		Moths			
		0	24	48	72
Number at risk	Only surgery	5095	2585	1450	458
	Surgery + chemotherapy	2143	975	626	409
	Neoadjuvant radiotherapy	397	162	73	29
	Adjuvant radiotherapy	1419	741	381	120

Treatments		Moths			
		0	24	48	72
Number at risk	Only surgery	3558	939	451	236
	Surgery + chemotherapy	3939	1128	553	343
	Neoadjuvant radiotherapy	214	107	84	22
	Adjuvant radiotherapy	3297	1289	650	408

Treatments		Moths			
		0	24	48	72
Number at risk	Only surgery	105	25	12	9
	Surgery + chemotherapy	111	39	15	10
	Neoadjuvant radiotherapy	118	47	25	12
	Adjuvant radiotherapy	79	22	10	7

Treatments		Moths			
		0	24	48	72
Number at risk	Only surgery	145	14	8	4
	Surgery + chemotherapy	193	40	8	4
	Neoadjuvant radiotherapy	47	20	12	5
	Adjuvant radiotherapy	170	41	10	6

Fig. 2 OS estimated with the Kaplan-Meier method for non- metastatic PDAC. A.OS estimated with the Kaplan-Meier method for PDAC patients with T1-3N0M0 stage receiving different treatment methods (surgery alone versus (vs.) adjuvant radiotherapy: $p = 0.223$; surgery alone vs. neoadjuvant radiotherapy: $p = 0.027$; surgery alone vs. surgery plus chemotherapy: $p = 0.007$;adjuvant radiotherapy vs. surgery plus chemotherapy: $p = 0.023$). B. OS estimated with the Kaplan-Meier method for PDAC patients with T1-3N + M0 stage receiving different treatment methods (surgery alone versus (vs.) adjuvant radiotherapy: $p < 0.001$; surgery alone vs. neoadjuvant radiotherapy: $p = 0.001$; surgery alone vs. surgery plus chemotherapy: $p < 0.001$;adjuvant radiotherapy vs. neoadjuvant radiotherapy: $p = 0.017$;adjuvant radiotherapy vs. surgery plus chemotherapy: $p < 0.001$). C. OS estimated with the Kaplan-Meier method for PDAC patients with T4N0M0 stage receiving different treatment methods (surgery alone versus (vs.) adjuvant radiotherapy: $p = 0.353$; surgery alone vs. neoadjuvant radiotherapy: $p < 0.001$; surgery alone vs. surgery plus chemotherapy: $p = 0.001$;adjuvant radiotherapy vs. neoadjuvant radiotherapy: $p < 0.001$;adjuvant radiotherapy vs. surgery plus chemotherapy: $p < 0.001$;neoadjuvant radiotherapy vs. surgery plus chemotherapy: $p < 0.001$). D. OS estimated with the Kaplan-Meier method for PDAC patients with T4N + M0 stage receiving different treatment methods (surgery alone versus (vs.) adjuvant radiotherapy: $p = 0.353$; surgery alone vs. neoadjuvant radiotherapy: $p < 0.001$; surgery alone vs. surgery plus chemotherapy: $p < 0.001$;adjuvant radiotherapy vs. neoadjuvant radiotherapy: $p < 0.001$;adjuvant radiotherapy vs. surgery plus chemotherapy: $p < 0.001$;neoadjuvant radiotherapy vs. surgery plus chemotherapy: $p < 0.001$)

Similarly, the 1:1 propensity score matching was used to obtain the balanced population of the neoadjuvant radiotherapy group and the only surgery group($n = 155$), neoadjuvant radiotherapy group and the adjuvant radiotherapy group ($n = 153$), neoadjuvant radiotherapy group and the surgery plus chemotherapy group ($n = 166$) in stage T1-3N + M0 PDAC patients. The OS of the neoadjuvant radiotherapy group was better than that of the only surgery group (HRs = 0.618; 95% CIs, 0.429–0.863; $P = 0.036$), but there was no difference with that of the operation plus chemotherapy group (HRs = 1.083; 95% CIs, 0.838–1.400; $P = 0.541$). The adjuvant radiotherapy

Table 3 Multivariate Cox analyses of treatment methods for OS ($n = 21,030$)

TNM Stage	Treatments	Multivariate HR (95% CI)	*P* value
T1-3N0M0			0.001
	Only surgery	Reference	
	Surgery + chemotherapy	0.896(0.827–0.970)	0.007
	Neoadjuvant radiotherapy	1.171(1.019–1.347)	0.027
	Adjuvant radiotherapy	0.950(0.874–1.032)	0.223
T1-3N + M0			< 0.001
	Only surgery	Reference	
	Surgery + chemotherapy	0.686(0.649–0.726)	< 0.001
	Neoadjuvant radiotherapy	0.751(0.635–0.887)	0.001
	Adjuvant radiotherapy	0.613(0.579–0.649)	< 0.001
T4N0M0			< 0.001
	Only surgery	Reference	
	Surgery + chemotherapy	0.588(0.424–0.814)	0.001
	Neoadjuvant radiotherapy	0.482(0.347–0.670)	< 0.001
	Adjuvant radiotherapy	0.858(0.621–1.185)	0.353
T4N + M0			< 0.001
	Only surgery	Reference	
	Surgery + chemotherapy	0.530(0.411–0.683)	< 0.001
	Neoadjuvant radiotherapy	0.338(0.215–0.532)	< 0.001
	Adjuvant radiotherapy	0.430(0.334–0.554)	< 0.001

OS Overall Survival, *CI* Confidence intervals, *HR* Hazard ratios

Table 4 Median survival and, 1-, 3-year OS of PDAC patients ($n = 21,030$)

TNM Stage	Treatments	Median survival	1-year OS	3-year OS
T1-3N0M0	Only surgery	21	70.14%	46.52%
	Surgery + chemotherapy	25	73.27%	49.36%
	Neoadjuvant radiotherapy	19	67.65%	39.87%
	Adjuvant radiotherapy	24	72.09%	48.16%
T1-3N + M0	Only surgery	10	38.65%	6.88%
	Surgery + chemotherapy	15	42.27%	14.85%
	Neoadjuvant radiotherapy	16	39.26%	12.34%
	Adjuvant radiotherapy	19	47.64%	18.63%
T4N0M0	Only surgery	7	27.14%	6.72%
	Surgery + chemotherapy	17	47.67%	19.36%
	Neoadjuvant radiotherapy	20	52.75%	26.47%
	Adjuvant radiotherapy	14	31.82%	8.73%
T4N + M0	Only surgery	6	7.28%	0.05%
	Surgery + chemotherapy	10	26.18%	6.54%
	Neoadjuvant radiotherapy	17	42.34%	16.56%
	Adjuvant radiotherapy	16	33.29%	9.86%

PDAC Pancreatic Ductal Adenocarcinoma, *OS* Overall Survival

Table 5 Univariate and Multivariate Cox analyses of treatment methods for OS after PSM

	Before PSM				After PSM			
	Univariate analysis	Multivariate analysis			Univariate analysis	Multivariate analysis		
TNM stage Treatment	*P*	HR	95%CI	P	P	HR	95%CI	P
T1-3N0M0	< 0.001			0.038	0.048			0.176
Only surgery		Reference	Reference	Reference		Reference	Reference	Reference
Neoadjuvant radiotherapy		1.486	1.315–1.679	0.038		1.164	0.934–1.449	0.176
T1-3N0M0	0.016			0.006	0.039			0.125
Neoadjuvant radiotherapy		Reference	Reference	Reference		Reference	Reference	Reference
Adjuvant radiotherapy		0.809	0.695–0.941	0.006		0.807	0.649–1.035	0.125
T1-3N0M0	0.001			0.001	0.034			0.025
Surgery plus chemotherapy		Reference	Reference	Reference		Reference	Reference	Reference
Neoadjuvant radiotherapy		1.285	1.107–1.491	0.001		1.280	1.045–1.574	0.025
T1-3N + M0	0.002			0.008	0.049			0.036
Only surgery		Reference	Reference	Reference		Reference	Reference	Reference
Neoadjuvant radiotherapy		0.795	0.671–0.942	0.008		0.618	0.429–0.863	0.036
T1-3N + M0	0.019			0.015	0.040			0.022
Adjuvant radiotherapy		Reference	Reference	Reference		Reference	Reference	Reference
Neoadjuvant radiotherapy		1.047	1.013–1.706	0.015		1.364	1.046–1.777	0.022
T1-3N + M0	0.035			0.795	0.021			0.541
Surgery plus chemotherapy		Reference	Reference	Reference		Reference	Reference	Reference
Neoadjuvant radiotherapy		1.023	0.863–1.212	0.795		1.083	0.838–1.400	0.541
T4NxM0	< 0.001			< 0.001	< 0.001			< 0.001
Only surgery		Reference	Reference	Reference		Reference	Reference	Reference
Neoadjuvant radiotherapy		0.459	0.349–0.602	< 0.001		0.466	0.331–0.657	< 0.001
T4NxM0	< 0.001			< 0.001	0.002			0.002
Adjuvant radiotherapy		Reference	Reference	Reference		Reference	Reference	Reference
Neoadjuvant radiotherapy		0.590	0.445–0.781	< 0.001		0.589	0.419–0.830	0.002
T4NxM0	< 0.001			0.040	0.028			0.028
Surgery plus chemotherapy		Reference	Reference	Reference		Reference	Reference	Reference
Neoadjuvant radiotherapy		0.752	0.573–0.987	0.040		0.707	0.519–0.963	0.028

PSM Propensity score matching, *OS* Overall Survival, *CI* Confidence intervals, *HR* Hazard ratios

group had the best prognosis (HRs = 1.364; 95% CIs, 1.046–1.777; $P = 0.022$).

The 1:1 propensity score matching was used to obtain the balanced population of the neoadjuvant radiotherapy group and the only surgery group($n = 104$), neoadjuvant radiotherapy group and the adjuvant radiotherapy group ($n = 102$), neoadjuvant radiotherapy group and the surgery plus chemotherapy group ($n = 138$) in stage T4 PDAC patients. The OS of neoadjuvant radiotherapy group was better than that of only surgery group (HRs = 0.466; 95% CIs, 0.331–0.657; $P < 0.001$), adjuvant radiotherapy group (HRs = 0.589; 95% CIs, 0.419–0.830; $P = 0.002$) and surgery plus chemotherapy group (HRs = 0.707; 95% CIs, 0.519–0.963; $P = 0.028$). The Kaplan-Meier curve of overall survival of PDAC patients after PSM were shown in Fig. 3.

Discussion

The surgical approach for PDAC mainly depends on the anatomical location of the tumor. Although the surgical resection rate and surgical safety of PDAC have been significantly improved, and the incidence of serious complications during perioperative period has been significantly reduced in the past 30 years, the main goal still remains the same: removal of all lesions visible to the naked eye and microscopically within the pancreas and drainage of the lymph nodes, known as marginal negative or R0 resection [14]. However, even after R0 resection, the prognosis of PDAC is not significantly improved, and the treatment of PDAC remains extremely challenging [9]. In this study, patients with non-metastatic PDAC who received surgery alone had the worst prognosis. The

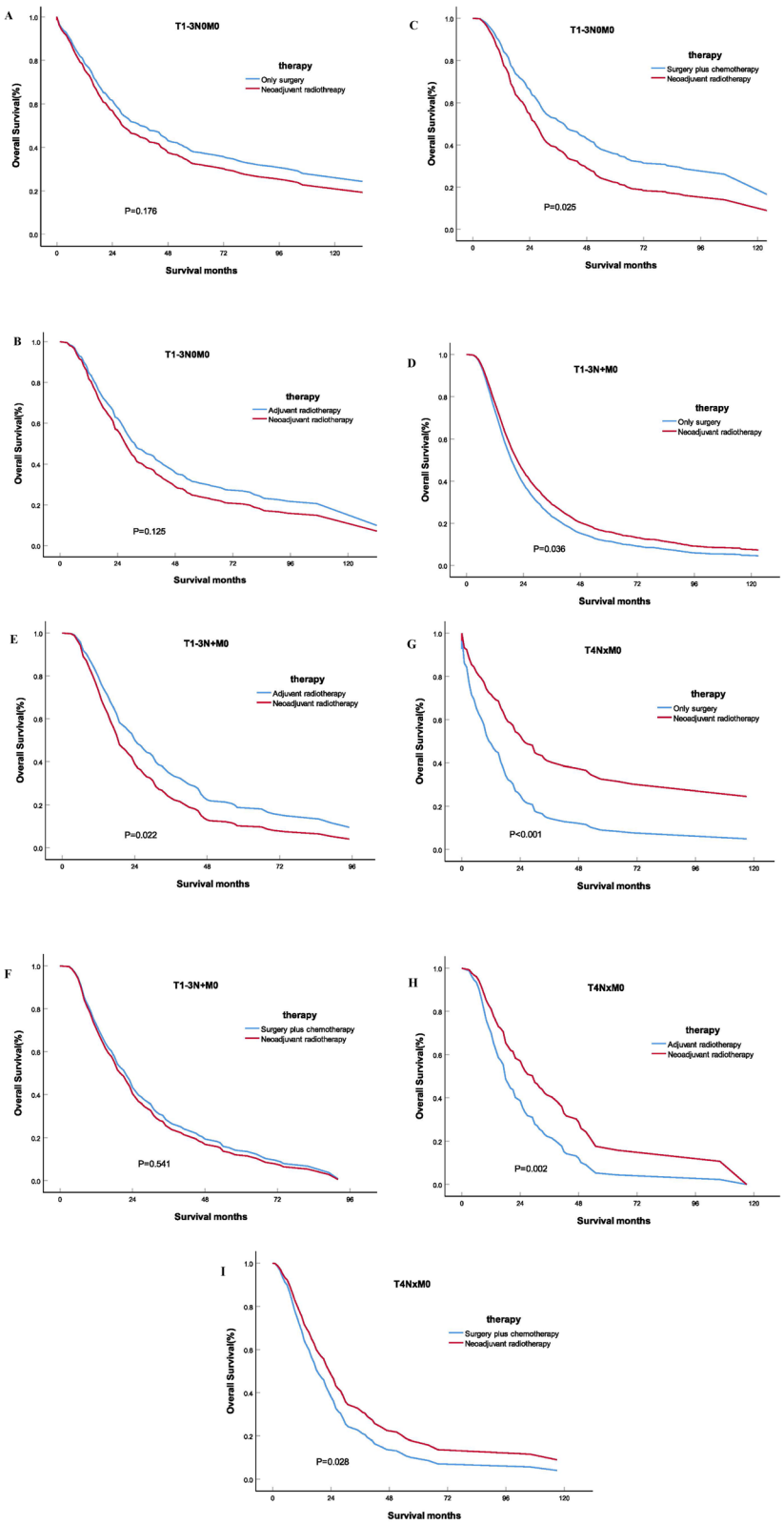


Fig. 3 (See legend on next page.)

(See figure on previous page.)
Fig. 3 The Kaplan-Meier curve of overall survival of PDAC patients after PSM. A.Comparison of OS between the neoadjuvant radiotherapy group and the only surgery group for T1-3N0M0 stage ($P = 0.176$); B. Comparison of OS between the neoadjuvant radiotherapy group and the adjuvant radiotherapy group for T1-3N0M0 stage ($P = 0.125$); C. Comparison of OS between the neoadjuvant radiotherapy group and the surgery plus chemotherapy group for T1-3N0M0 stage ($P = 0.025$); D. Comparison of OS between the neoadjuvant radiotherapy group and the only surgery group for T1-3N + M0 stage ($P = 0.036$); E. Comparison of OS between the neoadjuvant radiotherapy group and the adjuvant radiotherapy group for T1-3N + M0 stage ($P = 0.022$); F. Comparison of OS between the neoadjuvant radiotherapy group and the surgery plus chemotherapy group for T1-3N + M0 stage ($P = 0.541$); G. Comparison of OS between the neoadjuvant radiotherapy group and the only surgery group for T4 stage ($P < 0.001$); H. Comparison of OS between the neoadjuvant radiotherapy group and the adjuvant radiotherapy group for T4 stage ($P = 0.002$); I. Comparison of OS between the neoadjuvant radiotherapy group and the surgery plus chemotherapy group for T4 stage ($P = 0.028$).

main reason for this poor prognosis is local recurrence or distant metastasis of PDAC after surgery, which is a key factor affecting the long-term survival of patients. This showed that only surgical treatment of PDAC is far from enough, and we need to combine systematic adjuvant therapy. Therefore, the application value of neoadjuvant radiotherapy in PDAC has gradually become a hot topic, but there is still a big controversy.

The focus of this study was to determine whether neoadjuvant radiotherapy had a better effect on OS than postoperative radiotherapy, but the existing evidence remains controversial. Currently, it is generally accepted that neoadjuvant radiotherapy is superior to adjuvant radiotherapy mainly related to tumor response and preservation of normal tissues, including the following points [1]. The goal of neoadjuvant radiotherapy is to reduce the stage of the tumor and, in combination with R0 resection, increase the chance of survival. With effective treatment, a percentage of potentially unresectable tumors may be reduced in staging in order to be surgically resectable [2]. Neoadjuvant radiotherapy is more effective on well-oxygenated cells that cannot be surgically removed [3]. In approximately 25% of patients, postoperative adjuvant radiotherapy may be affected due to delayed postoperative recovery. However, delayed postoperative recovery does not affect the implementation of neoadjuvant radiotherapy [14, 4]. The use of neoadjuvant radiotherapy may help identify PDAC patients at high risk of early metastasis.

Therefore, neoadjuvant radiotherapy is considered to be applicable to borderline resectable PDAC and locally advanced PDAC. Some studies demonstrated that neoadjuvant radiotherapy can improve the R0 resection rate and the prognosis of patients with borderline resectable PDAC. After neoadjuvant radiotherapy, the median rate of resection and R0 resection of PDAC patients can reach 68 and 89% respectively. For patients who received neoadjuvant therapy and underwent surgical resection, the median OS range was 15.6 to 35 months. Compared with the group without neoadjuvant radiotherapy, the difference in median OS was statistically significant [15, 16]. In this study, patients with non-metastatic PDAC were divided into T1-3N0M0, T1-3N + M0, T4N0M0, T4N + M0 according to TNM stages, and the effects of different treatment regimens including neoadjuvant radiotherapy on the prognosis were analyzed. The results proved that neoadjuvant radiotherapy improves OS for T1-4N + M0/T4N0M0 PDAC patients. Moreover, for T4 patients, the effect of neoadjuvant radiotherapy on OS was significantly better than that of adjuvant radiotherapy and surgery plus chemotherapy. Therefore, the necessity of neoadjuvant radiotherapy should be emphasized in clinical practice for PDAC patients with stage T4.

However, the survival of T1-3N0M0 patients couldn't benefit from neoadjuvant radiotherapy according to the results of this study. Some scholars also questioned the use of neoadjuvant radiotherapy in early PDAC. Patients with resectable PDAC can initially be surgically removed, but neoadjuvant radiotherapy may delay the patient's surgical opportunity, making the lesions that could have been resected with R0 become unresectable or even distant metastases [17]. Especially in the process of neoadjuvant radiotherapy, if the patient has serious complications, such as biliary tract obstruction, this may aggravate the development of the disease, or even make the patient's physical condition worse, not suitable for surgical treatment. Another problem that must be considered is that, unlike surgery, the initiation of neoadjuvant radiotherapy requires definite pathological results. Given the anatomical location and structure of the tumor, biopsy is sometimes difficult to perform and may delay treatment. The specificity of endoscopic ultrasound-guided biopsy is 96%, but the sensitivity is only 85.92% and repeated examinations are required in 11% of cases [18].

A prospective, randomized, controlled phase II trial in Germany comparing neoadjuvant chemoradiotherapy with surgical priority for resectable pancreatic cancer was prematurely discontinued after 73 patients were enrolled. The existing results showed that there was no significant difference in R0 removal rate and median overall survival time between the two groups [19]. A meta-analysis published in 2019 included 11 clinical studies involving 2666 patients from the university of Texas southwestern medical center, Montefiore medical

center, erlangen university hospital, Germany, Tohoku university school of medicine, Japan, and others. The results showed that the R0 resection rate was improved in patients of resectable PDAC treated with neoadjuvant radiotherapy, but the overall survival time of the patients was not significantly increased [20]. Combined with the results of this study, the overall survival of surgery plus chemotherapy is significantly better than neoadjuvant radiotherapy and adjuvant radiotherapy, so it is recommended that patients with T1-3N0M0 should choose surgery plus chemotherapy as the priority.

A consensus has been reached on the mode of systemic therapy for PDAC under MDT [21]. For borderline resectable and locally advanced PDAC, neoadjuvant radiotherapy may transform patients who cannot be R0 resected or even inoperable into R0 resectable patients, thus extending survival time and benefiting the patients. In this study, a combination of neoadjuvant radiotherapy was recommended for patients with stage T4 PDAC. Whether neoadjuvant therapy can benefit patients with early resectable PDAC is still controversial. Our study suggested that T1-3N0M0 stage PDAC patients were preferred to receive surgery plus chemotherapy, while neoadjuvant radiotherapy was not recommended. In addition, T1-3N + M0 stage PDAC patients were preferentially recommended postoperative adjuvant radiotherapy. However, this study is only a retrospective analysis from a large database, and the results need to be further verified by prospective experiments. With the development of large clinical trials, high level of evidence-based medical evidence will continue to be presented, and the understanding of neoadjuvant radiotherapy for PDAC will be deepened, which may lead to a consensus on the existing controversies and treatment options in the future.

Similar to other studies using the SEER database as a data source, our study has limitations and requires careful interpretation of the results. First, while the SEER data included information about surgery, radiation, and chemotherapy, the details of these treatments (such as surgical margins, radiation dose, chemotherapy regiments, and chemotherapy sequence) were not recorded in the database. Second, the SEER database lacks some key clinical information that may be important for prognosis, such as tumor markers (CA19–9), the relationships between tumor and important blood vessels, and so on.

Conclusions

In summary, this retrospective study analyzed SEER database cases from 2004 to 2016 and made the following recommendations: 1. Among patients with non-metastatic PDAC, stage T1-4N + M0/T4N0M0 patients who received neoadjuvant radiotherapy, adjuvant radiotherapy, and surgery plus chemotherapy had longer OS than those who received surgery alone, while stage T1-3N0M0 patients did not benefit from neoadjuvant radiotherapy. 2. For patients with stage T1-3N0M0, surgery plus chemotherapy is clinically recommended as the preferred treatment. 3. For PDAC patients with stage T1-3N + M0, postoperative adjuvant radiotherapy has a better prognosis and adjuvant radiotherapy is preferred. 4. For stage T4 patients, neoadjuvant radiotherapy had significantly longer OS than adjuvant radiotherapy and surgery plus chemotherapy, which may be appropriate for guidelines to adopt a more proactive stance on using of neoadjuvant radiotherapy for stage T4 PDAC patients.

Supplementary information

Supplementary information accompanies this paper at https://doi.org/10.1186/s13014-020-01561-z.

Additional file 1: Table 1. Univariate and multivariate analyses of OS in the neoadjuvant radiotherapy group and the only surgery group for T1-3N0M0 PDAC patients.

Additional file 2: Table 2. Univariate and multivariate analyses of OS in the neoadjuvant radiotherapy group and the adjuvant radiotherapy group for T1-3N0M0 PDAC patients.

Additional file 3: Table 3. Univariate and multivariate analyses of OS in the neoadjuvant radiotherapy group and the surgery plus chemotherapy group for T1-3N0M0 PDAC patients.

Additional file 4: Table 4. Univariate and multivariate analyses of OS in the neoadjuvant radiotherapy group and the only surgery group for T1-3N + M0 PDAC patients.

Additional file 5: Table 5. Univariate and multivariate analyses of OS in the neoadjuvant radiotherapy group and the adjuvant radiotherapy group for T1-3N + M0 PDAC patients.

Additional file 6: Table 6. Univariate and multivariate analyses of OS in the neoadjuvant radiotherapy group and the surgery plus chemotherapy group for T1-3N + M0 PDAC patients.

Additional file 7: Table 7. Univariate and multivariate analyses of OS in the neoadjuvant radiotherapy group and the only surgery group for T4 PDAC patients.

Additional file 8: Table 8. Univariate and multivariate analyses of OS in the neoadjuvant radiotherapy group and the adjuvant radiotherapy group for T4 PDAC patients.

Additional file 9: Table 9. Univariate and multivariate analyses of OS in the neoadjuvant radiotherapy group and the surgery plus chemotherapy group for T4 PDAC patients.

Abbreviations

PDAC: Pancreatic Ductal Adenocarcinoma; OS: Overall Survival; SEER: Surveillance, Epidemiology, and End Results; CIs: Confidence intervals; HRs: Hazard ratios; MDT: Multi-disciplinary team; ISGPS: International Study Group on Pancreatic Surgery; US: United States; PSM: Propensity score matching

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Authors' contributions
Conceptualization: Dan Wang, Yuqiang Li, Cenap Güngör; Data curation: Chongshun Liu, Tingyu Yan, Chenglong Li, Qionghui Yang. Formal analysis: Dan Wang,Yang Xu, Lilan Zhao, Qian Pei, Fengbo Tan. Methodology: Dan Wang, Yuqiang Li, Qian Pei, Fengbo Tan. Writing-original draft: Dan Wang. Writing-review & editing: Yuqiang Li, Yuan Zhou, Cenap Güngör. All the authors read and approved the final manuscript.

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Availability of data and materials
The data from this study is publicly available in the national cancer institute's Surveillance, Epidemiology, and End Results (SEER) database at https://seer.cancer.gov/.

Ethics approval and consent to participate
This study is based on a retrospective analysis of the SEER database. There is no identifiable patient information in the SEER database, and all data is anonymous. Therefore, written informed consent was not required for this study. The survey was conducted in accordance with the ethical standards of the Helsinki Declaration and national and international norms. This study was approved by the institutional review board of our hospital.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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Supplementary table 1. Univariate and multivariate analyses of OS in the neoadjuvant radiotherapy group and the only surgery group for T1-3N0M0 PDAC patients.

		Before PSM				After PSM			
		Univariate	Multivariate analysis			Univariate	Multivariate analysis		
Characteristics	Level	P	HR	95%CI	P	P	HR	95%CI	P
Insurance Recode		<0.001			<0.001	0.004			0.004
	Insured		Reference	Reference	Reference		Reference	Reference	Reference
	No/unknown		1.253	1.135-1.383	<0.001		1.523	1.147-2.023	0.004
Marital status		<0.001			<0.001	0.624			NA
	Married		Reference	Reference	Reference				
	Single		1.248	1.138-1.369	<0.001				
	Unknown		1.017	0.820-1.261	0.880				
Age, years		<0.001			<0.001	<0.001			<0.001
	<65		Reference	Reference	Reference		Reference	Reference	Reference
	≥65		2.246	2.039-2.475	<0.001		1.564	1.256-1.948	<0.001
Race recode		0.004			0.784	0.819			NA
	White		Reference	Reference	Reference				
	Other		1.016	0.908-1.136	0.784				
Sex		0.023			0.001	0.356			NA
	Female		Reference	Reference	Reference				
	Male		1.163	1.065-1.270	0.001				
Tumor site		<0.001			<0.001	0.056			NA
	Pancreas Head		Reference	Reference	Reference				
	Pancreas Body Tail		0.550	0.494-0.611	<0.001				
	Pancreas Other		0.725	0.635-0.828	<0.001				
Grade		<0.001			<0.001	<0.001			0.001
	I		Reference	Reference	Reference		Reference	Reference	Reference
	II		2.950	2.597-3.352	<0.001		1.549	1.002-2.394	0.049
	III/IV		4.886	4.250-5.618	<0.001		1.851	1.168-2.932	0.009
	Unknown		1.654	1.413-1.936	<0.001		1.054	0.672-1.653	0.819
T stage		<0.001			<0.001	0.192			NA
	T1		Reference	Reference	Reference				
	T2		1.654	1.413-1.936	<0.001				
	T3		1.486	1.315-1.679	<0.001				
Treatment methods		<0.001			0.038	0.048			0.176
	Only surgery		Reference	Reference	Reference		Reference	Reference	Reference
	Neoadjuvant radiotherapy		1.486	1.315-1.679	0.038		1.164	0.934-1.449	0.176
Regional nodes examined		<0.001			0.590	0.073			NA
	<15		Reference	Reference	Reference				
	≥15		0.956	0.866-1.055	0.367				
	Unknown		1.074	0.770-1.497	0.674				

Supplementary table 2. Univariate and multivariate analyses of OS in the neoadjuvant radiotherapy group and the adjuvant radiotherapy group for T1-3N0M0 PDAC patients.

		Before PSM				After PSM			
		Univariate	Multivariate analysis			Univariate	Multivariate analysis		
Characteristics	Level	P	HR	95%CI	P	P	HR	95%CI	P
Insurance Recode		0.030			0.031	0.965			NA
	Insured		Reference	Reference	Reference				
	No/unknown		1.153	1.013-1.311	0.031				
Marital status		0.634			NA	0.832			NA
	Married								
	Single								
	Unknown								
Age, years		<0.001			0.001	0.467			NA
	<65		Reference	Reference	Reference				
	≥65		1.219	1.086-1.369	0.001				
Race recode		0.230			NA	0.850			NA
	White								
	Other								
Sex		0.028			0.057	0.687			NA
	Female		Reference	Reference	Reference				
	Male		1.118	0.996-1.254	0.057				
Tumor site		0.363			NA	0.592			NA
	Pancreas Head								
	Pancreas Body Tail								
	Pancreas Other								
Grade		0.003			<0.001	0.042			0.116
	I		Reference	Reference	Reference		Reference	Reference	Reference
	II		1.191	0.976-1.453	0.085		1.074	0.670-1.721	0.768
	III/IV		1.191	0.976-1.453	0.002		1.365	0.831-2.244	0.219
	Unknown		0.946	0.740-1.208	0.654		1.365	0.831-2.244	0.637
T stage		0.008			0.008	0.667			NA
	T1		Reference	Reference	Reference				
	T2		1.165	0.994-1.365	0.059				
	T3		1.331	1.110-1.595	0.002				
Treatment methods		0.016			0.006	0.039			0.125
Neoadjuvant radiotherapy			Reference	Reference	Reference		Reference	Reference	Reference
Adjuvant radiotherapy			0.809	0.695-0.941	0.006		0.807	0.649-1.035	0.125
Regional nodes examined		0.002			0.004	0.919			NA
	<15		Reference	Reference	Reference				
	≥15		0.816	0.718-0.927	0.002				
	Unknown		1.229	0.793-1.904	0.356				

Supplementary table 3. Univariate and multivariate analyses of OS in the neoadjuvant radiotherapy group and the surgery plus chemotherapy group for T1-3N0M0 PDAC patients.

		Before PSM				After PSM			
		Univariate	Multivariate analysis			Univariate	Multivariate analysis		
Characteristics	Level	P	HR	95%CI	P	P	HR	95%CI	P
Insurance Recode		0.001			0.012	0.813			NA
	Insured		Reference	Reference	Reference				
	No/unknown		1.210	1.043-1.404	0.012				
Marital status		0.637			NA	0.817			NA
	Married								
	Single								
	Unknown								
Age, years		<0.001			<0.001	0.001			0.002
	<65		Reference	Reference	Reference		Reference	Reference	Reference
	≥65		1.298	1.160-1.453	<0.001		1.422	1.133-1.785	0.002
Race recode		0.745			NA	0.559			NA
	White								
	Other								
Sex		0.985			NA	0.255			NA
	Female								
	Male								
Tumor site		0.274			NA	0.583			NA
	Pancreas Head								
	Pancreas Body Tail								
	Pancreas Other								
Grade		<0.001			<0.001	0.002			0.003
	I		Reference	Reference	Reference		Reference	Reference	Reference
	II		1.549	1.266-1.896	<0.001		1.451	0.936-2.250	0.096
	III/IV		2.135	1.736-2.627	<0.001		1.451	0.936-2.250	0.005
	Unknown		1.282	1.009-1.630	0.042		1.152	0.734-1.808	0.539
T stage		<0.001			<0.001	0.157			NA
	T1		Reference	Reference	Reference				
	T2		1.282	1.009-1.630	<0.001				
	T3		1.647	1.390-1.952	<0.001				
Treatment methods		0.001			0.001	0.034			0.025
Surgery plus chemotherapy			Reference	Reference	Reference		Reference	Reference	Reference
Neoadjuvant radiotherapy			1.285	1.107-1.491	0.001		1.280	1.045-1.574	0.025
Regional nodes examined		0.007			0.037	0.019			0.043
	<15		Reference	Reference	Reference		Reference	Reference	Reference
	≥15		0.885	0.507-0.991	0.011		0.935	0.722-1.210	0.609
	Unknown		0.866	0.488-1.535	0.621		2.521	1.649-3.070	0.015

Supplementary table 4. Univariate and multivariate analyses of OS in the neoadjuvant radiotherapy group and the only surgery group for T1-3N+M0 PDAC patients.

		Before PSM				After PSM			
		Univariate	Multivariate analysis			Univariate	Multivariate analysis		
Characteristics	Level	P	HR	95%CI	P	P	HR	95%CI	P
Insurance Recode		<0.001			0.004	0.977			NA
	Insured		Reference	Reference	Reference				
	No/unknown		1.140	1.044-1.245	0.004				
Marital status		<0.001			0.016	0.414			NA
	Married		Reference	Reference	Reference				
	Single		1.122	1.038-1.213	0.004				
	Unknown		1.063	0.864-1.309	0.562				
Age, years		<0.001			<0.001	0.001			<0.001
	<65		Reference	Reference	Reference		Reference	Reference	Reference
	≥65		1.504	1.382-1.637	<0.001		1.612	1.235-2.104	<0.001
Race recode		0.100			0.784	0.600			NA
	White		Reference	Reference	Reference				
	Other		1.016	0.908-1.136	0.784				
Sex		0.697			0.001	0.434			NA
	Female		Reference	Reference	Reference				
	Male		1.163	1.065-1.270	0.001				
Tumor site		<0.001			<0.001	0.211			NA
	Pancreas Head		Reference	Reference	Reference				
	Pancreas Body Tail		0.650	0.578-0.730	<0.001				
	Pancreas Other		0.843	0.741-0.958	0.009				
Grade		<0.001			<0.001	<0.001			<0.001
	I		Reference	Reference	Reference		Reference	Reference	Reference
	II		3.138	2.726-3.612	<0.001		2.337	1.335-4.090	0.003
	III/IV		4.180	3.618-4.828	<0.001		3.270	1.846-5.793	<0.001
	Unknown		1.855	1.515-2.271	<0.001		1.573	0.818-3.022	0.174
T stage		<0.001			<0.001	0.199			NA
	T1		Reference	Reference	Reference				
	T2		1.300	1.150-1.470	<0.001				
	T3		1.442	1.260-1.650	<0.001				
N stage		<0.001			<0.001	0.412			NA
	N1		Reference	Reference	Reference				
	N2		1.226	1.132-1.329	<0.001				
Treatment methods		0.002			0.008	0.049			0.036
Only surgery			Reference	Reference	Reference		Reference	Reference	Reference
Neoadjuvant radiotherapy			0.795	0.671-0.942	0.008		0.618	0.429-0.863	0.036
Regional nodes examined		0.915			NA	0.399			NA
	<15								
	≥15								
	Unknown								

Supplementary table 5. Univariate and multivariate analyses of OS in the neoadjuvant radiotherapy group and the adjuvant radiotherapy group for T1-3N+M0 PDAC patients.

		Before PSM				After PSM			
		Univariate	Multivariate analysis			Univariate	Multivariate analysis		
Characteristics	Level	P	HR	95%CI	P	P	HR	95%CI	P
Insurance Recode		0.006			0.009	0.165			NA
	Insured		Reference	Reference	Reference				
	No/unknown		1.125	1.030-1.229	0.009				
Marital status		0.765			NA	0.980			NA
	Married								
	Single								
	Unknown								
Age, years		0.101			NA	0.570			NA
	<65								
	≥65								
Race recode		0.704			NA	0.067			NA
	White								
	Other								
Sex		<0.001			0.001	0.318			NA
	Female		Reference	Reference	Reference				
	Male		1.139	1.054-1.231	0.001				
Tumor site		0.936			NA	0.114			NA
	Pancreas Head								
	Pancreas Body Tail								
	Pancreas Other								
Grade		<0.001			<0.001	0.247			NA
	I		Reference	Reference	Reference				
	II		1.439	1.239-1.670	<0.001				
	III/IV		1.733	1.489-2.018	<0.001				
	Unknown		1.234	0.988-1.540	0.064				
T stage		<0.001			<0.001	0.724			NA
	T1		Reference	Reference	Reference				
	T2		1.321	1.169-1.493	<0.001				
	T3		1.472	1.288-1.682	<0.001				
N stage		<0.001			<0.001	0.004			0.002
	N1		Reference	Reference	Reference		Reference	Reference	Reference
	N2		1.472	1.288-1.682	<0.001		1.709	1.212-2.411	0.002
Treatment methods		0.019			0.015	0.040			0.022
	Adjuvant radiotherapy		Reference	Reference	Reference		Reference	Reference	Reference
	Neoadjuvant radiotherapy		1.047	1.013-1.706	0.015		1.364	1.046-1.777	0.022
Regional nodes examined		<0.001			<0.001	0.340			NA
	<15		Reference	Reference	Reference				
	≥15		0.772	0.712-0.836	<0.001				
	Unknown		0.928	0.586-1.469	0.749				

Supplementary table 6. Univariate and multivariate analyses of OS in the neoadjuvant radiotherapy group and the surgery plus chemotherapy group for T1-3N+M0 PDAC patients.

		Before PSM				After PSM			
		Univariate	Multivariate analysis			Univariate	Multivariate analysis		
Characteristics	Level	P	HR	95%CI	P	P	HR	95%CI	P
Insurance Recode		0.042			0.121	0.260			NA
	Insured		Reference	Reference	Reference				
	No/unknown		1.086	0.978-1.206	0.121				
Marital status		0.680			NA	0.300			NA
	Married								
	Single								
	Unknown								
Age, years		<0.001			<0.001	0.025			0.007
	<65		Reference	Reference	Reference		Reference	Reference	Reference
	≥65		1.168	1.084-1.260	<0.001		1.430	1.102-1.854	0.007
Race recode		0.525			NA	0.595			NA
	White								
	Other								
Sex		0.522			NA	0.940			NA
	Female								
	Male								
Tumor site		0.405			NA	0.930			NA
	Pancreas Head								
	Pancreas Body Tail								
	Pancreas Other								
Grade		<0.001			<0.001	0.011			<0.001
	I		Reference	Reference	Reference		Reference	Reference	Reference
	II		1.279	1.103-1.483	0.001		2.359	1.329-4.185	0.003
	III/IV		1.672	1.441-1.940	<0.001		3.410	1.907-6.100	0.000
	Unknown		1.176	0.959-1.443	0.119		2.506	1.342-4.679	0.004
T stage		<0.001			<0.001	0.656			NA
	T1		Reference	Reference	Reference				
	T2		1.305	1.157-1.471	<0.001				
	T3		1.390	1.218-1.586	<0.001				
N stage		<0.001			<0.001	0.204			NA
	N1		Reference	Reference	Reference				
	N2		1.325	1.225-1.434	<0.001				
Treatment methods		0.035			0.795	0.021			0.541
Surgery plus chemotherapy			Reference	Reference	Reference		Reference	Reference	Reference
Neoadjuvant radiotherapy			1.023	0.863-1.212	0.795		1.083	0.838-1.400	0.541
Regional nodes examined		<0.001			<0.001	0.314			NA
	<15		Reference	Reference	Reference				
	≥15		0.826	0.765-0.892	<0.001				
	Unknown		0.761	0.470-1.233	0.267				

Supplementary table 7. Univariate and multivariate analyses of OS in the neoadjuvant radiotherapy group and the only surgery group for T4 PDAC patients.

		Before PSM				After PSM			
		Univariate	Multivariate analysis			Univariate	Multivariate analysis		
Characteristics	Level	P	HR	95%CI	P	P	HR	95%CI	P
Insurance Recode		0.017			0.275	0.529			NA
	Insured		Reference	Reference	Reference				
	No/unknown		1.161	0.888-1.518	0.275				
Marital status		0.011			0.624	0.149			NA
	Married		Reference	Reference	Reference				
	Single		1.007	0.780-1.302	0.955				
	Unknown		1.294	0.767-2.181	0.334				
Age, years		<0.001			<0.001	0.134			NA
	<65		Reference	Reference	Reference				
	≥65		1.752	1.378-2.228	<0.001				
Race recode		0.999			NA	0.470			NA
	White								
	Other								
Sex		0.629			NA	0.662			NA
	Female								
	Male								
Tumor site		0.723			NA	0.628			NA
	Pancreas Head								
	Pancreas Body Tail								
	Pancreas Other								
Grade		0.709			NA	0.107			NA
	I								
	II								
	III/IV								
	Unknown								NA
N stage		<0.001			0.002	0.121			
	N0		Reference	Reference	Reference				
	N1		1.485	1.146-1.925	0.003				
	N2		1.780	1.219-2.597	0.003				
Treatment methods		<0.001			<0.001	<0.001			<0.001
	Only surgery		Reference	Reference	Reference		Reference	Reference	Reference
	Neoadjuvant radiotherapy		0.459	0.349-0.602	<0.001		0.466	0.331-0.657	<0.001
Regional nodes examined		0.409			NA	0.729			NA
	<15								
	≥15								
	Unknown								

Supplementary table 8. Univariate and multivariate analyses of OS in the neoadjuvant radiotherapy group and the adjuvant radiotherapy group for T4 PDAC patients.

		Before PSM				After PSM			
		Univariate	Multivariate analysis			Univariate	Multivariate analysis		
Characteristics	Level	P	HR	95%CI	P	P	HR	95%CI	P
Insurance Recode		0.001			0.004	0.052			NA
	Insured		Reference	Reference	Reference				
	No/unknown		1.468	1.133-1.902	0.004				
Marital status		0.768			NA	0.731			NA
	Married								
	Single								
	Unknown								
Age, years		0.439			NA	0.866			NA
	<65								
	≥65								
Race recode		0.459			NA	0.728			NA
	White								
	Other								
Sex		0.041			0.042	0.302			NA
	Female		Reference	Reference	Reference				
	Male		1.277	1.009-1.615	0.042				
Tumor site		0.733			NA	0.473			NA
	Pancreas Head								
	Pancreas Body Tail								
	Pancreas Other								
Grade		0.136			NA	0.005			<0.001
	I						Reference	Reference	Reference
	II						1.991	0.709-5.595	0.191
	III/IV						4.269	1.547-11.785	0.005
	Unknown						3.031	1.067-8.612	0.037
N stage		0.013			0.615	0.492			NA
	N0		Reference	Reference	Reference				
	N1		0.936	0.709-1.234	0.637				
	N2		1.104	0.786-1.551	0.568				
Treatment methods		<0.001			<0.001	0.002			0.002
	Adjuvant radiotherapy		Reference	Reference	Reference		Reference	Reference	Reference
	Neoadjuvant radiotherapy		0.590	0.445-0.781	<0.001		0.589	0.419-0.830	0.002
Regional nodes examined		0.085			NA	0.733			NA
	<15								
	≥15								
	Unknown								

Supplementary table 9. Univariate and multivariate analyses of OS in the neoadjuvant radiotherapy group and the surgery plus chemotherapy group for T4 PDAC patients.

		Before PSM				After PSM			
		Univariate	Multivariate analysis			Univariate	Multivariate analysis		
Characteristics	Level	P	HR	95%CI	P	P	HR	95%CI	P
Insurance Recode		0.101			NA	0.532			NA
	Insured								
	No/unknown								
Marital status		0.005			0.080	0.674			NA
	Married		Reference	Reference	Reference				
	Single		1.257	0.971-1.627	0.083				
	Unknown		1.731	0.884-3.392	0.110				
Age, years		0.189			NA	0.818			NA
	<65								
	≥65								
Race recode		0.832			NA	0.717			NA
	White								
	Other								
Sex		0.328			NA	0.216			NA
	Female								
	Male								
Tumor site		0.236			NA	0.996			NA
	Pancreas Head								
	Pancreas Body Tail								
	Pancreas Other								
Grade		0.799			NA	0.677			NA
	I								
	II								
	III/IV								
	Unknown								
N stage		<0.001			<0.001	0.119			NA
	N0		Reference	Reference	Reference				
	N1		1.412	1.076-1.852	0.013				
	N2		2.464	1.736-3.497	<0.001				
Treatment methods		<0.001			0.040	0.028			0.028
Surgery plus chemotherapy			Reference	Reference	Reference		Reference	Reference	Reference
Neoadjuvant radiotherapy			0.752	0.573-0.987	0.040		0.707	0.519-0.963	0.028
Regional nodes examined		<0.025			0.001	0.468			NA
	<15		Reference	Reference	Reference				
	≥15		0.641	0.499-0.822	<0.001				
	Unknown		1.131	0.601-2.130	0.703				

1.2 The Survival Effect of Radiotherapy on Stage IIB/III Pancreatic Cancer Undergone Surgery in Different Age and Tumor Site Groups: A Propensity Scores Matching Analysis Based on SEER Database

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The Survival Effect of Radiotherapy on Stage IIB/III Pancreatic Cancer Undergone Surgery in Different Age and Tumor Site Groups: A Propensity Scores Matching Analysis Based on SEER Database

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Background: It remains controversial whether radiotherapy (RT) improves survival in patients with stage IIB/III PDAC. A growing number of studies have found that patients' age at diagnosis and tumor site not only affect prognosis, but also may lead to different treatment responses. Therefore, the purpose of this study was to verify whether the survival effect of radiotherapy in patients with stage IIB/III PDAC varies across age and tumor site groups.

Methods: The target population was selected from PDAC patients undergone surgery in the Surveillance, Epidemiology, and End Results (SEER) database between 2004 and 2016. This study performed the Pearson's chi-square test, Cox regression analysis, Kaplan-Meier (K-M) method, and focused on propensity frequency matching analysis.

Results: Neither neoadjuvant radiotherapy (nRT) nor adjuvant radiotherapy (aRT) patient group had probably improved survival among early-onset patients. For middle-aged patients, nRT seemed to fail to extend overall survival (OS), while aRT might improve the OS. Plus, both nRT and aRT were associated with improved survival in elderly patients. The aRT might be related with survival benefits in patients with pancreatic head cancer, while nRT was not. And RT in patients with PDAC at other sites did not appear to provide a survival benefit.

Conclusion: Carefully selected data from the SEER database suggested that age and tumor location may be the reference factors to guide the selection of RT for patients with stage IIB/III PDAC. These findings are likely to contribute to the development of personalized treatment for patients with stage IIB/III PDAC.

Keywords: pancreatic ductal adenocarcinoma, radiotherapy, SEER, Age, tumor site

INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) is considered to be one of the most common gastrointestinal malignancies in the world, with an estimated incidence of 60,430 cases in 2021 (1). The prognosis of PDAC is dismal due to the characteristics of strong invasiveness and early metastasis. Even among PDAC patients with resectable disease, the 5-year overall survival (OS) rate is only 17% (2, 3). Therefore, in addition to the improvement of surgical methods, an increasing attention has been paid to the adjuvant treatment of pancreatic cancer, especially radiotherapy and chemotherapy. A large number of studies have shown that adjuvant chemotherapy can significantly improve the survival of PDAC patients (4). Accordingly, NCCN emphasizes the implementation of 6-months adjuvant chemotherapy for all PDAC patients undergoing surgical resection (5).

Radiotherapy (RT) is also one of the important weapons against PDAC, including neoadjuvant radiotherapy (nRT), adjuvant radiotherapy (aRT) and palliative treatment. It works by delivering ionizing radiation directly to the primary tumor and regional lymph nodes, which may cause genetic damage and ultimately apoptosis of cancer cells (6). However, our previous study has shown that RT does not benefit the survival of PDAC patients with stage T1-3N0M0 (7). For surgically resected PDAC patients, the NCCN and American Society for Radiation Oncology (ASTRO) also recommend conventional aRT for only a subset of high-risk patients (including positive lymph nodes (stage IIB/III) and margins) (5, 8). Although the role of RT as a local treatment in minimizing local recurrence has been widely recognized, there is no consensus on whether it can improve the survival of patients with stage IIB/III, when to use it, and how best to use it (9, 10).

In recent years, many studies have confirmed that the survival outcome and treatment effect of PDAC patients vary with age (11). Younger patients with PDAC tend to be at a more advanced stage and have a poorer prognosis than older patients, possibly due to their aggressive oncological behavior (12). In addition, younger PDAC patients are more likely to benefit from surgery and adjuvant chemotherapy compared with older patients, according to some studies (13, 14). However, there is still a lack of large sample studies on RT in PDAC patients of different ages. Also, the significance of primary tumor site for prognosis and treatment of patients with PDAC is still controversial. Among resected PDACs, those tumors located at the head of the pancreas had worse overall survival (OS) compared with those at the body and tail of the pancreas (15). Other studies have proved that tumor location does not affect the prognosis of PDAC, but has an important influence on postoperative recurrence and treatment methods (16).

Given the above questions, we used the Surveillance, Epidemiology, and End Results (SEER) database, which collects cancer case data from every state in the United States, to verify whether the survival effect of RT for stage IIB/III PDAC patients was different among different age and tumor site groups.

Abbreviations: PDAC, Pancreatic Ductal Adenocarcinoma; RT, Radiotherapy; aRT, Adjuvant radiotherapy; nRT, Neoadjuvant radiotherapy; ASTRO, American Society for Radiation Oncology; SEER, Surveillance, Epidemiology, and End Results; OS, Overall Survival; CIs, Confidence intervals; HRs, Hazard ratios; US, United States; PSM, Propensity score matching; RNE, Regional nodes examined.

MATERIALS AND METHODS

Data Extraction and Screening

Data for this retrospective study was collected from the SEER database (from 1973 to 2016), which includes 18 population-based cancer registries covering approximately 30% of the US population. The target population was limited to PDAC patients pathologically confirmed by post-operative specimens between 2004 and 2016. Other important information extracted included: general basic information, TNM stage, treatment information (surgery, chemotherapy, RT, Regional nodes examined (RNE)) and follow-up. In addition, the T and N stage were recorded according to the 8th edition TNM stage system by combining tumor size. Exclusion criteria were as follows: not confirmed by postoperative pathology (n=54,652), non-PDAC patients (n=2,110), non-stage IIB/III patients (n=54,174), non-surgical patients (n=10,863) and survival months is 0 (n = 571). Ultimately, enrolled patients were divided into three groups (age<60, 60-69 and ≥70) by the age at diagnosis and two cohorts (pancreatic head and other site groups) by the site of the primary tumor (**Figure 1**).

Statistical Analysis

The endpoint of this study was overall survival (OS). Pearson's chi-square test was used to analyze differences between groups. Multivariate Cox proportional risk regression model was performed to analysis the hazard ratio (HR) and 95% confidence interval (CI). The survival analysis was carried out by the Log-rank test, and the survival curve was drawn by Kaplan-Meier (K-M) method. We performed propensity score matching (PSM) to eliminate the influence of other variables. All statistical analyses in this study were conducted by software SPSS 25.0(IBM, Armonk, NY, USA). All p values less than 0.05 generated in the study were considered statistically significant.

RESULTS

Characteristics and Survival Analysis of All Patients

The total population consisted of 11,865 PDAC patients with stage IIB/III, including 3,336 early-onset patients (age<60), 3,966 middle-aged patients (age: 60-69), and 4,563 elderly patients (age≥70). As shown in **Table 1**, there were significant differences in clinicopathological factors among these groups. The ratio of Grade III/IV was significantly higher in elderly patients with stage IIB/III PDAC compared to the other two subgroups (p<0.001). However, the proportion of T3 and T4 in early-onset patients was the highest among these three groups

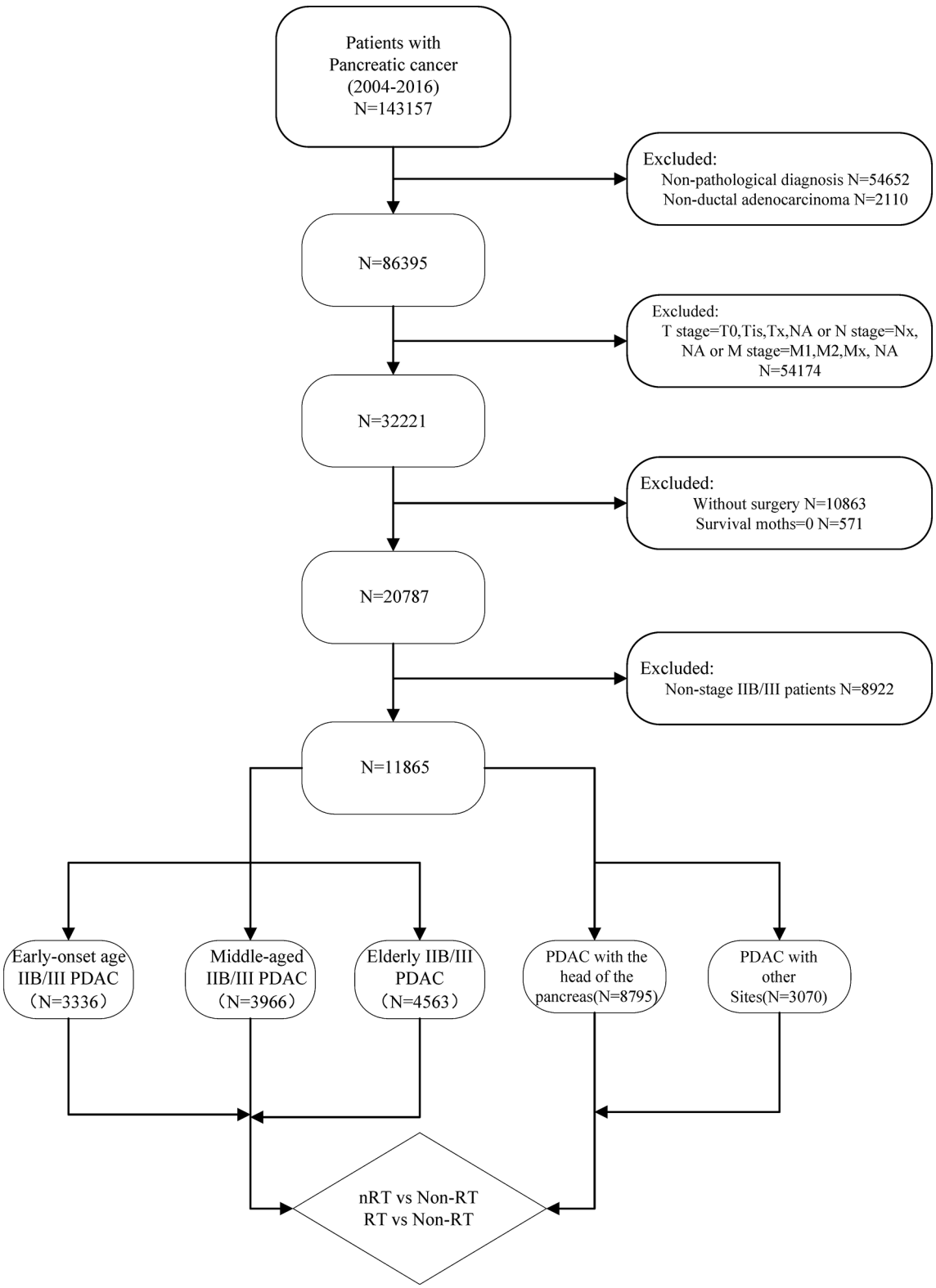

FIGURE 1 | Procedures for inclusion and exclusion of PDAC patients.

TABLE 1 | Characteristics of stage IIB/III PDAC cancer.

Characteristics	Total	Age groups			p-value	Site groups		p-value
		Age < 60	60-69	Age≥70		Pancreas Head	Other sites	
Insurance					<0.001			0.010
Insured	9622 (81.10%)	2569 (77.01%)	3269 (82.43%)	3784 (82.93%)		7084 (80.55%)	2538 (82.67%)	
No/unknown	2243 (18.90%)	767 (22.99%)	697 (17.57%)	779 (17.07%)		1711 (19.45%)	532 (17.33%)	
Marital status					<0.001			0.500
Married	7521 (63.39%)	2092 (62.71%)	2648 (66.77%)	2781 (60.95%)		5564 (63.26%)	1957 (63.75%)	
Single	3957 (33.35%)	1123 (33.66%)	1193 (30.08%)	1641 (35.96%)		2952 (33.56%)	1005 (32.74%)	
Unknown	387 (3.26%%)	121 (3.63%)	125 (3.15%)	141 (3.09%)		279 (3.18%)	108 (3.51%)	
Race					<0.001			0.001
White	9820 (82.76%)	2618 (78.48%)	3294 (83.06%)	3908 (85.65%)		7337 (83.42%)	2483 (80.88%)	
Other	2045 (17.24%)	718 (21.52%)	672 (16.94%)	655 (14.35%)		1458 (16.58%)	587 (19.12%)	
Gender					<0.001			0.213
Male	6113 (51.52%)	1843 (55.25%)	2089 (52.67%)	2181 (47.80%)		4561 (51.86%)	1552 (50.55%)	
Female	5752 (48.48%)	1493 (44.75%)	1877 (47.33%)	2382 (52.20%)		4234 (48.14%)	1518 (49.45%)	
Tumor site					0.001			
Pancreas Head	8795 (74.13%)	2409 (72.21%)	3013 (75.97%)	3373 (73.92%)				
Pancreas Body Tail and other	3070 (25.87%)	927 (27.79%)	953 (24.03%)	1190 (26.08%)				
Grade					<0.001			<0.001
Grade I	1410 (11.88%)	491 (14.72%)	449 (11.32%)	470 (10.30%)		912 (10.37%)	498 (16.22%)	
Grade II	5366 (45.23%)	1445 (43.32%)	1806 (45.54%)	2115 (46.35%)		4039 (45.92%)	1327 (43.22%)	
Grade III/IV	4219 (35.56%)	1090 (32.67%)	1439 (36.28%)	1690 (37.04%)		3239 (36.83%)	980 (31.92%)	
Unknown	870 (7.33%)	310 (9.29%)	272 (6.86%)	288 (6.31%)		605 (6.88%)	265 (8.64%)	
T stage					<0.001			<0.001
T1	1393 (11.74%)	427 (12.80%)	446 (11.25%)	520 (11.40%)		1125 (12.79%)	268 (8.73%)	
T2	6484 (54.65%)	1728 (51.80%)	2167 (54.64%)	2589 (56.74%)		5250 (59.69%)	1234 (40.20%)	
T3	3018 (25.44%)	874 (26.20%)	1019 (25.69%)	1125 (24.65%)		1788 (20.33%)	1230 (40.07%)	
T4	970 (8.17%)	307 (9.20%)	334 (8.42%)	329 (7.21%)		632 (7.19%)	338 (11.00%)	
N stage					0.101			<0.001
N0	414 (3.49%)	127 (3.81%)	140 (3.53%)	147 (3.22%)		241 (2.74%)	173 (5.64%)	
N1	7336 (61.83%)	2029 (60.82%)	2418 (60.97%)	2889 (63.31%)		5262 (59.83%)	2074 (67.56%)	
N2	4115 (34.68%)	1180 (35.37%)	1408 (35.50%)	1527 (33.47%)		3292 (37.43%)	823 (26.80%)	
Radiation					<0.001			<0.001
Non- RT	7735 (65.19%)	2008 (60.19%)	2402 (60.56%)	3325 (72.87%)		5610 (63.79%)	2125 (69.22%)	
nRT	378 (3.19%)	137 (4.11%)	147 (3.71%)	94 (2.06%)		276 (3.14%)	102 (3.32%)	
RT	3752 (31.62%)	1191 (35.70%)	1417 (35.73%)	1144 (25.07%)		2909 (33.07%)	843 (27.46%)	
Chemotherapy					<0.001			<0.001
Yes	8112 (68.37%)	2420 (72.54%)	2940 (74.13%)	2752 (60.31%)		6232 (70.86%)	1880 (61.24%)	
No/Unknown	3753 (31.63%)	916 (27.46%)	1026 (25.87%)	1811 (39.69%)		2563 (29.14%)	1190 (38.76%)	
RNE					<0.001			<0.001
<15	5286 (44.55%)	1481 (44.39%)	1661 (41.88%)	2144 (46.99%)		3698 (42.05%)	1588 (51.73%)	
≥15	6493 (54.72%)	1833 (54.95%)	2272 (57.29%)	2388 (52.33%)		5034 (57.24%)	1459 (47.52%)	
Unknown	86 (0.73%)	22 (0.66%)	33 (0.83%)	31 (0.68%)		63 (0.71%)	23 (0.75%)	
Age								0.001
<60						2409 (27.39%)	927 (30.20%)	
60-69						3013 (34.26%)	953 (31.04%)	
≥70						3373 (38.35%)	1190 (38.76%)	

PDAC, Pancreatic Ductal Adenocarcinoma; RT, Radiotherapy; aRT, Adjuvant radiotherapy; nRT, Neoadjuvant radiotherapy.

(p<0.001). What's more, the age of patients with stage IIB/III PDAC appears to influence treatment selection and execution to some extent. Elderly patients with stage IIB/III PDAC were less likely to receive RT (27.13%), chemotherapy (60.31%), or surgery with RNE≥15 (52.33%) than early-onset (RT: 39.81%, chemotherapy: 72.54%, surgery with RNE≥15: 54.95%) and middle-aged patients (RT: 39.44%, chemotherapy: 74.13%, surgery with RNE≥ 15: 57.29%).

In addition, 74.13% of primary tumors were located in the head of pancreas (8,795) and 25.87% in other sites (3,070) of the target population. Although the proportion of T3/T4 stages in patients with pancreatic head cancer is lower than tumors in other parts of the pancreas, more patients develop lymph node metastases. Similarly, patients with pancreatic head cancer tend to undergo RT (36.21%) and chemotherapy (70.86%) as well as surgery with RNE≥15 (57.24%) compared to patients with tumors in other sites of the pancreas (RT: 30.78%, chemotherapy: 61.24%, surgery with RNE≥ 15: 47.52%).

The results of univariate and multivariate cox proportional risk regression model (**Table 2**) indicated that the prognosis of all PDAC patients with stage IIB/III was closely related to insurance and marital status, gender, age at diagnosis, tumor location, tumor grade, tumor T and N stage, RT, chemotherapy and RNE (all P <0.001).

TABLE 2 | Univariate and multivariate analysis for OS of all stage IIB/III PDAC patients.

Characteristics	Level	Univariate analysis	Multivariate analysis		
		P	HR	95%CI	P
Insurance Recode		<0.001			<0.001
	Insured		Reference	Reference	Reference
	No/unknown		1.150	1.091-1.211	<0.001
Marital status		<0.001			<0.001
	Married		Reference	Reference	Reference
	Single		1.122	1.071-1.176	<0.001
	Unknown		1.031	0.912-1.167	0.622
Age, years		<0.001			<0.001
	<60		Reference	Reference	Reference
	60-69		1.178	1.114-1.246	<0.001
	≥70		1.445	1.369-1.526	<0.001
Race recode		0.449			
	White				
	Other				
Sex		0.010			<0.001
	Female		Reference	Reference	Reference
	Male		1.102	1.054-1.151	<0.001
Tumor site		<0.001			<0.001
	Pancreas Head		Reference	Reference	Reference
	Other sites		0.850	0.806-0.895	<0.001
Grade		<0.001			<0.001
	I		Reference	Reference	Reference
	II		2.107	1.940-2.288	<0.001
	III/IV		2.762	2.540-3.004	<0.001
	Unknown		1.530	1.363-1.718	<0.001
T stage		<0.001			<0.001
	T1		Reference	Reference	Reference
	T2		1.296	1.207-1.391	<0.001
	T3		1.418	1.311-1.534	<0.001
	T4		2.008	1.788-2.256	<0.001
N stage		<0.001			<0.001
	N0		Reference	Reference	Reference
	N1		1.264	1.069-1.451	0.005
	N2		1.667	1.427-1.948	<0.001
Radiotherapy		<0.001			<0.001
	Non- RT		Reference	Reference	Reference
	nRT		0.910	0.792-1.045	0.181
	RT		0.891	0.848-0.937	<0.001
Chemotherapy		<0.001			<0.001
	Yes		Reference	Reference	Reference
	No		1.326	1.259-1.396	<0.001
RNE		<0.001			<0.001
	<15		Reference	Reference	Reference
	≥15		0.822	0.786-0.860	<0.001
	Unknown		1.183	0.938-1.491	0.155

PDAC, Pancreatic Ductal Adenocarcinoma; RT, Radiotherapy; aRT, Adjuvant radiotherapy; nRT, Neoadjuvant radiotherapy; OS, Overall Survival; CI, Confidence intervals; HR, Hazard ratios; RNE, Regional nodes examined.

The Impact of RT on Early-Onset Patients With Stage IIB/III PDAC

According to the multivariate Cox regression model, neither nRT (p=0.531) nor aRT (p=0.106) improved OS in early-onset patients with stage IIB/III PDAC (**Figure 2A**). The K-M survival analysis showed that no significant association between nRT and OS (p=0.605), while aRT (p=0.004, HRs=1.132; 95% CIs, 1.038-1.235) developed worse OS compared to those with non-RT in early-onset patients (**Figure 2B**). The median survival of non-RT, nRT and aRT patients were 22, 22, and 21 months, respectively (**Table 3**). In order to reduce the interference of other variables, the balanced population of the non-RT and the nRT(n = 107 pairs), the non-RT and the RT(n = 812 pairs) were obtained by multiple 1:1 PSM for early-onset PDAC patients with stage IIB/III. Similarly, the survival curves after PSM indicated that nRT (p=0.427, **Figure 2C**) and aRT (p=0.873, **Figure 2D**) still did not seem to be associated with improved OS of early-onset patients with stage IIB/III PDAC.

The Impact of RT on Middle-Aged Patients With Stage IIB/III PDAC

Using similar methods, the multivariate Cox regression analysis and K-M survival analysis before matching showed that nRT

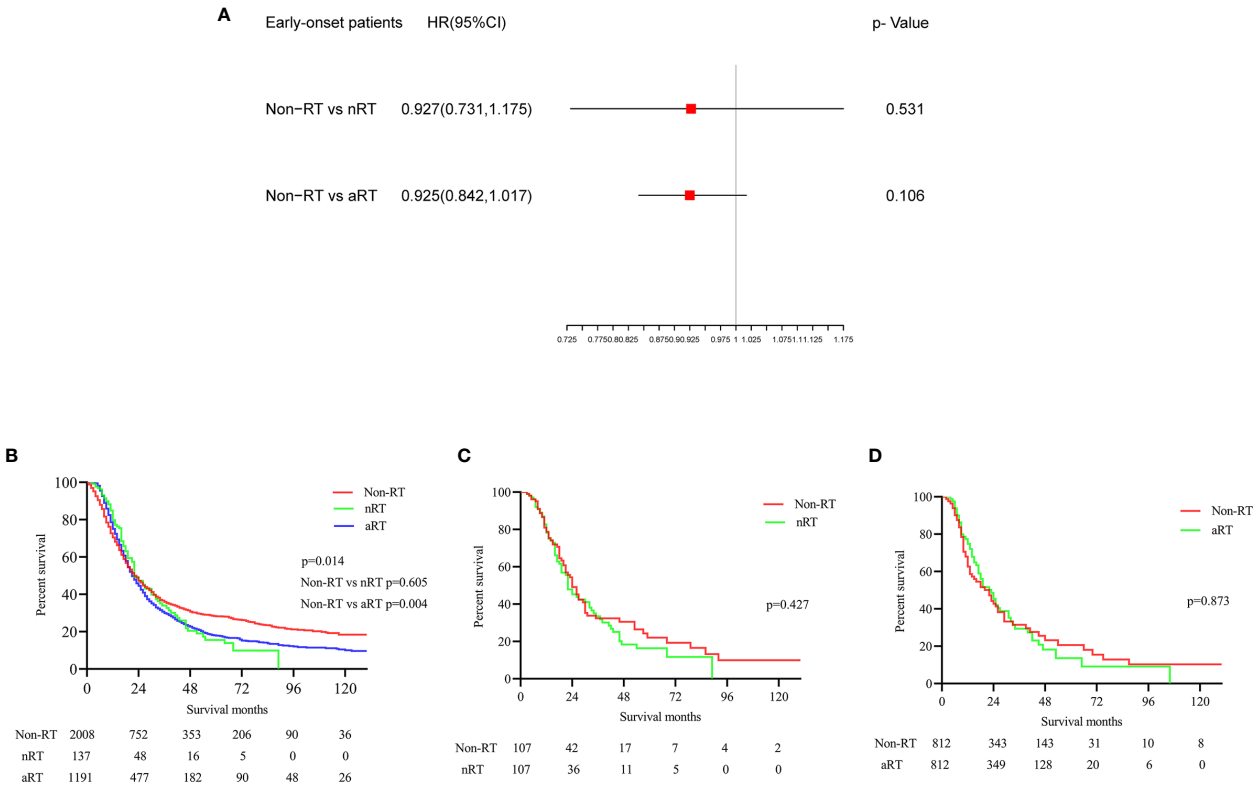

FIGURE 2 | The forest plot and the survival curves were used to demonstrate the effect of radiotherapy in early onset stage IIB/III PDAC patients. **(A)**. The forest plot for non-RT vs. nRT and non-RT vs. aRT in early onset stage IIB/III PDAC patients; **(B)**. The survival curve for total early onset stage IIB/III PDAC patients before PSM; **(C)**. The survival curve for non-RT vs. nRT in early onset stage IIB/III PDAC patients after PSM; **(D)**. The survival curve for non-RT vs. aRT in early onset stage IIB/III PDAC patients after PSM.

seemed to fail to prolong the OS of middle-aged patients with stage IIB/III PDAC (p=0.547; p=0.065), while aRT might improve the OS of patients (p=0.008, **Figure 3A**; p<0.001, HRs=0.869; 95% CIs, 0.806-0.938, **Figure 3B**). Median survival was 18, 21 and 23 months for patients receiving non-RT, nRT and aRT, respectively. The balanced populations of non-RT and nRT (n = 127 pairs), non-RT and aRT (n = 1067 pairs) were matched by 1:1 PSM. Further survival analysis found that nRT could not improve the OS (p=0.880, **Figure 3C**), and the OS of aRT was significantly better than that of non-RT in middle-aged PDAC patients with stage IIB/III (p=0.014, HRs=0.883; 95% CIs, 0.798-0.977, **Figure 3D**).

TABLE 3 | Median survival and, 1-, 3- and 5-year OS of stage IIB/III PDAC patients.

Groups	Treatments	Median survival	1-year OS	3-year OS	5-year OS
Age < 60	Non-RT	22	47.17%	26.01%	19.08%
	nRT	22	47.92%	9.33%	–
	RT	21	44.75%	16.33%	10.08%
60-69	Non-RT	18	38.83%	13.83%	9.67%
	nRT	21	45.50%	12.49%	6.58%
	RT	23	44.08%	13.85%	10.67%
Age≥70	Non-RT	13	29.17%	7.90%	3.75%
	nRT	23	47.17%	14.25%	10.41%
	RT	19	39.92%	10.08%	3.81%
Pancreas Head	Non-RT	16	32.25%	11.08%	7.58%
	nRT	20	47.16%	12.16%	–
	RT	22	43.42%	13.17%	8.33%
Other sites	Non-RT	20	45.08%	22.92%	15.91%
	nRT	24	52.75%	9.01%	7.25%
	RT	20	39.66%	12.58%	9.08%

PDAC, Pancreatic Ductal Adenocarcinoma; RT, Radiotherapy; aRT, Adjuvant radiotherapy; nRT, Neoadjuvant radiotherapy; OS, Overall Survival.

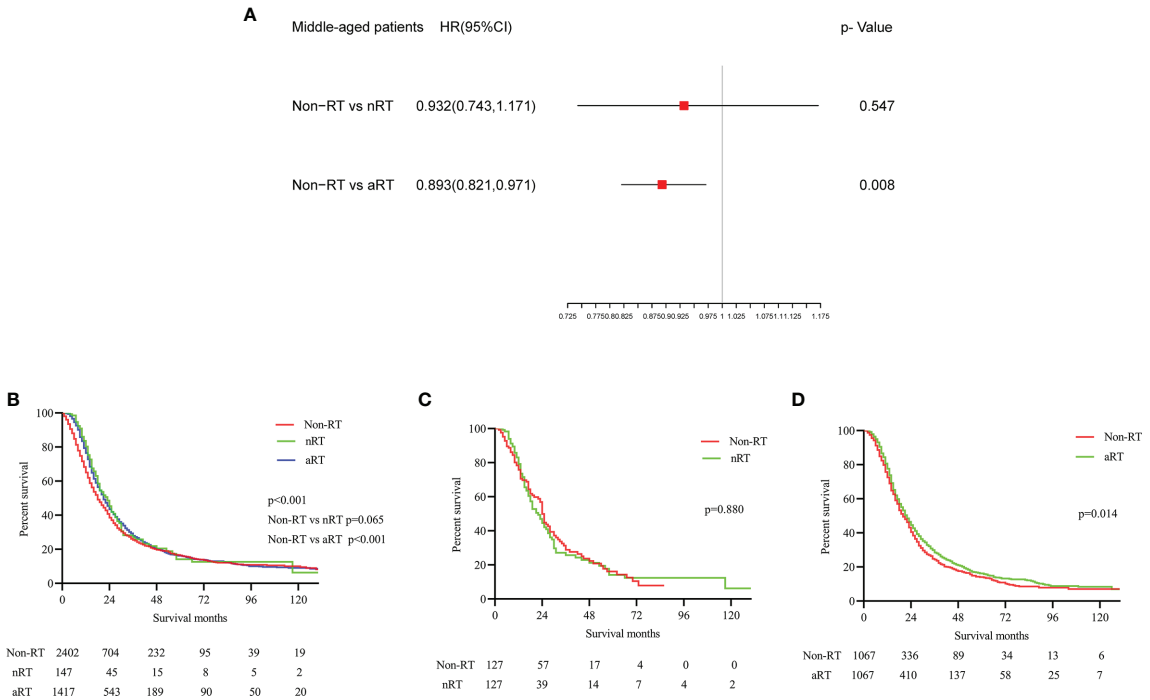

FIGURE 3 | The forest plot and the survival curves were used to demonstrate the effect of radiotherapy in middle-aged stage IIB/III PDAC patients. **(A)**. The forest plot for non-RT vs. nRT and non-RT vs. aRT in middle-aged stage IIB/III PDAC patients; **(B)**. The survival curve for total middle-aged stage IIB/III PDAC patients before PSM; **(C)**. The survival curve for non-RT vs. nRT in middle-aged stage IIB/III PDAC patients after PSM; **(D)**. The survival curve for non-RT vs. aRT in middle-aged stage IIB/III PDAC patients after PSM.

The Impact of RT on Elderly Patients With Stage IIB/III PDAC

Before PSM matching, both Cox multivariate regression analysis (**Figure 4A**) and K-M (**Figure 4B**) survival analysis showed that nRT and aRT might be related with survival benefits for elderly patients. The median survival for these three treatments were 13 (non-RT), 23(nRT) and 19 months(aRT), respectively. Similarly, the K-M survival analysis after matching suggested that nRT (p=0.004, HRs=0.848; 95% CIs, 0.755-0.953, **Figure 4C**) and aRT (p=0.002, HRs=0.853; 95% CIs, 0.770-0.944, **Figure 4D**) still seemed to provided significant survival benefits for elderly PDAC patients with stage IIB/III.

The Impact of RT on Stage IIB/III PDAC Patients With Different Tumor Sites

The same approaches were used to analyze patients with stage IIB/III PDAC at different sites. According to Cox multivariate regression analysis of pancreatic head cancer, there was no significant difference in OS between nRT patients and non-RT patients(p=0.250), while the OS of aRT patients was significantly better than that of non-RT patients (p<0.001, **Figure 5A**). The K-M survival curves suggested that both nRT and aRT were beneficial for OS in patients with pancreatic head cancer before PSM (all p<0.001, **Figure 5B**). The corresponding median survival were 16(non-RT), 20(nRT), and 22(aRT) months, respectively. The survival curve after PSM showed that although there was no significant difference in survival between the nRT and non-RT groups (p=0.445, **Figure 5C**), aRT still improved the OS of patients with pancreatic head cancer (p<0.001, HRs=0.867; 95% CIs, 0.807-0.932, **Figure 5D**).

For patients with stage IIB/III PDAC at other sites, the multivariate Cox regression analysis (**Figure 5E**) and K-M survival analysis without PSM (**Figure 5F**) showed that neither aRT nor nRT were associated with improved survival, which was further validated by survival analysis with PSM (**Figures 5G, H**). Median survival was 20, 24 and 20 months for patients undergone non-RT, nRT and aRT, respectively.

DISCUSSION

A variety of tumors, including pancreatic cancer, possess different molecular characteristics, biological behaviors and therapeutic responses in different age groups (17–19). For example, young patients and elderly patients with pancreatic cancer benefit from comprehensive treatment differently. Another study found that chemotherapy didn't seem to affect the prognosis of young patients with breast cancer, which is obviously inconsistent with most studies that are not grouped by age (20). In addition, a recent study focusing on stage II/III rectal cancer revealed that radiotherapy had different effects on the survival of patients at different ages (21). Moreover, treatment

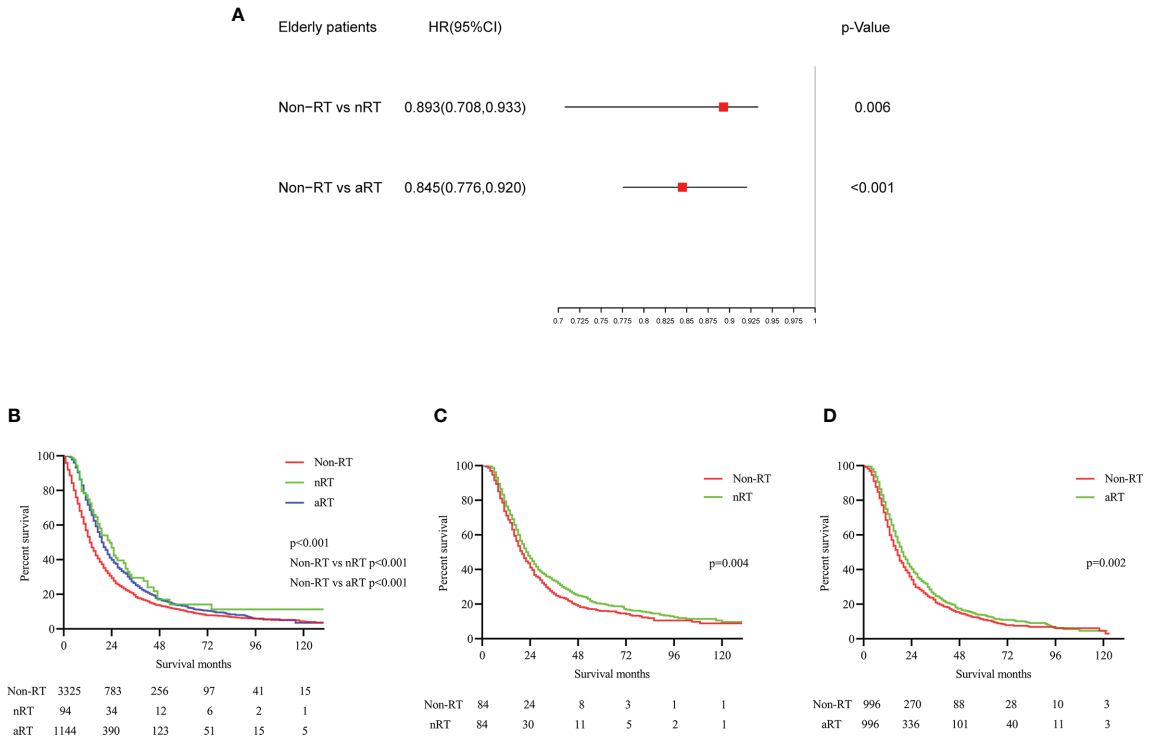

FIGURE 4 | The forest plot and the survival curves were used to demonstrate the effect of radiotherapy in elderly stage IIB/III PDAC patients. **(A)**. The forest plot for non-RT vs. nRT and non-RT vs. aRT in elderly stage IIB/III PDAC patients; **(B)**. The survival curve for total elderly stage IIB/III PDAC patients before PSM; **(C)**. The survival curve for non-RT vs. nRT in elderly stage IIB/III PDAC patients after PSM; **(D)**. The survival curve for non-RT vs. aRT in elderly stage IIB/III PDAC patients after PSM.

methods and postoperative recurrence methods are also diverse according to the different site of primary tumor of PDAC (16). These evidences prompted us to explore the impact of radiotherapy on survival in PDAC patients with stage IIB/III at different ages and sites through the SEER database. The results of our study showed that the survival effect of RT was not consistent in different age groups, but also in different tumor sites.

We found that RT failed to benefit the survival of patients with early-onset stage IIB/III PDAC through age stratification. Even before PSM, survival analysis indicated that aRT was a risk factor for prognosis, which was clearly at odds with the findings of most studies that do not group by age (22). Conventional wisdom has it that younger patients are more likely to withstand more aggressive treatments, because of their relatively good physical state (23). The data we selected also demonstrated that patients with early-onset PDAC underwent more extensive surgery (RNE≥15) and chemoradiotherapy than older patients. Better treatment utilization and the ability to tolerate intensive therapy will hopefully be associated with improved outcomes. However, our data do not support that increasing RT in early-onset patients improves prognosis. A retrospective study from the Ellis Fisher Cancer Center also found that younger pancreatic cancer patients who received more treatment did not have a greater survival benefit than older patients (24). This suggested that survival improvements in early-onset patients with stage IIB/III PDAC are more likely to depend on the development of new therapies and technologies, rather than more aggressive use of existing models.

Traditionally, RT has been considered to cause significant radiation toxicity to PDAC due to the presence of many radiation-sensitive organs (stomach, duodenum, liver, kidney and spinal cord) in the pancreatic anatomic region (25). Furthermore, the conventional wisdom has been that increasing age, comorbidities, and worsening physical conditions (such as frailty) increase the risk of chemotherapy intolerance, disease progression, and death (26). Therefore, the application of RT in elderly patients with PDAC is more cautious in real clinical practice. However, recent studies have found that age may not be a predictor of radiation-induced toxicity and that healthy status such as frailty are more closely associated with radiation toxicity. Frailty is a pathological condition characterized by the decline of various physiological systems, although related to age, but not equal to old age (27). In this study, the proportion of patients over 70 years old who received RT was significantly lower than that of patients with early onset, especially the ration of nRT was only 2.06%. However, survival analysis showed that aRT could prolong survival in middle-aged and elderly patients, and nRT improved survival in the elderly. It is necessary for us to re-evaluate the benefits and risks of RT in elderly PDAC patients. In fact, many analyses showed that in terms of radiotherapy tolerance and toxicity, the results of elderly

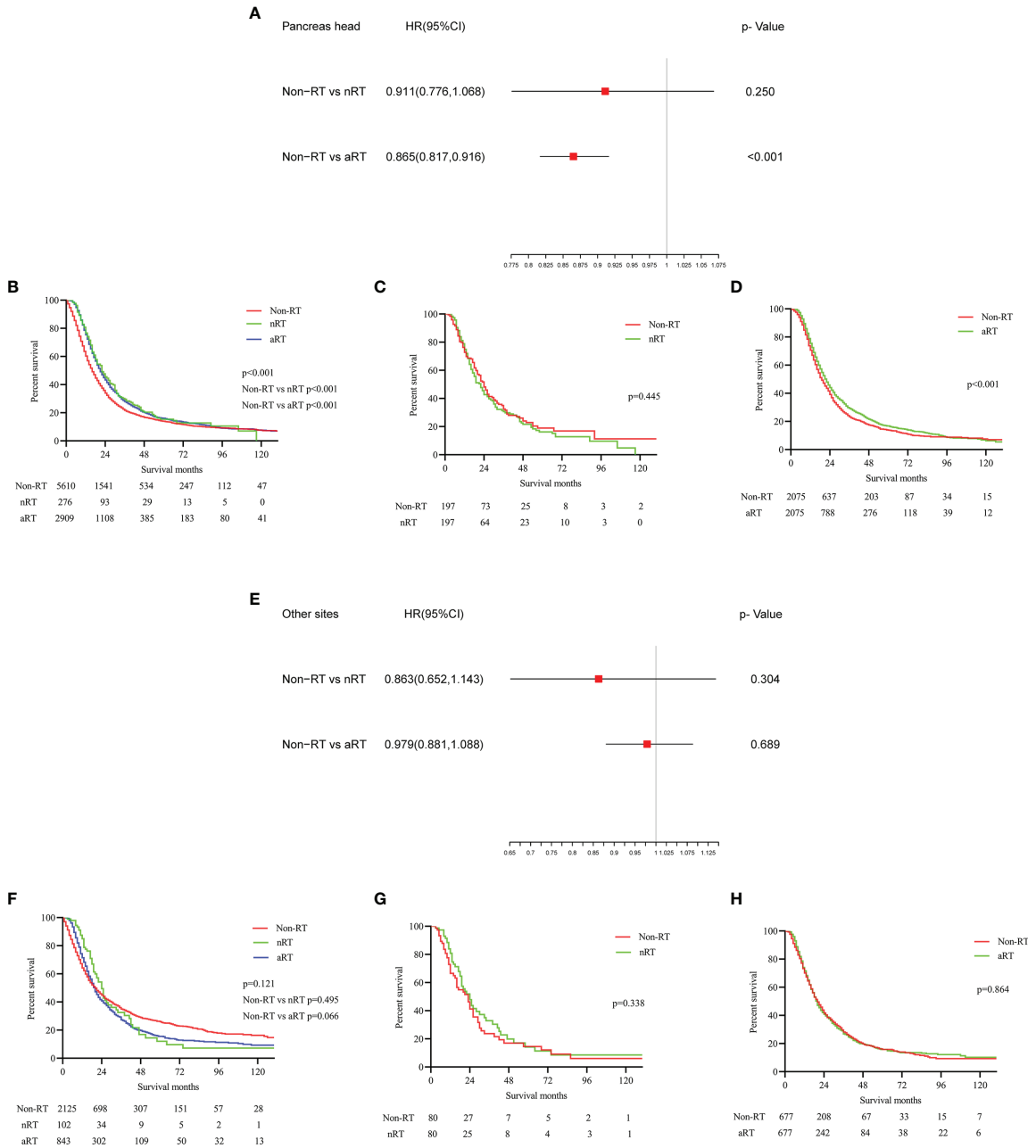

FIGURE 5 | The forest plots and the survival curves were used to demonstrate the effect of radiotherapy in stage IIB/III PDAC patients with different tumor sites. **(A)** The forest plot for non-RT vs. nRT and non-RT vs. aRT in patients with pancreatic head tumors; **(B)** The survival curve for total patients with pancreatic head tumors before PSM; **(C)** The survival curve for non-RT vs. nRT in patients with pancreatic head tumors after PSM; **(D)** The survival curve for non-RT vs. aRT in patients with pancreatic head tumors after PSM; **(E)** The forest plot for non-RT vs. nRT and non-RT vs. aRT in PDAC patients at other sites; **(F)** The survival curve for total PDAC patients at other sites before PSM; **(G)** The survival curve for non-RT vs. nRT in PDAC patients at other sites after PSM; **(H)** The survival curve for non-RT vs. aRT in PDAC patients at other sites after PSM.

patients were similar to those of the general population, including young patients (28, 29). In adjuvant therapy, radiotherapy and chemotherapy are carried out at the same time, which can eradicate residual microscopic or macroscopic disease caused by the special anatomy of the pancreatic lesion (22). Moreover, compared with aRT, nRT is associated with a significant reduction in local recurrence and treatment-related toxicity (9). Therefore, clinicians should pay attention to the use of aRT in patients over 60 years of age with stage IIB/III PDAC and nRT in patients over 70 years of age.

In addition, the effect of tumor anatomical site on the prognosis and treatment of pancreatic cancer has gradually become a

research hotspot in recent years. A retrospective study of 128 patients with pancreatic cancer from Japan showed that tumor location was not a prognostic factor for overall survival of locally advanced pancreatic cancer, although the clinical presentation of PDAC at different sites may differ (30). However, pancreatic head tumors had a higher rate of lymph node metastasis and a correspondingly poorer prognosis according to another propensity score-matched analysis (31). Another study, which analyzed germline and somatic mutations in 90 Chinese patients with pancreatic cancer, found differences in the mutation spectrum of pancreatic tumors at different anatomic sites, suggesting that treatment options for patients at different tumor sites may differ (32). In our experience, pancreatic head cancer had a worse prognosis than tumors in other sites. What's more, there were differences in the effects of RT in patients with stage IIB/III PDAC at different sites. The application of aRT can benefit the OS in patients with pancreatic head cancer, but not in patients with PDAC at other sites. Therefore, we suggested clinicians should also consider tumor site as an important factor in deciding radiotherapy options for pancreatic cancer.

To date, our study was the first to specifically investigate the impact of RT on survival in PDAC patients with stage IIB/III at different ages and tumor sites. As a retrospective, non-randomized study, selection bias and confounding factors inevitably interfered. Although we use PSM to try to compensate for these defects, there are still some confounding factors that cannot be identified and some known confounding factors that cannot be controlled. The degree of tumor invasion, health status (comorbidities and frailty), surgical complications and recovery are all important factors affecting the decision of radiotherapy. These variables cannot be obtained and coded directly in the SEER database, so they can only be controlled indirectly. Furthermore, the data was sourced from a public database (SEER) rather than a separate queue, and the available information was limited. For example, the SEER database does not provide ECOG performance status, resectability status, surgical margin status, radiotherapy target design, technique, and dose, which undoubtedly weakens the reliability of the conclusions of this study. In addition, the data only provided whether the patients underwent chemotherapy, so it was not possible to determine whether the patients underwent 5-fluorouracil-based regimen. Finally, genomic data from tumor samples also have great clinical reference value to guide prognosis and treatment, but this is also not recorded in the SEER database. These missing variables are critical to prognosis and need to be discussed in future studies.

In summary, this study was based on a stratified analysis of age and tumor location, highlighting the difference in the efficacy of RT in different subgroups of patients. Of course, the results of this study need to be further confirmed by prospective cohorts in patients with stage IIB/III PDAC.

CONCLUSION

Carefully selected data from the SEER database suggested that age and tumor location may be the reference factors to guide the selection of RT for patients with stage IIB/III PDAC. These findings may contribute to the development of individualized treatment for patients with stage IIB/III PDAC.

DATA AVAILABILITY STATEMENT

Publicly available datasets were analyzed in this study. This data can be found here: https://seer.cancer.gov/.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of Xiangya Hospital of Central South University. Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

Conceptualization: DW, CL, and CG. Data curation: HG, MT, and CLL. Formal analysis: DW, LZ, QP, and FT. Methodology: DW, YL, QP, and FT. Writing-original draft: DW. Writing review & editing: CL. Revise & proofread: DW, YL, CG, and CL. All the authors read and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2022.799930/full#supplementary-material

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Supplementary Table 1. Features of early-onset patients in the non-radiotherapy group and the neoadjuvant radiotherapy group before and after PSM.

	Before PSM			After PSM		
Characteristics	Non-	Neoadjuvant	P	Non-	Neoadjuvant	P
Insurance Recode			0.743			1.000
Insured	1595(79.43%)	111(81.02%)		86(80.37%)	87(81.31%)	
No/unknown	413(20.57%)	26(18.98%)		21(19.63%)	20(18.69%)	
Marital status			0.017			0.374
Married	1219(60.71%)	99(72.26%)		74(69.16%)	80(74.77%)	
Single	709(35.31%)	32(23.36%)		30(28.04%)	22(20.56%)	
Unknown	80(3.98%)	6(4.38%)		3(2.80%)	5(4.67%)	
Race			<0.001			1.000
White	1546(76.99%)	123(89.78%)		95(88.79%)	94(87.85%)	
Others	462(23.01%)	14(10.22%)		12(11.21%)	13(12.15%)	
Sex			0.307			0.891
Male	892(44.42%)	67(48.91%)		49(45.79%)	51(47.66%)	
Female	1116(55.58%)	70(51.09%)		58(54.21%)	56(52.34%)	
Tumor site			0.126			0.637
Pancreas Head	1377(68.58%)	103(75.18%)		78(72.90%)	82(76.64%)	
Pancreas Body Tail	631(31.42%)	34(24.82%)		29(27.10%)	25(23.36%)	
Grade			<0.001			0.346
I	376(18.73%)	7(5.10%)		3(2.80%)	7(6.54%)	
II	821(40.89%)	44(32.12%)		38(35.51%)	36(33.64%)	
III/IV	617(30.73%)	32(23.36%)		31(28.97%)	23(21.50%)	
Unknown	194(9.65%)	54(39.42%)		35(32.72%)	41(38.32%)	
T stage			<0.001			0.422
T1	252(12.55%)	6(4.38%)		6(5.61%)	6(5.61%)	
T2	1051(52.34%)	47(34.30%)		44(41.12%)	47(43.92%)	
T3	559(27.84%)	22(16.06%)		32(29.91%)	22(20.56%)	
T4	146(7.27%)	62(45.26%)		25(23.36%)	32(29.91%)	
N stage			<0.001			0.653
N0	54(2.69%)	46(33.58%)		16(14.95%)	19(17.76%)	
N1	1208(60.16%)	77(56.20%)		80(74.77%)	74(69.16%)	
N2	746(37.15%)	14(10.22%)		11(10.28%)	14(13.08%)	
Chemotherapy			<0.001			1.000
Yes	1142(56.87%)	137(100%)		107(100%)	107(100%)	
No/Unknown	866(43.13%)	0		0	0	
RNE			0.003			0.359
<15	891(44.37%)	75 (54.74%)		48(44.86%)	57(53.27%)	
≥15	1106(55.08%)	59(43.07%)		58(54.21%)	48(44.86%)	
Unknown	11(0.55%)	3(2.19%)		1(0.93%)	2(1.87%)	

Supplementary Table 2. Features of early-onset patients in the non-radiotherapy group and the adjuvant radiotherapy group before and after PSM.

	Before PSM			After PSM		
Characteristics	Non-	Adjuvant	P	Non-	Adjuvant	P
Insurance Recode			<0.001			1.000
Insured	1595(79.43%)	863(72.46%)		667(82.14%)	667(82.14%)	
No/unknown	413(20.57%)	328(27.54%)		145(17.86%)	145(17.86%)	
Marital status			0.034			0.966
Married	1219(60.71%)	774(64.99%)		537(66.13%)	537(66.13%)	
Single	709(35.31%)	382(32.07%)		268(33.00%)	267(32.88%)	
Unknown	80(3.98%)	35(2.94%)		7(0.87%)	8(0.99%)	
Race			0.076			0.715
White	1546(76.99%)	949(79.68%)		644(79.31%)	638(78.57%)	
Others	462(23.01%)	242(20.32%)		168(20.69%)	174(21.43%)	
Sex			0.820			0.960
Male	892(44.42%)	534(44.84%)		373(45.94%)	372(45.81%)	
Female	1116(55.58%)	657(55.16%)		439 (54.06%)	440(54.19%)	
Tumor site			<0.001			0.950
Pancreas Head	1377(68.58%)	929(78.00%)		650(80.05%)	651(80.17%)	
Pancreas Body Tail and	631(31.42%)	262(22.00%)		162(19.95%)	161(19.83%)	
Grade			<0.001			1.000
I	376(18.73%)	108(9.07%)		61(7.51%)	61(7.51%)	
II	821(40.89%)	580(48.70%)		407(50.12%)	407(50.12%)	
III/IV	617(30.73%)	441(37.03%)		317(39.04%)	317(39.04%)	
Unknown	194(9.65%)	62(5.20%)		27(3.33%)	27(3.33%)	
T stage			0.134			0.999
T1	252(12.55%)	169(14.19%)		95(11.70%)	96(11.82%)	
T2	1051(52.34%)	630(52.90%)		496(61.08%)	496(61.08%)	
T3	559(27.84%)	293(24.60%)		195(24.02%)	195(24.02%)	
T4	146(7.27%)	99(8.31%)		26(3.20%)	25(3.08%)	
N stage			0.385			1.000
N0	54(2.69%)	27(2.27%)		4(0.49%)	4(0.49%)	
N1	1208(60.16%)	744(62.47%)		497(61.21%)	497(61.21%)	
N2	746(37.15%)	420(35.26%)		311(38.30%)	311(38.30%)	
Chemotherapy			<0.001			1.000
Yes	1142(56.87%)	1141(95.80%)		780(96.06%)	780(96.06%)	
No/Unknown	866(43.13%)	50(4.20%)		32(3.94%)	32(3.94%)	
RNE			0.760			0.459
<15	891(44.37%)	515(43.24%)		339(41.75%)	317(39.04%)	
≥15	1106(55.08%)	668(56.09%)		469(57.76%)	489(60.22%)	
Unknown	11(0.55%)	8(0.67%)		4(0.49%)	6(0.74%)	

Supplementary Table 3. Features of middle-aged patients in the non-radiotherapy group and the neoadjuvant radiotherapy group before and after PSM.

	Before PSM			After PSM		
Characteristics	Non-	Neoadjuvant	P	Non-	Neoadjuvant	P
Insurance Recode			0.091			0.145
Insured	2045(85.14%)	133(90.48%)		105(82.68%)	114(89.76%)	
No/unknown	357(14.86%)	14(9.52%)		22(17.32%)	13(10.24%)	
Marital status			0.013			0.399
Married	1558(64.86%)	112(76.19%)		98(77.17%)	96(75.59%)	
Single	769(32.02%)	30(20.41%)		28(22.05%)	27(21.26%)	
Unknown	75(3.12%)	5(3.40%)		1(0.78%)	4(3.15%)	
Race			0.649			0.733
White	1995(83.06%)	125(85.03%)		105(82.68%)	108(85.04%)	
Others	407(16.94%)	22(14.97%)		22(17.32%)	19(14.96%)	
Sex			0.335			0.900
Male	1144(47.63%)	64(43.54%)		57(44.88%)	56(44.09%)	
Female	1258(52.37%)	83(56.46%)		70(55.12%)	71(55.91%)	
Tumor site			0.496			0.776
Pancreas Head	1792(74.60%)	106(72.11%)		92(72.44%)	95(74.80%)	
Pancreas Body Tail and	610(25.40%)	41(27.89%)		35(27.56%)	32(25.20%)	
Grade			<0.001			0.053
I	300(12.49%)	18(12.24%)		4(3.15%)	8(6.30%)	
II	1044(43.46%)	47(31.97%)		52(40.94%)	47(37.01%)	
III/IV	903(37.59%)	34(23.14%)		48(37.80%)	34(26.77%)	
Unknown	155(6.46%)	48(32.65%)		23(18.11%)	38(29.92%)	
T stage			<0.001			0.429
T1	288(11.99%)	2(1.36%)		3(2.36%)	2(1.57%)	
T2	1284(53.46%)	54(36.73%)		54(42.51%)	54(42.52%)	
T3	659(27.44%)	32(21.77%)		40(31.50%)	31(24.41%)	
T4	171(7.11%)	59(40.14%)		30(23.63%)	40(31.50%)	
N stage			<0.001			0.981
N0	66(2.75%)	42(28.57%)		25(19.69%)	25(19.69%)	
N1	1459(60.74%)	89(60.54%)		87(68.50%)	86(67.72%)	
N2	877(36.51%)	16(10.88%)		15(11.81%)	16(12.59%)	
Chemotherapy			<0.001			1.000
Yes	1456(60.62%)	145(98.64%)		126(99.21%)	125(98.43%)	
No/Unknown	946(39.38%)	2(1.36%)		1(0.79%)	2(1.57%)	
RNE			<0.001			0.508
<15	955(39.76%)	77(52.38%)		66(51.97%)	63(49.61%)	
≥15	1429(59.49%)	64(43.54%)		59(46.46%)	59(46.46%)	
Unknown	18(0.75%)	6(4.08%)		2(1.57%)	5(3.93%)	

Supplementary Table 4. Features of middle-aged patients in the non-radiotherapy group and the adjuvant radiotherapy group before and after PSM.

	Before PSM			After PSM		
Characteristics	Non-	Adjuvant	P	Non-	Adjuvant	P
Insurance Recode			<0.001			0.841
Insured	2045(85.14%)	1091(76.99%)		941(88.19%)	938(87.91%)	
No/unknown	357(14.86%)	326(23.01%)		126(11.81%)	129(12.09%)	
Marital status			0.023			1.000
Married	1558(64.86%)	978(69.02%)		766(71.79%)	766(71.79%)	
Single	769(32.02%)	394(27.81%)		286(26.81%)	286(26.81%)	
Unknown	75(3.12%)	45(3.17%)		15(1.40%)	15(1.40%)	
Race			0.871			1.000
White	1995(83.06%)	1174(82.85%)		888(83.22%)	888(83.22%)	
Others	407(16.94%)	243(17.15%)		179(16.78%)	179(16.78%)	
Sex			0.804			0.633
Male	1144(47.63%)	669(47.21%)		508(47.61%)	497(46.58%)	
Female	1258(52.37%)	748(52.79%)		559(52.39%)	570(53.42%)	
Tumor site			0.004			0.869
Pancreas Head	1792(74.60%)	1115(78.69%)		865(81.07%)	862(80.79%)	
Pancreas Body Tail	610(25.40%)	302(21.31%)		202(18.93%)	205(19.21%)	
Grade			<0.001			0.989
I	300(12.49%)	131(9.24%)		82(7.69%)	78(7.31%)	
II	1044(43.46%)	715(50.46%)		526(49.30%)	526(49.30%)	
III/IV	903(37.59%)	502(35.43%)		412(38.61%)	416(38.99%)	
Unknown	155(6.46%)	69(4.87%)		47(4.40%)	47(4.40%)	
T stage			0.010			0.992
T1	288(11.99%)	156(11.01%)		100(9.37%)	101(9.47%)	
T2	1284(53.46%)	829(58.50%)		667(62.52%)	664(62.23%)	
T3	659(27.44%)	328(23.15%)		248(23.24%)	247(23.15%)	
T4	171(7.11%)	104(7.34%)		52(4.87%)	55(5.15%)	
N stage			0.637			0.984
N0	66(2.75%)	32(2.26%)		18(1.69%)	19(1.78%)	
N1	1459(60.74%)	870(61.40%)		656(61.48%)	657(61.57%)	
N2	877(36.51%)	515(36.34%)		393(36.83%)	391(36.65%)	
Chemotherapy			<0.001			1.000
Yes	1456(60.62%)	1339(94.50%)		1006(94.28%)	1006(94.28%)	
No/Unknown	946(39.38%)	78(5.50%)		61(5.72%)	61(5.72%)	
RNE			0.019			0.367
<15	955(39.76%)	629(44.39%)		413(38.71%)	413(38.71%)	
≥15	1429(59.49%)	779(54.98%)		654(61.29%)	652(61.11%)	
Unknown	18(0.75%)	9(0.63%)		0	2(0.18%)	

Supplementary Table 5. Features of elderly patients in the non-radiotherapy group and the neoadjuvant radiotherapy group before and after PSM.

	Before PSM			After PSM		
Characteristics	Non-	Neoadjuvant	P	Non-	Neoadjuvant	P
Insurance Recode			0.060			0.766
Insured	2802(84.27%)	86(91.49%)		79(94.05%)	77(91.67%)	
No/unknown	523(15.73%)	8(8.51%)		5(5.95%)	7(8.33%)	
Marital status			0.418			0.627
Married	1975(59.40%)	62(65.96%)		53(63.10%)	57(67.86%)	
Single	1247(37.50%)	29(30.85%)		30(35.71%)	25(29.76%)	
Unknown	103(3.10%)	3(3.19%)		1(1.19%)	2(2.38%)	
Race			0.658			0.698
White	2842(85.47%)	79(84.04%)		66(78.57%)	69(82.14%)	
Others	483(14.53%)	15(15.96%)		18(21.43%)	15(17.86%)	
Sex			0.917			1.000
Male	1777(53.44%)	51(54.26%)		47(55.95%)	47(55.95%)	
Female	1548(46.56%)	43(45.74%)		37(44.05%)	37(44.05%)	
Tumor site			0.637			1.000
Pancreas Head	2441(73.41%)	67(71.28%)		61(72.62%)	61(72.62%)	
Pancreas Body Tail and	884(26.59%)	27(28.72%)		23(27.38%)	23(27.38%)	
Grade			<0.001			0.818
I	362(10.89%)	6(6.38%)		4(4.76%)	5(5.95%)	
II	1529(45.98%)	28(29.79%)		24(28.57%)	28(33.33%)	
III/IV	1243(37.38%)	24(25.53%)		27(32.14%)	22(26.19%)	
Unknown	191(5.75%)	36(38.30%)		29(34.53%)	29(34.53%)	
T stage			<0.001			0.086
T1	388(11.67%)	2(2.13%)		7(8.33%)	2(2.38%)	
T2	1892(56.90%)	35(37.23%)		26(30.96%)	35(41.67%)	
T3	839(25.23%)	15(15.96%)		24(28.57%)	15(17.86%)	
T4	206(6.20%)	42(44.68%)		27(32.14%)	32(38.09%)	
N stage			<0.001			0.621
N0	82(2.47%)	29(30.85%)		16(19.05%)	20(23.81%)	
N1	2125(63.91%)	53(56.38%)		58(69.05%)	52(61.90%)	
N2	1118(33.62%)	12(12.77%)		10(11.90%)	12(14.29%)	
Chemotherapy			<0.001			0.497
Yes	1599(48.09%)	94(100%)		82(97.62%)	84(100%)	
No/Unknown	1726(51.91%)	0		2(2.38%)	0	
RNE			0.876			0.821
<15	1573(47.31%)	46(48.94%)		42(50.00%)	41(48.81%)	
≥15	1728(51.97%)	47(50.00%)		40(47.62%)	42(50.00%)	
Unknown	24(0.72%)	1(1.06%)		2(2.38%)	1(1.19%)	

Supplementary Table 6. Features of elderly patients in the non-radiotherapy group and the adjuvant radiotherapy group before and after PSM.

	Before PSM			After PSM		
Characteristics	Non-	Adjuvant	P	Non-	Adjuvant	P
Insurance Recode			<0.001			1.000
Insured	2802(84.27%)	896(78.32%)		855(85.84%)	855(85.84%)	
No/unknown	523(15.73%)	248(21.68%)		141(14.16%)	141(14.16%)	
Marital status			0.003			0.563
Married	1975(59.40%)	744(65.03%)		624(62.65%)	647(64.96%)	
Single	1247(37.50%)	365(31.91%)		341(34.24%)	320(32.13%)	
Unknown	103(3.10%)	35(3.06%)		31(3.11%)	29(2.91%)	
Race			0.504			0.341
White	2842(85.47%)	987(86.28%)		843(84.64%)	858(86.14%)	
Others	483(14.53%)	157(13.72%)		153(15.36%)	138(13.86%)	
Sex			0.003			0.754
Male	1777(53.44%)	554(48.43%)		503(50.50%)	496(49.80%)	
Female	1548(46.56%)	590(51.57%)		493(49.50%)	500(50.20%)	
Tumor site			0.144			1.000
Pancreas Head	2441(73.41%)	865(75.61%)		775(77.81%)	775(77.81%)	
Pancreas Body Tail and	884(26.59%)	279(24.39%)		221(22.19%)	221(22.19%)	
Grade			0.179			1.000
I	362(10.89%)	102(8.92%)		84(8.43%)	84(8.43%)	
II	1529(45.98%)	558(48.78%)		488(49.00%)	488(49.00%)	
III/IV	1243(37.38%)	423(36.97%)		379(38.05%)	379(38.05%)	
Unknown	191(5.75%)	61(5.33%)		45(4.52%)	45(4.52%)	
T stage			0.560			1.000
T1	388(11.67%)	130(11.36%)		104(10.44%)	104(10.44%)	
T2	1892(56.90%)	662(57.87%)		618(62.05%)	618(62.05%)	
T3	839(25.23%)	271(23.69%)		226(22.69%)	226(22.69%)	
T4	206(6.20%)	81(7.08%)		48(4.82%)	48(4.82%)	
N stage			0.333			1.000
N0	82(2.47%)	36(30.85%)		19(1.91%)	19(1.91%)	
N1	2125(63.91%)	711(56.38%)		634(63.65%)	634(63.65%)	
N2	1118(33.62%)	397(12.77%)		343(34.44%)	343(34.44%)	
Chemotherapy			<0.001			1.000
Yes	1599(48.09%)	1059(92.57%)		913(91.67%)	913(91.67%)	
No/Unknown	1726(51.91%)	85(7.43%)		83(8.33%)	83(8.33%)	
RNE			0.527			1.000
<15	1573(47.31%)	525(45.89%)		439(44.08%)	439(44.08%)	
≥15	1728(51.97%)	613(53.58%)		557(55.92%)	557(55.92%)	
Unknown	24(0.72%)	6(0.53%)		0	0	

Supplementary Table 7. Features of patients with pancreatic head cancer in the non-radiotherapy group and the neoadjuvant radiotherapy group before and after PSM.

	Before PSM			After PSM		
Characteristics	Non-	Neoadjuvant	P	Non-	Neoadjuvant	P
Insurance Recode			0.039			1.000
Insured	4649(82.87%)	242(87.68%)		178(90.36%)	178(90.36%)	
No/unknown	961(17.13%)	34(12.32%)		19(9.64%)	19(9.64%)	
Marital status			0.054			0.259
Married	3445(61.41%)	185(67.03%)		130(65.99%)	142(72.08%)	
Single	1985(35.38%)	79(28.62%)		60(30.46%)	52(26.40%)	
Unknown	180(3.21%)	12(4.35%)		7(3.55%)	3(1.52%)	
Age			<0.001			0.484
< 60	1377(24.55%)	103(37.32%)		70(35.53%)	64(32.49%)	
60-69	1792(31.94%)	106(38.41%)		86(43.66%)	82(41.62%)	
≥70	2441(43.51%)	67(24.27%)		41(20.81%)	51(25.89%)	
Race			0.006			0.122
White	4656(82.99%)	246(89.13%)		161(81.73%)	173(87.81%)	
Others	954(17.01%)	30(10.87%)		36(18.27%)	24(12.18%)	
Sex			0.724			0.481
Male	2744(48.91%)	138(50.00%)		104(52.79%)	97(49.24%)	
Female	2866(51.09%)	138(50.00%)		93(47.21%)	100(50.76%)	
Grade			<0.001			1.000
I	633(11.28%)	19(6.88%)		12(6.09%)	12(6.09%)	
II	2504(44.63%)	86(31.16%)		75(38.07%)	75(38.07%)	
III/IV	2110(37.62%)	72(26.09%)		51(25.89%)	51(25.89%)	
Unknown	363(6.47%)	99(35.87%)		59(29.95%)	59(29.95%)	
T stage			<0.001			0.092
T1	725(12.92%)	10(3.62%)		21(10.66%)	8(4.06%)	
T2	3380(60.25%)	119(43.12%)		93(47.21%)	103(52.28%)	
T3	1169(20.84%)	52(18.84%)		38(19.29%)	41(20.82%)	
T4	336(5.99%)	95(34.42%)		45(22.84%)	45(22.84%)	
N stage			<0.001			1.000
N0	110(1.96%)	70(25.36%)		28(14.21%)	28(14.21%)	
N1	3349(59.70%)	173(62.68%)		139(70.56%)	139(70.56%)	
N2	2151(38.34%)	33(11.96%)		30(15.23%)	30(15.23%)	
Chemotherapy			<0.001			1.000
Yes	3195(56.95%)	275(99.64%)		197(100%)	197(100%)	
No/Unknown	2415(43.05%)	1(0.36%)		0	0	
RNE			<0.001			1.000
<15	2303(41.05%)	138(50.00%)		90(45.69%)	90(45.69%)	
≥15	3267(58.24%)	131(47.46%)		106(53.81%)	106(53.81%)	
Unknown	40(0.71%)	7(2.54%)		1(0.50%)	1(0.50%)	

Supplementary Table 8. Features of patients with pancreatic head cancer in the non-radiotherapy group and the adjuvant radiotherapy group before and after PSM.

	Before PSM			After PSM		
Characteristics	Non-	Adjuvant	P	Non-	Adjuvant	P
Insurance Recode			<0.001			1.000
Insured	4649(82.87%)	2193(75.39%)		1780(85.78%)	1780(85.78%)	
No/unknown	961(17.13%)	716(24.61%)		295(14.22%)	295(14.22%)	
Marital status			<0.001			0.988
Married	3445(61.41%)	1934(66.48%)		1444(69.59%)	1442(69.49%)	
Single	1985(35.38%)	888(30.53%)		608(29.30%)	609(29.35%)	
Unknown	180(3.21%)	87(2.99%)		23(1.11%)	24(1.16%)	
Age			<0.001			0.981
< 60	1377(24.55%)	929(31.94%)		612(29.49%)	607(29.25%)	
60-69	1792(31.94%)	1115(38.33%)		788(37.98%)	788(37.98%)	
≥70	2441(43.51%)	865(29.73%)		675(32.53%)	680(32.77%)	
Race			0.405			0.475
White	4656(82.99%)	2435(83.71%)		1728(83.28%)	1745(84.10%)	
Others	954(17.01%)	474(16.29%)		347(16.72%)	330(15.90%)	
Sex			0.033			0.827
Male	2744(48.91%)	1352(46.48%)		957(46.12%)	964(46.46%)	
Female	2866(51.09%)	1557(53.52%)		1118(53.88%)	1111(53.54%)	
Grade			<0.001			0.929
I	633(11.28%)	260(8.94%)		135(6.51%)	134(6.46%)	
II	2504(44.63%)	1449(49.81%)		1029(49.59%)	1039(50.07%)	
III/IV	2110(37.62%)	1057(36.34%)		827(39.86%)	826(39.81%)	
Unknown	363(6.47%)	143(4.91%)		84(4.04%)	76(3.66%)	
T stage			0.202			0.989
T1	725(12.92%)	390(13.41%)		231(11.13%)	225(10.84%)	
T2	3380(60.25%)	1751(60.19%)		1395(67.23%)	1397(67.33%)	
T3	1169(20.84%)	567(19.49%)		381(18.36%)	386(18.60%)	
T4	336(5.99%)	201(6.91%)		68(3.28%)	67(3.23%)	
N stage			0.899			0.971
N0	110(1.96%)	61(2.10%)		17(0.82%)	18(0.87%)	
N1	3349(59.70%)	1740(59.81%)		1254(60.43%)	1248(60.14%)	
N2	2151(38.34%)	1108(38.09%)		804(38.75%)	809(38.99%)	
Chemotherapy			<0.001			1.000
Yes	3195(56.95%)	2762(94.95%)		1961(94.51%)	1961(94.51%)	
No/Unknown	2415(43.05%)	147(5.05%)		114(5.49%)	114(5.49%)	
RNE			0.120			0.905
<15	2303(41.05%)	1257(43.21%)		792(38.17%)	792(38.17%)	
≥15	3267(58.24%)	1636(56.24%)		1280(61.69%)	1281(61.73%)	
Unknown	40(0.71%)	16(0.55%)		3(0.14%)	2(0.10%)	

Supplementary Table 9. Features of PDAC patients at other sites in the non-radiotherapy group and the neoadjuvant radiotherapy group before and after PSM.

	Before PSM			After PSM		
Characteristics	Non-	Neoadjuvant	P	Non-	Neoadjuvant	P
Insurance Recode			0.677			0.521
Insured	1793(84.38%)	88(86.27%)		65(81.25%)	69(86.25%)	
No/unknown	332(15.62%)	14(13.73%)		15(18.75%)	11(13.75%)	
Marital status			<0.001			0.062
Married	1307(61.51%)	88(86.27%)		56(70.00%)	67(83.75%)	
Single	740(34.82%)	12(11.77%)		23(28.75%)	11(13.75%)	
Unknown	78(3.67%)	2(1.96%)		1(1.25%)	2(2.50%)	
Age			0.006			0.196
< 60	631(29.69%)	34(33.33%)		36(45.00%)	25(31.25%)	
60-69	610(28.71%)	41(40.20%)		29(36.25%)	35(43.75%)	
≥70	884(41.60%)	27(26.47%)		15(18.75%)	20(25.00%)	
Race			0.606			0.563
White	1727(81.27%)	81(79.41%)		65(81.25%)	61(76.25%)	
Others	398(18.73%)	21(20.59%)		15(18.75%)	19(23.75%)	
Sex			0.187			0.268
Male	1069(50.31%)	44(43.14%)		44(55.00%)	36(45.00%)	
Female	1056(49.69%)	58(56.86%)		36(45.00%)	44(55.00%)	
Grade			<0.001			0.592
I	405(19.06%)	12(11.76%)		10(12.50%)	11(13.75%)	
II	890(41.88%)	33(32.35%)		25(31.25%)	27(33.75%)	
III/IV	653(30.73%)	18(17.65%)		20(25.00%)	13(16.25%)	
Unknown	177(8.33%)	39(38.24%)		25(31.25%)	29(36.25%)	
T stage			<0.001			0.068
T1	203(9.55%)	0		4(5.00%)	0	
T2	847(39.86%)	17(16.67%)		9(11.25%)	17(21.25%)	
T3	888(41.79%)	17(16.67%)		22(27.50%)	17(21.25%)	
T4	187(8.80%)	68(66.66%)		45(56.25%)	46(57.50%)	
N stage			<0.001			0.351
N0	92(4.33%)	47(46.08%)		33(41.25%)	30(37.50%)	
N1	1443(67.91%)	46(45.10%)		33(41.25%)	41(51.25%)	
N2	590(27.76%)	9(8.82%)		14(17.50%)	9(11.25%)	
Chemotherapy			<0.001			1.000
Yes	1002(47.15%)	101(99.02%)		78(97.50%)	79(98.75%)	
No/Unknown	1123(52.85%)	1(0.98%)		2(2.50%)	1(1.25%)	
RNE			0.008			0.765
<15	1116(52.52%)	60(58.82%)		41(51.25%)	44(55.00%)	
≥15	996(46.87%)	39(38.24%)		37(46.25%)	33(41.25%)	
Unknown	13(0.61%)	3(2.94%)		2(2.50%)	3(3.75%)	

Supplementary Table 10. Features of PDAC patients at other sites in the non-radiotherapy group and the adjuvant radiotherapy group before and after PSM.

	Before PSM			After PSM		
Characteristics	Non-	Adjuvant	P	Non-	Adjuvant	P
Insurance Recode			<0.001			1.000
Insured	1793(84.38%)	657(77.94%)		585(86.41%)	585(86.41%)	
No/unknown	332(15.62%)	186(22.06%)		92(13.59%)	92(13.59%)	
Marital status			0.031			0.781
Married	1307(61.51%)	562(66.67%)		457(67.50%)	462(68.24%)	
Single	740(34.82%)	253(30.01%)		207(30.58%)	199(29.40%)	
Unknown	78(3.67%)	28(3.32%)		13(1.92%)	16(2.36%)	
Age			<0.001			0.772
< 60	631(29.69%)	262(31.08%)		213(31.46%)	203(29.99%)	
60-69	610(28.71%)	302(35.82%)		249(36.78%)	248(36.63%)	
≥70	884(41.60%)	279(33.10%)		215(31.76%)	226(33.38%)	
Race			0.453			0.171
White	1727(81.27%)	675(80.07%)		554(81.83%)	534(78.88%)	
Others	398(18.73%)	168(19.93%)		123(18.17%)	143(21.12%)	
Sex			0.266			0.254
Male	1069(50.31%)	405(48.04%)		355(52.44%)	334(49.34%)	
Female	1056(49.69%)	438(51.96%)		322(47.56%)	343(50.66%)	
Grade			<0.001			0.218
I	405(19.06%)	81(9.61%)		55(8.12%)	60(8.86%)	
II	890(41.88%)	404(47.92%)		323(47.71%)	333(49.19%)	
III/IV	653(30.73%)	309(36.65%)		250(36.93%)	253(37.37%)	
Unknown	177(8.33%)	49(5.81%)		49(7.24%)	31(4.58%)	
T stage			0.074			0.750
T1	203(9.55%)	65(7.71%)		49(7.24%)	46(6.79%)	
T2	847(39.86%)	370(43.89%)		327(48.30%)	325(48.01%)	
T3	888(41.79%)	325(38.55%)		268(39.59%)	264(39.00%)	
T4	187(8.80%)	83(9.85%)		33(4.87%)	42(6.20%)	
N stage			0.728			0.834
N0	92(4.33%)	34(4.03%)		14(2.07%)	17(2.51%)	
N1	1443(67.91%)	585(69.40%)		479(70.75%)	481(71.05%)	
N2	590(27.76%)	224(26.57%)		184(27.18%)	179(26.44%)	
Chemotherapy			<0.001			1.000
Yes	1002(47.15%)	777(92.17%)		615(90.84%)	615(90.84%)	
No/Unknown	1123(52.85%)	66(7.83%)		62(9.16%)	62(9.16%)	
RNE			0.177			0.629
<15	1116(52.52%)	412(48.87%)		318(46.97%)	329(48.60%)	
≥15	996(46.87%)	424(50.30%)		356(52.59%)	343(50.66%)	
Unknown	13(0.61%)	7(0.83%)		3(0.44%)	5(0.74%)	

1.3 Neoadjuvant radiotherapy for locoregional Siewert type II gastroesophageal junction adenocarcinoma: A propensity scores matching analysis

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RESEARCH ARTICLE

Neoadjuvant radiotherapy for locoregional Siewert type II gastroesophageal junction adenocarcinoma: A propensity scores matching analysis

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Data Availability Statement: The data from this study is publicly available in the national cancer institute's Surveillance, Epidemiology, and End Results (SEER) database at https://seer.cancer.gov/. The URL of the database is http://seer.cancer.gov/ and the RRID of the database is nif-0000-21366.

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Abstract

Objective

To analyze the effect of neoadjuvant radiotherapy (nRT) on prognosis in patients with locoregional Siewert type II gastroesophageal junction adenocarcinoma (GEA).

Method

All patients pathologically diagnosed as Siewert type II GEA between 2004 and 2015 were retrieved from the Surveillance, Epidemiology and Final Results (SEER) database. We analyzed the impact of different treatment regimens on the prognosis in each stage. Survival analysis was performed by Kaplan-Meier (K-M) method. Multivariate Cox model and propensity score matching was further used to verify the results.

Results

4,160 patients were included in this study. The efficacy of nRT was superior to that of adjuvant radiotherapy (aRT) ($p = 0.048$), which was the same as that of surgery combined with chemotherapy ($p = 0.836$), but inferior to the overall survival (OS) of surgical treatment alone ($p<0.001$) in T1-2N0M0 patients. Patients receiving nRT had distinctly better survival than those receiving surgical treatment alone ($p = 0.008$), but had similar survival compared with patients treated with aRT ($p = 0.989$) or surgery combined with chemotherapy ($p = 0.205$) in the T3N0/T1-3N+M0 subgroup. The efficacy of nRT is clearly stronger than that of surgical therapy alone ($p<0.001$), surgery combined with chemotherapy ($p<0.001$), and aRT ($p = 0.008$) in patients with T4 stage. The survival analysis results were consistent before and after propensity score matching.

Conclusion

In these carefully selected patients, the present study made the following recommendations: nRT can improve the prognosis of patients with T3N0M0/T1-3N+M0 and T4 Siewert type II

Competing interests: The authors have declared that no competing interests exist.

Abbreviations: GEA, Gastroesophageal junction adenocarcinoma; GEJ, Gastroesophageal junction; SEER, Surveillance, Epidemiology, and End Results; nRT, Neoadjuvant radiotherapy; aRT, Adjuvant radiotherapy; PSM, Propensity score matching; OS, Overall survival; K-M, Kaplan-Meier; HR, Hazard ratio; RNE, Regional nodes examined; CI, Confidence interval.

GEA, and it seems to be a better treatment for T4 patients. Surgery alone seems to be sufficient, and nRT is not conducive to prolonging the survival of Siewert II GEA patients with T1-2N0M0 stage. Of course, further prospective trials are needed to verify this conclusion.

Introduction

It was estimated that about 18,000 new cases and 13,000 deaths from esophageal cancer occur in the United States in 2020 [1]. Adenocarcinoma, accounting for 75% of esophagus cancers, is mainly located in the lower esophagus and gastroesophageal junction (GEJ) in the US, and its incidence has raised significantly since the 1970s [2]. Most patients with gastroesophageal junction adenocarcinoma (GEA) often have a terrible prognosis, with a 5-year survival of less than 25%, because of late-stage diagnosis and rapid spread [3]. Siewert classification is ground on the anatomical distance between the tumor center and the GEJ, which divides GEA into three grouplets: Siewert type I, type II, and type III [4] and is now widely used in clinical practice. Siewert type I (distal esophageal adenocarcinoma) originates from the specialized intestinal area of the esophagus (such as Barrett's esophagus), which can infiltrate the esophagus-gastric junction from above(located 1–5 cm above the GEJ); Siewert type II (cardia cancer) originates from the junction of the esophagus and stomach(located 1cm above the GEJ to 2cm below); Siewert type III (subcardial gastric carcinoma) refers to the esophagogastric junction and the distal esophagus are infiltrated from the bottom inward(located 2–5 cm below the GEJ) [4]. It has been agreed, clinically, that type I and III GEA can be staged and treated with reference to carcinoma of esophagus and gastric cancer, respectively, due to the similarity in pathology and biological behavior [5]. Although the latest TNM staging system (8th edition) classifies Siewert type II as esophageal cancer, it is difficult to determine whether the origin is gastric cancer or esophageal cancer, so the optimal treatment has been controversial.

At present, surgery is the basis for the treatment of Siewert type II GEA patients without distant metastasis, and the pivotal goal is to achieve radical resection. However, the treatment outcome of only surgery is often disappointing, which has prompted the development of multimodal therapy for GEA [6]. Neoadjuvant chemotherapy is superior to surgical treatment alone for resectable esophagus cancer and GEA in some randomized clinical trials [7,8] and has been widely used clinically. Currently, neoadjuvant chemotherapy for type II GEA is mainly aimed at patients with locally advanced tumors that invade the gastric wall to a depth of T3 or T4, and it is expected that surgical resection is difficult or cannot achieve R0 resection. Its main chemotherapy regimen mainly refers to the neoadjuvant chemotherapy regimen for gastric cancer [9]. In addition, neoadjuvant radiotherapy (nRT) is mainly used to control local disease and improve marginal negative resection. However, because of the contradictory results of some clinical trials [10–12], whether patients with GEA can benefit from nRT is still inconclusive and needs further study.

Moreover, the necessity of nRT for the treatment of cavity organ tumors is controversial and some studies have shown that nRT does not improve the survival of these patients [13]. In addition, radiotherapy may lead to edema, fibrosis, and normal tissue structure disorder in the surrounding tissues of the tumor, which makes it difficult for the surgeon to perform radical resection and increases the probability of postoperative complications [14,15]. Therefore, some researchers have proposed to exclude radiotherapy in the treatment of rectal cancer [14]. Does the idea of abandoning radiotherapy apply to all cavity organ tumors? Therefore, this

study aims to explore the significance of nRT for Siewert II tumor patients, so as to propose individualized treatment strategies.

This study tried to use the information from the specific cancer database, the Surveillance, Epidemiology, and End Results (SEER) database, and divided the treatment strategies into surgery-only cohort, nRT cohort, adjuvant radiotherapy (aRT) cohort, and surgery plus chemotherapy cohort to analyze the influence of nRT on the prognosis of non-metastatic Siewert II GEA patients.

Methods

Data provenience

The present study extracted GEA cases from the database through SEER Stat software. The SEER database incorporates basic demographic data and some clinical characteristics, mainly from 18 cancer registration centers, accounting for about 28% of the American populace [16]. This study is based on a retrospective analysis in the SEER database and has no identifiable patient information in the database, which is anonymous. Therefore, written informed consent is not required in this study. The study is based on the ethical standards of the Helsinki Declaration as well as national and international norms.

Patient population

GEA patients are derived from the up-to-date version of the SEER database with additional treatment fields (SEER 18, 1973–2014 varying), which was based on the November 2016 submission and was released in March 2018. Although there is no specific Siewert classification in this database, we classified cancers whose 'Primary Site' is 'C16.0-Cardia NOS' and 'CS v0204 + Schema' is 'EsophagusGEJunction' as Siewert type II GEA referring to previous studies [17,18]. We retrieved all Siewert type II GEA patients diagnosed pathologically between the years 2004–2015 from the SEER database. The extracted information mainly incorporated basic information (age, sex, race, insurance, and marital status), specific pathological data (tumor grade, pathological type, TNM stage), treatment information (operation, chemotherapy and radiotherapy), other clinical data (lymph node dissection, tumor size) and follow-up data. The database used the 7th (2010–2105) and 6th (2004–2015) TNM staging systems from 2004 to 2015, so we converted the 6th edition to the 7th edition based on CS Extension and CS Lymph Nodes. We selected patients with surgery code 30–80 from the SEER database, which means that these patients have received at least partial gastrectomy. This study only included patients with non-metastatic GEA (T1-4NxM0), and the specific process of inclusion and exclusion can be seen in **Fig 1**. Both neoadjuvant radiotherapy and adjuvant radiotherapy patients received chemotherapy after screening. We divided the treatment strategy into four cohorts: surgery cohort (patients only received surgery), surgery combined with chemotherapy cohort (patients underwent surgery and chemotherapy, without radiotherapy), and nRT cohort (patients treated with nRT and surgical treatment, with chemotherapy), aRT cohort (patients received surgical treatment combined with chemotherapy and aRT).

Statistical analyses

Overall survival (OS), that is, from the time of diagnosis of GEA to death or the last follow-up, was the principal end point of the study. First, the chi-square test was applied to compare patient characteristics between treatment groups. The log-rank test was utilized to estimate and analyze patients' 3-year, 5-year, and median OS. We performed univariate and multivariate Cox models to analyze patients in each group and to determine risk ratios (HR) and 95%

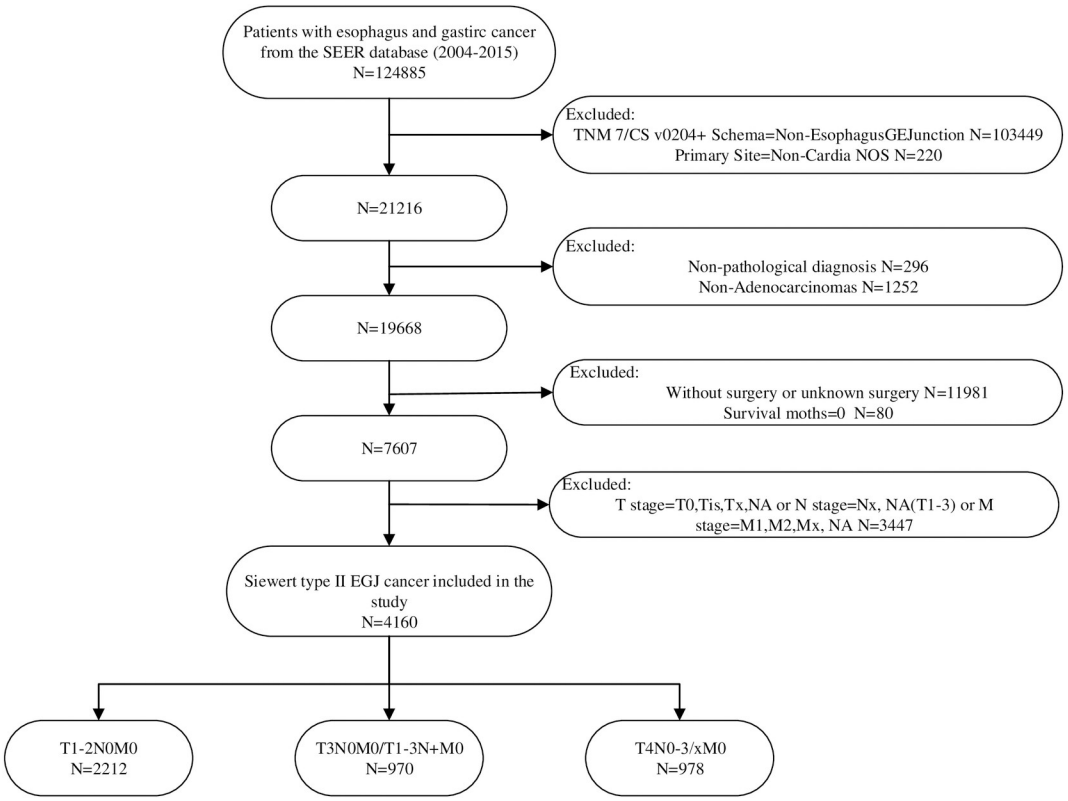

Fig 1. Inclusion and exclusion procedures for Siewert type II EGA patients from SEER database.

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confidence intervals (CI). This study uses propensity score matching to reduce the possibility of various treatment selection biases. Insurance, marital status, age, race, gender, pathological type, tumor grade, T stage, RNE and tumor size were used as matching criteria to estimate propensity scores in the T1-2N0M0 group. In addition to the above indicators, N stage was added as a matching criterion to estimate the propensity score in the T3N0M0/T1-3N+M0 and T4N0-3/xM0 group. Propensity score matching pairs were identified without replacement using a 1:1 nearest neighbor matching algorithm with caliper width determined by the recommendation from Austin (0.002 of the standard deviation of the logit of the PSs). All statistical analyses in this study were run under SPSS 26.0 software, and the inspection level of all statistical analyses was set to p-value less than 0.05. In addition, GraphPad Prism 8 software was used to draw the Kaplan-Meier (K-M) survival curve.

Result

Basic characteristics of the patients

Overall, after screening, 4,160 GEA patients were finally incorporated in this study. nRT was carried out in 24.57% (1,022) of the total population and around 12.19% (507) underwent aRT. About 45.70% (1,901) of patients received chemotherapy. The majority of the study group were married white, and 56.80% were older than 65. Most of the patients studied were in T1 stage, accounting for 42.54% (1,770), and 23.51% (978) were in T4 stage. Patients with tumor grades III and IV account for a high proportion (41.26%) of the population. The basic clinical and pathological features of the subjects were displayed in **Table 1**.

Table 1. The basic clinicopathological features of patients with Siewert type II EGA.

Features	T1-2N0M0(N = 2212)	T3N0M0/T1-3N+M0(N = 970)	T4N0-3/xM0 (N = 978)
	Number (%)	Number (%)	Number (%)
Insurance Recode			
No/Unknown	660(29.84%)	221(22.78%)	498(50.92%)
Insured	1552(70.16%)	749(77.22%)	480(49.08%)
Marital status			
Single/Unknown	730(33.00%)	317(32.68%)	340(34.76%%)
Married	1482(67.00%)	653(67.32%)	638(65.24%)
Race			
Non-whites	212(9.58%)	103(10.62%)	130(13.29%)
White	2000(90.42%)	867(89.38%)	848(86.71%)
Age			
<65	834(37.70%)	429(44.23%)	534(54.60%)
≥65	1378(62.30%)	541(55.77%)	444(45.40%)
Sex			
Female	510(23.06%)	186(19.18%)	218(22.29%)
Male	1702(76.94%)	784(80.82%)	760(77.71%)
Histology			
Adenocarcinomas	2056(92.95%)	809(83.40%)	784(80.16%)
Cystic, mucinous and serous neoplasms	156(7.05%)	161(16.60%)	194(19.84%)
Grade			
I	310(14.01%)	52(5.36%)	34(3.48%)
II	927(41.91%)	325(33.51%)	257(26.28%)
III/IV	636(28.75%)	519(53.51%)	636(65.03%)
Unknown	339(15.33%)	74(7.62%)	51(5.21%)
T stage			
T1	1760(79.57%)	10(1.03%)	-
T2	452(20.43%)	27(2.78%)	-
T3	-	933(96.19%)	-
T4	-	-	978(100%)
N stage			
N0	2212(100%)	746(76.90%)	185(18.92%)
N1	-	104(10.72%)	40(4.09%)
N2	-	70(7.22%)	13(1.33%)
N3	-	50(5.16%)	15(1.53%)
Unknown	-	-	725(74.13%)
Therapy			
Surgery alone	1721(77.80%)	240(24.74%)	235(24.03%)
Surgery + chemotherapy	114(5.15%)	139(14.34%)	182(18.61%)
nRT	269(12.17%)	473(48.76%)	280(28.63%)
aRT	108(4.88%)	118(12.16%)	281(28.73%)
RNE			
<15	1537(69.48%)	513(52.89%)	503(51.43%)
≥15	638(28.85%)	441(45.46%)	456(46.63%)
Unknown	37(1.67%)	16(1.65%)	19(1.93%)
Tumor size			
<3cm	883(39.92%)	82(8.45%)	29(2.97%)
≥3cm and <5cm	669(30.24%)	441(45.46%)	360(36.81%)

(*Continued*)

Table 1. (Continued)

Features	T1-2N0M0(N = 2212)	T3N0M0/T1-3N+M0(N = 970)	T4N0-3/xM0 (N = 978)
	Number (%)	Number (%)	Number (%)
≥5cm	120(5.42%)	301(31.04%)	431(44.07%)
Unknown	540(24.42%)	146(15.05%)	158(16.15%)

Abbreviations GEA: Gastroesophageal junction adenocarcinoma; nRT: Neoadjuvant radiotherapy; aRT: Adjuvant radiotherapy; RNE: Regional nodes examined.

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Survival analysis before PSM

First, the results of Cox regression model analysis in the entire group showed that age, marital and insurance status, grade, pathological type, T stage, N stage, treatment mode, and regional lymph node examination (RNE) are closely related to OS (Table 2). The tumor outcomes of nRT, aRT, and surgery combined with chemotherapy were significantly better than surgery alone for patients with non-stage IV Siewert type II GEA (p = 0.004). The influences of various therapy modes on the prognosis of patients were further analyzed in subgroups of different stages. The K-M curve of OS in each stage was manifested in Fig 2.

About 12.16% of patients received nRT in the T1-2N0M0 subgroup. The efficacy of nRT is superior to that of aRT (HR 0.738, 95%CI 0.533–0.920; p = 0.048), and it is the same as that of surgery plus chemotherapy (HR 0.996, 95%CI 0.699–1.336; p = 0.836). Nonetheless, the overall survival of patients who only received surgery was indeed longer than that of nRT in patients with T1-2N0M0 stage (HR 0.674, 95%CI 0.539–0.842; p<0.001) (Fig 3A–3C). The median survival was 70, 46, 95, and 114 months for nRT, aRT, surgery combined with chemotherapy, and surgery alone cohorts, respectively (Table 3).

The nRT was administered to 48.76% of patients in the T3N0/T1-3N+M0 subgroup. The prognosis of patients undergoing nRT distinctly won upon that of patients undergoing surgical treatment alone (HR 0.765, 95%CI 0.621–0.943; p = 0.008), with median survival times of 48 and 39 months, respectively. There was no striking disparity in the survival between nRT and aRT cohort (HR 1.002, 95%CI 0.766–1.311; p = 0.989; Median survival: 51 months) or surgery combined with chemotherapy cohort (HR 1.183, 95%CI 0.898–1.559; p = 0.205; Median survival: 42 months) (Fig 3D–3F).

Only 28.63% of patients received nRT in the T4 subgroup, but the efficacy of nRT was markedly superior to that of surgery alone (HR 0.323, 95%CI 0.265–0.392; p<0.001), surgery combined with chemotherapy (HR 0.657, 95%CI 0.523–0.825; p<0.001), and aRT (HR 0.775, 95%CI 0.640–0.938; p = 0.008), with median survival of 31 months, 10 months, 20 months, and 26 months, respectively (Fig 3G–3I).

Survival analysis after PSM

The multiple 1:1 PSM to compare different treatment regimens created three new comparison subgroups in stage T1-2N0M0 patients: nRT versus surgery alone (n = 252 pairs), nRT versus surgery combined with chemotherapy (n = 114 pairs), and nRT versus aRT (n = 108 pairs). Further K-M analysis found there was no striking disparity between the OS of the nRT cohort and the surgery combined with the chemotherapy cohort (HR 1.096, 95%CI 0.764–1.573; p = 0.615), and the survival advantage compared with the aRT cohort disappeared (HR 1.228, 95%CI 0.866–1.742; p = 0.237), while the survival of the surgical treatment cohort was still significantly superior to the nRT cohort (HR 0.702, 95%CI 0.541–0.909; p = 0.005) (Fig 4A–4C).

The PSM analysis of stage T3N0M0/T1-3N+M0 patients, which contained 234 ones per matched group, indicated the OS of nRT was superior to surgery alone (HR 1.256, 95% CI

Table 2. The Cox regression model analysis for OS of all Siewert type II GEA patients.

		Univariate analysis	Multivariate analysis		
Features	**classification**	**P**	**HR**	**95%CI**	**P**
Insurance status		<0.001			<0.001
	No/unknown		Reference	Reference	Reference
	Insured		0.848	0.775–0.929	<0.001
Marital status		<0.001			<0.001
	Single/Unknown		Reference	Reference	Reference
	Married		0.832	0.761–0.908	<0.001
Age, years		<0.001			<0.001
	<65		Reference	Reference	Reference
	≥65		1.773	1.619–1.941	<0.001
Race recode		0.068			
	No-whites				
	White				
Sex		0.373			
	Female				
	Male				
Histology		<0.001			0.038
	Adenocarcinomas		Reference	Reference	Reference
	Cystic, mucinous and serous neoplasms		1.134	1.007–1.278	0.038
Grade		<0.001			<0.001
	I		Reference	Reference	Reference
	II		1.084	0.910–1.290	0.368
	III/IV		1.425	1.197–1.696	<0.001
	Unknown		0.831	0.665–1.038	0.103
T stage		<0.001			<0.001
	T1		Reference	Reference	Reference
	T2		1.590	1.360–1.859	<0.001
	T3		1.816	1.564–2.109	<0.001
	T4		2.260	1.869–2.733	<0.001
N stage		<0.001			<0.001
	N0		Reference	Reference	Reference
	N1		1.550	1.234–1.946	<0.001
	N2		1.914	1.427–2.567	<0.001
	N3		2.892	2.160–3.870	<0.001
	Unknown		1.712	1.439–2.037	<0.001
Treatment methods		<0.001			0.004
	Surgery alone		Reference	Reference	Reference
	Surgery plus chemotherapy		0.898	0.757–0.961	0.046
	nRT		0.838	0.739–0.949	0.005
	aRT		0.824	0.714–0.950	0.008
RNE		0.042			<0.001
	<15		Reference	Reference	Reference
	≥15		0.703	0.641–0.771	<0.001
	Unknown		0.865	0.614–1.217	0.405
Tumor size		<0.001			0.126
	<3cm		Reference	Reference	Reference
	≥3cm and <5cm		1.089	0.950–1.247	0.220

(*Continued*)

Table 2. (Continued)

		Univariate analysis	Multivariate analysis		
Features	**classification**	**P**	**HR**	**95%CI**	**P**
	≥5cm		1.196	1.024–1.397	0.024
	Unknown		1.127	0.973–1.305	0.112

Abbreviations GEA: Gastroesophageal junction adenocarcinoma; nRT: Neoadjuvant radiotherapy; aRT: Adjuvant radiotherapy; RNE: Regional nodes examined; OS: Overall survival; HR: Hazard ratio; CI: Confidence interval.

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1.011–1.585; p = 0.042). In addition, nRT has no obvious survival superiority compared with aRT (HR 0.966, 95% CI 0.685–1.362; p = 0.840) after matching (n = 107 pairs). Similarly, no significant disparities in OS could be identified between the nRT and the surgery combined with chemotherapy groups (HR 1.133, 95% CI 0.813–1.580; p = 0.447) after PSM analysis (n = 124 pairs) (**Fig 4D–4F**).

The 1:1 PSM analysis among stage T4 patients, in which 96 patients treated with nRT were matched to 96 patients undergoing surgery alone, yielded OS favored the nRT cohort (HR 0.523, 95% CI 0.378–0.721; p <0.001). Versus the surgery plus chemotherapy group, the nRT group manifested a distinctly longer survival (HR 0.769, 95% CI 0.596–0.993; p = 0.033) after PSM analysis (n = 152 pairs). And matched patients with nRT, after matching (n = 249 pairs), were related to a significantly better OS than the aRT cohort (HR 0.752, 95% CI 0.597 to 0.942; p = 0.045) (**Fig 4G–4I**). The characteristics of patients before and after PSM in each group are shown in S1–S9 Tables.

Discussion

Surgical resection, as the main treatment for most operable GEA patients, has always been associated with poor survival, which may be due to the relative difficulty of some patients to achieve radical resection or some patients still have distant metastases after radical resection [19]. For this reason, the neoadjuvant therapy has become to be the most shining star in the field of clinical treatment of GEA, including preoperative chemotherapy and radiotherapy. Existing studies have confirmed that neoadjuvant chemotherapy is superior to surgery alone and is a comprehensive treatment method that is easily accepted by GEA patients [20,21]. Although some randomized trials have been conducted so far, the treatment of nRT in GEA patients remains controversial. The CROSS trial is a multiagency phase III clinical trial in which 366 ones with esophageal cancer or GEA were randomly allotted to the surgical-only, preoperative or postoperative chemoradiotherapy groups, confirming that preoperative chemoradiotherapy is superior to surgical treatment alone and that preoperative treatment is the standard treatment [22]. However, the results of a comparative study showed that preoperative radiotherapy did not significantly improve the OS of the lower esophagus and GEA [23]. What's more, another large retrospective analysis showed that nRT seems to enhance the venture of death among patients with resectable GEA [24].

Hence, we believe that non-metastatic GEA patients should be further staged to discuss the effect of nRT, rather than considered as a whole. First of all, although radical surgical resection and adjuvant treatment provide the possibility of curing localized diseases, most patients with clinical T3 and T4 tumors have a poor prognosis, especially T4 stage [25]. What's more, if patients with esophageal cancer have lymph node metastasis, the prognosis is generally frustrating, and adjuvant therapy is recommended [26]. In addition, whether induction therapy

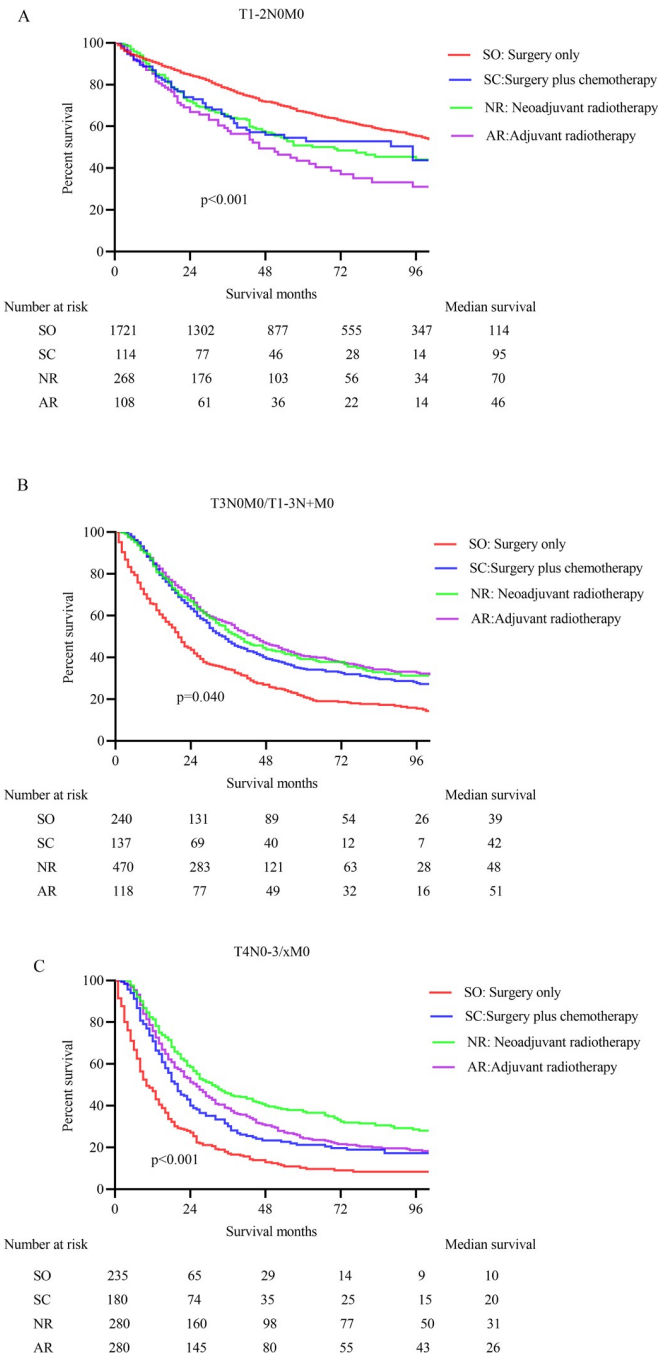

Fig 2. The overall survival estimated with the Kaplan-Meier method for non- metastatic Siewert type II EGA patients. A. The OS analysis of different treatment methods in T1-2N0M0 stage ($p<0.001$); B. The OS analysis of different treatment methods in T3N0/T1-3N+M0 stage ($p = 0.040$); C. The OS analysis of different treatment methods in T4 stage ($p<0.001$).

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can improve the survival of patients with early localized disease (T1-2N0M0) is now a fierce controversy [27,28]. With these questions in mind, GEA patients were separated into three subgroups: T1-2N0M0, T3N0/T1-3N+M0, and T4NxM0 to analyze the influence of various therapy options including nRT on the prognosis.

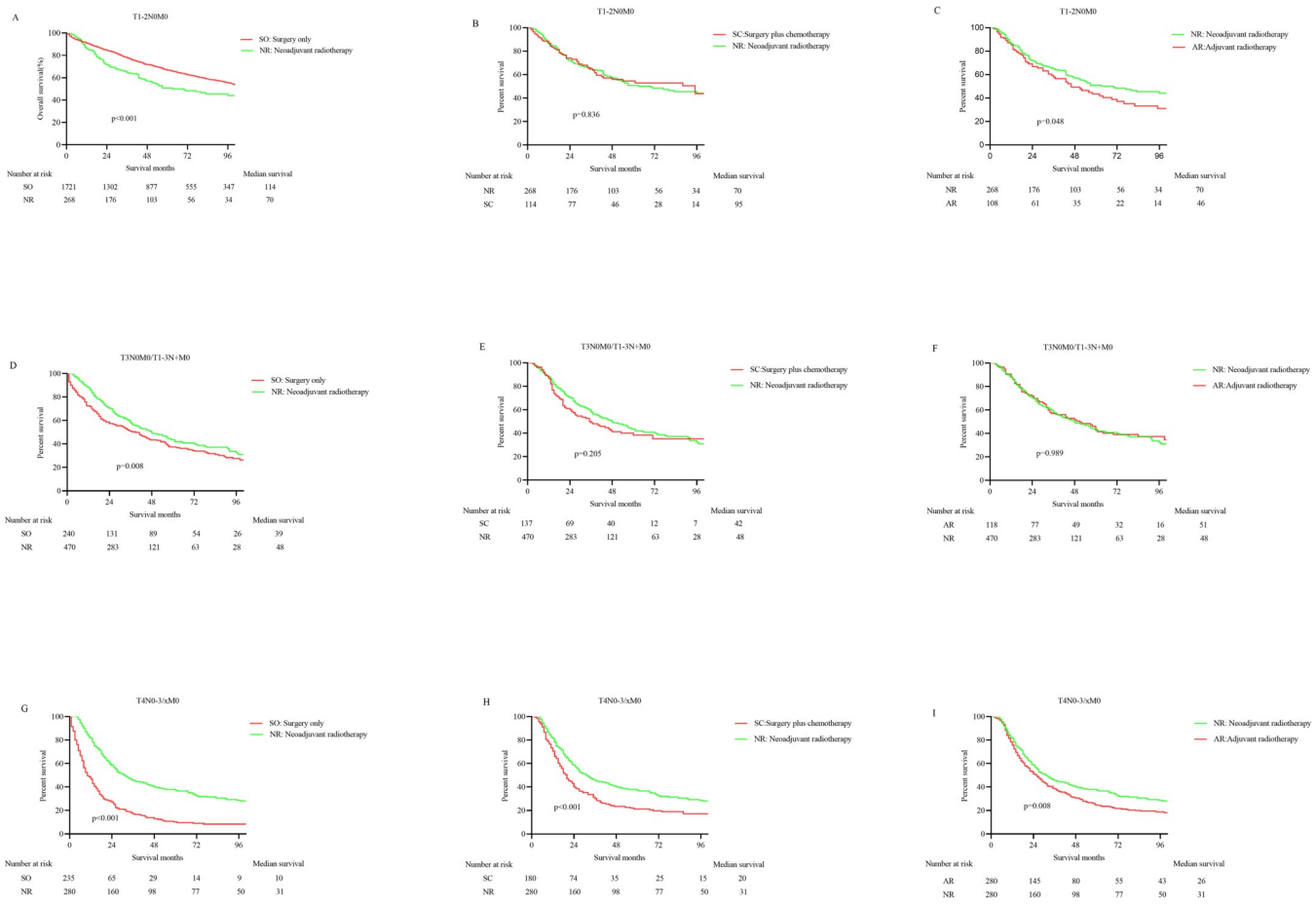

Fig 3. The K-M curves for OS in non- metastatic Siewert type II EGA patients at different stages before PSM. A. Surgery only vs Neoadjuvant radiotherapy in T1-2N0M0; B. Surgery combined with chemotherapy vs Neoadjuvant radiotherapy in T1-2N0M0; C. Neoadjuvant radiotherapy vs Adjuvant radiotherapy in T1-2N0M0; D. Surgery only vs Neoadjuvant radiotherapy in T3N0/T1-3N+M0; E. Surgery combined with chemotherapy vs Neoadjuvant radiotherapy in T3N0/T1-3N+M0; F. Neoadjuvant radiotherapy vs Adjuvant radiotherapy in T3N0/T1-3N+M0; G. Surgery only vs Neoadjuvant radiotherapy in T4; H. Surgery combined with chemotherapy vs Neoadjuvant radiotherapy in T4; I. Neoadjuvant radiotherapy vs Adjuvant radiotherapy in T4.

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For all we know, our study is the only study to evaluate the impact of nRT on the prognosis of non-metastatic GEA in different stages. Firstly, the results revealed that nRT was detrimental to prolonged survival in T1-2N0M0 patients. Not only for GEA but also for pancreatic cancer, the question whether neoadjuvant therapy should be used in early-stage patients has always been a question. The reason for opposing neoadjuvant therapy for patients with early resectable cancer is that neoadjuvant therapy may cause patients to miss the best opportunity for surgery, making lesions that could be resectable at R0 progress to incurable resection, or even distant metastases [29,30]. Our consequences are confirmed by other retrospective researches, indicating that routine use of neoadjuvant induction therapy may be adverse rather than beneficial to survival in all T1-2N0M0 patients [31]. The real challenge for stage T1-2 esophageal or GEA remains to perfect the precision of the inspection of microscopic lymph node metastases, but currently imaging and endoscopy methods seem to be inadequate [31]. In addition, the T1-2N0M0 stage esophageal cancer or GEA is a localized disease in which the tumor infiltrates into the submucosal layer and may increase the risk of lymph node metastasis, but removal of tumor lesions and local lymph node dissection may be adequate to bring the disease under control, and additional neoadjuvant or adjuvant therapy may have no

Table 3. Multivariate Cox analysis of OS with various treatment methods, median survival and 3-year and 5-year OS.

TNM Stage	Treatments	Multivariate HR (95% CI)	P value	Median survival	3-year OS	5-year OS
T1-2N0M0			<0.001			
Only surgery		Reference		114	77.91%	66.94%
Surgery + chemotherapy		1.499(1.121–2.004)	0.006	95	64.82%	54.57%
nRT		1.465(1.195–1.795)	<0.001	70	64.62%	50.81%
aRT		1.829(1.402–2.386)	<0.001	46	57.83%	43.54%
T3N0/T1-3N+M0			0.008			
Only surgery		Reference		39	40.81%	27.39%
Surgery + chemotherapy		0.803(0.503–0.968)	0.041	42	54.66%	40.03%
nRT		0.755(0.612–0.932)	0.009	48	56.94%	42.61%
aRT		0.716(0.534–0.958)	0.025	51	58.06%	43.59%
T4N0-3/xM0			<0.001			
Only surgery		Reference		10	17.06%	9.74%
Surgery + chemotherapy		0.594(0.476–0.740)	<0.001	20	30.16%	21.29%
nRT		0.347(0.263–0.449)	<0.001	31	45.80%	37.08%
aRT		0.584(0.498–0.689)	<0.001	26	38.59%	24.35%

Abbreviations OS: Overall survival; HR: Hazard ratio; CI: Confidence interval; nRT: Neoadjuvant radiotherapy; aRT: Adjuvant radiotherapy.

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prognostic benefit [32]. Therefore, combined with our results, only surgery is advised as the main therapy for patients with stage T1-2N0M0 GEA.

The results of a European multicenter retrospective study, which collected data from 30 European centers of patients undergoing esophageal/ GEA surgery, suggest a remarkable survival advantage from nRT for T3N0M0 carcinoma of esophagus [33]. This also further confirms our findings that T3N0M0 should be considered as a locally advanced esophageal cancer like T1-3N+M0, which can benefit from neoadjuvant therapy, but the risk of postoperative complications will not increase significantly. The nRT, aRT, and surgery combined with chemotherapy all can prominently improve OS compared to only surgery for the large subgroup of T3N0/T1-3N+M0 patients, but the best treatment plan still needs further study. In addition, a review also has yielded similar results, showing that multimodal treatment combined with surgery, radiotherapy, and neoadjuvant therapy can improve the prognosis of most locally advanced operable esophageal and gastric adenocarcinomas, but there are still some controversies about the best treatment [34].

We observed that nRT improved the OS of T3N0M0/T1-3N+M0 and T4 stage GEA patients. Especially for T4 patients, nRT has a significantly better impact on survival than aRT and surgery combined with chemotherapy. Most of the GEA patients with stage T4 invade adjacent structures (such as lung, large blood vessels, and trachea), and the prognosis is greatly dismal. Although modern surgical techniques have been significantly improved, these tumors are generally regarded as not directly surgically treated, which has also led to the increasingly prominent role of neoadjuvant therapy [35]. It is clear that patients with R0 resection have a longer survival period than R1 or R2 resection [36]. The nRT can transform unresectable or even inoperable tumors into resectable lesions, which cannot be achieved by postoperative adjuvant therapy. Analyses have shown that the median overall resection rate of T4 disease is 59% (35%-78%), and the R0 resection rate is 36.5% (32%-44%); this effect is mainly due to the role of neoadjuvant chemoradiotherapy [37]. Such achievement should enable patients with T4 stage esophagus or GEA without metastasis to be completely cured after R0 resection, thereby prolonging survival [38]. Therefore, a combination of nRT is likely the best choice

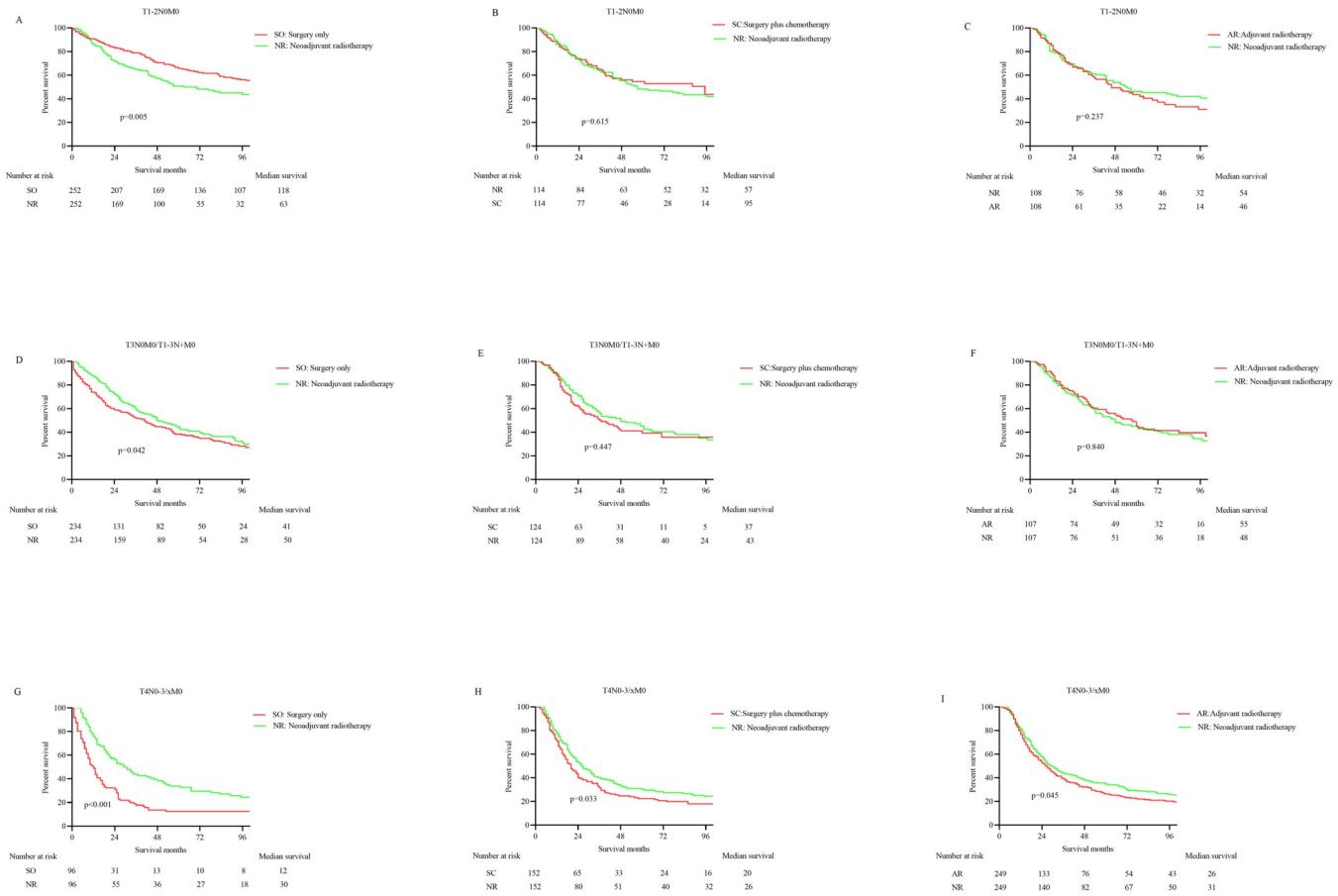

Fig 4. The K-M curves for OS in non- metastatic Siewert type II EGA patients at different stages after PSM. A. Surgery only vs Neoadjuvant radiotherapy in T1-2N0M0; B. Surgery combined with chemotherapy vs Neoadjuvant radiotherapy in T1-2N0M0; C. Neoadjuvant radiotherapy vs Adjuvant radiotherapy in T1-2N0M0; D. Surgery only vs Neoadjuvant radiotherapy in T3N0/T1-3N+M0; E. Surgery combined with chemotherapy vs Neoadjuvant radiotherapy in T3N0/T1-3N+M0; F. Neoadjuvant radiotherapy vs Adjuvant radiotherapy in T3N0/T1-3N+M0; G. Surgery only vs Neoadjuvant radiotherapy in T4; H. Surgery combined with chemotherapy vs Neoadjuvant radiotherapy in T4; I. Neoadjuvant radiotherapy vs Adjuvant radiotherapy in T4.

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when deciding the optimal scheme for treating patients with T4 GEA. Yet, the use of nRT in T4 patients is not ideal (only 28.63%) according to data extracted from the SEER database. Hence, the clinical importance of nRT for T4 GEA patients cannot be overemphasized.

Although we have extracted a large number of patient data with follow-up information from the SEER database, some of the inherent limitations of the database are related to the current research. However, as a national database, the SEER database does not provide information about the specific plan, dose, and duration of radiotherapy and chemotherapy. We can only determine whether the patient receives radiotherapy or chemotherapy and the sequence of radiotherapy and surgery. Among them, the information of radiation dose is particularly important. For example, a crossover test has shown that preoperative radiotherapy has survival benefits for GEA patients, but the dose of radiotherapy used is much lower than the dose often used in conventional neoadjuvant radiotherapy. Toxic and side effects caused by radiotherapy are an important issue that cannot be ignored in clinical practice. As the radiation dose increases, the toxicity may further increase. Different medical institutions in the United States have different radiation doses and techniques used in preoperative radiotherapy, which is a difference that cannot be balanced by the use of PSM in this study.

Another shortcoming is that there is no information on the patient's tumor regression after radiotherapy, which has a great impact on the patient's follow-up treatment and long-term survival. The SEER database, despite this limitation, is still a valuable database for studying cancer treatment. In addition, this study, as a retrospective analysis, perform propensity score matching to reduce some defects such as selection bias, but the conclusions should be ulteriorly proved by randomized controlled trials.

Conclusions

In these carefully selected patients, the present study made the following recommendations: nRT can improve the prognosis of patients with T3N0M0/T1-3N+M0 and T4 Siewert type II GEA, and it seems to be a better treatment for T4 patients. Surgery alone seems to be sufficient, and nRT is not conducive to prolonging the survival of Siewert II GEA patients with T1-2N0M0 stage. Of course, further prospective trials are needed to verify this conclusion.

Supporting information

S1 Table. Features of stage T1-2N0M0 patients in the surgery only group and the neoadjuvant radiotherapy group before and after PSM.
(DOCX)

S2 Table. Features of stage T1-2N0M0 patients in the surgery plus chemotherapy group and the neoadjuvant radiotherapy group before and after PSM.
(DOCX)

S3 Table. Features of stage T1-2N0M0 patients in the adjuvant radiotherapy group and the neoadjuvant radiotherapy group before and after PSM.
(DOCX)

S4 Table. Features of stage T3N0M0/T1-3N+M0 patients in the surgery only group and the neoadjuvant radiotherapy group before and after PSM.
(DOCX)

S5 Table. Features of stage T3N0M0/T1-3N+M0 patients in the surgery plus chemotherapy group and the neoadjuvant radiotherapy group before and after PSM.
(DOCX)

S6 Table. Features of stage T3N0M0/T1-3N+M0 patients in the adjuvant radiotherapy group and the neoadjuvant radiotherapy group before and after PSM.
(DOCX)

S7 Table. Features of stage T4 patients in the surgery only group and the neoadjuvant radiotherapy group before and after PSM.
(DOCX)

S8 Table. Features of stage T4 patients in the surgery plus chemotherapy group and the neoadjuvant radiotherapy group before and after PSM.
(DOCX)

S9 Table. Features of stage T4 patients in the adjuvant radiotherapy group and the neoadjuvant radiotherapy group before and after PSM.
(DOCX)

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Validation: Yuan Zhou.

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Writing – original draft: Yuan Zhou, MengXiang Tian, Dan Wang.

Writing – review & editing: Yuan Zhou, Cenap Güngör, Dan Wang.

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Supplementary Table 1. Features of stage T1-2N0M0 patients in the surgery only group and the neoadjuvant radiotherapy group before and after PSM.

	Before PSM			After PSM		
Characteristics	Srugery only	Neoadjuvant	P	Srugery only	Neoadjuvant	P
Insurance Recode			0.295			1.000
No/Unknown	523(30.39%)	73(27.24%)		67(26.59%)	67(26.59%)	
Insured	1198(69.61%)	195(72.76%)		185(73.41%)	185(73.41%)	
Marital status			0.094			1.000
Single/Unknown	577(33.53%)	76(28.36%)		69(27.38%)	69(27.38%)	
Married	1144(66.47%)	192(71.64%)		183(72.62%)	183(72.62%)	
Race			0.036			0.375
Non-whites	172(9.99%)	16(5.97%)		20(7.94%)	14(5.56%)	
White	1549(90.01%)	252(90.03%)		232(92.06%)	238(94.44%)	
Age			<0.001			1.000
<60	613(35.62%)	131(48.88%)		118(46.83%)	118(46.83%)	
≥60	1108(64.38%)	137(51.12%)		134(53.17%)	134(53.17%)	
Sex			<0.001			0.522
Female	422(24.52%)	39(14.55%)		38(15.08%)	33(13.10%)	
Male	1299(75.48%)	229(85.45%)		214(84.92%)	219(86.90%)	
Histology			0.005			1.000
Adenocarcinomas	1610(93.55%)	237(88.43%)		224(88.89%)	224(88.89%)	
Cystic, mucinous and	111(6.45%)	31(11.57%)		28(11.11%)	28(11.11%)	
Grade			<0.001			0.070
I	272(15.80%)	16(5.97%)		22(8.73%)	15(5.95%)	
II	725(42.13%)	112(41.79%)		111(44.05%)	108(42.86%)	
III/IV	447(25.97%)	103(38.43%)		101(40.08%)	94(37.30%)	
Unknown	277(16.10%)	37(13.81%)		18(7.14%)	35(13.89%)	
T stage			<0.001			1.000
T1	1480(86.00%)	134(50.00%)		131(51.98%)	131(51.98%)	
T2	241(14.00%)	134(50.00%)		121(48.02%)	121(48.02%)	
RNE			0.005			1.000
<15	1219(70.83%)	163(60.82%)		154(61.11%)	154(61.11%)	
≥15	477(27.72%)	99(36.94%)		94(37.30%)	94(37.30%)	
Unknown	25(1.45%)	6(2.24%)		4(1.59%)	4(1.59%)	
Tumor size			<0.001			0.683
<3cm	756(43.93%)	60(22.39%)		64(25.40%)	56(22.22%)	
≥3cm and <5cm	501(29.11%)	91(33.96%)		91(36.11%)	86(34.13%)	
≥5cm	70(4.07%)	32(11.94%)		26(10.32%)	29(11.51%)	
Unknown	394(22.89%)	85(31.71%)		71(28.17%)	81(32.14%)	

Supplementary Table 2. Features of stage T1-2N0M0 patients in the surgery plus chemotherapy group and the neoadjuvant radiotherapy group before and after PSM.

	Before PSM			After PSM		
Characteristics	surgery plus	Neoadjuvant	P	surgery plus	Neoadjuvant	P
Insurance Recode			0.868			0.563
No/Unknown	32(28.07%)	73(27.24%)		32(28.07%)	36(31.58%)	
Insured	82(71.93%)	195(72.76%)		82(71.93%)	78(68.42%)	
Marital status			0.254			0.391
Single/Unknown	39(34.22%)	76(28.36%)		39(34.22%)	32(28.07%)	
Married	75(65.78%)	192(71.64%)		75(65.78%)	82(71.93%)	
Race			0.019			0.397
Non-whites	15(13.16%)	16(5.97%)		15(13.16%)	10(8.77%)	
White	99(86.84%)	252(90.03%)		99(86.84%)	104(91.23%)	
Age			0.787			1.000
<60	54(47.37%)	131(48.88%)		54(47.37%)	54(47.37%)	
≥60	60(52.63%)	137(51.12%)		60(52.63%)	60(52.63%)	
Sex			0.054			0.128
Female	26(22.81%)	39(14.55%)		26(22.81%)	17(14.91%)	
Male	88(77.19%)	229(85.45%)		88(77.19%)	97(85.09%)	
Histology			0.768			1.000
Adenocarcinomas	102(89.47%)	237(88.43%)		102(89.47%)	102(89.47%)	
Cystic, mucinous and	12(10.53%)	31(11.57%)		12(10.53%)	12(10.53%)	
Grade			0.914			0.831
I	7(6.14%)	16(5.97%)		7(6.14%)	5(4.39%)	
II	45(39.47%)	112(41.79%)		45(39.47%)	43(37.72%)	
III/IV	48(42.11%)	103(38.43%)		48(42.11%)	48(42.11%)	
Unknown	14(12.28%)	37(13.81%)		14(12.28%)	18(15.78%)	
T stage			0.018			0.082
T1	72(63.16%)	134(50.00%)		72(63.16%)	59(51.75%)	
T2	42(36.84%)	134(50.00%)		42(36.84%)	55(48.25%)	
RNE			0.282			0.965
<15	60(52.63%)	163(60.82%)		60(52.63%)	62(54.39%)	
≥15	52(45.62%)	99(36.94%)		52(45.62%)	50(43.86%)	
Unknown	2(1.75%)	6(2.24%)		2(1.75%)	2(1.75%)	
Tumor size			0.434			0.338
<3cm	27(23.68%)	60(22.39%)		27(23.68%)	27(23.68%)	
≥3cm and <5cm	47(41.23%)	91(33.96%)		47(41.23%)	35(30.70%)	
≥5cm	10(8.77%)	32(11.94%)		10(8.77%)	12(10.53%)	
Unknown	30(26.32%)	85(31.71%)		30(26.32%)	40(35.09%)	

Supplementary Table 3. Features of stage T1-2N0M0 patients in the adjuvant radiotherapy group and the neoadjuvant radiotherapy group before and after PSM.

	Before PSM			After PSM		
Characteristics	Adjuvant	Neoadjuvant	P	Adjuvant	Neoadjuvant	P
Insurance Recode			0.640			0.659
No/Unknown	32(29.63%)	73(27.24%)		32(29.63%)	35(32.41%)	
Insured	76(70.37%)	195(72.76%)		76(70.37%)	73(67.59%)	
Marital status			0.193			0.469
Single/Unknown	38(35.19%)	76(28.36%)		38(35.19%)	33(30.56%)	
Married	70(64.81%)	192(71.64%)		70(64.81%)	75(69.44%)	
Race			0.005			0.252
Non-whites	9(8.33%)	16(5.97%)		9(8.33%)	4(3.70%)	
White	99(91.67%)	252(90.03%)		99(91.67%)	104(96.30%)	
Age			0.006			1.000
<60	36(33.33%)	131(48.88%)		36(33.33%)	36(33.33%)	
≥60	72(66.67%)	137(51.12%)		72(66.67%)	72(66.67%)	
Sex			0.166			0.201
Female	22(20.37%)	39(14.55%)		22(20.37%)	14(12.96%)	
Male	86(76.63%)	229(85.45%)		86(76.63%)	94(87.04%)	
Histology			0.008			0.280
Adenocarcinomas	106(98.15%)	237(88.43%)		106(98.15%)	102(94.44%)	
Cystic, mucinous and	2(1.85%)	31(11.57%)		2(1.85%)	6(5.56%)	
Grade			0.072			0.074
I	15(13.89%)	16(5.97%)		15(13.89%)	6(5.56%)	
II	45(41.67%)	112(41.79%)		45(41.67%)	38(35.18%)	
III/IV	37(34.26%)	103(38.43%)		37(34.26%)	47(43.52%)	
Unknown	11(10.18%)	37(13.81%)		11(10.18%)	17(15.74%)	
T stage			0.002			0.069
T1	73(67.59%)	134(50.00%)		73(67.59%)	60(55.56%)	
T2	35(32.41%)	134(50.00%)		35(32.41%)	48(44.44%)	
RNE			<0.001			0.897
<15	94(87.04%)	163(60.82%)		94(87.04%)	96(88.89%)	
≥15	10(9.26%)	99(36.94%)		10(9.26%)	9(8.33%)	
Unknown	4(3.70%)	6(2.24%)		4(3.70%)	3(2.78%)	
Tumor size			0.029			0.207
<3cm	40(37.04%)	60(22.39%)		40(37.04%)	26(24.07%)	
≥3cm and <5cm	30(27.78%)	91(33.96%)		30(27.78%)	34(31.48%)	
≥5cm	8(7.40%)	32(11.94%)		8(7.40%)	12(11.11%)	
Unknown	30(27.78%)	85(31.71%)		30(27.78%)	36(33.34%)	

Supplementary Table 4. Features of stage T3N0M0/T1-3N+M0 patients in the surgery only group and the neoadjuvant radiotherapy group before and after PSM.

	Before PSM			After PSM		
Characteristics	Srugery only	Neoadjuvant	P	Srugery only	Neoadjuvant	P
Insurance Recode			<0.001			0.161
No/Unknown	80(33.33%)	87(18.51%)		79(33.76%)	65(27.78%)	
Insured	160(66.67%)	383(81.49%)		155(66.24%)	169(72.22%)	
Marital status			0.051			0.174
Single/Unknown	91(37.92%)	144(30.64%)		88(37.61%)	74(31.62%)	
Married	149(62.08%)	326(69.36%)		146(62.39%)	160(68.38%)	
Race			0.006			0.386
Non-whites	34(14.17%)	36(7.66%)		32(13.68%)	17(7.26%)	
White	206(85.83%)	434(92.34%)		202(86.32%)	217(92.74%)	
Age			<0.001			1.000
<60	56(23.33%)	247(52.55%)		56(23.93%)	56(23.93%)	
≥60	184(76.67%)	223(47.45%)		178(76.07%)	178(76.07%)	
Sex			0.002			0.125
Female	63(26.25%)	77(16.38%)		61(26.07%)	47(20.09%)	
Male	177(73.75%)	393(83.62%)		173(73.93%)	187(79.91%)	
Histology			0.198			0.128
Adenocarcinomas	209(87.08%)	392(83.40%)		203(86.75%)	191(81.62%)	
Cystic, mucinous and	31(12.92%)	78(16.60%)		31(13.25%)	43(18.38%)	
Grade			<0.001			0.544
I	11(4.58%)	30(6.38%)		11(4.70%)	17(7.26%)	
II	97(40.42%)	153(32.55%)		94(40.17%)	94(40.17%)	
III/IV	125(52.08%)	227(48.30%)		122(52.14%)	119(50.86%)	
Unknown	7(2.92%)	60(12.77%)		7(2.99%)	4(1.71%)	
T stage			0.421			1.000
T1	1 (0.42%)	7(1.49%)		1(0.43%)	1(0.43%)	
T2	6(2.50%)	10(2.13%)		4(1.71%)	4(1.71%)	
T3	233(97.08%)	453(96.38%)		229(97.86%)	229(97.86%)	
N stage			0.002			1.000
N0	207(86.25%)	369(78.51%)		207(88.46%)	207(88.46%)	
N1	15(6.25%)	50(10.64%)		13(5.56%)	13(5.56%)	
N2	8(3.33%)	42(8.94%)		7(2.99%)	7(2.99%)	
N3	10(4.17%)	9(1.91%)		7(2.99%)	7(2.99%)	
RNE			0.327			1.000
<15	126(52.50%)	266(56.60%)		123(52.56%)	123(52.56%)	
≥15	112(46.67%)	196(41.70%)		110(47.01%)	110(47.01%)	
Unknown	2(0.83%)	8(1.70%)		1(0.43%)	1(0.43%)	
Tumor size			<0.001			0.319
<3cm	18(7.50%)	49(10.43%)		18(7.69%)	28(11.97%)	
≥3cm and <5cm	115(47.92%)	208(44.26%)		112(47.86%)	99(42.31%)	
≥5cm	94(39.17%)	116(24.68%)		91(38.89%)	90(38.46%)	
Unknown	13(5.41%)	97(20.63%)		13(5.56%)	17(7.26%)	

Supplementary Table 5. Features of stage T3N0M0/T1-3N+M0 patients in the surgery plus chemotherapy group and the neoadjuvant radiotherapy group before and after PSM.

	Before PSM			After PSM		
Characteristics	Srugery plus	Neoadjuvant	P	Srugery plus	Neoadjuvant	P
Insurance Recode			0.752			0.076
No/Unknown	27(19.71%)	87(18.51%)		24(19.35%)	37(29.84%)	
Insured	110(80.29%)	383(81.49%)		100(80.65%)	87(70.16%)	
Marital status			0.623			0.259
Single/Unknown	45(32.85%)	144(30.64%)		39(31.45%)	31(25.00%)	
Married	92(67.15%)	326(69.36%)		85(68.55%)	93(75.00%)	
Race			0.338			0.535
Non-whites	14(10.22%)	36(7.66%)		11(8.87%)	15(12.10%)	
White	123(89.78%)	434(92.34%)		113(91.13%)	109(87.90%)	
Age			0.071			1.000
<60	60(43.80%)	247(52.55%)		56(45.16%)	56(45.16%)	
≥60	77(56.20%)	223(47.45%)		68(54.84%)	68(54.84%)	
Sex			0.768			0.866
Female	21(15.33%)	77(16.38%)		20(16.13%)	22(17.74%)	
Male	116(84.67%)	393(83.62%)		104(83.87%)	102(82.26%)	
Histology			0.397			1.000
Adenocarcinomas	110(80.29%)	392(83.40%)		101(81.45%)	101(81.45%)	
Cystic, mucinous and	27(19.71%)	78(16.60%)		23(18.55%)	23(18.55%)	
Grade			0.001			0.207
I	6(4.38%)	30(6.38%)		5(4.03%)	10(8.06%)	
II	36(26.28%)	153(32.55%)		34(27.42%)	41(33.06%)	
III/IV	90(65.69%)	227(48.30%)		80(64.52%)	65(52.42%)	
Unknown	5(3.65%)	60(12.77%)		5(4.03%)	8(6.46%)	
T stage			0.686			1.000
T1	1 (0.73%)	7(1.49%)		1(0.81%)	1(0.81%)	
T2	4(2.92%)	10(2.13%)		3(2.42%)	3(2.42%)	
T3	132(96.35%)	453(96.38%)		120(96.77%)	120(96.77%)	
N stage			<0.001			1.000
N0	95(69.34%)	369(78.51%)		95(76.61%)	95(76.61%)	
N1	17(12.41%)	50(10.64%)		15(12.10%)	15(12.10%)	
N2	11(8.03%)	42(8.94%)		10(8.06%)	10(8.06%)	
N3	14(10.22%)	9(1.91%)		4(3.23%)	4(3.23%)	
RNE			0.008			1.000
<15	57(41.61%)	266(56.60%)		53(42.74%)	53(42.74%)	
≥15	76(55.47%)	196(41.70%)		68(54.84%)	68(54.84%)	
Unknown	4(2.92%)	8(1.70%)		3(2.42%)	3(2.42%)	
Tumor size			0.400			0.843
<3cm	12(8.76%)	49(10.43%)		12(9.68%)	13(10.48%)	
≥3cm and <5cm	59(43.07%)	208(44.26%)		53(42.74%)	46(37.10%)	
≥5cm	43(31.39%)	116(24.68%)		36(29.03%)	40(32.26%)	
Unknown	23(16.78%)	97(20.63%)		23(18.55%)	25(20.16%)	

Supplementary Table 6. Features of stage T3N0M0/T1-3N+M0 patients in the adjuvant radiotherapy group and the neoadjuvant radiotherapy group before and after PSM.

	Before PSM			After PSM		
Characteristics	Adjuvant	Neoadjuvant	P	Adjuvant	Neoadjuvant	P
Insurance Recode			0.283			1.000
No/Unknown	27(22.88%)	87(18.51%)		22(20.56%)	22(20.56%)	
Insured	91(77.12%)	383(81.49%)		85(79.44%)	85(79.44%)	
Marital status			0.837			0.354
Single/Unknown	35(29.66%)	144(30.64%)		32(29.91%)	25(23.36%)	
Married	83(70.34%)	326(69.36%)		75(70.09%)	82(76.64%)	
Race			0.008			0.087
Non-whites	19(16.10%)	36(7.66%)		17(15.89%)	8(7.48%)	
White	99(83.90%)	434(92.34%)		90(84.11%)	99(92.52%)	
Age			0.743			0.784
<60	64(54.24%)	247(52.55%)		57(53.27%)	55(51.40%)	
≥60	54(45.76%)	223(47.45%)		50(46.73%)	52(48.60%)	
Sex			0.218			0.479
Female	25(21.19%)	77(16.38%)		22(20.56%)	17(15.89%)	
Male	93(78.81%)	393(83.62%)		85(79.44%)	90(84.11%)	
Histology			0.241			0.733
Adenocarcinomas	93(78.81%)	392(83.40%)		87(81.45%)	84(81.45%)	
Cystic, mucinous and	25(21.19%)	78(16.60%)		20(18.55%)	23(18.55%)	
Grade			0.001			0.765
I	5(4.24%)	30(6.38%)		5(4.67%)	8(7.48%)	
II	36(30.51%)	153(32.55%)		33(30.84%)	29(27.10%)	
III/IV	75(63.56%)	227(48.30%)		67(62.62%)	67(62.62%)	
Unknown	2(1.69%)	60(12.77%)		2(1.87%)	3(2.80%)	
T stage			0.186			0.101
T1	1 (0.85%)	7(1.49%)		1(0.93%)	6(5.61%)	
T2	6(5.08%)	10(2.13%)		5(4.67%)	8(7.48%)	
T3	111(94.07%)	453(96.38%)		101(94.40%)	93(86.91%)	
N stage			<0.001			1.000
N0	74(62.71%)	369(78.51%)		74(69.16%)	74(69.16%)	
N1	22(18.64%)	50(10.64%)		19(17.76%)	19(17.76%)	
N2	9(7.63%)	42(8.94%)		7(6.54%)	7(6.54%)	
N3	13(11.02%)	9(1.91%)		7(6.54%)	7(6.54%)	
RNE			0.896			0.704
<15	64(54.24%)	266(56.60%)		56(52.34%)	54(50.47%)	
≥15	52(44.07%)	196(41.70%)		49(45.79%)	49(45.79%)	
Unknown	2(1.69%)	8(1.70%)		2(1.87%)	4(3.74%)	
Tumor size			<0.001			0.154
<3cm	3(2.54%)	49(10.43%)		3(2.80%)	5(4.67%)	
≥3cm and <5cm	54(45.76%)	208(44.26%)		50(46.73%)	49(45.79%)	
≥5cm	48(40.68%)	116(24.68%)		43(40.19%)	32(29.91%)	
Unknown	13(11.02%)	97(20.63%)		11(10.28%)	21(19.63%)	

Supplementary Table 7. Features of stage T4 patients in the surgery only group and the neoadjuvant radiotherapy group before and after PSM.

	Before PSM			After PSM		
Characteristics	Srugery only	Neoadjuvant	P	Srugery only	Neoadjuvant	P
Insurance Recode			<0.001			1.000
No/Unknown	141(60.00%)	110(39.29%)		53(55.21%)	53(55.21%)	
Insured	94(40.00%)	170(60.71%)		43(44.79%)	43(44.79%)	
Marital status			<0.001			1.000
Single/Unknown	107(45.53%)	77(27.50%)		29(30.21%)	29(30.21%)	
Married	128(54.47%)	203(72.50%)		67(69.79%)	67(69.79%)	
Race			<0.001			0.391
Non-whites	42(17.87%)	17(6.07%)		15(15.63%)	10(10.42%)	
White	193(82.13%)	263(93.93%)		81(84.37%)	86(89.58%)	
Age			<0.001			1.000
<60	70(29.79%)	186(66.43%)		46(47.92%)	46(47.92%)	
≥60	165(70.21%)	94(33.57%)		50(52.08%)	50(52.08%)	
Sex			0.001			0.066
Female	65(27.66%)	45(16.07%)		24(25.00%)	13(13.54%)	
Male	170(72.34%)	235(83.93%)		72(75.00%)	83(86.46%)	
Histology			0.066			0.687
Adenocarcinomas	189(80.43%)	242(86.43%)		80(83.33%)	83(86.46%)	
Cystic, mucinous and	46(19.57%)	38(13.57%)		16(16.67%)	13(13.54%)	
Grade			0.006			1.000
I	7(2.98%)	14(5.00%)		2(2.08%)	2(2.08%)	
II	58(24.68%)	87(31.07%)		25(26.04%)	25(26.04%)	
III/IV	160(68.08%)	152(54.29%)		67(69.80%)	67(69.80%)	
Unknown	10(4.26%)	27(9.64%)		2(2.08%)	2(2.08%)	
N stage			0.312			1.000
N0	53(22.55%)	62(22.14%)		23(23.96%)	23(23.96%)	
N1	7(2.98%)	16(5.71%)		1(1.04%)	1(1.04%)	
N2	1(0.43%)	5(1.79%)		-	-	
N3	3(1.28%)	2(0.71%)		-	-	
Nx	171(72.76%)	195(69.65%)		72(75.00%)	72(75.00%)	
RNE			0.327			0.140
<15	136(57.87%)	176(62.86%)		53(55.21%)	65(67.71%)	
≥15	96(40.85%)	98(35.00%)		42(43.75%)	29(30.21%)	
Unknown	3(1.28%)	6(2.14%)		1(1.04%)	2(2.08%)	
Tumor size			<0.001			0.754
<3cm	6(2.55%)	11(3.93%)		2(2.08%)	2(2.08%)	
≥3cm and <5cm	94(40.00%)	107(38.21%)		40(41.67%)	42(43.75%)	
≥5cm	115(48.94%)	88(31.43%)		45(46.88%)	47(48.96%)	
Unknown	20(8.51%)	74(26.43%)		9(9.37%)	5(5.21%)	

Supplementary Table 8. Features of stage T4 patients in the surgery plus chemotherapy group and the neoadjuvant radiotherapy group before and after PSM.

	Before PSM			After PSM		
Characteristics	Srugery plus	Neoadjuvant	P	Srugery plus	Neoadjuvant	P
Insurance Recode			0.327			1.000
No/Unknown	79(43.89%)	110(39.29%)		63(41.45%)	63(41.45%)	
Insured	101(56.11%)	170(60.71%)		89(58.55%)	89(58.55%)	
Marital status			0.480			0.697
Single/Unknown	55(30.56%)	77(27.50%)		42(27.63%)	39(25.66%)	
Married	125(69.44%)	203(72.50%)		110(72.37%)	113(74.34%)	
Race			0.001			0.396
Non-whites	29(16.11%)	17(6.07%)		23(15.13%)	17(11.18%)	
White	151(83.89%)	263(93.93%)		129(84.87%)	135(88.82%)	
Age			0.161			1.000
<60	108(60.00%)	186(66.43%)		96(63.16%)	96(63.16%)	
≥60	72(40.00%)	94(33.57%)		56(36.84%)	56(36.84%)	
Sex			0.170			0.365
Female	38(21.11%)	45(16.07%)		30(19.74%)	23(15.13%)	
Male	142(78.89%)	235(83.93%)		122(80.26%)	129(84.87%)	
Histology			0.002			1.000
Adenocarcinomas	135(75.00%)	242(86.43%)		126(82.89%)	126(82.89%)	
Cystic, mucinous and	45(25.00%)	38(13.57%)		26(17.11%)	26(17.11%)	
Grade			0.002			1.000
I	3(1.67%)	14(5.00%)		3(1.97%)	3(1.97%)	
II	41(22.78%)	87(31.07%)		37(24.34%)	37(24.34%)	
III/IV	128(71.11%)	152(54.29%)		107(70.39%)	107(70.39%)	
Unknown	8(4.44%)	27(9.64%)		5(3.30%)	5(3.30%)	
N stage			0.061			1.000
N0	26(14.44%)	62(22.14%)		22(14.47%)	22(14.47%)	
N1	6(3.33%)	16(5.71%)		5(3.29%)	5(3.29%)	
N2	5(2.78%)	5(1.79%)		1(0.66%)	1(0.66%)	
N3	5(2.78%)	2(0.71%)		-	-	
Nx	138(76.67%)	195(69.65%)		124(81.58%)	124(81.58%)	
RNE			<0.001			0.749
<15	65(36.11%)	176(62.86%)		59(38.82%)	65(42.76%)	
≥15	110(61.11%)	98(35.00%)		89(58.55%)	84(55.26%)	
Unknown	5(2.78%)	6(2.14%)		4(2.63%)	3(1.98%)	
Tumor size			0.004			0.318
<3cm	5(2.78%)	11(3.93%)		5(3.29%)	3(1.97%)	
≥3cm and <5cm	53(29.44%)	107(38.21%)		46(30.26%)	59(38.82%)	
≥5cm	87(48.33%)	88(31.43%)		72(47.37%)	51(33.55%)	
Unknown	35(19.45%)	74(26.43%)		29(19.08%)	39(25.66%)	

Supplementary Table 9. Features of stage T4 patients in the adjuvant radiotherapy group and the neoadjuvant radiotherapy group before and after PSM.

	Before PSM			After PSM		
Characteristics	Adjuvant	Neoadjuvant	P	Adjuvant	Neoadjuvant	P
Insurance Recode			0.002			0.418
No/Unknown	147(52.50%)	110(39.29%)		119(47.79%)	110(41.45%)	
Insured	133(47.50%)	170(60.71%)		130(52.21%)	139(58.55%)	
Marital status			0.037			0.052
Single/Unknown	100(35.71%)	77(27.50%)		87(34.94%)	66(26.51%)	
Married	180(64.29%)	203(72.50%)		162(65.06%)	183(73.49%)	
Race			0.001			1.000
Non-whites	42(15.00%)	17(6.07%)		15(6.02%)	16(6.42%)	
White	238(85.00%)	263(93.93%)		234(93.98%)	233(93.58%)	
Age			0.096			1.000
<60	167(59.64%)	186(66.43%)		159(63.86%)	159(63.86%)	
≥60	113(40.36%)	94(33.57%)		90(36.14%)	90(36.14%)	
Sex			0.012			0.459
Female	69(24.64%)	45(16.07%)		42(16.87%)	36(14.46%)	
Male	211(75.36%)	235(83.93%)		207(83.13%)	213(85.54%)	
Histology			0.004			0.111
Adenocarcinomas	216(77.14%)	242(86.43%)		203(81.53%)	216(86.75%)	
Cystic, mucinous and	64(22.86%)	38(13.57%)		46(18.47%)	33(13.25%)	
Grade			<0.001			0.058
I	10(3.57%)	14(5.00%)		10(4.02%)	13(5.22%)	
II	71(25.36%)	87(31.07%)		68(27.31%)	76(30.52%)	
III/IV	194(69.29%)	152(54.29%)		168(67.47%)	148(59.44%)	
Unknown	5(1.78%)	27(9.64%)		3(1.20%)	12(4.82%)	
N stage			<0.001			1.000
N0	44(15.71%)	62(22.14%)		44(17.67%)	44(17.67%)	
N1	11(3.93%)	16(5.71%)		6(2.41%)	6(2.41%)	
N2	2(0.71%)	5(1.79%)		2(0.80%)	2(0.80%)	
N3	5(1.79%)	2(0.71%)		2(0.80%)	2(0.80%)	
Nx	218(77.86%)	195(69.65%)		195(78.32%)	195(78.32%)	
RNE			<0.001			0.160
<15	125(44.64%)	176(62.86%)		125(50.20%)	146(58.63%)	
≥15	150(53.57%)	98(35.00%)		119(47.79%)	98(39.36%)	
Unknown	5(1.79%)	6(2.14%)		5(2.01%)	5(2.01%)	
Tumor size			<0.001			0.059
<3cm	7(2.50%)	11(3.93%)		6(2.41%)	10(4.02%)	
≥3cm and <5cm	105(37.50%)	107(38.21%)		105(42.17%)	107(42.97%)	
≥5cm	120(42.86%)	88(31.43%)		91(36.55%)	88(35.34%)	
Unknown	48(17.14%)	74(26.43%)		47(18.87%)	44(17.67%)	

1.4 A Nomogram for Predicting Lymph Nodal Metastases in Patients with Appendiceal Cancers: An Analysis of SEER Database

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ORIGINAL RESEARCH

A Nomogram for Predicting Lymph Nodal Metastases in Patients with Appendiceal Cancers: An Analysis of SEER Database

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ABSTRACT

Backgrounds: Appendiceal cancers are usually diagnosed after appendectomy accidentally. The need for subsequent right hemicolectomy in these patients was determined by the potential risk of regional lymph node (LN) metastasis. Establishing a nomogram to forecast the potential risk of lymph node metastasis of appendiceal cancer could help in the next step of treatment.

Methods: Patients with appendiceal cancer undergoing surgery was queried in the American cancer database of Surveillance, Epidemiology and End Results database from 2004 to 2016. A nomogram was established based on Logistic regression model.

Results: Finally, 3,075 patients were diagnosed with appendectomy cancer from 2004 to 2016. Among them, there were 2028 (65.9%) cases with negative lymph nodes, 1047 (34.1%) cases with positive lymph nodes. Risk factors associated with lymph node metastasis include age, histological type, tissue grade, T stage, distant metastasis, and tumor size. We drew the ROC curves of the training group (0.754, $P < 0.001$) and the validation group (0.775, $P < 0.001$) respectively. C-index values of predictions were 0.772 (95%CI, 0.750-0.793) and 0.776 (95%CI, 0.746-0.807), and Brier score were 0.178 and 0.172 in training and validation group respectively. All of them showed excellent performance of the nomogram in our study.

Conclusion: A new nomogram was created to assess the potential risk of LN metastasis in patients of appendiceal cancer by utilizing age, tumor histology, tumor pathologic grade, tumor size, T-stage, and M-stage. The nomogram could provide a strong reference for the right hemicolectomy and facilitate clinic decision.

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KEYWORDS
Appendiceal cancer; nodal metastases; surveillance epidemiology and end results database; nomogram; right hemicolectomy; metastases

Introduction

The current epidemiological survey showed that the annual incidence of appendiceal cancer was about 0.12 per 100,000 people [1,2], which presented that appendiceal cancer is an infrequent cancer with mounting incidence. Furthermore, the prognosis of appendiceal cancer is poor since the aggressive malignancy and a late stage at diagnosis [1]. Moreover, most of patients with appendiceal cancer cannot be diagnosed preoperatively and usually found incidentally following routine appendectomy for signs and symptoms of acute appendicitis [3–5]. With the development of medical technology, more options, including simple appendectomy, right hemicolectomy and even large debulking procedures with the hyperthermic intraperitoneal chemotherapy, are available for the therapies of appendiceal cancer. However, it is controversial regarding the best treatment for appendiceal cancer [6–10].

It is a great challenge for surgeons to determine whether right hemicolectomy is appropriate to be performed for those patients, who was diagnosed as appendiceal cancer during surgery, with unknown status of lymph node (LN) metastasis [11]. Currently, the treatment of appendiceal adenocarcinoma mainly referred to the treatment guidelines for colon cancer, but there was no specific treatment guidelines [12]. Besides, some research recommended that performance of local right hemicolectomy should be based on tumor size and histology [13,14]. The treatment guidelines, published by National Comprehensive Cancer Network (NCCN), recommended that patients with $\leq$ 2 cm appendiceal carcinoid tumors can be treated by appendectomy alone. However, right hemicolectomy was recommended for appendiceal neuroendocrine tumor larger than 2 cm since the risk of LN metastasis increased with growing tumor [14]. The European society of neuroendocrine tumor (ENETS) appendix neuroendocrine occult cancer guidelines suggested right-side colon resection for patients with any of the following: 1 to 2 cm but edge positive or undefined, or

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deep in the appendix, the high level or vascular invasion, and all appendices neuroendocrine tumor patients $> 2\,cm$[13]. Although previous studies assessed the potential risk of LN metastasis, there was a lack of large-scale national database studies which could quantify the overall risk of LN metastasis in appendiceal cancer patients [15–17].

Therefore, the purpose of this study was to construct nomogram based on clinical factors by assessing the potential risk of LN metastasis in patients of appendiceal cancer by analyzing the SEER database.

Materials and methods

Patients source

The data of patients were derived from the Surveillance, Epidemiology, and End Results (SEER) database in this retrospective analysis. SEER database is the U.S. authoritative cancer statistics database, which records the incidence, mortality, and disease of millions of patients with malignant tumors in some states and counties in the U.S. Currently, SEER collects and releases cancer incidence and survival data from population-based cancer registries covering almost 34.6 percent of the U.S. population [18]. The SEER database is designed to reduce the cancer burden on the U.S. population. Tumor information in the database is standardized and regularly updated with SEERStat software. Tumor researchers all over the world obtain some data through application, which provides a good source of data for clinical researchers who lack clinical research data. In addition, SEER database has a large sample size and strong statistical efficacy, which makes studies based on SEER database of high clinical reference value.

Inclusion/exclusion criteria

The target population of this study was limited to the appendiceal cancer patients with surgical treatment in SEER database from 2004 to 2016. The following information for each patient was collected: Insurance, Age at diagnosis, Race, Sex, Histology, Regional nodes examined, AJCC T stage, AJCC M stage, Regional nodes positive, lymph nodes status and metastatic status, CS tumor size. Histopathology was classified using Histology recode - broad groupings and divided into cystic, mucinous and serous neoplasms, adenocarcinomas and adenomas, other. Tumor grades were classified according to SEER criteria: Grade I: Well differentiated; Grade II: Moderately differentiated; Grade III: Poorly differentiated; Grade IV: Undifferentiated and unknown. Lymph node metastasis was categorized according to Regional nodes positive: positive, negative and unknown. T and M stage were classified using the AJCC guidelines. Tumor size was classified according to CS Tumor size code: 999 as Unknown, 001-019, 991 and 992 as $< 2\,cm$, 020-988 and 993-995 as $\geq 2\,cm$, 000 as No mass/tumor found. Exclusion criteria: No regional lymph node examined (Regional nodes examined code: 0,99), unknown status regarding tumor grade, T stage, metastasis and tumor size. The final study sample contained 3,075 patients. (Figure 1). These samples were stochastically divided into two groups, a training group (n = 2,050) and a validation group (n = 1,025).

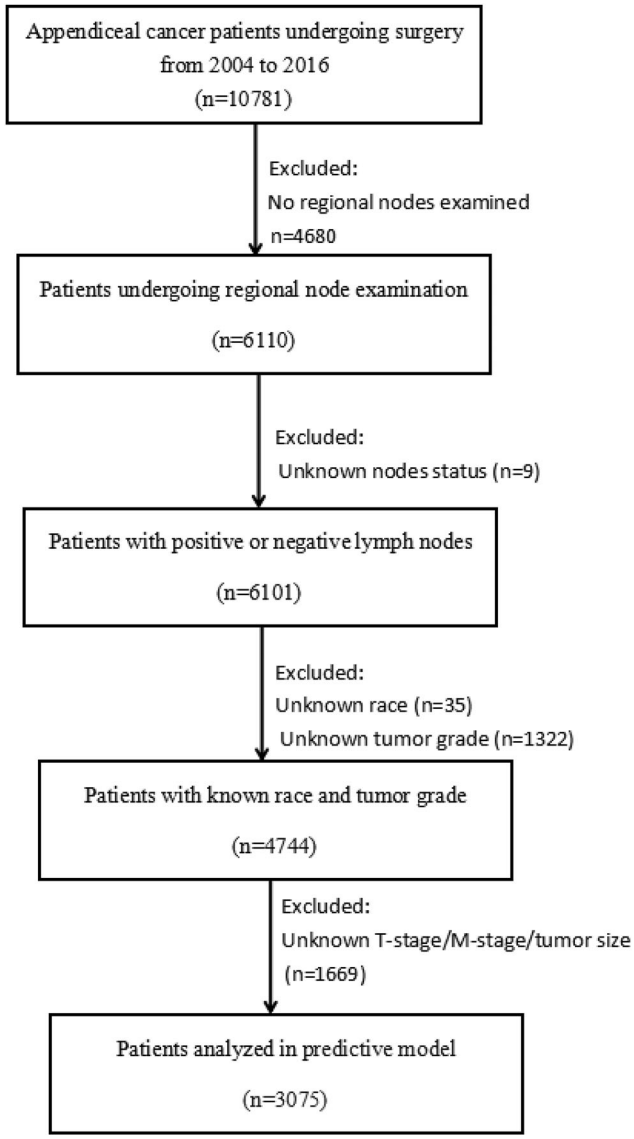

Figure 1. Inclusion and exclusion flowchart.

Statistical analyses

Firstly, Chi-square test was utilized for intergroup analysis. Then the single factor and multiple logistic regression models were analyzed. A 95% confidence interval (CI) and an odds ratio (OR) were used to evaluate. Variables with statistical differences in univariate analysis were involved in the model of multivariate logistic regression. On the basis of multiple logistic regression model, nomogram was constructed by software R 3.4.1 (Developed by the Institute for Statistics and Mathematics, Vienna, Austria; http://www.rproject.org/). IBM SPSS statistics trial ver. 25.0 (IBM, Armonk, NY, USA). The study stipulated all reported p-values ≤ 0.05 had statistical significance.

Table 1. Characteristics of patients in the training and validation group.

	Training group(n = 2050)			Validation group(n = 1025)		
Characteristic	Positive(n = 702)	Negative(n = 1348)	P	Positive(n = 345)	Negative(n = 680)	P
Age(years)			0.236			0.339
<50	148(21.08%)	297(22.03%)		84(24.35%)	159(23.38%)	
50-64	268(38.18%)	525(38.95%)		141(40.87%)	247(36.32%)	
65-79	213(30.34%)	422(31.30%)		95(27.54%)	211(31.04%)	
≥80	73(10.40%)	104(7.72%)		25(7.24%)	63(9.26%)	
Gender			0.809			0.459
Female	369(52.56%)	701(52.00%)		186(53.91%)	350(51.47%)	
Male	333(47.44%)	647(48.00%)		159(46.09%)	330(48.53%)	
Race			0.350			0.138
White	566(80.63%)	1103(81.82%)		275(79.71%)	570(83.82%)	
Black	81(11.54%)	162(11.02%)		44(12.75%)	60(8.82%)	
Other	55(7.83%)	83(6.16%)		26(7.54%)	50(7.36%)	
Histology			0.095			0.063
Adenomas and adenocarcinomas	407(57.98%)	725(53.78%)		170(49.27%)	372(54.71%)	
Cystic, mucinous and serous neoplasms	288(41.03%)	615(45.62%)		167(48.41%)	302(44.41%)	
Other	7(0.99%)	8(0.60%)		8(2.32%)	6(0.88%)	
Grade			<0.01			<0.01
Grade I	98(13.96%)	521(38.65%)		52(15.07%)	279(41.03%)	
Grade II	278(39.60%)	624(46.29%)		111(32.17%)	290(42.65%)	
Grade III	273(38.89%)	176(13.06%)		154(44.64%)	101(14.85%)	
Grade IV	53(7.55%)	27(2.00%)		28(8.12%)	10(1.47%)	
T stage			<0.01			<0.01
T1	27(3.85%)	228(16.91%)		9(2.61%)	104(15.29%)	
T2	26(3.70%)	169(12.54%)		11(3.19%)	75(11.03%)	
T3	219(31.20%)	466(34.57%)		85(24.64%)	248(36.47%)	
T4	430(61.25%)	485(35.98%)		240(69.56%)	253(37.21%)	
M stage			<0.01			<0.01
M0	390(55.56%)	1040(77.15%)		178(51.59%)	535(78.68%)	
M1	312(44.44%)	308(22.85%)		167(48.41%)	145(21.32%)	
Tumor size			<0.01			<0.01
<2cm	98(13.96%)	427(31.68%)		36(10.43%)	206(30.29%)	
≥2cm	604(86.04%)	921(68.32%)		309(59.57%)	474(69.71%)	

Table 2. Adjusted odds ratio (OR) with 95% confidence interval (CI) and p value for selected tumor and demographic characteristics as indicators of lymph node metastasis among appendiceal cancer patients.

Characteristics	OR	95%CI	P Value
Age(years)			0.017
<50	0.738	0.490-1.111	0.146
50-64	0.563	0.385-0.824	0.003
65-79	0.641	0.435-0.944	0.024
≥80	Reference		1.000
Histology			<0.001
Adenomas and adenocarcinomas	1.453	0.465-4.537	0.520
Cystic, mucinous and serous neoplasms	0.713	0.228-2.232	0.561
Other	Reference		1.000
Grade			<0.001
Grade I	0.157	0.092-0.269	<0.001
Grade II	0.292	0.176-0.486	<0.001
Grade III	0.793	0.470-1.338	0.385
Grade IV	Reference		1.000
T stage			<0.001
T1	0.298	0.187-0.475	<0.001
T2	0.309	0.193-0.493	<0.001
T3	0.713	0.560-0.908	0.006
T4	Reference		1.000
M stage			<0.001
M0	0.459	0.360-0.585	<0.001
M1	Reference		1.000
Tumor size			<0.001
<2cm	0.585	0.443-0.772	<0.001
≥2cm	Reference		1.000

Result

Demographics

This study enrolled 3,075 patients, including 2028 (65.9%) cases with negative LN and 1047 (34.1%) cases with positive LN. According to the 2:1 random grouping principle, patients were separated training team and validation team. The specific clinical data of the two groups of patients can be seen in Table 1. The percentages of patients with LN metastasis in the training cohort and the validation cohort were 34.2% (702/2050) and 33.6% (345/1075) respectively. The percentage of patients with distant metastases in the two groups was

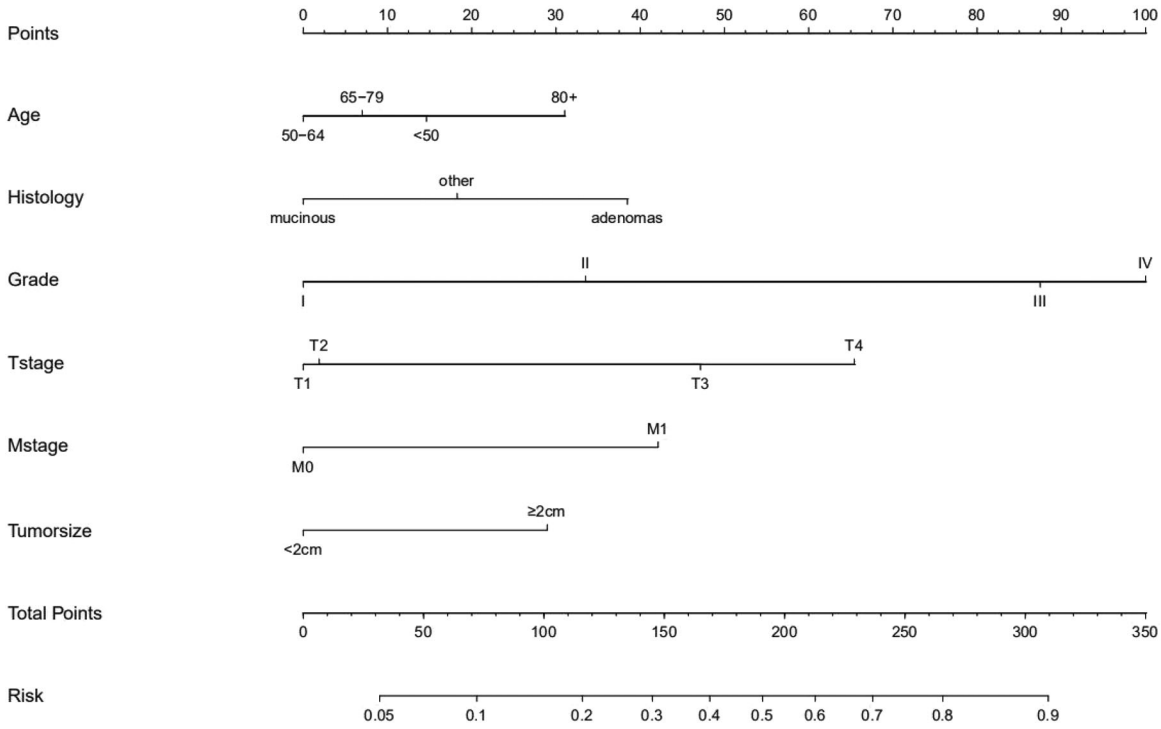

Figure 2. Nomograms for predicting nodal metastases in patients with appendiceal cancers.

Table 3. Model performance following internal validation.

	Training group	Validation group
C-index	0.772(0.750-0.794)	0.776(0.746-0.807)
Brier-score	0.178	0.172

30.2% (620/2050) and 30.4% (312/1025) respectively. Patients with high tumor grade ($p < 0.001$), Distance metastasis ($p < 0.001$), advanced T-stage ($p < 0.001$), and tumor size ($p < 0.001$) were related with LN positive disease.

Establishment of metastatic nomogram

The independent lymph node metastatic odds ratios (ORs) for Age, Gender, Race, Tumor pathologic grade, Tumor histology, T stage, distance metastasis and Tumor size for the logistic model were listed in Table 2. The most of characteristics highly associated with lymph node metastasis except gender and race. The crucially independent hazard factors determined by multivariate analyses were incorporated to form a nomogram for predicting lymph node metastasis. First, each risk variable was assigned a score using the score scale at the top of each nomogram; the ratio at the bottom of every nomogram (summing up the scales of all variables) was then utilized to forecast lymph node metastasis rates. The nomogram of LN metastasis forecast showed that tumor pathologic grade contributed the most to lymph node metastasis, then T stage, M stage, Histology, Age and tumor size (Figure 2).

Verification of lymph node metastatic nomogram

The internal verification for nomograms was carried out by Brier score, C-index, calibration and receiver operating

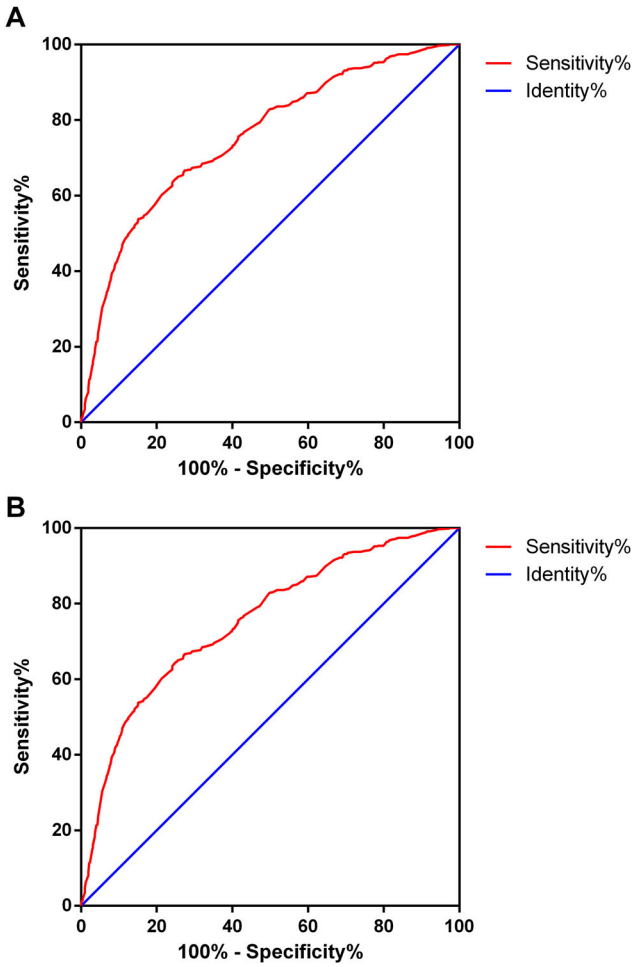

Figure 3. Area under the ROC of the nomogram in A the training cohort and B the validation cohort.

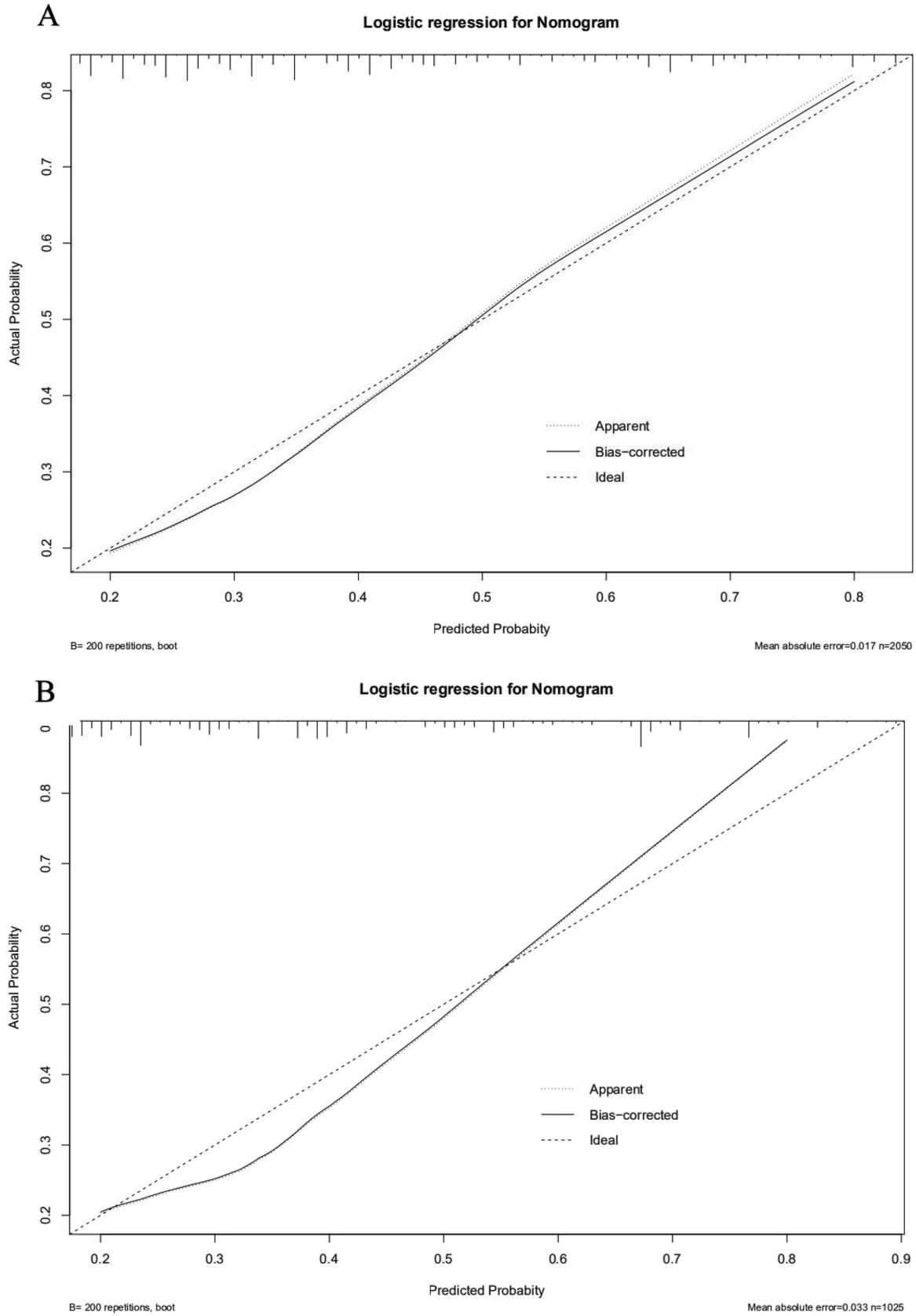

Figure 4. The calibration curves for predictions of nodal metastases in patients with appendiceal cancers A in the training cohort and B in the validation cohort.

characteristic (ROC) curve. C-index values of predictions were 0.772 (95% CI, 0.750-0.794) and 0.776 (95% CI, 0.746-0.807), and Brier score were 0.178 and 0.172 in training and validation group respectively (Table 3). Both of them suggested that these models made accurate predictions. The value of area under the ROCs were 0.754($p < 0.001$) in the

primary cohort and 0.775($p < 0.001$) in the validation cohort (Figure 3A and B), showing outstanding sensitivity and specificity of the nomogram. Through the calibration curves (Figure 4A and B), the forecast of nomogram testified to have superior accordance with actual LN metastasis.

Discussion

It is critical to assess the potential hazard of LN metastasis for patients diagnosed as appendiceal cancer after simple appendectomy. Therefore, we established a nomogram that correlated with the cumulative risk score for LN metastasis in appendiceal cancer patients, based primarily on clinical pathology and demographic variables obtained at the initial diagnosis in this study. A risk assessment system combining patient age, tumor grade, tumor histology, T-stage, M-stage and tumor size can effectively and accurately predict the likelihood of lymph node metastasis. It could also be included into clinical practice to direct the monitoring and treatment strategies of patients with appendiceal cancer.

Major international guidelines were controversial for the scope of surgery for appendiceal cancer diagnosed during incidental appendectomy [19]. The treatment guidelines, published by the NANETS and ENETS, both recommended patients with $\geq$ 2 cm appendiceal carcinoid tumors can be treated by right hemicolectomy and the NANETS guidelines recommended all appendiceal goblet cell cancers can be treated by right hemicolectomy. Within these guidelines, patients with 1 to 2 cm neuroendocrine tumors and any single high-risk feature were recommended to undergo right hemicolectomy [13,14]. However, there is still no clear consensus on whether patients with appendiceal cancer need to receive right hemicolectomy [20,21]. Although a predictive model of the potential risk of LN metastasis in the overall appendix cancer was studied by Ryan W. et al, it lacked the characterization of the nomogram and ignored some other important clinical factors [22,23]. Therefore, in order to guide clinical treatment better, this study was dedicated to establishing a complete scoring system and nomogram to make up for these shortcomings.

In this study, the potential risk of LN metastasis had a bearing on age, tumor grade, tumor histology, T stage, M stage and tumor size in appendiceal cancer patients. Among them, tumor grade was the most principal hazard factor of LN metastasis in this nomogram. Patients of undifferentiated appendiceal cancer owned the highest risk of LN metastasis which were consistent with most previous studies [24–27]. Moreover, T stage could also be used as an important predictive factors of LN metastasis for appendiceal cancer, which was confirmed by these research of Ryan W. Day and Partelli S [22,28]. The study of Mosquera C et al displayed that tumor size was associated with lymph node metastasis of appendicoma [23]. This study verified that patients with tumors $\geq$2 cm suffered a higher risk of LN metastasis than those <2 cm. Interestingly, the risk of lymph node metastasis did not increase completely with age. In fact, patients over 80-year old suffered the highest risk of lymph node metastasis but those less than 50 years old not the lowest. Moreover, this study found that lymph node metastasis related to distant metastasis closely. Previous studies also reported that patients' age and distant metastasis were related with LN metastasis in patients with appendiceal cancer [22,23].

We recognized several limitations in this study, such as the innate deficiencies of using SEER data. First, this study was a kind of retrospective study which might have selection bias because not all the appendiceal cancer patients had routine tests for lymph node dissection, under which circumstance the incidence of LN metastasis might be underestimated. In addition, due to the lack of data, some factors that previous studies confirmed that associated with LN metastasis in patients of appendiceal cancer were not included in this study, such as tumor lymphangiogenesis infiltration and carcinoembryonic antigen [29–32].

Despite these deficiencies, there were a good few advantages in our study: big data analysis could resent the treatment and outcome of appendiceal cancer better in U.S. In addition, we specifically studied predictive factors of LN metastasis in appendiceal cancer and mapped the nomogram. Visualization of risk factors can better guide the clinical decisions [33].

Conclusion

A new nomogram was created to assess the potential risk of LN metastasis in patients of appendiceal cancer by utilizing age, tumor histology, tumor pathologic grade, tumor size, T-stage, and M-stage. The nomogram could provide a strong reference for the right hemicolectomy and facilitate clinic decision.

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Disclosure statement

The authors declare that they have no competing interests.

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Ethics approval

Due to the public nature of all data, this study does not need the approval of the ethics committee.

Informed consent

As this study is a retrospective study, informed consent of patients was waived.

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1.5 Nomograms predicting overall survival and cancer-specific survival for patients with appendiceal cancer after surgery

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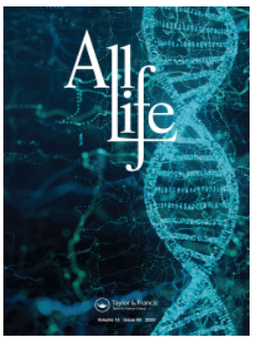

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Nomograms predicting overall survival and cancer-specific survival for patients with appendiceal cancer after surgery

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ABSTRACT

In order to establish nomograms that could forecast the postoperative survival for patients with appendiceal cancer after surgery, this study collected 5945 patients with surgically removed appendiceal cancer from the Surveillance, Epidemiology, and End Results database. Overall survival (OS) and cancer-specific survival (CSS) were analyzed by Cox regression analysis and nomograms. The population was randomly separated into a training group ($n = 3963$) and a validation group ($n = 1982$). Age, histological grade, T stage, N stage, regional nodes examination, tumor size, and CEA were independent prognostic factors for OS and were used in the nomogram. In addition, radiotherapy and chemotherapy were independent prognostic factors for CSS. The C-index values of the nomograms predicting postoperative OS and CSS were 0.76 (95% CI 0.74–0.78) and 0.80 (95% CI 0.78–0.82) in the training group and 0.77 (95% CI 0.74–0.79) and 0.81 (95% CI 0.78–0.84) in the validation group. Moreover, nomograms were better than traditional American Joint Committee on Cancer (AJCC) TNM 8th Edition Staging System in predicting prognosis derived from the results of DCA and ROC curves. In a word, we constructed new nomograms based on a large database that can accurately predict the OS and CSS of patients with appendiceal cancer after surgery.

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Appendiceal cancer; Overall survival; Cancer-specific survival; Nomogram; SEER database; AJCC TNM

Introduction

Appendiceal cancer, with reported incidences ranging from 0.1% to 17%, is a rare gastrointestinal cancer that accounts for only 4% of all intestinal tumors (Marmor et al. 2015; Siddharthan et al. 2019). Moreover, appendiceal cancer is associated with a fairly high mortality rate. The poor survival rate, to some extent, is due to higher rates of misdiagnosis and missed diagnosis. Appendiceal cancer is often misdiagnosed as acute inflammatory appendicitis as a result of appendix masses blocking the appendix, abnormal imaging findings of enlarged or perforated appendix, and symptoms of abdominal right lower quadrant pain (Siddharthan et al. 2019). Furthermore, recent studies testified that the morbidity and mortality of appendiceal cancer were on the rise (Shaib et al. 2017; Siegel et al. 2019). Therefore, appendiceal cancer should have been got more and more attention from surgeons and scholars.

The appendiceal adenocarcinoma, containing mucous, non-mucous (colonic), and signet-ring cell adenocarcinoma (McCusker et al. 2002; Ciarrocchi et al. 2016), ranks as the most primary malignancy among various pathological subtypes of appendiceal cancer (Ciarrocchi et al. 2015). Yet there is limited information on the treatment of appendiceal adenocarcinoma. The National Comprehensive Cancer Network (NCCN) recommends systemic chemotherapy for appendiceal adenocarcinoma in accordance with the NCCN guidelines for colon cancer because of the lack of large sample data (Benson et al. 2017). However, are the treatment methods fit to appendiceal cancer? It is unclear, especially for patients after surgery, which, mainly right hemicolectomy, is current the main treatment for appendiceal cancer (Turaga et al. 2013).

The Surveillance, Epidemiology, and End Results (SEER) database is the recognized authority on cancer

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statistics, recording the morbidity and mortality of patients with malignant tumors in the United States. SEER program publishes data about cancer incidence and survival rates based on population-based cancer registries that cover almost 34.6% of the U.S. population (Li et al. 2019). Nomogram can transform the complex regression model into a visual graph, making the results of the prediction model more readable and convenient for evaluation, and is able to provide the accuracy of individual prognostic prediction (Iasonos et al. 2008; Balachandran et al. 2015). In addition, it should be noted that some tumors in the American Joint Committee on Cancer (AJCC) TNM 8th Edition Staging System indicate that in a future version, they will consider nomogram for patient specific prognostic assessments (Lydiatt et al. 2017).

Therefore, the aim of our study was to create nomograms predicting postoperative overall survival (OS) and cancer-specific survival (CSS) in patients with appendiceal cancer after surgery based on the SEER database.

Material and methods

Patients

The study collected the data of all patients with appendiceal cancer from the SEER database during 2004–2016. The selection criteria were as follows: (1) patients with pathological diagnosis of appendiceal adenocarcinoma (histology recode: 8140–8389 and 8440–8499); (2) patients undergoing resection and with exact TNM stage information (refer to the AJCC TNM 8th Edition Staging System); (3) patients without distant metastases before surgery. According to these criteria, a total of 5945 patients were included in the study. The detailed screening process is shown in Figure 1. In this study, detailed information about patients with appendiceal cancer contained the age of diagnosis, race, gender, pathological grade, pathological type, TNM stage, type of surgery, radiotherapy and chemotherapy, regional nodes examination (RNE), tumor size, and CEA level. With reference to previous data (Enblad et al. 2018) and lymph node dissection experience in colorectal cancer, we grouped the number of lymph node examinations into 0–4, 4–7, 8–11, and ≥ 12.

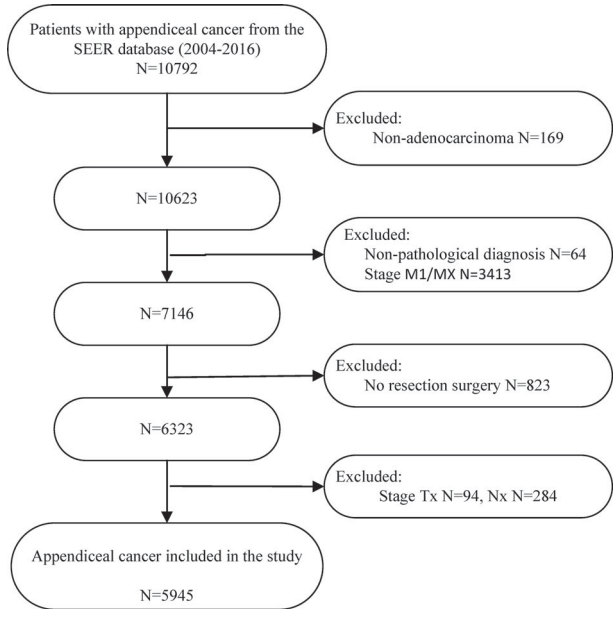

Figure 1. Flow chart of case inclusion and exclusion.

Statistical analysis

First, the appendiceal cancer patients meeting the inclusion criteria were randomly assigned to the training group ($n = 3963$) or the validation group ($n = 1982$) employing the randomization function of SPSS25.0 (IBM, Armonk, NY, USA). We used the R statistical software version 3.5 (http://www.r-project.org) with the survival and rms packages to build nomograms, and risk Regression package to evaluate the performance of the nomograms. SPSS 25.0 software was also utilized for univariate and multivariate Cox proportional hazard regression analysis to assess prognostic factors. Variables were calculated through the hazard ratio (HR) and the corresponding 95% confidence intervals (CI). The concordance index (C-index), the calibration diagram, the decision curve analysis (DCA) and time-dependent receiver operating characteristic (ROC) curve were used to evaluate the effect of nomograms. This study exists two primary endpoints, OS and CSS. OS was defined as the time interval between diagnosis and death due to any cause or the time of last follow-up with patients still alive. CSS was computed from the time of diagnosis to the time of death attributed to appendiceal cancer or still alive at last follow-up censored. In this study, all p values ≤ 0.05 were statistically significant.

Table 1. The basic and clinical features of appendiceal cancer.

Variables	Training group (n = 3963), n %		Validation group (n = 1982), n %		Total (n = 5945), n %	
Age						
< 50	1341	33.84%	654	33.00%	1995	33.56%
50–64	1352	34.12%	683	34.46%	2035	34.23%
65–79	952	24.02%	493	24.87%	1445	24.30%
≥ 80	318	8.02%	152	7.67%	470	7.91%
Race						
White	3303	83.35%	1664	83.96%	4967	83.55%
Black	394	9.94%	190	9.59%	584	9.82%
Other/unknown	266	6.71%	128	6.45%	394	6.63%
Sex						
Female	2070	52.23%	1022	51.56%	3092	52.01%
Male	1893	47.77%	960	48.44%	2853	47.99%
Grade						
Grade I	1579	39.84%	797	40.21%	2376	39.97%
Grade II	1171	29.55%	567	28.61%	1738	29.23%
Grade III- IV	451	11.38%	238	12.01%	689	11.59%
unknown	762	19.23%	380	19.17%	1142	19.21%
Histology						
Adenocarcinomas	2879	72.65%	1467	74.02%	4346	73.10%
cystic, mucinous and serous neoplasms	1084	27.35%	515	25.98%	1599	26.90%
T stage						
Tis-T1	1365	34.44%	729	36.78%	2094	35.22%
T2	444	11.20%	182	9.18%	626	10.53%
T3	1284	32.40%	639	32.24%	1923	32.35%
T4	870	21.96%	432	21.80%	1302	21.90%
N stage						
N0	3316	83.67%	1693	85.42%	5009	84.26%
N1	482	12.16%	214	10.80%	696	11.71%
N2	165	4.17%	75	3.78%	240	4.03%
Surgery						
Appendectomy	1906	48.09%	964	48.64%	2870	48.28%
Colectomy	2057	51.91%	1018	51.36%	3075	51.72%
Radiation						
Yes	71	1.79%	33	1.66%	104	1.75%
No/Unknown	3892	98.21%	1949	98.34%	5841	98.25%
Chemotherapy						
Yes	837	21.12%	414	20.89%	1251	21.04%
No/Unknown	3126	78.88%	1568	79.11%	4694	79.96%
Regional nodes examined						
0–3	1466	36.99%	761	38.43%	2227	37.46%
4–7	193	4.87%	111	5.60%	304	5.11%
8–11	276	6.96%	135	6.81%	411	6.91%
≥ 12	1996	50.37%	963	48.59%	2959	49.77%
unknown	32	0.81%	12	0.57%	44	0.75%
Tumor Size						
< 2cm	1587	40.05%	845	42.63%	2432	40.91%
≥ 2cm	1534	38.71%	718	36.23%	2252	37.88%
Unknown	842	21.24%	419	21.14%	1261	21.21%
CEA						
Positive	272	6.86%	111	5.60%	383	6.44%
Negative	525	13.25%	257	12.97%	782	13.15%
unknown	3166	79.89%	1614	81.43%	4780	80.41%

Results

Basic characteristics of the patients

A total of 5945 patients were involved in the study. Randomization was performed according to the ratio of 2:1, with 3963 patients in the training group and 1982 patients in the validation group. The detail information of patients, including age at diagnosis, race, gender, histological grade, type of pathology, TNM stage, RNE, type of surgery, radiotherapy and chemotherapy, tumor size and CEA was shown in Table 1. The total population was mainly female (3092, 52.01%). About 67.79% of the total population were younger than 65 years. A total of 2870(48.28%) patients underwent appendectomy and 3075(51.72%) underwent colectomy. 2959 patients (49.77%) examined more than 12 lymph nodes. The number of patients receiving chemotherapy was 1251, about 21.04%. Only 104 (1.75%) patients underwent radiotherapy.

Table 2. Univariate and multivariate analysis of OS in the training group.

	Univariate analysis	Multivariate analysis		
Characteristics	*P*	HR	95% CI	*P*
Age	0.000			0.000
< 50		Reference		
50–64		1.601	1.280–2.001	0.000
65–79		2.473	1.977–3.093	0.000
≥ 80		5.716	4.460–7.328	0.000
Race	0.064			
White		NA		
Black				
Other/unknown				
Sex	0.337			
Female		NA		
Male				
Grade	0.000			0.000
Grade I		Reference		
Grade II		1.427	1.174–1.734	0.000
Grade III–IV		1.839	1.458–2.320	0.000
Unknown		1.245	0.994–1.559	0.057
Histology	0.000			
Adenocarcinomas		Reference		
cystic, mucinous and serous neoplasms		0.980	0.843–1.139	0.788
T stage	0.000			0.000
Tis-T1		Reference		
T2		1.005	0.737–1.371	0.975
T3		1.213	0.954–1.543	0.115
T4		1.932	1.501–2.487	0.000
N stage	0.000			0.000
N0		Reference		
N1		1.594	1.300–1.955	0.000
N2		3.294	2.573–4.215	0.000
Surgery	0.093			
Appendectomy		NA		
Colectomy				
Radiation	0.000			
Yes		Reference		
No/Unknown		0.856	0.607–1.206	0.373
Chemotherapy	0.000			
Yes		Reference		
No/Unknown		0.939	0.782–1.128	0.502
Regional nodes examined	0.000			0.000
0–3		Reference		
4–7		0.844	0.632–1.128	0.252
8–11		0.878	0.685–1.126	0.306
≥ 12		0.588	0.489–0.706	0.000
unknown		0.779	0.430–1.410	0.409
Tumor size	0.000			0.012
< 2 cm		Reference		.
≥ 2 cm		1.343	1.087–1.660	0.006
unknown		1.362	1.095–1.694	0.006
CEA	0.000			0.000
Positive		Reference		
Negative		0.605	0.472–0.776	0.000
unknown		0.695	0.567–0.851	0.000

OS, Overall survival; CI, confidence interval; HR, hazard ratio; NA, Not Apply.

Construction of the OS and CSS nomograms

In the univariate Cox regression analysis, we discovered that both of OS and CSS did not relate to race, gender, and type of surgery in appendiceal cancer patients after surgery. Variables with significant difference in the univariate analysis were further involved in multivariate analysis. The multivariate analysis identified that postoperative OS related to 7 variables, including age at diagnosis, histological grade, T stage, N stage, RNE, tumor tissue size, and CEA (Table 2). The multivariate analysis demonstrated that postoperative CSS was associated with nine variables, including age at diagnosis, histological grade, T stage, N stage, RNE, radiotherapy and chemotherapy, tumor tissue size, and CEA (Table 3).

All of the independent prognostic factors were utilized to erect the predictive nomograms for OS and

Table 3. Univariate and multivariate analysis of CSS in the training group.

	Univariate analysis	Multivariate analysis		
Characteristics	*P*	HR	95%CI	*P*
Age	0.000			0.000
< 50		Reference		
50–64		1.231	0.939–1.613	0.132
65–79		1.672	1.258–2.224	0.000
≥ 80		3.206	2.242–4.584	0.000
Race	0.338			
White		NA		
Black				
Other/unknown				
Sex	0.895			
Female		NA		
Male				
Grade	0.000			0.000
Grade I		Reference		
Grade II		1.711	1.282–2.284	0.000
Grade III- IV		2.158	1.557–2.992	0.000
unknown		1.387	0.984–1.955	0.062
Histology	0.000			
Adenocarcinomas		Reference		
cystic, mucinous and serous neoplasms		1.078	0.878–1.325	0.472
T stage	0.000			0.000
Tis-T1		Reference		
T2		1.890	1.040–3.432	0.037
T3		2.600	1.585–4.266	0.000
T4		4.537	2.739–7.516	0.000
N stage	0.000			0.000
N0		Reference		
N1		1.903	1.459–2.483	0.000
N2		4.285	3.120–5.883	0.000
Surgery	0.382			
Appendectomy		NA		
Colectomy				
Radiation	0.000			
Yes		Reference		
No/Unknown		0.594	0.402–0.878	0.009
Chemotherapy	0.000			
Yes		Reference		
No/Unknown		.768	0.605–0.975	0.030
Regional nodes examined	0.000			0.001
0–3		Reference		
4–7		0.977	0.651–1.467	0.912
8–11		0.723	0.500–1.046	0.085
≥ 12		0.588	0.447–0.775	0.000
unknown		0.780	0.356–1.712	0.536
Tumor Size	0.000			0.025
< 2cm		Reference		
≥ 2cm		1.547	1.096–2.185	0.013
unknown		1.619	1.132–2.316	0.008
CEA	0.000			0.001
Positive		Reference		
Negative		0.562	0.405–0.780	0.001
unknown		0.629	0.479–0.825	0.001

OS, Cancer-specific survival; CI, confidence interval; HR, hazard ratio; NA, Not Apply.

CSS in this study. The prognostic nomograms for estimating the 2-, 3-, and 5-year CSS and OS was displayed in Figure 2. The nomogram assigned a score to each prognostic variable. These scores were added to the total scores of the 2-, 3-, and 5-year OS and CSS prediction scales for patients with appendiceal cancer after surgery to construct an internally validated prediction nomogram.

Verification of the OS and CSS nomograms

We used multiple methods to verify the predictive effects of the nomogram, including the C-index, the calibration diagram, the decision curve analysis and time-dependent ROC curve. The C-index of OS and CSS nomograms was 0.76 (95% CI 0.74–0.78) and 0.80 (95% CI 0.78–0.82) in training group, respectively. The

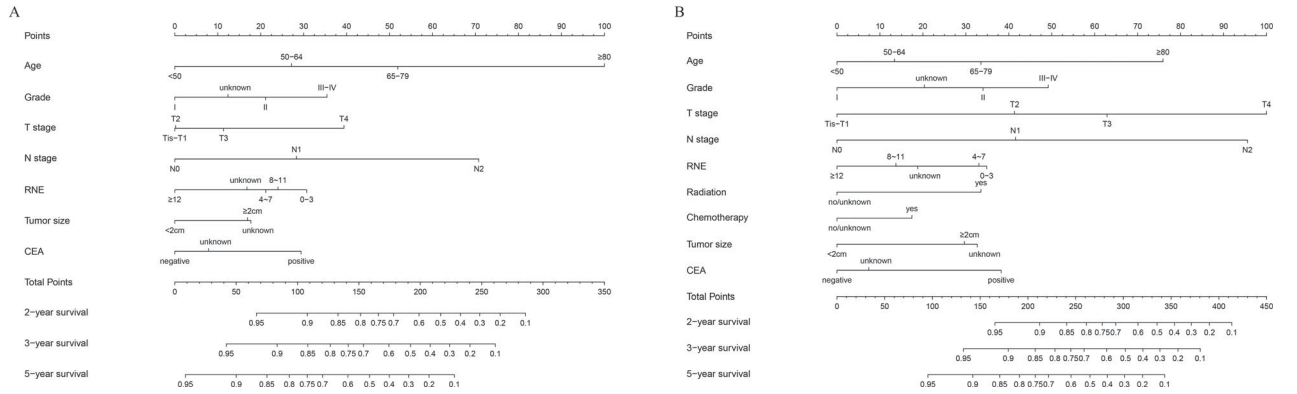

Figure 2. Nomograms that predict 2-year, 3-year, and 5-year overall survival (A) and cancer-specific survival (B) in patients with appendiceal cancer after surgery.

C-index for the validation group was 0.77 (OS, 95% CI 0.74–0.79) and 0.81 (CSS, 95% CI 0.78–0.84). These results attested that our prognostic nomograms were fairly accurate. And the calibration diagram indicated that the actual survival rate was very compatible with the nomogram prediction (Figure 3). The DCA curves suggested that the OS and CSS nomograms were superior to AJCC TNM 8th Edition Staging System regarding the predictive effect (Figure 4). It could be seen from time-dependent ROC curve results that nomograms have a better sensitivity and specificity comparing with AJCC TNM 8th Edition Staging System (Figure 5).

Patient risk stratification

The cut-off values of the OS total score obtained through X-tile analysis were 98 and 163. According to the cut-off values, patients were divided into low-risk, moderate-risk and high-risk groups. The Kaplan–Meier analysis found that the low-risk group held the best prognosis, with the 5-year survival rate reaching 88.1%. Followed by the moderate-risk group (the 5-year survival rate of 66.5%), and the high-risk group (the 5-year survival rate of 31.8%) (Figure 6A). The cut-off values of the CSS total score obtained through X-tile analysis were 161 and 241. Depending on the cutoff values, the low-risk group showed the best prognosis with a 5-year survival rate of 94.2%, followed by the moderate-risk group with a 5-year survival rate of 77.3%. The high-risk group existed the worst prognosis with a 5-year survival rate of 43.8% (Figure 6-B). Similarly, among the OS and CSS total scores of the validation group, the low-risk group had the best prognosis, the moderate-risk group followed, and the high-risk group had the worst prognosis (Figure 7).

Discussion

Appendiceal cancer is a rare tumor with a high degree of malignancy and an increasing incidence, and the main comprehensive treatment principles of appendiceal cancer mainly refer to right colon cancer. Although surgical and other treatments have made progress in local tumor control for appendiceal cancer, mortality remains high and long-term survival is worse than for colon cancer (Son et al. 2016). Therefore, to provide a personalized estimate of OS and CSS and risk stratification, we developed two nomograms to combine the independent risk prognostic factors after survival analysis for patients with postoperative appendiceal cancer.

Several obvious advantages can be found in this study compared with previous studies that established appendiceal cancer nomograms. First of all, we are the first to build nomograms specifically for the survival of patients with appendiceal cancer after surgery, while the previous nomograms did not specifically serve postoperative patients and was limited to mucinous adenocarcinoma (Xie et al. 2016; Yan et al. 2019). Furthermore, compared to the previous two studies which only included 1404 and 3234 patients (Xie et al. 2016; Yan et al. 2019), our nomogram was based on a larger data study, which included 5945 patients, and was validated in 1982 patients. Second, we included more commonly used prognostic factors in clinical practice compared with previous nomograms, such

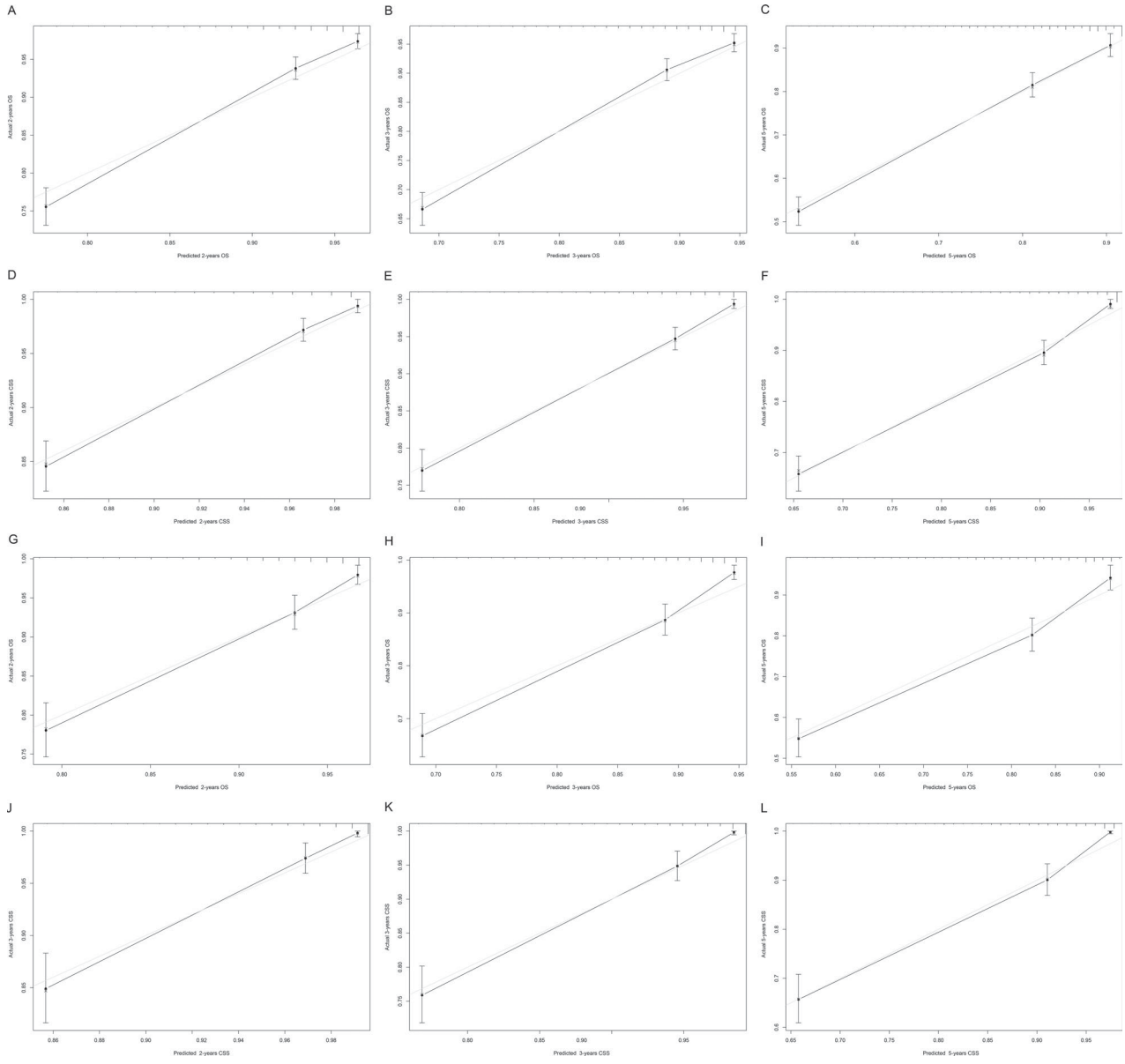

Figure 3. The calibration curve of nomograms. 2-year (A), 3-year (B), 5-year (C) overall survival nomogram calibration curves, 2-year (D), 3-year (E), 5-year (F) cancer-specific survival nomogram calibration curves in the training group; 2-year (G), 3-year (H), 5-year (I) overall survival nomogram calibration curves, 2-year (J), 3-year (K), 5-year (L) cancer-specific survival nomogram calibration curves in the validation group.

Note: The dashed line indicates an excellent match between actual survival results (*y*-axis) and nomogram predictions (*x*-axis). The closer the dotted line to the point, the higher the prediction accuracy. OS, overall survival; CSS, cancer-specific survival.

as preoperative CEA, chemotherapy and tumor size, which means that the prognosis of patients with appendiceal cancer can be more accurately predicted. Finally, the capability of our nomograms was assessed by C-index, DCA, ROC and calibration curve compared with previous studies. Both C-index and area under the curve are greater than 0.7, indicating that the model has a high accuracy, and the calibration curve is in good agreement with the 45° reference line. In addition, according to ROC analysis, the cut-off value was obtained for risk stratification, and the patients assigned to the high-risk group had a lower survival rate.

Our nomograms contained several prognostic factors commonly used in clinical practice. Age, pathological grade and T stage were key factors affecting the prognosis of patients with postoperative appendiceal cancer. Our research suggested that older age, poorly differentiated or undifferentiated pathological grade and deeper local tumor invasion lead to a worse

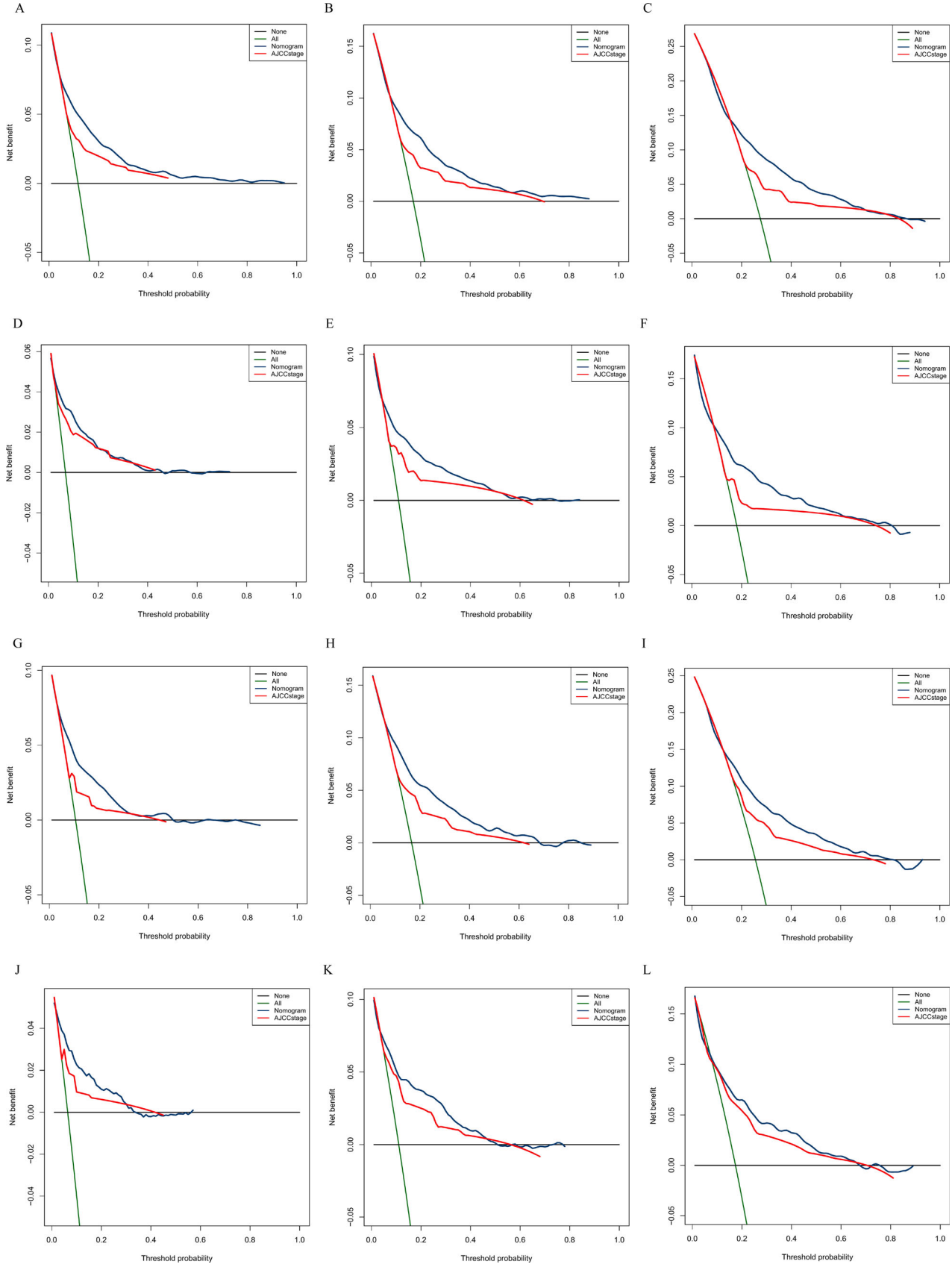

Figure 4. Decision curve analysis for nomograms compared with AJCC TNM. DCA curves of 2-year (A), 3-year (B), 5-year (C) overall survival nomogram, DCA curves of 2-year (D), 3-year (E), 5-year (F) cancer-specific survival nomogram in training group; DCA curves of 2 years (G), 3 years (H), and 5 years (I) total survival nomogram, DCA curves of 2 years (J), 3 years (K), 5 years (L) cancer-specific survival nomograms in the validation group. AJCC, American Joint Committee on Cancer.

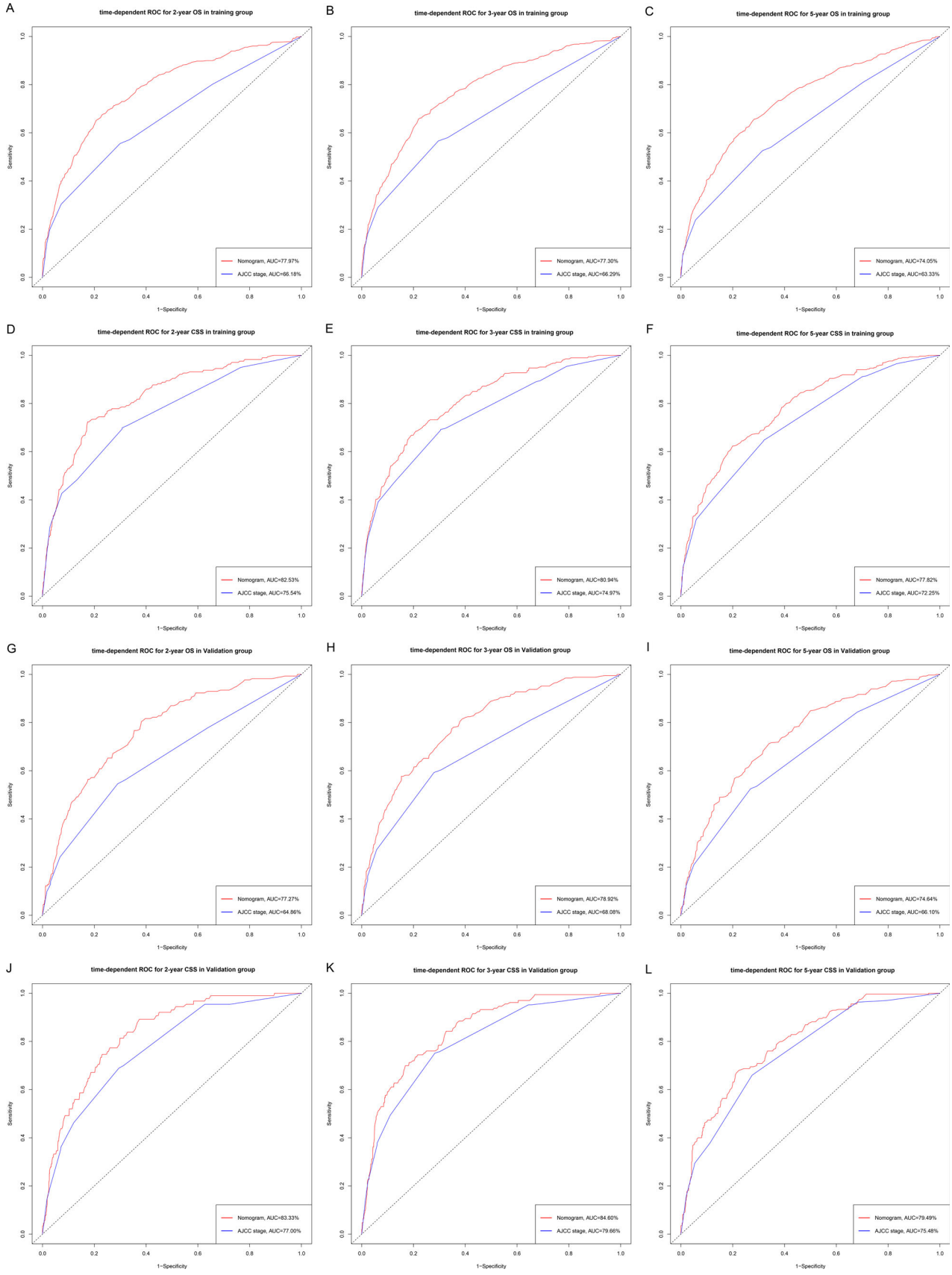

Figure 5. ROC curves of nomograms. ROC curves of 2-year (A), 3-year (B), 5-year (C) overall survival nomogram, ROC curves of 2-year (D), 3-year (E), 5-year (F) cancer-specific survival nomogram in training group; ROC curves of 2 years (G), 3 years (H), and 5 years (I) total survival nomogram, ROC curves of 2 years (J), 3 years (K), 5 years (L) cancer-specific survival nomograms in the validation group. ROC, receiver operating characteristic; OS, overall survival; CSS, cancer-specific survival.

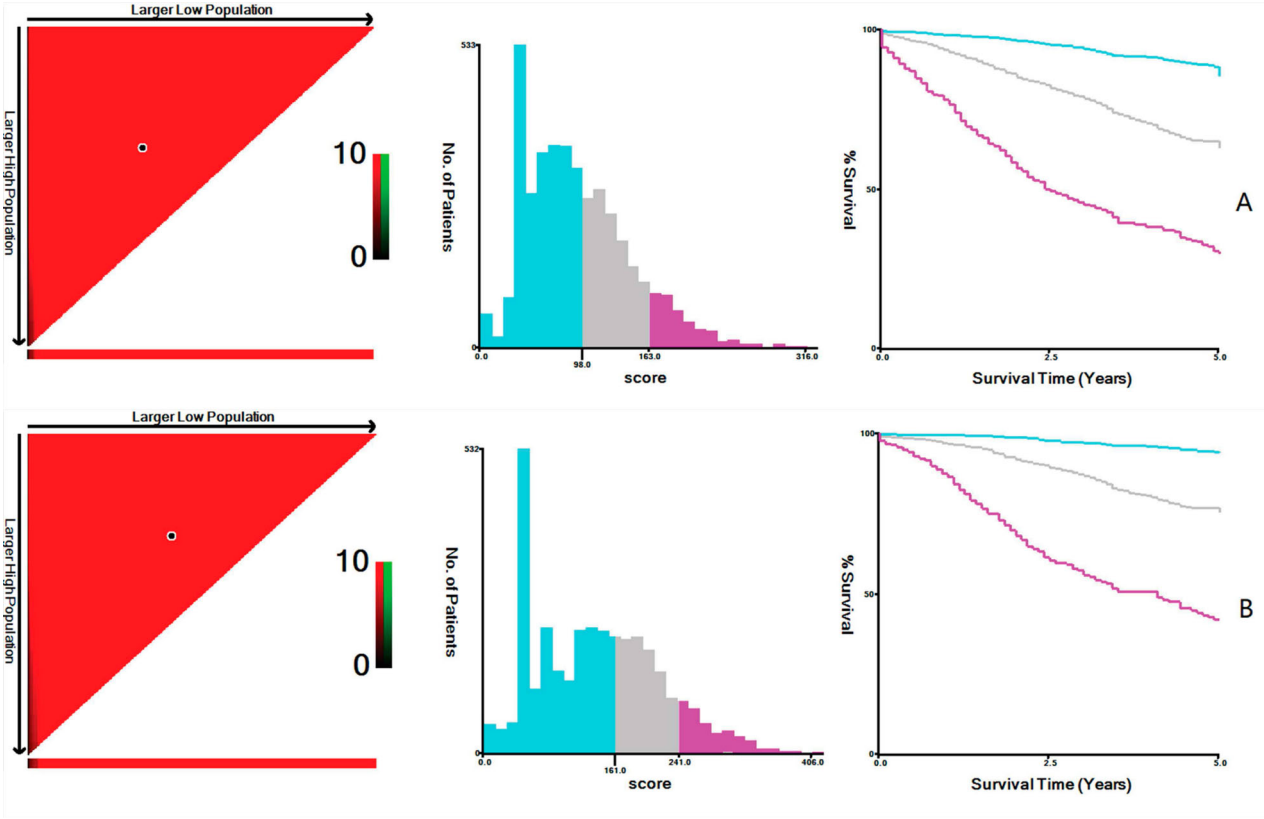

Figure 6. X-tile analysis is used to determine the cut-off value of the OS(A) total score and CSS (B)total score. Note: Cutoff values of OS total score: 98 and 163; cutoff values of CSS total score: 161 and 241. Histograms and Kaplan Meier analysis are based on these cutoffs. OS, overall survival; CSS, cancer-specific survival.

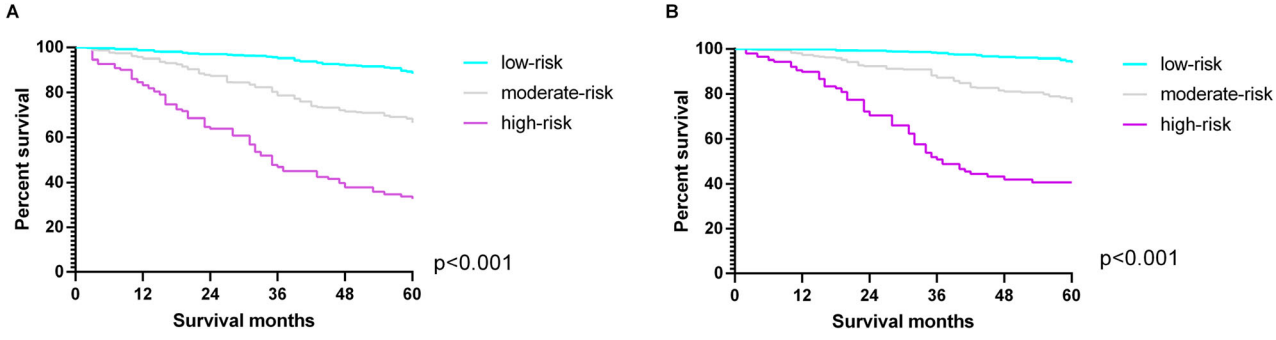

Figure 7. K–M survival curves in validation group. A: K–M survival curve of OS; B: K–M survival curve of CSS. OS, overall survival; CSS, cancer-specific survival.

prognosis, which is consistent with the results of other researches that have studied the relationship between these factors and the prognosis of appendiceal cancer (Turaga et al. 2012; Overman et al. 2013; Shaib et al. 2017). Previous study demonstrated that lymph node metastasis and CEA were important predictors of OS (Alexandraki et al. 2016; Ihemelandu et al. 2017). N stage and CEA were also closely associated with postoperative OS and CSS in patients with appendiceal cancer, that is, patients with lymph node metastasis owned a worse prognosis and patients with elevated CEA levels hold poor postoperative OS and CSS. This phenomenon may be attributed to lymph node metastasis and elevated CEA suggesting a strong likelihood of recurrence (Nash et al. 2015; Wang et al. 2020). We found that the RNE affected postoperative OS and CSS in patients with appendiceal cancer and patients with more than 12 examination numbers possessed the best prognosis. Similarly, Fleischmann et al. claimed that patients who examined 12 or more regional lymph

nodes had better OS and CSS comparing those with RNE < 12 (Fleischmann et al. 2017). The result displayed the important significance of removing a sufficient number of lymph nodes during surgery for appendiceal cancer.

More importantly, there are some interesting and meaningful findings in this study. Some researches revealed that multidisciplinary therapies, especially adjuvant chemotherapy and radiotherapy after surgical resection, have been increasingly applied to treat patients with resectable gastrointestinal cancer (Ragnhammar et al. 2001; Blum et al. 2016; Wu et al. 2020). However, it is still uncertain whether comprehensive therapy can improve the survival rate of patients with appendiceal cancer. Asare et al. announced that chemoradiotherapy cannot improve the survival for patients with appendiceal cancer (Asare et al. 2016), which were consistent with the results of this study. Moreover, the nomogram predicting postoperative CSS indicated that radiotherapy and chemotherapy may play as risk factors for patients with resectable appendiceal cancer. Which may be because of the toxic side effects of chemoradiation. Therefore, oncologist needs to further explore the specific chemotherapy regimen for appendiceal cancer rather than utilize the current chemotherapeutic strategy, which mainly learned from the experience of colorectal cancer (Tejani et al. 2014). Previous studies confirmed that tumor size is adverse prognostic factor for patients with appendiceal cancer (Kyang et al. 2019). It was closely related to postoperative OS and CSS in patients with appendiceal cancer that patients with tumors larger than 2 cm owned a worse prognosis comparing with those with tumors smaller than 2 cm. Thus we suggested that it is necessary to learn some experience regarding the staging system from some other tumors, such as Gastrointestinal Stromal Tumors (GIST) and pancreatic cancer, which incorporated the tumor size into the tumor staging system.

At present, the tumor stage of appendiceal cancer mainly depends on the AJCC TNM System. However, the results of previous studies indicated that the TNM system is not very ideal to evaluate the prognosis for appendiceal cancer (Xie et al. 2016). Our nomograms showed a clear advantage over the AJCC TNM 8th Edition Staging System. The time-dependent ROC curves showed that the nomograms provided a higher sensitivity and specificity comparing the AJCC staging system. The DCA curve showed that the nomograms possessed superior clinical value with the superior net benefits and net reduction in interventions per 100 patients.

Our study owned several advantages as well as limitations. The limitation was that some clinical factors, which may affect the prognosis of appendiceal cancer, were not included in the SEER database, such as intraoperative intraperitoneal chemotherapy (IPC) and cancerous emboli in the lymphatic vessels and blood vessels. In addition, this study was a retrospective study and needs to be further verified by a prospective study. Despite some limitations, our study, based on a large sample of 5945 patients, greatly reduced potential bias in the analysis. In addition, we successfully constructed the novel nomograms that could be considered as useful prognostic models with excellent predictive function to assess the OS and CSS for postoperative appendiceal cancer.

Conclusion

We constructed new nomograms based on a large database that can accurately predict the OS and CSS of patients with appendiceal cancer after surgery. The new nomograms call into question the current treatment strategies for appendiceal cancer, which primarily is based on chemoradiotherapy of colorectal cancer. It is urgent to further explore the treatment options suiting for appendiceal cancer.

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Disclosure statement

No potential conflict of interest was reported by the author(s).

Data accessibility

The data that support the findings of this study are openly available in the Accessing the 1975-2016 SEER data at https://seer.cancer.gov/data/access.html. The URL of the database is http://seer.cancer.gov/ and the RRID of the database is nif-0000-21366.

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1.6 Specific survival nomograms based on SEER database for small intestine adenocarcinoma

Wang D, Li C, Li Y, Liu W, Zhao L, Güngör C, Tan F, Zhou Y.
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Original Article

Specific survival nomograms based on SEER database for small intestine adenocarcinoma

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Background: Small intestine cancers, as an extremely rare tumor type, account only for 3% of all gastrointestinal tumors. Small intestine adenocarcinoma (SIA), representing approximately one-third of all small bowel cancers, has received relatively little attention, both in research efforts and clinical cognizance. Owing to anatomical proximity and rarity, small bowel adenocarcinomas are frequently grouped with colorectal adenocarcinomas. Therefore, a large SIA patient cohort is needed to develop and validate new nomogram prognostic models specific to SIA patients.

Methods: Patients diagnosed with SIA between 2004 and 2016 were extracted from the Surveillance, Epidemiology, and Final Results (SEER) database. All patients were randomly assigned to the training cohort and the validation cohort (2:1). The basic clinical information, detailed pathological staging, and treatment information of the patients were included in the analysis. Nomograms were shaped following the evaluations of the Cox regression model and verified using the decision curve analysis (DCA), time-dependent receiver operating characteristic (ROC) curves, concordance index (C-index), and calibration curves.

Results: The entire group comprised 6,947 patients with small intestine adenocarcinoma. According to the results of the multivariate Cox regression analysis, ten variables, including marital status, age, pathological grade, tumor location, T (tumor), N (nodes), M (metastasis) stage, surgery, chemotherapy, and regional nodes examined (RNE), were independent predictors of both of overall survival (OS) and cancer-specific survival (CSS). All significant variables were used to create the nomograms for OS and CSS. Various methods verified the reliability of the nomograms. The C-indexes of the OS and CSS nomogram were 0.756 (95% CI, 0.748–0.764) and 0.771 (95% CI, 0.761–0.781) in the training cohort and 0.748 (95% CI, 0.736–0.760) and 0.767 (95% CI, 0.752–0.781) in the validation cohort. The calibration curve showed good agreement between the nomogram prediction and actual survival. DCA indicated a clear net benefit of these new forecasting models.

Conclusions: This study built and verified nomograms to predict OS and CSS for rare SIA, which appear to be excellent tools to augment the clinically available evidence to facilitate the discussion between SIA patients and clinicians regarding therapeutic choice.

Keywords: Small intestine adenocarcinoma (SIA); overall survival; cancer-specific survival; nomogram; SEER database

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Introduction

The small intestine accounts for more than 75% of the gastrointestinal tract and 90% of its mucosal surface. Nonetheless, small intestine cancer, as an extremely rare tumor type, accounts for only 3% of all gastrointestinal tumors (1). With an estimated 3,600 new cases per year diagnosed in Europe and 5,300 new cases per year in the USA (2,3), small intestine cancers have a comparable incidence rate to testicular cancer, Hodgkin lymphoma, chronic myeloid leukemia, and anal cancer (1). The common histological types of small bowel tumors include carcinoids, adenocarcinomas, lymphomas, and sarcomas. Small intestine adenocarcinoma (SIA), representing approximately one-third of all small bowel cancers (4), receives relatively little attention, both in research efforts and clinical cognizance.

Owing to anatomical proximity and rarity, the clinical management for SIA follows that of colorectal adenocarcinomas. Despite several notable molecular similarities (5,6), SIA differs from colorectal cancer (CRC) in that it involves the low bacterial load, dilute liquid contents, higher levels of lymphoid aggregates and IgA levels (7) and worse outcomes (8,9). Therefore, it is necessary to better predict the prognosis of SIA patients under the existing diagnosis and treatment models.

Previous studies have suggested that factors affecting the prognosis of SIA patients include age, tumor stage, surgery, radiotherapy and chemotherapy (2). However, these variables have only been used as single indicators, which cannot accurately predict the survival of SIA patients. To overcome the limitations of a single predictor, a new nomogram prediction model was needed. Nomogram refers to visible representations of mathematical models that can combine certain features to estimate specific endpoints. The practical graphical display of the nomogram allows us to make easy and prompt predictions in clinical practice. Considering the rarity of SIA, large databases, such as the Surveillance, Epidemiology, and End Results database (SEER database), are excellent resources that can provide some necessary clinical data. SEER database has been widely used to examine the incidence and outcome patterns of various familiar cancers.

Therefore, prognostic nomograms for patients with SIA were created to assess overall survival (OS) and cancer-specific survival (CSS) based on the SEER database.

We present the following article in accordance with the TRIPOD reporting checklist (available at https://dx.doi.org/10.21037/apm-21-600).

Methods

Subject selection

A retrospective analysis involved 7,831 pathologically diagnosed SIA patients in the SEER database from 2004 to 2016. Patients with small intestine adenocarcinoma (ICD-O-3: 8140, 8143, 8144, 8145, 8210, 8220, 8211, 8255, 8260, 8261, 8262, 8263, 8310, 8480, 8481, 8490) were the target population in this study. The exclusion criteria were as follows: 1. Diagnosed at autopsy or death certificate; 2. Survival months = 0; 3. Tumor size =0; 4. All of the T, N, and M stages were blank. Exclusion process are displayed in *Figure 1*. The random grouping was then executed at a ratio of 2:1(training group, n=4,631, and validation group, n=2,316).

Prognostic variables

The information involving gender, marital status, age at diagnosis, race, histological type, grade, T (tumor), N (nodes), M (metastasis) stages, surgery, regional nodes examined (RNE), radiotherapy, and chemotherapy were acquired for each patient. The tumor sites of the patients were classified as duodenum, jejunum, ileum, and unknown. T stage was divided into T1-2, T3-4, and Tx. N stage and M stage were described as N0, N+, Nx, and M0, M1, Mx. Histologic type was classified as adenocarcinomas and mucinous cell carcinoma/signet ring cell carcinoma. Based on previous data and experience with lymph node dissection of colorectal cancer, the frequency of lymph node examination was divided into 0–4, 4–7, 8–11, ≥12, and unknown. All patients were inconsistently separated into two groups (training group, n=4,631 and validation group, n=2,316).

Follow up

In this study, OS and CSS were taken as endpoints. OS was defined as the time interval between the first diagnosis and death from any cause. CSS was defined as the time interval between the first diagnosis and death specific to SIA. We analyzed the 1-year, 3-year, and 5-year CSS and OS.

Statistical analysis

First, SIA patients meeting the inclusion criteria were randomly assigned at a 2:1 ratio to the training group (n=4,631) or validation group (n=2,316) using the randomization function in SPSS 26.0. In addition, SPSS 26.0 software was used for univariate and multivariate Cox

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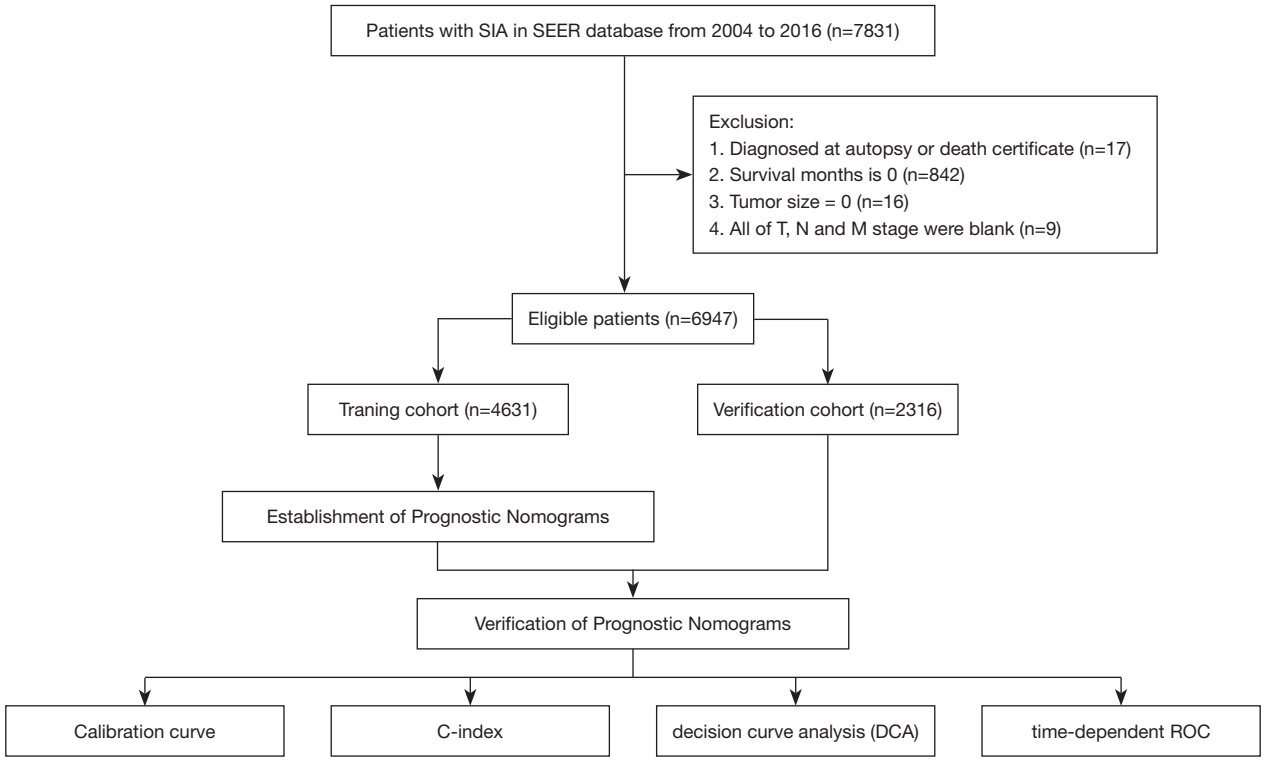

Figure 1 The workflow chart.

proportional risk regression analyses to assess and identify independent prognostic factors. The P value in the Cox regression model was set at 0.1 in univariate analysis. Additionally, all P values of less than 0.05 were considered significant. Variables were calculated using hazard ratios (HR) and corresponding 95% confidence intervals (CI).

We utilized the R statistical software version 3.5 (http://www.r-project.org) with the survival and RMS package to construct the histogram and the risk regression software package to evaluate the performance of the histogram. Various methods including decision curve analysis (DCA), time-dependent receiver operating characteristic (ROC) curves, concordance index (C-index) as well as calibration curves were used to verify the differential advantage of the histogram. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Results

Characteristics of patients with SIA

The entire cohort comprised 6,947 patients with small intestine adenocarcinoma. The characteristics of the SIA patients in this study are displayed in *Table 1*. The cohort comprised predominantly elderly patients (>60, 69.47%) with 13-month median survival. Overall,11.75% of patients were diagnosed with mucinous cell carcinoma (MCC) or signet ring cell carcinoma (SRCC). Duodenum was the main site of the small intestine adenocarcinoma (57.64%). Patients with synchronous metastases accounted for 30.39% of cases. Moreover, 37.11% of patients missed surgical resection, and only 43.70% of patients underwent chemotherapy.

Establishment of prognostic nomograms

Univariate Cox regression analyses were used for preliminary screening of prognostic factors, and multivariate Cox regression analyses were subsequently utilized to confirm the independent prognostic factors and the weight of factors affecting OS and CSS, presented as the odds ratio (OR). The preliminary prognostic factors (P value <0.1 in the univariate analyses) were included in the multivariate Cox regression model for analysis. Ten variables, including age, marital status, tumor location, pathological grade, T stage, N stage, M stage, surgery, chemotherapy, and RNE, were confirmed

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Table 1 Characteristics of patients with small intestine adenocarcinoma in the training and validation group

Characteristics	Total (n=6,947)		Training group (n=4,631)		Validation group (n=2,316)	
	N	%	N	%	N	%
Gender						
Female	3,183	45.82%	2,105	45.45%	1,078	46.55%
Male	3,764	54.18%	2,526	54.55%	1,238	53.45%
Age (years)						
≤50	849	12.22%	579	12.50%	270	11.66%
51–60	1,272	18.31%	836	18.05%	436	18.83%
61–70	1,815	26.13%	1,216	26.26%	599	25.86%
>70	3,011	43.34%	2,000	43.19%	1,011	43.65%
Marital status						
Married	3,852	55.45%	2,553	55.13%	1,299	56.09%
Unmarried/NOS	3,095	44.55%	2,078	44.87%	1,017	43.91%
Race						
White	5,211	75.01%	3,466	74.84%	1,745	75.35%
Black	1,238	17.82%	837	18.07%	401	17.31%
Other/NOS	498	7.17%	328	7.08%	170	7.34%
Tumor location						
Duodenum	4,004	57.64%	2,671	57.68%	1,333	57.56%
Jejunum	1,044	15.03%	706	15.25%	338	14.59%
Ileum	880	12.67%	582	12.57%	298	12.87%
Other/NOS	1,019	14.67%	672	14.51%	347	14.98%
Pathological grade						
I	541	7.79%	367	7.92%	174	7.51%
II	2,971	42.77%	1,968	42.50%	1,003	43.31%
III-IV	2,131	30.68%	1,429	30.86%	702	30.31%
Unknown	1,304	18.77%	867	18.72%	437	18.87%
Histologic type						
Adenocarcinomas	6,131	88.25%	4,109	88.73%	2,022	87.31%
MCC/SRCC	816	11.75%	522	11.27%	294	12.69%
T stage						
T1-2	1,230	17.71%	818	17.66%	412	17.79%
T3-4	4,546	65.44%	3,044	65.73%	1,502	64.85%
Tx	1,171	16.86%	769	16.61%	402	17.36%

Table 1 (*continued*)

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Table 1 (*continued*)

Characteristics	Total (n=6,947)		Training group (n=4,631)		Validation group (n=2,316)	
	N	%	N	%	N	%
N stage						
N0	3,595	51.75%	2,399	51.80%	1,196	51.64%
N+	2,548	36.68%	1,704	36.80%	844	36.44%
Nx	804	11.57%	528	11.40%	276	11.92%
M stage						
M0	4,495	64.70%	2,968	64.09%	1,527	65.93%
M1	2,111	30.39%	1,434	30.97%	677	29.23%
Mx	341	4.91%	229	4.94%	112	4.84%
Surgery						
Yes	4,369	62.89%	2,918	63.01%	1,451	62.65%
No/Unknown	2,578	37.11%	1,713	36.99%	865	37.35%
Radiotherapy						
Yes	614	8.84%	413	8.92%	201	8.68%
No/Unknown	6,333	91.16%	4,218	91.08%	2,115	91.32%
Chemotherapy						
Yes	3,036	43.70%	2,024	43.71%	1,012	43.70%
No/Unknown	3,911	56.30%	2,607	56.29%	1,304	56.30%
RNE						
<4	3,576	51.48%	2,352	50.79%	1,224	52.85%
4–7	767	11.04%	547	11.81%	220	9.50%
8–11	610	8.78%	408	8.81%	202	8.72%
≥12	1,742	25.08%	1,149	24.81%	593	25.60%
NOS	252	3.63%	175	3.78%	77	3.32%
OS	13 (4–35)		13 (4–35)		13 (4–34)	
CSS	13 (4–35)		13 (4–35)		13 (4–34)	

MCC, mucinous cell carcinoma; SRCC, signet ring cell carcinoma; RNE, regional nodes examined; NOS, not otherwise specified; OS, overall survival; CSS, cancer-specific survival.

as independent predictors of both OS (*Table 2*) and CSS (*Table 3*) in this study.

The nomograms predicting 1-, 3-, and 5-year OS and CSS were created using the ten variables (*Figure 2*). Adding up the scores related to each variable and projecting total scores to the bottom scales allowed us to easily calculate the estimated 1-, 3-, and 5-year OS and CSS probabilities.

Verification of prognostic nomograms

To identify the discriminating superiority of the nomograms, various methods involving decision curve analysis (DCA),

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Table 2 Univariable and multivariable Cox regression model analyses of OS for nomogram

Characteristics	Univariable analysis				Multivariable analysis			
	OR	95% CI lower	95% CI upper	P value	OR	95% CI lower	95% CI upper	P value
Gender				0.313				
Female		Reference		1		NA		
Male	0.965	0.900	1.034	0.313				
Age(years)				<0.001				<0.001
≤50		Reference		1		Reference		1
51–60	1.180	1.025	1.359	0.022	1.078	0.935	1.243	0.300
61–70	1.514	1.329	1.726	<0.001	1.309	1.147	1.494	<0.001
>70	2.139	1.893	2.417	<0.001	1.637	1.443	1.858	<0.001
Marital status				<0.001				<0.001
Married		Reference		1		Reference		1
Unmarried/NOS	1.351	1.260	1.448	<0.001	1.205	1.122	1.293	<0.001
Race				0.224				
White		Reference		1		NA		
Black	1.044	0.953	1.144	0.354				
Other/NOS	1.116	0.973	1.280	0.117				
Tumor location				<0.001				<0.001
Duodenum		Reference		1		Reference		1
Jejunum	0.525	0.471	0.585	<0.001	0.769	0.683	0.865	<0.001
Ileum	0.564	0.503	0.632	<0.001	0.903	0.798	1.022	0.106
Other/NOS	0.820	0.742	0.907	<0.001	1.102	0.988	1.230	0.082
Pathological grade				<0.001				<0.001
I		Reference		1		Reference		1
II	1.108	0.957	1.283	0.170	1.090	0.940	1.264	0.255
III-IV	1.547	1.334	1.795	<0.001	1.447	1.244	1.684	<0.001
Unknown	2.276	1.950	2.656	<0.001	1.093	0.931	1.283	0.279
Histologic type				0.635				
Adenocarcinomas		Reference		1		NA		
MCC/SRCC	0.974	0.872	1.087	0.635				
T stage				<0.001				0.001
T1-2		Reference		1		Reference		1
T3-4	0.888	0.808	0.976	0.014	1.216	1.096	1.350	<0.001
Tx	2.385	2.126	2.675	<0.001	1.166	1.026	1.326	0.019

Table 2 (*continued*)

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Table 2 (*continued*)

Characteristics	Univariable analysis				Multivariable analysis			
	OR	95% CI lower	95% CI upper	P value	OR	95% CI lower	95% CI upper	P value
N stage				<0.001				<0.001
N0		Reference		1		Reference		1
N+	1.127	1.044	1.216	0.002	1.395	1.281	1.519	<0.001
Nx	2.491	2.243	2.767	<0.001	1.146	1.006	1.304	0.040
M stage				<0.001				<0.001
M0		Reference		1		Reference		1
M1	2.891	2.680	3.118	<0.001	2.053	1.879	2.244	<0.001
Mx	2.658	2.298	3.074	<0.001	1.177	0.986	1.405	0.071
Surgery				<0.001				<0.001
Yes		Reference		1		Reference		1
No/Unknown	3.911	3.631	4.213	<0.001	2.462	2.182	2.777	<0.001
Radiotherapy				0.859				
Yes		Reference		1		NA		
No/Unknown	0.989	0.878	1.114	0.859				
Chemotherapy				<0.001				<0.001
Yes		Reference		1		Reference		1
No/Unknown	1.276	1.189	1.370	<0.001	1.568	1.448	1.697	<0.001
RNE				<0.001				<0.001
<4		Reference		1		Reference		1
4–7	0.448	0.399	0.503	<0.001	0.827	0.722	0.947	0.006
8–11	0.372	0.324	0.428	<0.001	0.723	0.615	0.848	<0.001
≥12	0.338	0.307	0.371	<0.001	0.637	0.561	0.723	<0.001
NOS	0.814	0.683	0.971	0.022	0.788	0.658	0.945	0.010

MCC, mucinous cell carcinoma; SRCC, signet ring cell carcinoma; RNE, regional nodes examined; NOS, not otherwise specified; NA, unavailable.

time-dependent receiver operating characteristic (ROC) curves, concordance index (C-index), as well as calibration curves were used in this study. The C-indexes of the OS nomogram were 0.756 (95% CI, 0.748–0.764) and 0.748 (95% CI, 0.736–0.760) in the training and verification group, respectively, which were higher compared to those of the AJCC stage for OS (0.613 (95% CI, 0.600–0.625) in the training cohort and 0.626 (95% CI, 0.609–0.643) in the verification cohort). The differences between the nomogram and AJCC stage in the prediction of CSS were similar. The C-indexes of a nomogram predicting CSS were 0.771 (95% CI, 0.761–0.781) in the training and 0.767 (95% CI, 0.752–0.781) in the verification cohort. Additionally, the AJCC stage illustrated inferior value of c-index (0.659 (95% CI, 0.643–0.675) in the training and 0.670 (95% CI, 0.648–0.692) in the verification cohort) (*Table 4*).

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Table 3 Univariable and multivariable Cox regression model analyses of CSS for nomogram

Characteristics	Univariable analysis				Multivariable analysis			
	OR	95% CI lower	95% CI upper	P value	OR	95% CI lower	95% CI upper	P value
Gender				0.717				
Female		Reference		1		NA		
Male	0.983	0.897	1.077	0.717				
Age(years)				<0.001				<0.001
≤50		Reference		1		Reference		1
51–60	1.135	0.964	1.337	0.129	1.080	0.916	1.274	0.358
61–70	1.472	1.262	1.716	<0.001	1.339	1.146	1.565	<0.001
>70	1.843	1.596	2.128	<0.001	1.497	1.288	1.739	<0.001
Marital status				<0.001				0.001
Married		Reference		1		Reference		1
Unmarried/NOS	1.296	1.182	1.420	<0.001	1.173	1.069	1.288	0.001
Race				0.932				
White		Reference		1		NA		
Black	1.010	0.898	1.136	0.867				
Other/NOS	1.033	0.865	1.233	0.722				
Tumor location				<0.001				0.002
Duodenum		Reference		1		Reference		1
Jejunum	0.549	0.478	0.630	<0.001	0.800	0.686	0.931	0.004
Ileum	0.528	0.452	0.617	<0.001	0.878	0.740	1.040	0.132
Other/NOS	0.843	0.733	0.969	0.016	1.108	0.955	1.287	0.176
Pathological grade				<0.001				<0.001
I		Reference		1		Reference		1
II	1.285	1.041	1.585	0.019	1.200	0.970	1.483	0.093
III-IV	1.927	1.561	2.380	<0.001	1.626	1.312	2.016	<0.001
Unknown	2.848	2.291	3.541	<0.001	1.205	0.962	1.509	0.104
Histologic type				0.983				
Adenocarcinomas		Reference		1		NA		
MCC/SRCC	0.998	0.866	1.151	0.983				
T stage				<0.001				<0.001
T1-2		Reference		1		Reference		1
T3-4	1.093	0.953	1.252	0.203	1.438	1.239	1.669	<0.001
Tx	2.983	2.541	3.502	<0.001	1.314	1.103	1.566	0.002

Table 3 (*continued*)

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Table 3 (*continued*)

Characteristics	Univariable analysis				Multivariable analysis			
	OR	95% CI lower	95% CI upper	P value	OR	95% CI lower	95% CI upper	P value
N stage				<0.001				<0.001
N0		Reference		1		Reference		1
N+	1.336	1.211	1.474	<0.001	1.505	1.349	1.679	<0.001
Nx	2.801	2.429	3.230	<0.001	1.153	0.973	1.366	0.101
M stage				<0.001				<0.001
M0		Reference		1		Reference		1
M1	3.670	3.327	4.048	<0.001	2.465	2.192	2.771	<0.001
Mx	2.842	2.292	3.525	<0.001	1.303	1.014	1.673	0.039
Surgery				<0.001				<0.001
Yes		Reference		1		Reference		1
No/Unknown	4.271	3.876	4.705	<0.001	2.640	2.240	3.112	<0.001
Radiotherapy				0.650				
Yes		Reference		1		NA		
No/Unknown	0.967	0.834	1.120	0.650				
Chemotherapy				0.055				<0.001
Yes		Reference		1		Reference		
No/Unknown	1.094	0.998	1.198	0.055	1.545	1.393	1.714	<0.001
RNE				<0.001				0.003
<4		Reference		1		Reference		1
4–7	0.404	0.346	0.471	<0.001	0.811	0.672	0.978	0.029
8–11	0.353	0.293	0.425	<0.001	0.799	0.642	0.996	0.046
≥12	0.334	0.296	0.376	<0.001	0.708	0.596	0.842	<0.001
NOS	0.843	0.666	1.067	0.156	0.843	0.662	1.074	0.168

MCC, mucinous cell carcinoma; SRCC, signet ring cell carcinoma; RNE, regional nodes examined; NOS, not otherwise specified; NA, unavailable.

Time-dependent ROC at 1-, 3-, and 5-years were conducted to confirm higher sensitivity and specificity of the nomograms in predicting the prognosis of SIA patients compared to the AJCC stage. The 1-, 3-, and 5-year AUC values of the nomogram were 83.38%, 83.82% and 83.58% for OS compared to63.18%, 67.85%, and 69.13% for AJCC stage, respectively, in the training group (*Figure 3A-C*). The AUC values of the nomogram were also superior to AJCC stage (1-year OS: 82.84% *vs.* 69.40%; 3-year OS: 81.87% *vs.* 69.87%; 5-year OS: 81.33% *vs.* 70.62%) in verification group (*Figure 3D-F*). In addition, the nomogram performed better for CSS compared to the AJCC stage in both of training (1-year CSS: 84.50% *vs.* 67.81%; 3-year CSS: 85.59% *vs.* 73.13%; 5-year CSS: 85.87% *vs.* 75.43%) (*Figure 3G-I*) and verification cohorts (1-year CSS: 85.30% *vs.* 68.97%; 3-year CSS: 83.10% *vs.* 73.81%; 5-year CSS:

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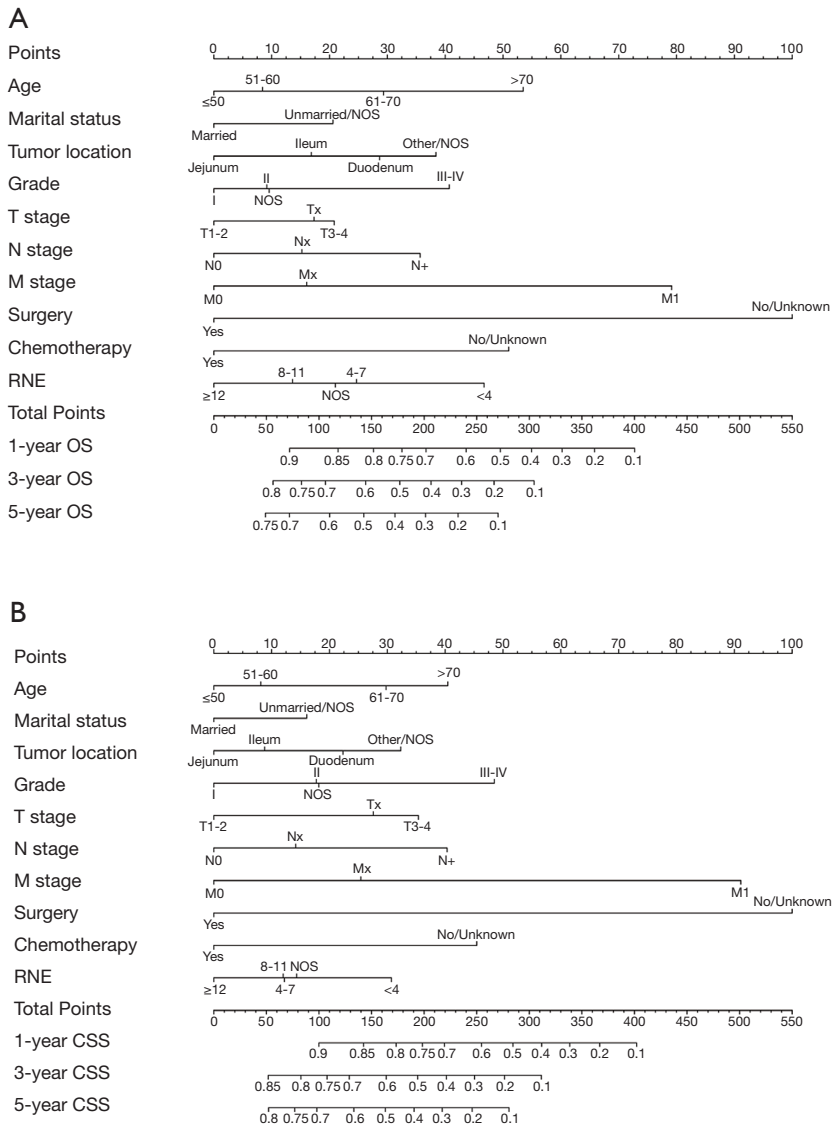

Figure 2 The nomograms for SIA patients. (A) Predicting OS. (B) Predicting CSS. SIA, small intestine adenocarcinoma; OS, overall survival; CSS, cancer-specific survival.

Table 4 The C-indices for predicting overall survival and cancer-specific survival

Groups	OS		CSS	
	C-index	95% CI	C-index	95% CI
Training group-Nomogram	0.756	0.748–0.764	0.771	0.761–0.781
Training group-AJCC stage	0.613	0.600–0.625	0.659	0.643–0.675
Validation group-Nomogram	0.748	0.736–0.760	0.767	0.752–0.781
Validation group-AJCC stage	0.626	0.609–0.643	0.670	0.648–0.692

OS, overall survival; CSS, cancer-specific survival; C-index, index of concordance; CI, confidence interval.

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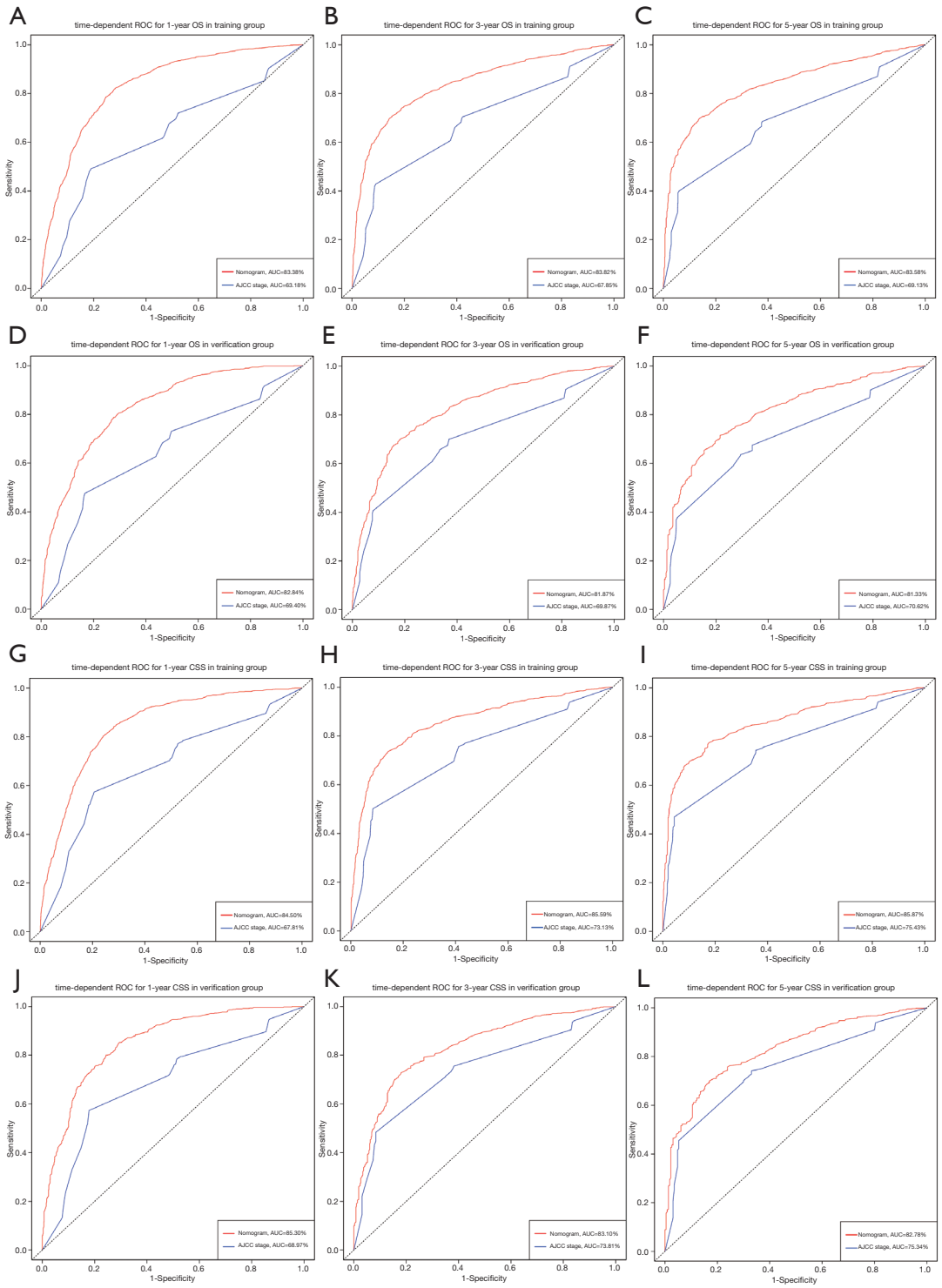

Figure 3 AUC values of ROCs of the nomograms and AJCC stage. (A-C) (training group): 1-year OS (83.38% *vs.* 63.18%); 3-year OS (83.82% *vs.* 67.85%); 5-year OS (83.58% *vs.* 69.13%). (D-F) (verification group): 1-year OS (82.84% *vs.* 69.40%); 3-year OS (81.87% *vs.* 69.87%); 5-year OS (81.33% *vs.* 70.62%). (G-I) (training group): 1-year CSS (84.50% *vs.* 67.81%); 3-year CSS (85.59% *vs.* 73.13%); 5-year CSS (85.87% *vs.* 75.43%). (G-I) (verification group): 1-year CSS (85.30% *vs.* 68.97%); 3-year CSS (83.10% *vs.* 73.81%); 5-year CSS (82.78% *vs.* 75.34%). OS, overall survival; CSS, cancer-specific survival.

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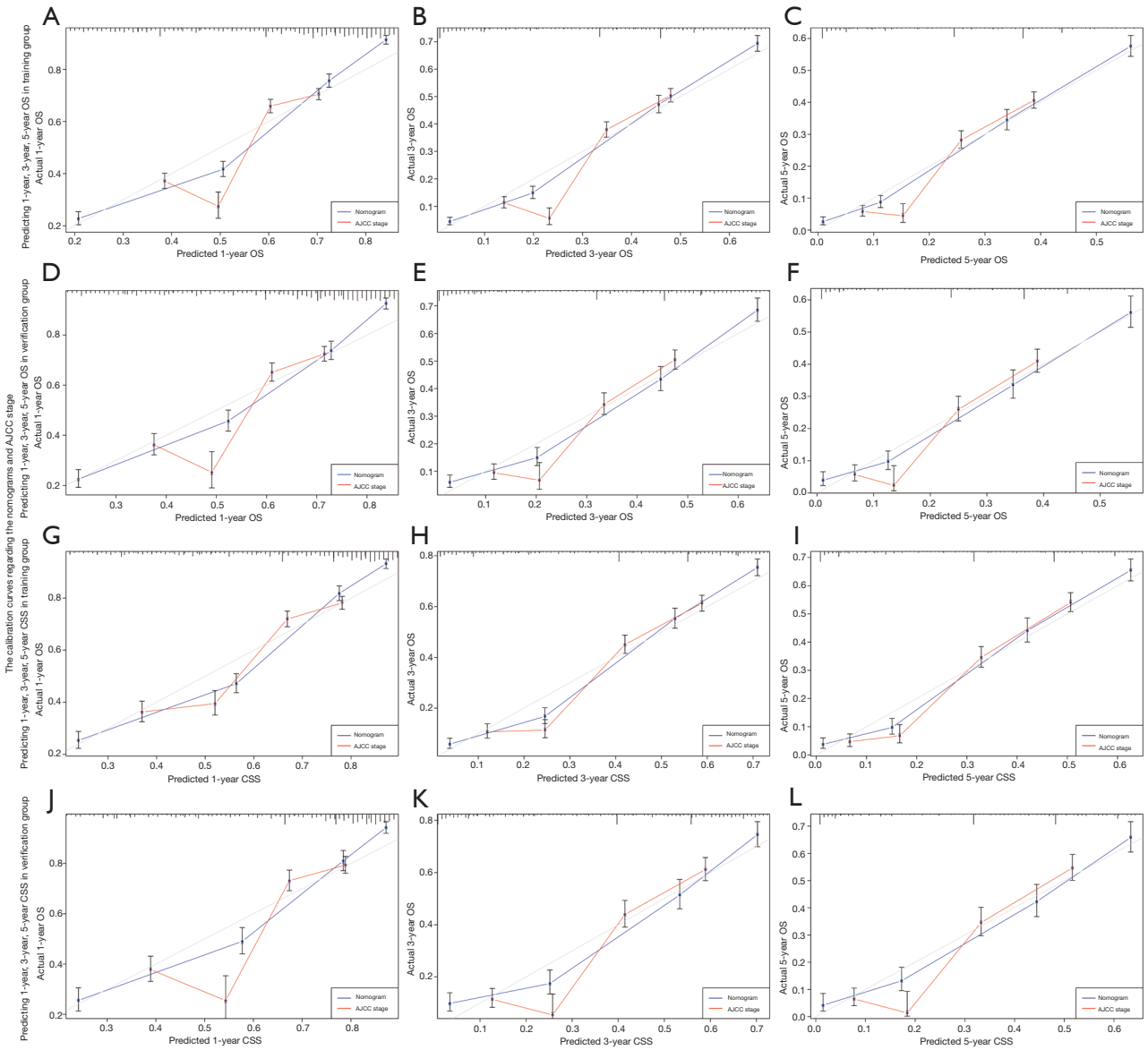

Figure 4 The calibration curves regarding the nomograms (blue lines) and AJCC stage (red lines). (A-C) (training group): predicting 1-year, 3-year, 5-year OS. (D-F) (verification group): predicting 1-year, 3-year, 5-year OS. (G-I) (training group): predicting 1-year, 3-year, 5-year CSS. (J-L) (verification group): predicting 1-year, 3-year, 5-year CSS. OS, overall survival; CSS, cancer-specific survival.

82.78% *vs*. 75.34%) (*Figure 3J-L*).

In addition, nomograms hold the minor deviations from the reference line comparing with the AJCC stage in calibration curves for both of OS (*Figure 4A-F*) and CSS (*Figure 4G-L*), which demonstrating a high degree of reliability. DCA curves for the novel nomograms and AJCC stage are presented in *Figure 5A-F* for OS and *Figure 5G-L* for CSS. Compared to the AJCC stage, the DCA of the nomograms showed superior net benefits, indicating that the nomograms in this study have a better clinical application than the AJCC stage.

Risk stratification

The prognostic scores of all independent variables were assigned based on the established nomogram, and the optimal cut-off values were calculated using X-tile based on the total scores. According to the cut-off values of the

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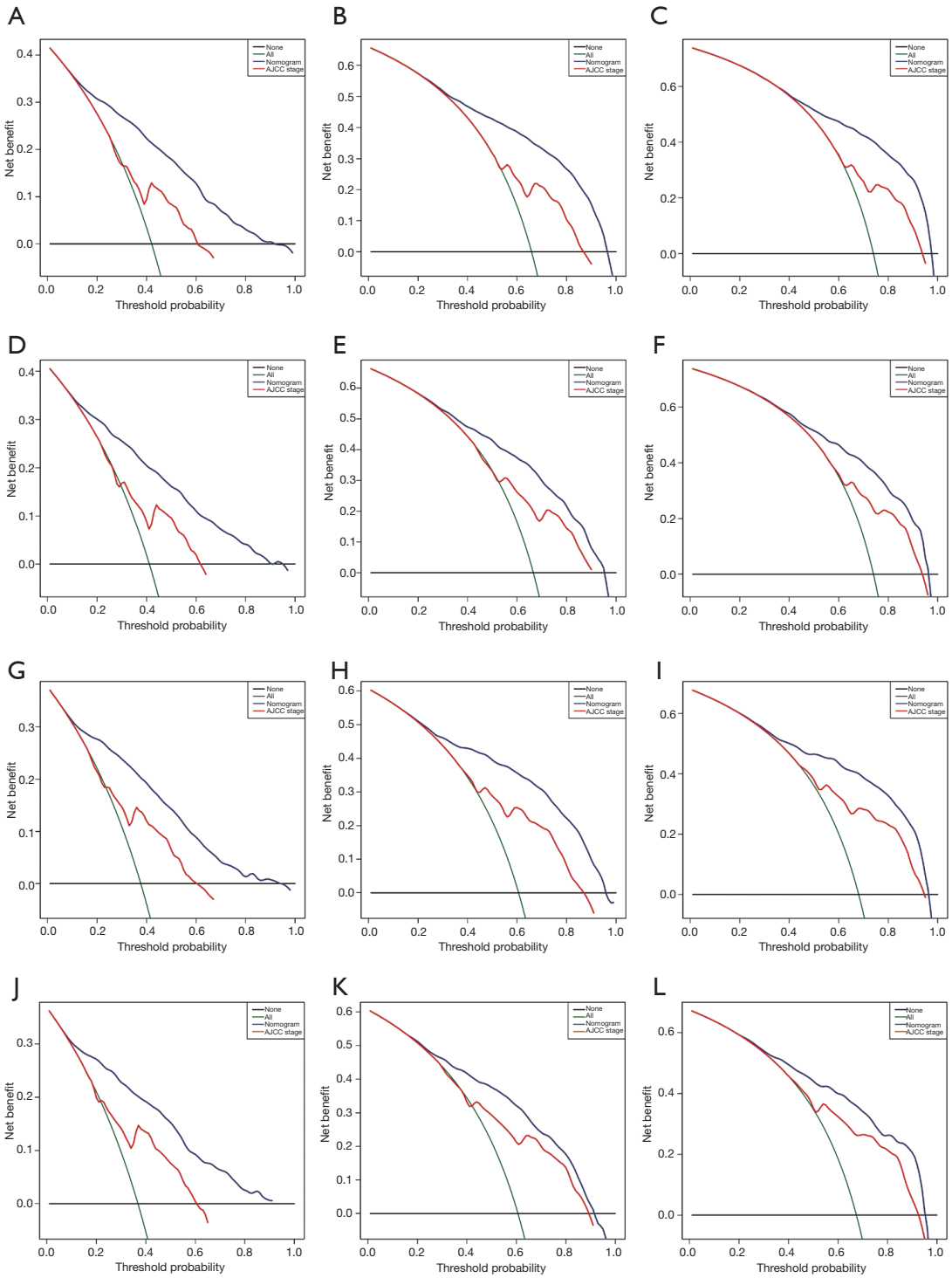

Figure 5 Decision curve analysis regarding the nomograms and AJCC stage. (A-C) (training group): for the 1-year, 3-year, 5-year OS. (D-F) (verification group): for the 1-year, 3-year, 5-year OS. (G-I) (training group): for the 1-year, 3-year, 5-year CSS. (J-L) (verification group): for the 1-year, 3-year, 5-year CSS. OS, overall survival; CSS, cancer-specific survival.

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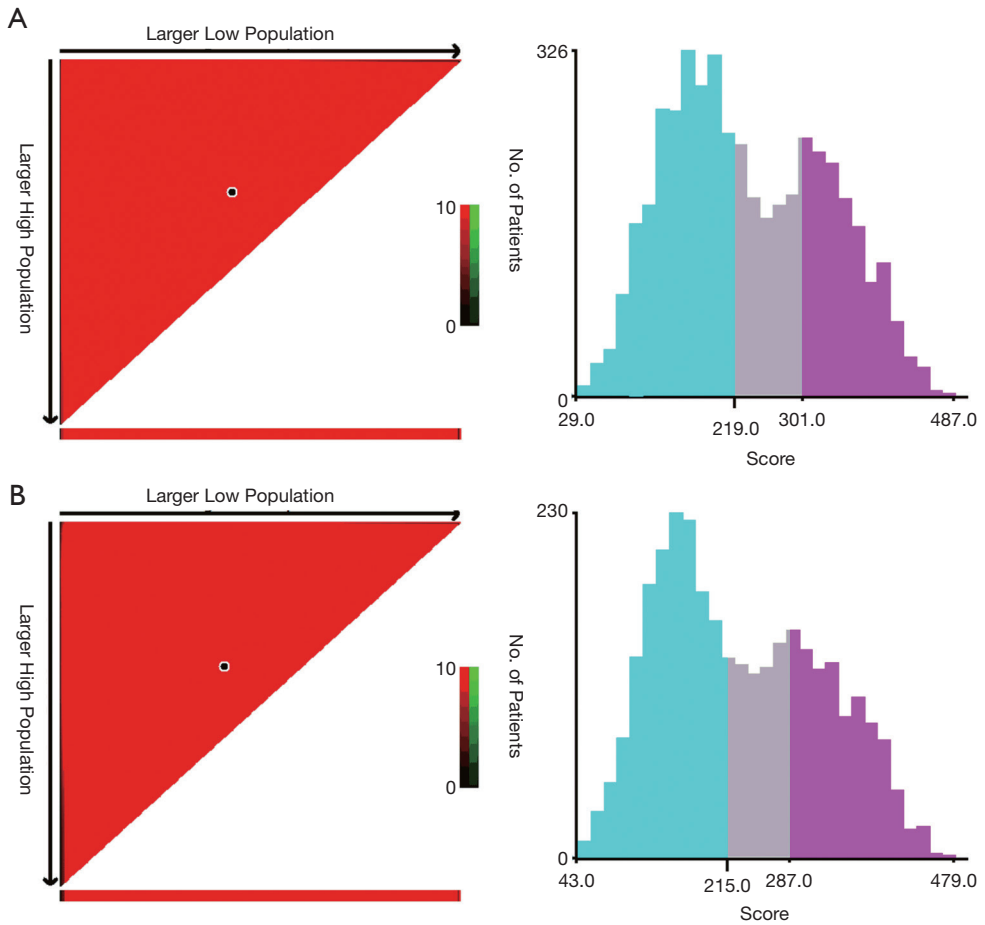

Figure 6 The cut-off values were calculated using X-tile based on the total scores. (A) The cut-off values were 219 and 301 for OS. (B) The cut-off values were 215 and 287 for CSS. OS, overall survival; CSS, cancer-specific survival.

nomogram for OS, patients with SIA were divided into low-risk (score ≤219), moderate-risk (219< score ≤301), and high-risk (score >301) (*Figure 6A*). In addition, patients with SIA were classified as low-risk (score ≤215), moderate-risk (215< score ≤287), and high-risk (score >287) for CSS (*Figure 6B*).

The Kaplan-Meier survival curves were subsequently delineated, as shown in *Figure* 7. The low-risk group had the highest 5-year OS rate (46.95% in training cohort and 44.61% in verification cohort), followed by the moderate-risk group (10.07% in training cohort and 10.97% in verification cohort) and high-risk group (2.43% in training cohort and 3.81% in verification cohort) (*Figure 7A* and *B*). Similarly, the high-risk group in the training and verification cohorts had the lowest 5-year CSS rates of 3.07% and 4.03%, respectively, followed by the moderate-risk group (12.87% in the training cohort and 17.39% in the verification cohort) and low-risk group (55.96% in the training cohort and 53.78% in the verification cohort) (*Figure 7C* and *D*). A statistically significant difference in survival outcomes was observed between the three groups (P<0.001).

Discussion

To our knowledge, this is the first large-database study specifically designed to describe the prognostic factors in SIA patients. This study developed and effectively validated prognostic OS and CSS nomograms for patients with SIA that could be better incorporated into clinical practice to guide surveillance and management strategies based on tumor and demographic variables.

SIA is usually diagnosed at an advanced disease stage due to the lack of specific symptoms and effective diagnostic

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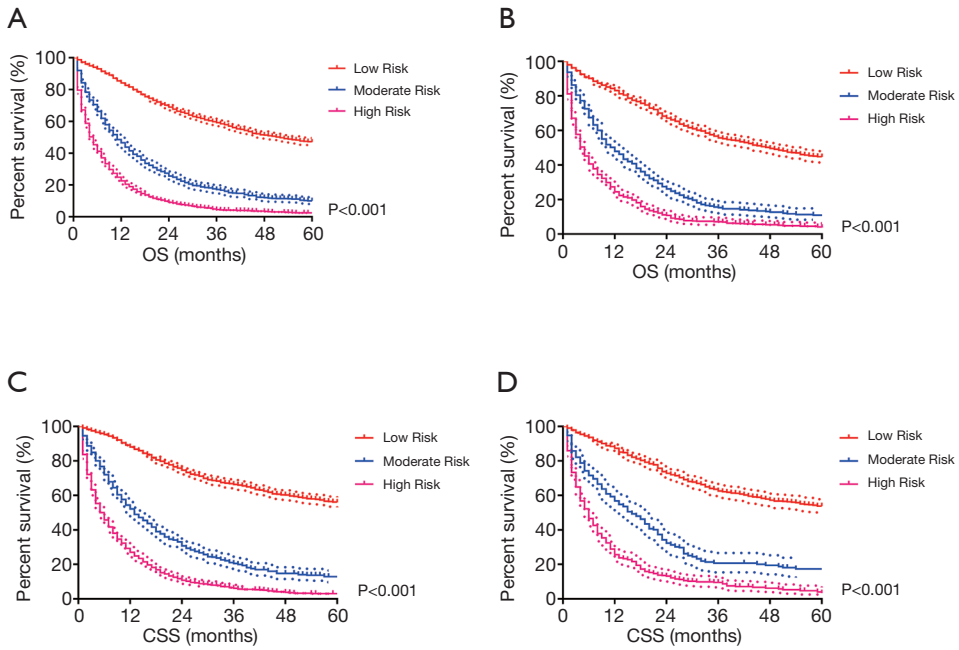

Figure 7 Survival analysis in the subgroup according to the risk stratification of the total score. (A,B) Low-risk group had the highest 5-year OS rate (46.95% in training cohort and 44.61% in verification cohort), followed by the moderate-risk group (10.07% in training cohort and 10.97% in verification cohort) and high-risk group (2.43% in training cohort and 3.81% in verification cohort). (C,D) High-risk group had the lowest 5-year CSS rate of 3.07% and 4.03% in the training and verification cohorts respectively, followed by the moderate-risk group (12.87% in training cohort and 17.39% in verification cohort) and low-risk group (55.96% in training cohort and 53.78% in verification cohort).

tools. The routine gastroduodenoscopy can assess only tumors in the proximal location of the small intestine, which explains the previous findings reporting that the rate of metastatic disease at diagnosis reached 32–33% in patients with SIA (10,11), similar to this study (30.39%). Moreover, 37.11% of SIA patients missed the surgical resection at the time of diagnosis. It is, therefore, necessary to explore tumor markers and diagnostic methods for SIA with adequate sensitivity and specificity.

The study demonstrated that tumor location was associated with survival rates. Similarly, Howe *et al*. (12) demonstrated worse cancer-specific survival in patients with duodenum compared to those with jejunal or ileal cancers. Nicholl *et al*. (13) revealed that patients with ileal tumors had a better OS compared to those with jejunal cancer by analyzing 1,444 patients with SIA. The nomograms were consistent with the results of these previous studies. Most importantly, patients with unclear tumor location suffered the greatest risk of survival among all SIA.

Based on the American Joint Committee on Cancer (AJCC) staging system, the tumor stage is the single most important prognostic factor in small bowel adenocarcinomas. The nomograms manifested clear advantages over the AJCC stage. First, the time-dependent ROC indicated that the nomograms had higher sensitivity and specificity. Second, minor deviations from the reference line demonstrated a high degree of reliability of the nomograms. Furthermore, DCA curves showed the nomograms facilitated better clinical decisions. The nomograms also considered the weight of the T, N, and M stages. More importantly, this study believed that the prognostic scoring system should consider treatment strategies and demographic factors, which would improve predictive performance and clinical decisions for individuals.

Surgical resection is the therapeutic mainstay for SIA presenting as a locoregional disease. The nomograms displayed that missed surgery was the worst prognostic factor, even worse than metastatic disease. The pancreaticoduodenectomy with negative margins and an adequate lymph-node evaluation should be performed for the first and second portions of the duodenum. Wide local excision and regional lymph-node dissection are indicated

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for the third and fourth portions of the duodenum and Jejunum or ileal adenocarcinomas. The distal or terminal ileum should be treated by right colectomy. Moreover, the number of regional lymph nodes to be evaluated should be determined. Using the SEER database, two recent researches distinguished either ≥8 or ≥10 lymph nodes as the optimal number (13,14). This study's findings are inconsistent with previous research since survival benefits were significantly greater for patients with more than 12 RNE, referring to colorectal cancer, compared to 8–11 RNE.

The number of patients with adjuvant chemotherapy increased from 8.1% in 1985 to 22.2% in 2005 in the National Cancer Database (4,15). In this study, 43.70% of SIA patients, a relatively low percentage, received chemotherapy in this study, which included data from 2004–2016. Adjuvant chemotherapy was expected to be beneficial despite the lack of randomized trials. A retrospective study including 54 patients revealed that adjuvant therapy was associated with improvement of DFS (HR 0.27; 95% CI, 0.07–0.98, P=0.05) in multivariate analysis (16). Czaykowski revealed that patients with chemotherapy had 15.6-month OS, while those without chemotherapy only had 7.7-month OS in the data from the registry of British Columbia (17). Moreover, a previous study showed an obvious increase in overall survival in the chemotherapy cohort (12 *vs.* 2 months, P=0.02) (9). Similarly, the prognosis in this study was significantly better for patients in the chemotherapy group compared to the non-chemotherapy group. The intuitive nomograms can also be used to encourage patients with small bowel cancer to receive treatment actively.

A small sample study reported that radiotherapy demonstrated a trend towards improved 5-year overall survival (18). However, this study with data from the SEER database cannot support this tendency. Clinicians need to re-evaluate the value of radiotherapy, as radiation may injure the small intestine and surrounding tissues. Besides, the difference between MCC/SRCC, being considered highly malignant, and adenocarcinomas was non-significant. In addition, age, marital status, and pathological grade were also related to the survival of small bowel cancer, which was consistent with colorectal cancer (19-22).

The advantages of the nomograms are (I) superior survival prediction ability to the AJCC stage, (II) ability to determine the value of treatment strategies, and (III) ability to distinguish more than 12 RNE as the optimal number. This study had some limitations. First, as a retrospective study, the nomograms still need to be validated by prospective studies in the future. Second, this study did not include some important factors, such as CEA and CA-199, among others, which were missing in the SEER database. However, the excellent sensitivity, specificity, and outstanding clinical value of the nomograms for SIA are the strengths of this study.

Conclusions

This study built and verified nomograms to predict OS and CSS for rare SIA, showing that they may serve as an excellent tool to augment the clinically available evidence to facilitate the discussion between SIA patients and clinicians regarding therapeutic choice.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/apm-21-600). Dr. Fengbo Tan reports receiving the following funding: The Nature Scientific Foundation of China (Grant No.81702956), The Strategy-Oriented Special Project of Central South University in China (Grant No. ZLXD2017003), The Natural Science Foundation of Hunan Province (Grant No.2020JJ4903 and 2020JJ5920) and The Colorectal cancer medical seed research fund project named "Effect and mechanism of

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YAP1 on EGFR resistance in K-ras wild-type metastatic colorectal cancer" from the Beijing Bethune Public Welfare Foundation. Dr. Dan Wang reports receiving funding from China Scholarship Council. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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2. Overview (Presentation of the publications)

In recent decades and due to changes in diet structure, environmental pollution, aging population and other factors, the global incidence of cancer is increasing, making cancer a major global public health problem (Siegel et al., 2022). Despite the advances in diagnostic equipment, surgical techniques and cutting-edge new treatment options, the prognosis for most advanced cancers remains dismal. According to GLOBOCAN, there were an estimated 19,292,789 new cancer cases and 9,958,133 cancer deaths worldwide in 2020 (Sung et al., 2021). Malignant tumors of the digestive system, including pancreatic and colorectal cancers, are one of the leading causes of death.

In particular, pancreatic cancer, one of the deadliest cancers in the world, is a devastating malignant disease with a median survival of 3-6 months and a 5-year survival rate of less than 5% (Ryan et al., 2014). Despite improvements in treatment modalities, the overall survival has barely changed in the past few decades, with mortality rates approaching morbidity. The latter is may be due to the following challenges in pancreatic cancer treatment: 1) although chemotherapy is widely used, resistance to chemotherapy is common. 2) whether radiotherapy can improve the survival of patients with pancreatic cancer is still controversial and is not widely used (Long et al., 2014). 3) most patients diagnosed with pancreatic cancer lack the opportunity for radical surgery because of its frequent detection in an advanced stage (Güngör et al., 2014; Yu et al., 2015). The phenomenon of missing early diagnosis due to insidious onset also exists in some other gastrointestinal tumors, such as gastro-esophageal junction adenocarcinoma (GEA), appendiceal cancer and small bowel cancer. Most patients with GEA often have a devastating prognosis, with a 5-year survival of less than 25%, because of late-stage diagnosis and rapid spread (Pennathur et al., 2013). Although appendiceal cancer and small bowel cancer are relatively rare, their incidence is increasing, and they are prone to misdiagnosis due to their special anatomical location, leading to poor prognosis (Raghav and Overman, 2013; Kyang et al., 2019).

In order to solve the above-mentioned problems, my research mainly included the following two parts: 1) Clinical projects: exploring the individualized treatment modes for pancreatic cancer and other gastrointestinal tumors and establishing relevant prediction models. 2) Basic experimental studies: Methods: Western blot, MTT proliferation and viability assays, apoptosis, immunochemistry, virus-mediated knockdown and overexpression studies and a series of other experiments were conducted to explore the effect of LRRN-1 on chemotherapy resistance and related mechanisms in pancreatic ductal adenocarcinoma (PDAC) cells.

2.1 Effect of neoadjuvant radiotherapy on survival of non-metastatic pancreatic ductal adenocarcinoma: a SEER database analysis

Only about 20% of PDAC patients who underwent surgical resection achieve long-term remission, which may be related to the high rate of recurrence after surgery (Tsai and Evans, 2016). The concerpt of the neoadjuvant therapy is gaining more and more attention by physicians and scholars due to the dismal survival rates. Based on a retrospective analysis of significant adjuvant chemotherapy studies in the 1970s, Du et al. firstly proposed the application of a neoadjuvant therapy (chemotherapy before surgery), which extended disease-free survival in 1982 (Du et al., 2015). Additionally, the neoadjuvant therapy concept expanded to preoperative radiotherapy and chemoradiotherapy. In 1990, the term of neoadjuvant therapy was first described in PDAC (Moss and Lee, 2010). The Fox Chase cancer center reported that neoadjuvant chemotherapy and radiotherapy improved the resectability of locally advanced PDAC (Moss and Lee, 2010). Moreover, the treatment model for PDAC was changed from "surgical-first" to a "multi-disciplinary team" (MDT) with advances in medical technology and treatment concepts in the past decades (Gedge, 2017). The application of neoadjuvant chemotherapy for patients with PDAC is widely recognized today (Hackert et al., 2016; Youngwirth et al., 2017). However, the role of neoadjuvant radiotherapy in PDAC is still under debate due to the lack of reliable data. Currently, neoadjuvant radiotherapy is mainly used for borderline resectable PDAC as well as locally advanced PDAC and may improve the marginal negative resection rate and local control rate (Greenblatt et al., 2011; Chung et al., 2017). However, it is unclear whether neoadjuvant radiotherapy improves survival of PDAC patients. Further, it is still highly controversial and requires further discussion about whether patients with initially resectable PDAC may have a benefit from neoadjuvant radiotherapy.

The patient cohort used in this study was created from custom data (additional treatment fields) of the Surveillance, Epidemiology, and End Results (SEER) Program. PDAC diagnosed by surgical histopathology between 2004 -2016 was selected. Combined with tumor size, T and N staging were recorded on basis of the 8th edition of TNM staging system. The study was limited to patients with non-metastatic PDAC (any T with any N and M0). The patients were divided into the following four groups according to the treatment methods: 1. Only surgery group (No radiation or chemotherapy); 2. Surgery + chemotherapy group (without radiation); 3. Neoadjuvant radiotherapy group (Neoadjuvant radiotherapy + surgery with or without chemotherapy); 4. Adjuvant radiotherapy group (surgery + adjuvant radiotherapy with or without chemotherapy). The oncological outcomes of different treatments were analyzed by propensity score matching (PSM) analysis.

The interesting findings of this study include:(1). Among patients with non-metastatic PDAC, stage T1-4N + M0/T4N0M0 patients who received neoadjuvant radiotherapy, adjuvant radiotherapy, and surgery + chemotherapy had longer overall survival (OS) than those who received surgery alone, while stage T1-3N0M0 patients did not benefit from neoadjuvant radiotherapy. (2). For patients with stage T1-3N0M0, surgery + chemotherapy is clinically recommended as the frontline treatment. (3). Postoperative adjuvant radiotherapy has a better prognosis and adjuvant radiotherapy is preferred for PDAC patients with stage T1-3N + M0. (4). For stage T4 patients, neoadjuvant radiotherapy had significantly longer OS than adjuvant radiotherapy and surgery + chemotherapy, which may be appropriate for guidelines to adopt a more proactive stance on using of neoadjuvant radiotherapy for stage T4 PDAC patients.

As discussed in the limitations of this study, other important factors such as age and tumor site may also influence the specific selection and efficacy of radiotherapy (Sonohara et al., 2021). In order to further investigate this, we conducted a study to explore the efficacy of radiotherapy in PDAC patients with different ages and tumor sites (introduced in section 2.2).

2.2 The Survival Effect of Radiotherapy on Stage IIB/III Pancreatic Cancer Undergone Surgery in Different Age and Tumor Site Groups: A Propensity Scores Matching Analysis Based on SEER Database

Radiotherapy (RT) is one of the important clinical weapons against PDAC, including neoadjuvant radiotherapy (nRT), adjuvant radiotherapy (aRT) and palliative treatment. It works by delivering ionizing radiation directly to the primary tumor and regional lymph nodes, which may cause genetic damage and ultimately apoptosis of cancer cells (Khanna and Jackson, 2001). However, our previous study has shown that RT does not have a benefit on survival of PDAC patients with stage T1-3N0M0 (introduced in section 2.1). For surgically resected PDAC patients, the National Comprehensive Cancer Network (NCCN) and American Society for Radiation Oncology (ASTRO) also recommend conventional aRT for only a subset of high-risk patients (including positive lymph nodes (stage IIB/III) and margins) (Palta et al., 2019; Tempero et al., 2021). Although the role of RT as a local treatment in minimizing local recurrence has been widely recognized, there is no consensus on whether it may improve the survival of patients with stage IIB/III (Chadha et al., 2016; Grossberg et al., 2020). In recent years, many studies have confirmed that the survival outcome and treatment effect of PDAC patients vary with age (Nipp et al., 2018). Younger (<50 years) patients with PDAC tend to be at a more advanced stage and have a poorer prognosis than older (≥50 years) patients, possibly

due to their aggressive oncological behavior (Primavesi et al., 2019). In addition, younger PDAC patients are more likely to benefit from surgery and adjuvant chemotherapy compared to elderly patients (Ansari et al., 2019; Saadat et al., 2021). However, there is still a lack of large sample studies on RT in PDAC patients of different ages. Also, the significance of primary tumor site for prognosis and treatment of patients with PDAC is still controversial. Among resected PDACs, those tumors located in the head of the pancreas and had worse OS compared with those located in the body and tail of the pancreas (Winer et al., 2019). Other studies have proved that tumor location does not affect the prognosis of PDAC, but has an important influence on postoperative recurrence and treatment methods (Takeda et al., 2020). Given the above questions, the purpose of the present study was to to verify whether the survival effect of RT for stage IIB/III PDAC patients was different among different age and tumor site groups.

Data for this retrospective study were collected from the SEER database. The target population was limited to pathologically confirmed PDAC patients by post-operative specimens between 2004 - 2016. The data demonstrated that patients with early-onset (<60 years) PDAC underwent more extensive surgery (regional nodes examined (RNE)⩾15) and chemoradiotherapy than elderly (⩾70 years) patients. Better treatment utilization and the ability to tolerate intensive therapy will hopefully be associated with improved outcomes. However, our data do not support that an increasing RT in early-onset patients improves prognosis. The survival analysis showed that aRT could prolong survival in middle-aged (60 - 69 years) and elderly patients, and nRT improved survival only in the elderly. Therefore, it is necessary to re-evaluate the benefits and risks of RT in elderly PDAC patient populations. Moreover, the application of aRT can increase the OS in patients with pancreatic head cancer, but not in patients with PDAC located at other sites.

Based on the these results our research puts forward the following suggestions: (1) survival improvements in early-onset patients with stage IIB/III PDAC are more likely to depend on the development of new therapies and technologies, rather than more the aggressive use of already existing models; (2) clinicians should pay attention to the use of aRT in patients over 60 years of age with stage IIB/III PDAC and nRT in patients over 70 years of age; (3) the tumor site should also be considered as an important factor when deciding on radiotherapy for PDAC.

Combined with Section 2.1 and this part of the study, tumor stage, age and tumor site may also be reference factors for PDAC patients to decide for radiotherapy. These findings may contribute to the development of individualized treatment options for PDAC patients. However, it should not be ignored that chemotherapy resistance is also a major clinical challenge in the treatment landscape of PDAC patients.

Therefore, my basic experimental research work included a better understanding of molecular mechanisms promoting chemotherapy resistance in PDAC.

In the group of Dr. Güngör, the abundant expression of LRRN1 was previously identified through RNA-Seq experiments including the comparative expression levels between chemoresistant and sensitive PDAC cells. Interestingly, LRNN1 gene expression levels were substantially higher in chemoresistant PDAC cells, compared to the chemosenstive counterpart.

Leucine-rich repeat neuronal protein-1 (LRRN1) is a type I transmembrane protein with extracellular leucine-rich repeats. LRRN1 belongs to the mammalian leucine-rich neuronal protein family (LRRN1-LRRN5) (Hamano et al., 2004). LRRN proteins have a high degree of homology and are expressed mainly in nervous tissues, with small amounts in lung, heart, liver and kidney. Studies have shown that LRRN proteins plays an important role in neural development and regeneration (Tossell et al., 2011; Bando et al., 2013). In addition to their expression in normal tissues, LRRN family members are also expressed in various tumors. LRRN2 is amplified and overexpressed in glioblastoma and anaplastic astrocytoma, and LRRN3 has been isolated and cloned from rat fibrosarcoma cells (Fukamachi et al., 2001). Furthermore, LRRN1 has been identified as a prognostic factor for high-risk neuroblastoma, promoting tumor cell proliferation (Hossain et al., 2008). LRRN1 restrains AP-1 activity by inhibiting the Fas/FasL pathway, thereby reducing the apoptosis of gastric cancer cells (Liu et al., 2019). However, a potential role of LRRN1 in PDAC is not known so far. For this reason, we investigated the potential molecular role of LRRN1 in PDAC cells. First, we investigated the expression level of LRRN1 protein in different PDAC cell lines and normal pancreatic cells (HPDE). LRRN1 expression was substantially higher in L3.6pl^{res} (gemcitabine-resistant), Panc-1, Paca-5072 (primary PDAC cell line) and Paca-5061 (primary PDAC cell line), but was low in HPDE, Bxpc3 and L3.6pl^{wt} (gemcitabine-sensitive). Lentivirus-mediated stable LRRN1-knockdown cells (shRNA) (L3.6pl^{res} and Panc-1) and LRRN1-overexpression cell clones (Bxpc3 and L3.6pl^{wt}) were established to analyze the molecular function of LRRN1 in PDAC cells.

Application of MTT viability assays suggested that LRRN1 expression was associated with gemcitabine resistance. Gemcitabine-treated LRRN1-overexpression cells (Bxpc3 and L3.6pl^{wt}; Myc-DDK) showed increased proliferation *in vitro,* compared to the respective control cells, while sh-LRRN1-knockdown cells showed significantly reduced *in vitro* cell proliferation and viability. Moreover, the quantification of cell apoptosis demonstrated that the LRRN1 knockout cell lines were sensitive to gemcitabine treatment. To investigate whether LRRN1 is inducible by chemotherapy, LRRN1 low expression cell lines (Bxpc3 and L3.6pl^{wt})

were treated with increasing concentrations of chemotherapeutics (gemcitabine/ Oxaliplatin) to further demonstrate an association between LRRN1 expression and chemotherapy resistance. These results manifested that LRRN1 expression is inducible by chemotherapy in a dose-dependent manner in chemosensitive PDAC cells.

It has very recently been shown that LRRN1 exerts its biological function through HIF-1α/Notch signaling pathway in PDAC cells (Zhang et al., 2021). Hypoxic conditions lead to overexpression of HIF-1α, which can overcome hypoxic stress by initiating angiogenesis and regulating cell metabolism, thereby promoting tumor growth and metastasis (Korbecki et al., 2021). PDAC, unlike other solid tumors, has an abundance of stromal cells and extracellular matrix, but lacks vascularization, resulting in severe and persistent hypoxia within the tumor micromilieu (Tao et al., 2021). A Hypoxic microenvironment has a wide range of effects on the biological behavior or malignant phenotype of pancreatic cancer cells, including metabolic reprogramming, invasion and metastasis, and pathological angiogenesis, which synergically promote the occurrence and drug resistance in pancreatic cancer (Tao et al., 2021). Therefore, we sought to investigate whether LRRN1 expression is associated with hypoxia in PDAC cells. Surprisingly, western blot results suggested that LRRN1 expression was increased in PDAC cancer cells under hypoxia conditions (150μM $CoCl_2$), compared to normoxy. Apoptosis assays further showed that following hypoxia treatment, LRRN1-knockdown cells showed an increased apoptotic rate, compared to control cells. Hence, these results suggested that hypoxia can induce LRRN1 gene expression in PDAC cells.

Another study demonstrated that LRRN1 protects human embryonic stem cells from post-translational degradation or modification by inhibiting the nuclear localization of pluripotent related proteins (OCT4, NANOG, SOX2) through AKT phosphorylation, thus maintaining pluripotency and self-renewal potential (Liao et al., 2018). The hypoxic microenvironment may promote therapeutic resistance of pancreatic cancer by influencing and regulating cancer stemness (Tao et al., 2021). Therefore, we hypothesized that LRRN1 might promote the pluripotency of pancreatic cancer stem cells by regulating the stability of different transcription factors, thereby promoting drug resistance and tumor progression in PDAC cells. The main pluripotent transcription factors include OCT4, NANOG and SOX2 (McKnight et al., 2010). Interstingly, we found significant differences in the expression level of these pluripotency factors between drug-resistant and sensitive cell lines. OCT4, NANOG and SOX2 were highly expressed in Panc-1 and L3.6pl^{res} cells, but low in Bxpc-3 and L3.6pl^{wt} cells, which was consistent with LRRN1 expression in these cells. Furthermore, the expression of OCT4, NANOG, and SOX2 changed with the expression level of LRRN1 in stable LRRN1-

knockdown and overexpression cell lines. In summary, we found that LRRN1 was abundantly expressed in drug-resistant PDAC cells. LRRN1 expression in PDAC cells is inducible by certain stress factors like hypoxia and chemotherapeutics and ultimately promote chemotherapy resistance by regulating various transcription factors involved in pluripotency.Additionally, we further investigate whether LRRN1 could be used as a potential marker for the diagnosis and/ or drug resistance in patients with PDAC considering the the above-mentioned characteristics. As a membrane protein, we were able to detect the LRRN1protein extracellularly as secreted in the cell culture media of different PDAC cell lines and LRRN1-overexpression cell clones (Bxpc3 and L3.6pl^{wt}). Interestingly, the secretion of LRRN1 into cell culture media of PDAC cell lines was significantly higher than that of normal pancreas cell lines. Surprisingly, LRRN1 was stable and highly expressed in the culture medium of gemcitabine-resistant cell line (L3.6pl^{res}) and was low expressed in the culture medium of gemcitabine-sensitive cell (L3.6pl^{wt}), which was exactly consistent with its expression detected in the respective cell lysates. Thus, we concluded that LRRN1 is a secreted protein in PDAC cells and a potential diagnostic marker for drug resistance. As one of the most common and important post-translational modifications of various membrane and extracellular proteins, glycosylation plays an important role in various biological processes such as cellular communication and protein transport (Pinho et al., 2013; Dalziel et al., 2014). Protein glycosylation in cancer occur mainly as O-glycan and N-glycan structures, which is closely related to cancer metastasis and drug resistance (Greville et al., 2016; Esmail and Manolson, 2021). LRRN1 protein expressed in human embryonic stem cells is glycosylated by N-linkage (Liao et al., 2018). There is no single information available about LRRN1 glycosylation in PDAC in the literature. For the molecular dissection of LRRN1 glycosylation in PDAC cells, we treated cell lysates and cell culture media with different digestive enzymes (PNGase F, O-Glycosidase and Protein Deglycosylation Mix II) to investigate the potential glycosylation level of LRRN1 in PDAC cells. The results showed that LRRN1 protein expressed and secreted by PDAC cells, was strongly modified by N-linked glycosylation. Of course, this conclusion needs to be further verified by detecting the expression of LRRN1 in blood and tissue samples of pancreatic cancer patients. In future studies, we will further investigate the post-translational modification of LRRN1 by using PDAC patient tissues and organoid cell cultures.

Based on the comprehensive analysis of clinical data, we believed that chemotherapy resistance is an important clinical obstacle for the individualized treatment landscape of pancreatic cancer. We confirmed that LRRN1 is closely associated with chemotherapy resistance in pancreatic cancer through a series of experiments, which is not only a potential

marker for determining drug resistance, but also a promising new therapeutic target. Moreover, we will continue to explore the molecular mechanisms of LRRN1 in a xenograft mouse model of PDAC.

2.3 Neoadjuvant radiotherapy for locoregional Siewert type II gastroesophageal junction adenocarcinoma (GEA): A propensity scores matching analysis

Siewert classification is based on the anatomical distance between the tumor center and the gastroesophageal junction (GEJ), which divides GEA into three grouplets: Siewert type I, type II, and type III and is now widely used in clinical practice. **Siewert type I** (distal esophageal adenocarcinoma) originates from the specialized intestinal area of the esophagus (such as Barrett's esophagus), which can infiltrate the GEJ from above (located 1-5cm above the GEJ). **Siewert type II** (cardia cancer) originates from the junction of the esophagus and stomach (located 1cm above the GEJ to 2cm below). **Siewert type III** (subcardial gastric carcinoma) refers to the esophagogastric junction and the distal esophagus are infiltrated from the bottom inward (located 2-5cm below the GEJ) (Rudiger Siewert et al., 2000). It has been agreed, clinically, that type I and III GEA can be staged and treated with reference to carcinoma of esophagus and gastric cancer, respectively, due to the similarity in pathology and biological behavior (Zhu et al., 2019). Although the latest TNM staging system (8^{th} edition) classifies Siewert type II as esophageal cancer, it is difficult to determine whether the origin is gastric or esophageal cancer, so the optimal treatment has been controversial.

At present, surgery is the basis for the treatment of Siewert type II GEA patients without distant metastasis, and the pivotal goal is to achieve radical resection. However, the treatment outcome of only surgery is often disappointing, which has prompted the development of multimodal therapy regimens for GEA (Cunningham et al., 2006). Neoadjuvant chemotherapy is superior to surgical treatment alone for resectable esophageal cancer and GEA in randomized clinical trials and has been widely used (Sjoquist et al., 2011; Kidane et al., 2015). Currently, neoadjuvant chemotherapy for type II GEA is mainly aimed at patients with locally advanced tumors that invade the gastric wall to a depth of T3 or T4, and it is expected that surgical resection is difficult or cannot achieve R0 resection. It's main chemotherapy regimen mainly refers to the neoadjuvant chemotherapy regimen for gastric cancer (Lutz et al., 2019). In addition, nRT is mainly used to control local disease and to improve marginal negative resection. However, because of contradictory results of some clinical trials (Altorki and Harrison, 2017; Deng et al., 2017), it is still not clear whether patients with GEA can benefit from nRT and needs therefore further investigations. Moreover, the necessity of nRT for the treatment of

cavity organ tumors is also controversial and studies have shown that nRT does not improve the survival of these patients (Sclafani and Cunningham, 2014). Moreover, radiotherapy may lead to edema, fibrosis, and normal tissue structure disorder in the surrounding tissues of the tumor, which makes it difficult for the surgeon to perform radical resection and ultimately increases the probability of postoperative complications (Geisler et al., 2004; Hu et al., 2017). For this reason, researchers have proposed to exclude radiotherapy in the treatment of rectal cancer. Does the idea of abandoning radiotherapy apply to all cavity organ tumors? Therefore, this study aimed to explore the significance of nRT for Siewert II tumor patients to propose individualized treatment strategies.

We retrieved all Siewert type II GEA patients diagnosed pathologically between the years 2004 - 2015 from the SEER database. Patients were divided into four groups according to treatment strategies: surgery cohort (patients only received surgery), surgery combined with chemotherapy cohort (patients underwent surgery and chemotherapy, without radiotherapy), and nRT cohort (patients treated with nRT and surgical treatment, with chemotherapy), aRT cohort (patients received surgical treatment combined with chemotherapy and aRT). 4.160 patients were included in this study. The efficacy of nRT was superior to that of aRT ($p=0.048$), which was the same as that of surgery combined with chemotherapy ($p=0.836$), but inferior to the OS of surgical treatment alone ($p<0.001$) in T1-2N0M0 patients. Patients receiving nRT had distinctly better survival than those receiving surgical treatment alone ($p=0.008$), but had similar survival rates compared to patients treated with aRT ($p=0.989$) or surgery combined with chemotherapy ($p=0.205$) in the T3N0/T1-3N+M0 subgroup. The efficacy of nRT is clearly stronger than that of surgical therapy alone ($p<0.001$), surgery combined with chemotherapy ($p<0.001$), and aRT ($p = 0.008$) in patients with T4 stage. The survival analysis results were consistent before and after the propensity score matching. Based on the results of the analysis, the following recommendations were made for the individualized treatment of GEA: nRT can improve the prognosis of patients with T3N0M0/T1-3N+M0 and T4 Siewert type II GEA, and it seems to be a better treatment for T4 patients. Surgery alone seems to be sufficient, and nRT is not conducive to prolong the survival of Siewert II GEA patients with T1-2N0M0 stage. Of course, further prospective trials are needed to verify this conclusion.

2.4 A Nomogram for Predicting Lymph Nodal Metastases in Patients with Appendiceal Cancers: An Analysis of SEER Database

Most of the patients suffering from appendiceal cancer cannot be diagnosed preoperatively and usually found incidentally following routine appendectomy for signs and symptoms of

acute appendicitis (Xu et al., 2021). With the development of medical technology, more options, including simple appendectomy, right hemicolectomy and even large debulking procedures with the hyperthermic intraperitoneal chemotherapy, are available for the therapies of appendiceal cancer. However, it is controversial regarding the best treatment for appendiceal cancer (Pawa et al., 2018; Brighi et al., 2020). It is a great challenge for surgeons to determine whether right hemicolectomy is appropriate to be performed for those patients, who were diagnosed with appendiceal cancer during surgery, with an unknown status of lymph node (LN) metastasis (Rault-Petit et al., 2019). Currently, the treatment of appendiceal adenocarcinoma mainly referred to the treatment guidelines of colon cancer, but there were no specific treatment guidelines (Whitfield et al., 2012). Besides, other studies recommended that performance of local right hemicolectomy should be based on tumor size and histology (Boudreaux et al., 2010; Pape et al., 2016). The treatment guidelines, published by the NCCN, recommended that patients with 2cm appendiceal carcinoid tumors can be treated by appendectomy alone. However, right hemicolectomy was recommended for appendiceal neuroendocrine tumors larger than 2cm since the risk of LN metastasis increased with growing tumor (Boudreaux et al., 2010). The ENETS Consensus Guidelines for Neuroendocrine Neoplasms of the Appendix suggested right-side colon resection for patients with any of the following: 1-2cm but edge positive or undefined, or deep in the appendix, the high level of vascular invasion, and all appendices neuroendocrine tumor > 2cm (Pape et al., 2016). Although previous studies assessed the potential risk of LN metastasis, there were a lack of large-scale national database studies which may quantify the overall risk of LN metastasis in appendiceal cancer patients (Ciarrocchi et al., 2016; Daskalakis et al., 2020). Therefore, the purpose of this study was to construct nomograms based on clinical factors by assessing the potential risk of LN metastasis in patients suffering from appendiceal cancer by analyzing the SEER database.

The target population of this study was limited to the appendiceal cancer patients with surgical treatment in SEER database from 2004 - 2016. Finally, 3.075 patients diagnosed with appendiceal cancer were enrolled. Among them, 2.028 (65.9%) cases with negative lymph nodes and 1.047 (34.1%) cases with positive lymph nodes. Risk factors associated with lymph node metastasis included age, histological type, tissue grade, T stage, distant metastasis, and tumor size. Visualization of risk factors can better guide the clinical decisions (Li et al., 2018). A new nomogram was created to assess the potential risk of LN metastasis in patients with appendiceal cancer by utilizing age, tumor histology, tumor pathologic grade, tumor size, T-stage, and M-stage. This nomogram could provide a strong support for the right hemicolectomy and may facilitate clinic decision.

To further achieve individualized treatment options of patients with appendiceal cancer, it is necessary to explore which of the clinic-pathological factors can be used as prognostic factors and which of them might have a potential impact on survival. Therefore, nomograms predicting OS and cancer-specific survival (CSS) of patients with appendiceal cancer were build in the following study (introduced in section 2.5).

2.5 Nomograms predicting overall survival and cancer-specific survival for patients with appendiceal cancer after surgery

Appendiceal cancer, with reported incidences ranging from 0.1% to 17%, is a rare gastrointestinal cancer that accounts for only 4% of all intestinal tumors (Shaib et al., 2017). However, in recent years the morbidity and mortality rates of appendiceal cancer patients are stepwise increasing (Siddharthan et al., 2019). The appendiceal adenocarcinoma, containing mucous, non-mucous (colonic), and signet-ring cell adenocarcinoma ranks as the most primary malignancy among various pathological subtypes of appendiceal cancer (Ciarrocchi et al., 2015). However, there is limited information available on the treatment of appendiceal adenocarcinoma. The NCCN recommends systemic chemotherapy for appendiceal adenocarcinoma in accordance with the NCCN guidelines for colon cancer because of lack of large sample data (Benson et al., 2017). In principle, the treatment of advanced appendiceal adenocarcinoma freuquently incorporates agents utilized for colon cancer. However, it is still unclear, especially for patients following surgery (mainly right hemicolectomy), which of the currently available treatment options may have a benefit for patients with appendiceal cancer (Tejani et al., 2014). Nomograms can transform the complex regression model into a visual graph, making the results of the prediction model more readable and convenient for evaluation, and is able to provide the accuracy of individual prognostic prediction (Balachandran et al., 2015). Nervertheless, the aim of our study was to create nomograms predicting postoperative OS and CSS in patients with appendiceal cancer after surgery based on the SEER database.

This study collected 5.945 patients with surgically removed appendiceal cancer from the Surveillance, Epidemiology, and End Results (SEER) database. The results showed that age, histological grade, T stage, N stage, regional nodes examination, tumor size, and CEA were independent prognostic factors for OS and were used in the nomogram. However, chemoradiotherapy did not improve OS of appendiceal cancer. Asare et al. announced that chemoradiotherapy cannot improve OS for patients with appendiceal cancer (Asare et al., 2016), which were consistent with the results of this study. Moreover, the nomogram for prediction of

postoperative CSS indicated that radiotherapy and chemotherapy may play a certain role as risk factors for patients with resectable appendiceal cancer, because of the toxic side effects of chemoradiation. Therefore, oncologist needs to further explore the specific chemotherapy regimen for appendiceal cancer rather than utilize the current chemotherapeutic strategy, which mainly learned from the experience of colorectal cancer (Son et al., 2016). Previous studies confirmed that tumor size is an adverse prognostic factor for patients with appendiceal cancer (Kyang et al., 2019). It was closely related to postoperative OS and CSS in patients with appendiceal cancer, and that patients with tumors > 2cm owned a worse prognosis compared with those having tumors < 2cm.

Thus, we suggest that it is necessary to incorporate tumor size into the tumor staging system by referring to other tumors, such as gastrointestinal stromal tumors (GIST) and pancreatic cancer. At present, the tumor stage of appendiceal cancer mainly depends on the TNM System of American Joint Committee on Cancer (AJCC). The results of previous studies indicated that the TNM system is not good enough to evaluate the prognosis of appendiceal cancer (Wu et al., 2016). The time-dependent ROC curves showed that the nomograms provided a higher sensitivity and specificity compared to the AJCC staging system.

Finally, we constructed new nomograms based on a large database that can accurately predict the OS and CSS of patients with appendiceal cancer after surgery, which also provides a reference for the individualized treatment of appendiceal cancer.

2.6 Specific survival nomograms based on SEER database for small intestine adenocarcinoma

Small intestine cancer, as an extremely rare tumor type, accounts for only 3% of all gastrointestinal tumors (Raghav and Overman, 2013). Small intestine adenocarcinoma (SIA), representing approximately one-third of all small bowel cancers (Bilimoria et al., 2009), received relatively less attention, both in research efforts and the clinic. Owing to anatomical proximity and rarity, the clinical management of SIA follows that of colorectal adenocarcinomas. Despite several notable molecular similarities, SIA differs from colorectal cancer (CRC) in that it involves the low bacterial load, dilute liquid contents, higher levels of lymphoid aggregates and IgA levels and worse outcomes (Halfdanarson et al., 2010). Therefore, it is necessary to better predict the prognosis of SIA patients under the existing diagnostic and treatment models. Considering the rarity of SIA, large databases, such as the SEER database,

are excellent resources that can provide big clinical data. Hence, prognostic nomograms for patients with SIA were created to assess OS and CSS based on the SEER database.

The entire group comprised 6.947 patients with small intestine adenocarcinoma. According to the results of the multivariate Cox regression analysis, ten variables, including marital status, age, pathological grade, tumor location, T (tumor), N (nodes), M (metastasis) stage, surgery, chemotherapy, and regional nodes examined (RNE), were independent predictors of both of OS and CSS. All significant variables were used to create the nomograms for OS and CSS. Surgical resection is the therapeutic gold standard for SIA, presented as a locoregional disease. The nomograms displayed that missed surgery was the worst prognostic factor, even worse than metastatic disease. The pancreaticoduodenectomy with negative margins and an adequate lymph-node evaluation should be performed for the first and second portions of the duodenum. Wide local excision and regional lymph-node dissection are indicated for the third and fourth portions of the duodenum and Jejunum or ileal adenocarcinomas. The distal or terminal ileum should be treated by right colectomy. Moreover, the number of regional lymph nodes to be evaluated should be determined. Using the SEER database, two recent researches distinguished either ≥8 or ≥10 lymph nodes as the optimal number (Nicholl et al., 2010; Overman et al., 2010). This study's findings are inconsistent with previous research, since the survival benefits were significantly higher for patients with more than 12 RNE, referring to colorectal cancer, compared to 8-11 RNE. In this study, 43.70% of SIA patients, a relatively low percentage, received chemotherapy in this study, which included data from 2004 - 2016. Adjuvant chemotherapy was expected to be beneficial despite the lack of randomized trials. The prognosis in this study was significantly better for patients in the chemotherapy group compared to the non-chemotherapy group. The intuitive nomograms may also be used to encourage patients with small bowel cancer to receive treatment actively. A small sample study reported that radiotherapy demonstrated a trend towards an improved 5-year overall survival. However, this study with data from the SEER database cannot support this tendency. For this reason, clinicians need to re-evaluate the value of radiotherapy, as radiation may damage the small intestine and/or surrounding tissues.

This study built and verified specific nomograms to predict OS and CSS for rare SIA, showing that they may serve as an excellent tool to augment the clinically available evidence to facilitate the discussion between SIA patients and clinicians regarding their therapeutic choice.

3. Summary/Zusammenfassung

A detailed analysis of the effects of radiotherapy on survival in different subgroups of pancreatic cancer and gastroesophageal junction adenocarcinoma：

i) Neoadjuvant radiotherapy is recommended for patients with stage T4 non-metastatic PDAC, and adjuvant radiotherapy is preferred for patients with stage T1-3N+M0 PDAC. However, neoadjuvant radiotherapy did not improve the survival of T1-3N0M0 patients, and surgery combined with chemotherapy was the first choice for their treatment.

ii) Age and tumor location may be the reference factors to guide the selection of radiotherapy for patients with stage IIB/III PDAC. It is necessary for clinicians to re-evaluate the benefits and risks of radiotherapy in elderly PDAC patients.

iii) Neoadjuvant radiotherapy can improve the prognosis of patients with T3N0M0/T1-3N+M0 and T4 Siewert type II GEA, and it seems to be a better treatment choice for T4 patients. Surgery alone seems to be sufficient, and neoadjuvant radiotherapy is not beneficial to prolong survival of Siewert II GEA patients with T1-2N0M0 stage.

Constructing nomograms to predict lymph node metastasis and prognosis of patients with appendiceal cancer:

iv) A new nomogram was created to assess the potential risk of lymph node metastasis in patients with appendiceal cancer, which may provide a strong reference for the right hemicolectomy and facilitate clinic decision.

v) The novel nomograms that could be considered as useful prognostic models with excellent predictive function to assess the OS and CSS for postoperative appendiceal cancer.

Building nomograms predicting OS and CSS for patients with SIA:

vi) The nomograms to predict OS and CSS for rare SIA, which appeared to be excellent tools to augment the clinically available evidence to facilitate the discussion between SIA patients and clinicians regarding therapeutic choice.

3. Zusammenfassung

Eine detaillierte Analyse der Auswirkungen der Strahlentherapie auf das Überleben in verschiedenen Untergruppen von Bauchspeicheldrüsenkrebs und Adenokarzinomen des gastroösophagealen Übergangs:

i) Eine neoadjuvante Strahlentherapie wird eher für Patienten mit nicht-metastasiertem PDAC im Stadium T4 empfohlen, und eine adjuvante Strahlentherapie wird für Patienten mit einem PDAC im Stadium T1-3N+M0 bevorzugt. Die neoadjuvante Strahlentherapie verbesserte jedoch nicht das Überleben von T1-3N0M0-Patienten, und eine Operation in Kombination mit einer Chemotherapie war die erste und bessere Wahl für ihre Behandlung.

ii) Das Alter und die Lokalisation des Tumors können Referenzfaktoren für die Auswahl der Strahlentherapie bei Patienten mit PDAC im Stadium IIB/III sein. Wir müssen den Nutzen und die Risiken der Strahlentherapie bei älteren PDAC-Patienten neu diskutieren und bewerten.

iii) Eine neoadjuvante Strahlentherapie kann die Prognose von Patienten mit T3N0M0/T1-3N+M0 und T4-Siewert-Typ-II-GEA verbessern und scheint eine bessere Behandlung für T4-Patienten zu sein. Eine Operation allein scheint ausreichend zu sein, und eine neoadjuvante Strahlentherapie ist nicht förderlich für eine Verlängerung des Überlebens von Siewert-II-GEA-Patienten im T1-2N0M0-Stadium.

Konstruktion von Nomogrammen zur Vorhersage von Lymphknotenmetastasen und Prognosen von Patienten mit Blinddarmkrebs:

iv) Ein neues Nomogramm wurde erstellt, um das potenzielle Risiko von Lymphknotenmetastasen bei Patienten mit Blinddarmkrebs zu bewerten, das eine starke Referenz für die rechte Hemikolektomie liefert und die klinische Entscheidung erleichtern könnte.

v) Die neuartigen Nomogramme, die als nützliche Prognosemodelle mit ausgezeichneter Vorhersagefunktion zur Beurteilung des OS und des CSS für postoperativen Blinddarmkrebs angesehen werden könnten.

Erstellung von Nomogrammen zur Vorhersage von OS und CSS für Patienten mit SIA:

vi die Nomogramme zur Vorhersage von OS und CSS bei seltener SIA, die hervorragende Instrumente zu sein scheinen, um die klinisch verfügbare Evidenz zu erweitern, und um die Diskussion zwischen SIA-Patienten und Ärzten über die therapeutische Wahl zu erleichtern.

4. List of abbreviations

AJCC: American Joint Committee on Cancer

GEA: gastroesophageal junction adenocarcinoma

PDAC: pancreatic ductal adenocarcinoma

SEER: Surveillance, Epidemiology, and End Results

PSM: propensity score matching

OS: overall survival

RT: radiotherapy

nRT: neoadjuvant radiotherapy

aRT: adjuvant radiotherapy

ASTRO: American Society for Radiation Oncology

RNE: regional nodes examined

GEJ: gastroesophageal junction

LN: lymph node

NCCN: National Comprehensive Cancer Network

CSS: cancer-specific survival

GIST: Gastrointestinal Stromal Tumors

SIA: Small intestine adenocarcinoma

CRC: colorectal cancer

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6. Declaration of the contribution to the publications

Publication: **Wang D**, Liu C, Zhou Y, Yan T, Li C, Yang Q, Xu Y, Zhao L, Pei Q, Tan F, Güngör C, Li Y. Effect of neoadjuvant radiotherapy on survival of non-metastatic pancreatic ductal adenocarcinoma: a SEER database analysis. Radiat Oncol. 2020 May 13;15(1):107. doi: 10.1186/s13014-020-01561-z. PMID: 32404114; PMCID: PMC7222314.
Contribution of Dan Wang: Study Design; Data Collection; Statistical Analysis; Data Interpretation; Manuscript Preparation; Literature Search.
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Publication: **Wang D**, Ge H, Tian M, Li C, Zhao L, Pei Q, Tan F, Li Y, Ling C, Güngör C. The Survival Effect of Radiotherapy on Stage IIB/III Pancreatic Cancer Undergone Surgery in Different Age and Tumor Site Groups: A Propensity Scores Matching Analysis Based on SEER Database. Front Oncol. 2022 Jan 31; 12:799930. doi: 10.3389/fonc.2022.799930. PMID: 35174085; PMCID: PMC8841859.
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Publication: Zhou Y, Tian M, Güngör C, **Wang D**. Neoadjuvant radiotherapy for locoregional Siewert type II gastroesophageal junction adenocarcinoma: A propensity scores matching analysis. PLoS One. 2021 May 12;16(5): e0251555. doi: 10.1371/journal.pone.0251555. PMID: 33979405; PMCID: PMC8115852.
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Publication: **Wang D**, Liu C, Yan T, Li C, Güngör C, Yang Q, Xu Y, Zhao L, Pei Q, Tan F, Li Y. A Nomogram for Predicting Lymph Nodal Metastases in Patients with Appendiceal Cancers:

An Analysis of SEER Database. J Invest Surg. 2021 Aug;34(8):924-930. doi: 10.1080/08941939.2019.1711467. PMID: 31931634.
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8. Curriculum Vitae

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9. Eidesstattliche Versicherung

Ich versichere ausdrücklich, dass ich die Arbeit selbständig und ohne fremde Hilfe verfasst, andere als die von mir angegebenen Quellen und Hilfsmittel nicht benutzt und die aus den benutzten Werken wörtlich oder inhaltlich entnommenen Stellen einzeln nach Ausgabe (Auflage und Jahr des Erscheinens), Band und Seite des benutzten Werkes kenntlich gemacht habe.
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