Overall survival in patients with metastatic pancreatic cancer after surgically primary tumor resected: a SEER-based nomogram analysis

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Research

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Abstract

Background

This study aimed to establish and validate a nomogram to predict overall survival in patients with metastatic pancreatic cancer (mPC) after surgically primary tumor resected.

Methods

All mPC patients who underwent primary tumor resection at SEER database between 2004 and 2016 were identified. We randomly assigned two-thirds of the patients to the training group and one third to the validation group. In the training group, the Kaplan–Meier survival analysis was used to analyze survival outcomes. A univariate and multivariate cox regression analysis was used to identify significant prognostic factors for establishing a nomogram. The predictive accuracy and discriminative ability were measured by the concordance index (C-index) and risk group stratification.

Results

A total of 742 patients were included for analysis. Four significant prognostic factors were obtained and included in the nomogram. The nomogram showed an acceptable discrimination ability (C- index:0.711) and good calibration and was further validated in the validation cohort (C- index: 0.727). The nomogram total points (NTP) had the potential to stratify patients into 2-risk groups with a median OS of 11 and 4.5 months ($P < 0.001$), respectively.

Conclusions

The nomogram can provide considerable accuracy individual prediction OS outcomes in patients with metastatic pancreatic cancer undergone primary tumor surgery and it can guide clinicians to make decisions in the clinical therapies.

Introduction

Pancreatic cancer (PC) is a fatal disease with poor prognosis and high mortality[1, 2]. It is predicted that pancreatic cancer is to be the second leading cause of cancer-associated mortality in the United States by 2030[3]. Although great advances have been made in surgery, radiotherapy and chemotherapy, the five-year survival rate for pancreatic cancer remains below 8 percent in the United States[4]. Surgical resection remains the mainstay of treatment for PC patients. However, mostly on account of the absence of the specific clinical feature, patients are diagnosed with an advantaged stage and lost the best chance of surgery[5]. The liver is the most common site of metastasis in PC patients. Meanwhile, It was revealed that those patients with liver metastasis had poorest prognoses than other site metastases[6]. Fortunately, some studies have shown that surgical resection of primary tumors can prolong the survival time of patients with metastatic pancreatic cancer (mPC)[7]. However, there is currently a lack of an

effective prognostic tool to predict the survival of mPC patients with surgical resection of the primary tumor.

Currently, a nomogram has been widely used in clinical prognosis prediction of cancer patients because of its' simple and exact [8, 9]. In addition, nomograms are useful for clinicians to deal with difficult conditions without uniform clinical guidelines. Compared to the traditional AJCC TNM stage, nomogram can predict the survival of patients more accurately [10, 11]. Besides, TNM stage can't provide a prognosis prediction for mPC patients with primary tumor resection, it is necessary to build a more personalized prognostic tool that can provide a more precise prognosis prediction for mPC patients with surgically resected primary tumor. There was already research about the nomogram for predicting survival in mPC patients [12]. However, nomograms for predicting survival time of mPC patients with surgically resected primary tumor are scarce.

Therefore, we intended to build a nomogram with the data from SEER database to better predict individualized prognosis in mPC patients with surgically resected primary tumor.

Materials And Methods

Patients selection

The data of this study was obtained from the Surveillance, Epidemiology, and End Results (SEER) 18-Registry (1973–2015dataset) (with additional treatment fields). We extracted data using the SEER*Stat software Version 8.3.6 by SEER ID (18986-Nov2018). The selection criteria were as follows: first, the pancreatic cancer patients were chosen based on the International Classification of Disease codes (ICD-O-3), including carcinoma (8010/3,8020/3), adenocarcinoma (8140/3), and infiltrating duct carcinoma (8500/3). Second, we limited our study from 2004 to 2016. Third, patients with one primary tumor only were included in the study. The exclusion criteria were as follows: (1) patients with no distant metastases; (2) patients with no surgery of primary site or unknown surgery information; (3) without certain grade information.

Data Collection

The following variables were extracted in the analysis: age at diagnosis, gender, race, marital status, tumor size, extension, regional nodes positive, site of metastases, surgery to the primary and metastases, scope regional LN surgery, TNM stage, chemotherapy recode, radiation recode, survival months and vital status. The primary endpoint was overall survival (OS), which was defined as the time from diagnosis to death due to any cause. The survival time of patients who were still alive at the end of the follow-up period was used as a censored. Ethical consent was not needed because no special personal information was recorded in the SEER database.

Statistical analysis

The statistical analyses were performed using R software version 3.6.2 (http://www.r-project.org) for windows and SPSS software (Inc., Chicago, USA, version 23). The significant level was set at 0.05 and all tests were two-sided. Categorical data were presented as frequency and percentage and tested with the Chi-square test.

For nomogram construction and validation, two-thirds of patients were assigned into the training group and one-third of patients were assigned into the validation group. The baseline characteristics of both groups were compared by the chi-square test. In the validation group, significant prognostic variables were obtained by univariate and multivariate Cox regression analyses. According to the result of multivariate analysis, independent prognostic factors were further selected to develop a nomogram to predict the probability of survival at 6-months,12-months, and 24-months. Discrimination was evaluated by using a concordance index (C-index). For reducing bias, Bootstraps with 1000 resamples in the training group and validation group were used for these activities. Besides, we use the calibration plot to compare the difference both predicted survival probability and the actual survival.

Risk Group Stratification Based On The Nomogram Total Points

To further discriminate OS, we categorized the patients into low-risk and high-risk groups based on nomogram total points (NTP). The optimal value of the cut-off for NTP was decided by the receiver operating characteristic (ROC) curve. The Kaplan-Meier survival curves were used to reveal the stratification of OS in both risk groups. Also, the cut-off value was then applied to the validation group and the Kaplan-Meier survival curves were also performed.

Result

Clinicopathological characteristics

A total of 742 eligible mPC patients with primary tumor surgery between 2004 and 2016 were included in the study (Figure.1). Among them, there were 494 cases in the training group and 248 cases in the validation group. The baseline characteristics of patients did not differ significantly between these 2 groups (Table 1). In the whole group, there were 383 (51.6%) males and 359 (48.4%) females. Most of them were white (n = 597, 80.5%) and married (n = 494, 66.6%). The most common tumor sites were the pancreatic head (n = 401, 54.0%), followed by the pancreatic tail (n = 176, 23.7%). The main grade of them were moderate differentiation (n = 340, 45.8%) and poor differentiation (n = 322, 43.4%). As for treatment, besides primary tumor resection, most of patients received chemotherapy (n = 443,59.7%), while surgery of metastases (n = 230, 31.0%) and radiotherapy (n = 93, 12.5%) were relatively less. By the end of follow-up, 644 (86.8%) patients had died and 98 (13.2%) patients were still alive (as a censored). The median survival time was 7 months.

Table 1
Baseline characteristics of the study patients

	Total	Training group	Validation group	P-Value
n(%)	(n = 742)	(n = 494)	(n = 248)	
Age				0.642
65	383(51.6)	252(51.0)	131(52.8)	
≥ 65	359(48.4)	242(49.0)	117(47.2)	
Sex				0.276
Male	383(51.6)	248(50.2)	135(54.4)	
Female	359(48.4)	246(49.8)	113(45.6)	
Race				0.988
White	597(80.5)	398(80.6)	199(80.2)	
Black	76(10.2)	50(10.1)	26(10.5)	
Other	69(9.3)	46(9.3)	23(9.3)	
Primary site				0.826
Head	401(54.0)	273(55.3)	128(51.6)	
Body	55(7.4)	36(7.3)	19(7.7)	
Tail	176(23.7)	114(23.1)	62(25.0)	
Other	110(14.9)	71(14.1)	39(15.7)	
Grade				0.220
	65(8.8)	36(7.3)	29(11.7)	
	340(45.8)	227(46.0)	113(45.6)	
	322(43.4)	220(44.5)	102(41.1)	
	15(2.0)	11(2.2)	4(1.6)	
Marital status				0.345
Married	494(66.6)	332(67.2)	162(65.3)	
Unmarried	92(12.4)	65(13.2)	27(10.9)	
Other	156(21.0)	97(19.6)	59(23.8)	
T stage				0.780

	Total	Training group	Validation group	P-Value
n(%)	(n = 742)	(n = 494)	(n = 248)	
T1	13(1.8)	8(1.6)	5(2.0)	
T2	64(8.6)	40(8.1)	24(9.7)	
T3	466(62.8)	310(62.8)	156(62.9)	
T4	171(23.0)	119(24.1)	52(21.0)	
Unspecific	28(3.8)	17(3.4)	11(4.4)	
N stage				0.244
N0	212(28.6)	143(28.9)	69(27.8)	
N1	508(68.5)	340(68.8)	168(67.7)	
Unspecific	22(2.9)	11(2.3)	11(4.5)	
Surgery of metastases				0.125
Yes	230(31.0)	144(29.1)	86(34.7)	
No/Unknown	512(69.0)	350(70.9)	162(65.3)	
Resected number of regional LN				0.216
None	105(14.2)	70(14.2)	35(14.1)	
1–3	59(8.0)	32(6.5)	27(10.9)	
≥ 4	554(74.7)	376(76.1)	178(71.8)	
Unspecific	24(3.1)	16(3.2)	8(3.2)	
Radiotherapy				0.493
Yes	93(12.5)	59(11.9)	34(13.7)	
No/Unknown	649(87.5)	435(88.1)	214(86.3)	
Chemotherapy				0.519
Yes	443(59.7)	299(60.5)	144(58.1)	
No/Unknown	299(40.3	195(39.5)	104(41.9)	

Independent Prognostic Factors Of OS In The Training Group

As listed in Table 2, the result of the univariate analysis revealed that grade, T stage, N stage, resected number of regional LN, radiotherapy and chemotherapy was statistically significant associations with OS. Furthermore, all significant prognostic factors that were selected by univariate cox analysis were included in the multivariable Cox proportional hazards model. The multivariate analysis displayed that grade (p□0.001), T stage (p = 0.001), resected number of regional LN (p = 0.023) and chemotherapy (p□0.001) were independent prognostic factors of OS. Patients with advanced grade (HR = 1.821 for moderately differentiated, 95% CI: 1.223–2.711; HR = 2.379 for poorly differentiated, 95% CI: 1.594–3.551; HR = 5.058 for undifferentiated, 95% CI: 2.458–10.407), advanced T stage (HR = 1.975 for T2 stage, 95% CI: 0.773–5.045; HR = 2.722 for T3 stage, 95% CI: 1.112–6.660; HR = 3.716 for undifferentiated, 95% CI: 1.497–9.227), less number of regional LN resected (HR = 0.766 for 1–3 regional LN resected, 95% CI: 0.484–1.213; HR = 0.612 for ≥ 4 regional LN resected, 95% CI: 0.444–0.842) suffered from inferior survival outcome. As for treatment, patients with receiving chemotherapy have a better survival outcome than no receiving chemotherapy (HR = 2.453, 95% CI: 1.981–3.037), while the metastatic site's surgery was not significant associations with OS (P > 0.05). Beyond that, Kaplan-Meier survival curves turned out the OS differences about stratification by these factors were all statistically significant (Fig. 2).

Table 2
Univariate and multivariate analyses of overall survival in the training group

	Univariate analysis		Multivariate analysis	
	HR(95%CI)	P-Value	HR(95%CI)	P-Value
Age		0.112		
65	1			
≥ 65	1.165(0.965–1.407)			
Sex		0.324		
Male	1			
Female	0.910(0.753–1.098)			
Race		0.559		
White	1			
Black	1.029(0.750–1.413)			
Other	0.834(0.592–1.175)			
Primary site		0.352		
Head	1			
Body	0.988(0.683–1.432)			
Tail	0.946(0.746-1.200)			
Other	1.243(0.948–1.630)			
Grade		0.001		0.001
	1		1	
	1.407(0.957–2.068)		1.821(1.223–2.711)	
	1.752(1.192–2.577)		2.379(1.594–3.551)	
	3.684(1.839–7.380)		5.058(2.458–10.407)	
Marital status		0.600		
Married	1			
Unmarried	1.097(0.817–1.473)			
Other	1.117(0.879–1.419)			

	Univariate analysis		Multivariate analysis	
T stage		0.001		0.001
T1	1		1	
T2	1.980(0.777–5.042)		1.975(0.773–5.045)	
T3	2.158(0.890–5.237)		2.722(1.112–6.660)	
T4	3.279(1.335–8.055)		3.716(1.497–9.227)	
Unspecific	6.081(2.231–16.578)		4.321(1.521–12.275)	
N stage		0.001		0.391
N0	1		1	
N1	1.018(0.825–1.255)		1.164(0.919–1.475)	
Unspecific	3.419(1.832–6.382)		1.263(0.626–2.547)	
Surgery of metastases		0.782		
Yes	1			
No/Unknown	0.971(0.789–1.196)			
Resected number of regional LN		0.001		0.023
None	1		1	
1–3	0.747(0.483–1.154)		0.766(0.484–1.213)	
≥ 4	0.589(0.454–0.765)		0.612(0.444–0.842)	
Unspecific	0.860(0.483–1.530)		0.775(0.425–1.413)	
Radiotherapy		0.034		0.460
Yes	1		1	
No/Unknown	1.373(1.025–1.839)		1.121(0.828–1.518)	
Chemotherapy		0.001		0.001
Yes	1		1	
No/Unknown	2.237(1.841–2.717)		2.453(1.981–3.037)	

Nomogram And Risk Classification

Based on the result of cox multivariate analysis, grade (p□0.001), T stage, resected number of regional LN and chemotherapy were integrated into establishing a nomogram (Fig. 3). This model showed that grade and chemotherapy had the greatest effect on prognosis, followed by the T stage and resected number of regional LN. Each subtype within these variables had a corresponding score on the point scale. By adding the scores of each selected variable, we can easily calculate the likelihood of survival at 6-,12-,24-months. In the training group and validation group, the C-index for OS was 0.711 and 0.727, respectively, which indicated that the nomogram had an accepted discernible ability. The calibration curves for predicting 6-months, 12-months and 24-months survival probability in the training group and validation group were shown in Fig. 4.

We divided the training group into two subgroups according to the optimal NTP cut-off value, which was identified by the ROC curve. The NTP cut-off value was 115.5. The patients were divided into low-risk subgroups (NTP□115.5,n = 244) and high-risk subgroups (NTP ≥ 115.5□n = 250). The median OS of both groups was 12 months and 4.5 months, respective. In the validation group, the same cut-off value was used to grouping. The median OS of low-risk was also 13 months and 4 months. The Kaplan-Meier survival curves were used to reveal the stratification of OS in the training and validation groups (Fig. 5-A and B).

Discussion

In clinical practice, such a dilemma often happens: patients are found to have a distant metastatic site but the primary tumor can be surgically resected. In such a case, surgery is sometimes performed based on the surgeon's experience and personal desire, but whether it has an impact on survival is not clearly defined. Several studies had demonstrated that surgical resection of a primary tumor can prolong the survival time of mPC[6, 13, 14]. Besides, a study based on the seer database, through propensity score matching, concluded that patients with metastatic pancreatic cancer could benefit from primary tumor resection[15]. Thus, primary site surgery should be recommended for patients who are in the good physical condition and have a desire for surgery. However, the absence of an efficient prognostic tool for OS in mPC patients with surgically primary tumors resection results in the difficulty in making decisions on the choice of treatment regimens. Thus, we built and validated a novel nomogram to predict the OS of mPC with primary tumors resection based on the SEER database. The result demonstrated that this model revealed an acceptable discernibility and calibration in predicting the OS of those patients. Besides, patients were divided into the low-risk group and high-risk group according to the cut off value of NTP. The results indicated that patients in the low-risk group had a significantly better prognosis than those in the high-risk group. Similar results were verified in the validation group. Based on the different risk groups with different potential outcomes, we can choose the risk-adapted treatment strategies for those patients.

In this study, tumor grade, T grade, resected number of regional LN and chemotherapy were confirmed as independent prognostic factors of mPC with primary tumor resection. The grade is one of the strongest independent prognostic factors. Tumor grading reflects the biological behavior of the tumor and plays an

important role in prognosis. It has been demonstrated that tumor differentiation is an independent influencing factor for predicting OS in other similar studies [16, 17]. In our study, the HR of OS increased with the degree of tumor differentiation decreases, and patients who were well-differentiation suffered better survival than poor-differentiation patients. Several studies also advised that tumor grade should be incorporated into the current TNM classification, because novel TNMG staging system enables more accurate prognosis prediction within particular clinical stages[18, 19]. Chemotherapy is an important treatment method for advanced pancreatic cancer. Studies have shown that concurrent chemoradiotherapy [20–21] after the induction of effective chemotherapy [22–24] can alleviate symptoms and improve the survival of patients for advanced pancreatic cancer with a good systemic condition. According to the National Comprehensive Center Network (NCCN) guidelines (Version 1.2017), patients with metastatic disease were recommended to choose corresponding chemotherapy regimens based on the condition of patients. Sultana et al[25] conducted a meta-analysis of a total of 9970 patients with locally advanced and metastatic pancreatic cancer in 51 randomized controlled studies, and found that chemotherapy significantly improved the survival rate of patients compared to the best supportive treatment. Compared with chemotherapy alone, chemotherapy combined with surgery can even increase the resection rate of partial metastatic pancreatic cancer [26]. Similar to the above result, it was found that chemotherapy therapy improved survival time in mPC patients with primary tumor resection (HR = 2.453 for no receiving chemotherapy, 95% CI: 1.981–3.037). Lymph node metastasis is considered to be an important prognostic factor for pancreatic cancer and other gastrointestinal tumors. Pancreatic cancer often metastasizes to distant lymph nodes through complex pathways and develops as a systemic disease[27]. In the early stage of the resectable pancreas, appropriate regional lymph node dissection can reduce the probability of postoperative recurrence and benefit the survival of patients, but the specific number of lymph nodes removed has not been agreed [28–29]. At present, there are few studies on whether primary resection of metastatic pancreatic cancer combined with regional lymph node dissection is beneficial for survival. In our study, Cox multivariate analysis showed that N staging was not an independent prognostic factor in mPC patients with surgically primary resection. However, combined regional lymph node removal can benefit the survival of mPC patients, and the number of lymph nodes removed is positively correlated with survival outcome(HR = 0.766 for 1–3 regional LN resected, 95% CI: 0.484–1.213; HR = 0.612 for ≥ 4 regional LN resected, 95% CI: 0.444–0.842). This result revealed that the resected number of regional LN was identified as an independent prognostic factor.

Nomograms are graphical representations of statistical prediction models that provide the probability of survival for a given outcome [30]. Thus, the variables included in a nomogram should be easily available and measurable. In our study, the nomogram is simple to use and provides a quantitative prognosis for individual patients. Besides, our study uses four variables that are easily accessible in clinical work, making the use of nomogram more convenient. In some studies [31],the preoperative pain was included in the nomogram for pancreatic cancer. Although pain is the common symptom of patients with metastasis pancreatic cancer，it is so subjective and the clinical significance remains unclear，which makes the result of prognosis prediction inaccurate. Yi-Nan Shen et al[32] study showed that radiological

parameters played important parts in the diagnosis and treatment of pancreatic cancers with venous invasion. However, it is difficult to measure and obtain, it is very inconvenient for clinical use.

There are some limitations to this study. First, although the SEER database is large, many important variables are not recorded,such as the level of CA199, specific chemotherapy regimens and so on. As we know, different chemotherapy regimens have a great influence on the prognosis of patients. Current mainstream chemotherapy regimens include FOLFIRINOX and Gemcitabine plus nab-paclitaxel. That will be a major part of our future research. Second, although the established nomogram has good identification capabilities, further validation based on a large external cohort is required. Third, the data in the SEER database is retrospective data, so selection bias is unavoidable.

In conclusion, we developed and validated a novel nomogram for predicting the survival of mPC patients with primary tumors resection. What's more, our model performed well in both the training and validation groups. It can be used to calculate individualized survival prediction and provide better treatment allocation in mPC patients with surgically primary tumor resection.

Abbreviations

mPC: Metastatic pancreatic cancer; OS: Overall survival; LN: lymph nodes; NTP: Nomogram Total Points; NCCN: National Comprehensive Center Network; ROC: Receiver Operating Characteristic. ICD-O-3: International Classification of Diseases for Oncology,Third Edition; K-M: Kaplan-Meier. SEER: Surveillance, Epidemiology,and End Results.

Declarations

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Availability of data and materials

The datasets analyzed during the current study are available in the SEER repository (https://seer.cancer.gov/).

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable.

Author Contributions

Maoen Pan and Heguang Huang designed the study. Yuanyuan Yang and Xiaoting Wu contributed to get access to data and statistical analysis. Maoen Pan drafted the manuscript. Heguang Huang and Yuanyuan Yang critically revised the paper. All authors read and approved the final manuscript.

Competing interests

The authors have no conflicts of interest to declare.

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Figures

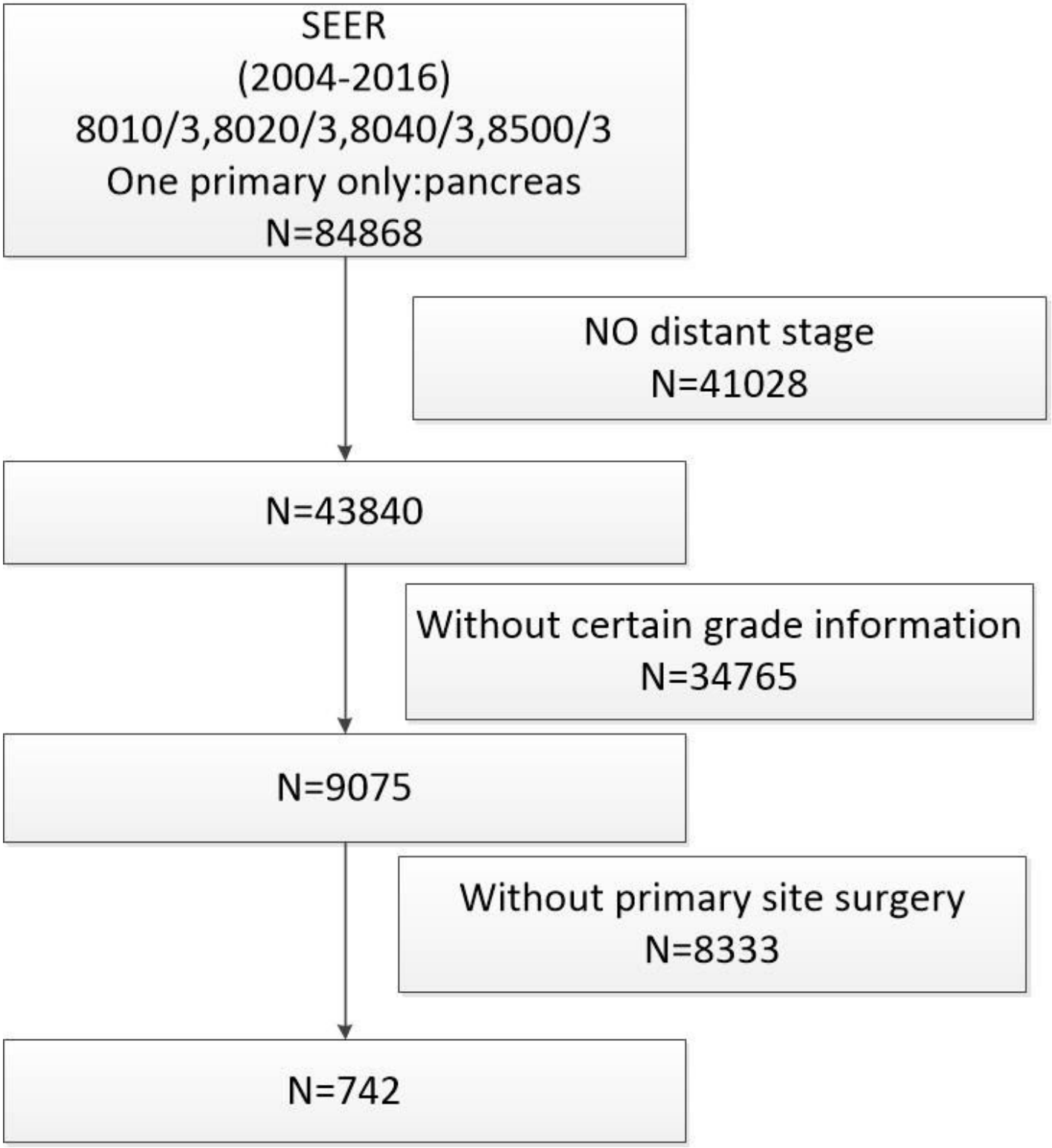

Figure 2

Flow chart depicting the selection of mPC patients with primary site surgery.

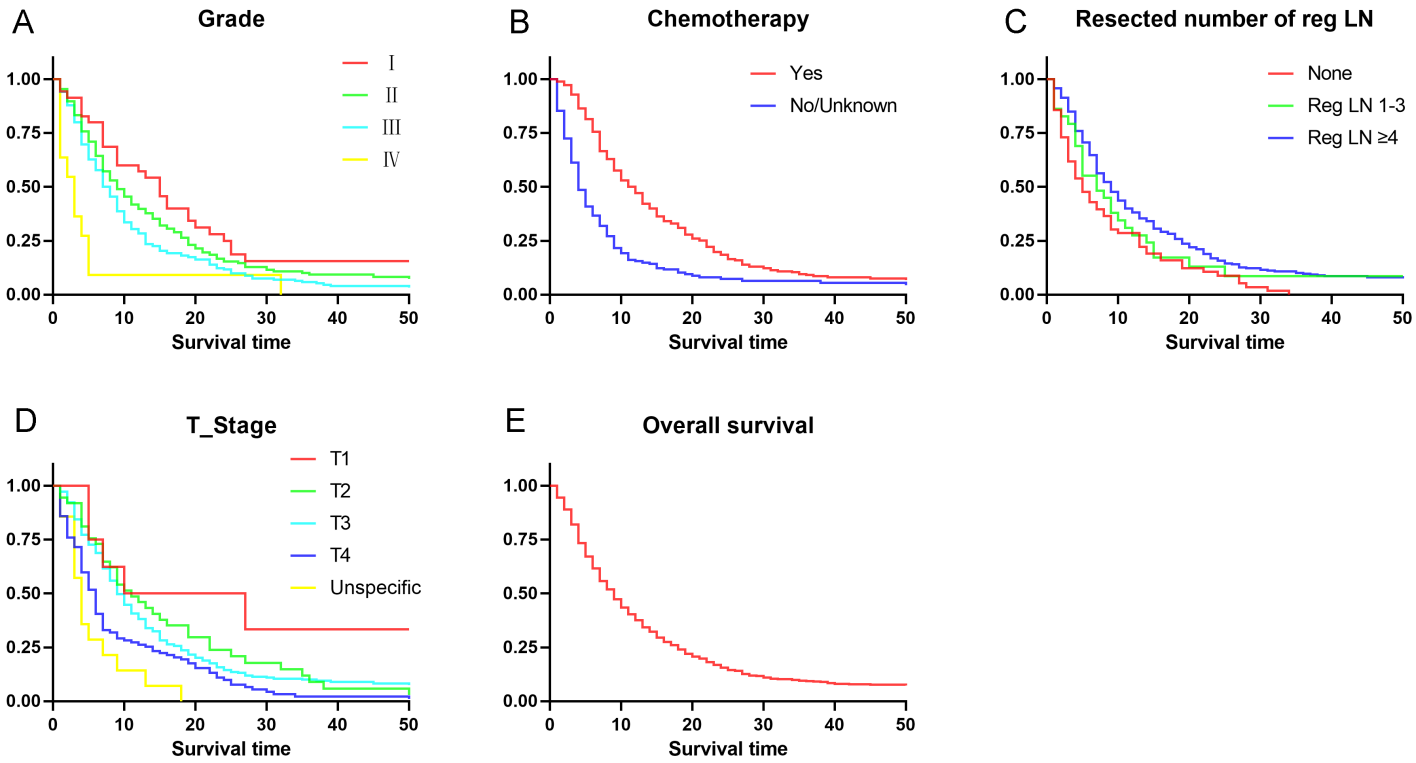

Figure 4

Kaplan-Meier OS curves stratified by patient characteristics: (A)Grade; (B) Chemotherapy; (C) Resected number of reg LN; (D) T_Stage; (E) Overall survival.

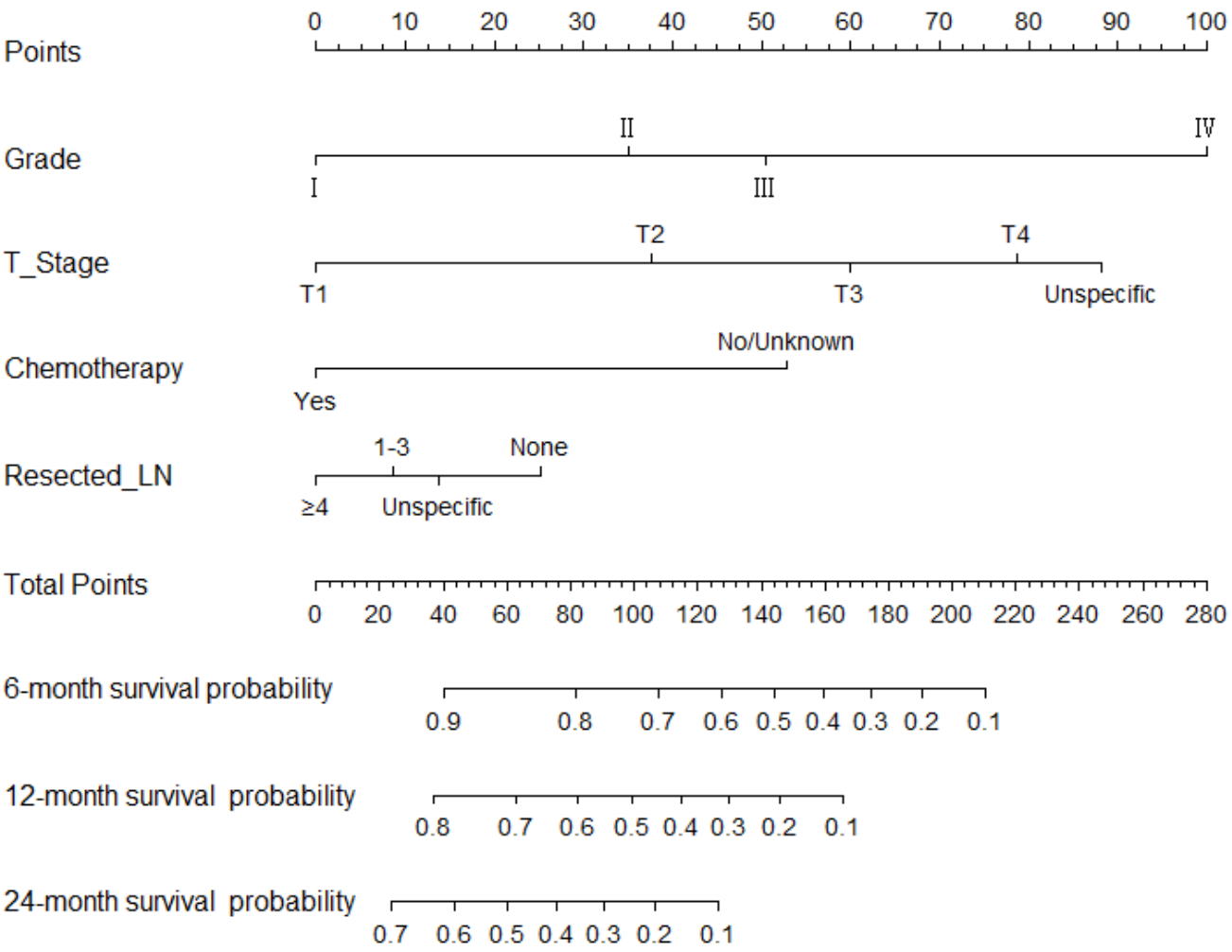

Figure 6

The prognostic nomogram for OS. Assign points to each risk factor by drawing a line up from the corresponding value to the point line. The total points of the four risk factors is calculated and find it on the total points line. A line is drawn down to read the corresponding predictions of 6-, 12-, and 24- month survival probabilities.

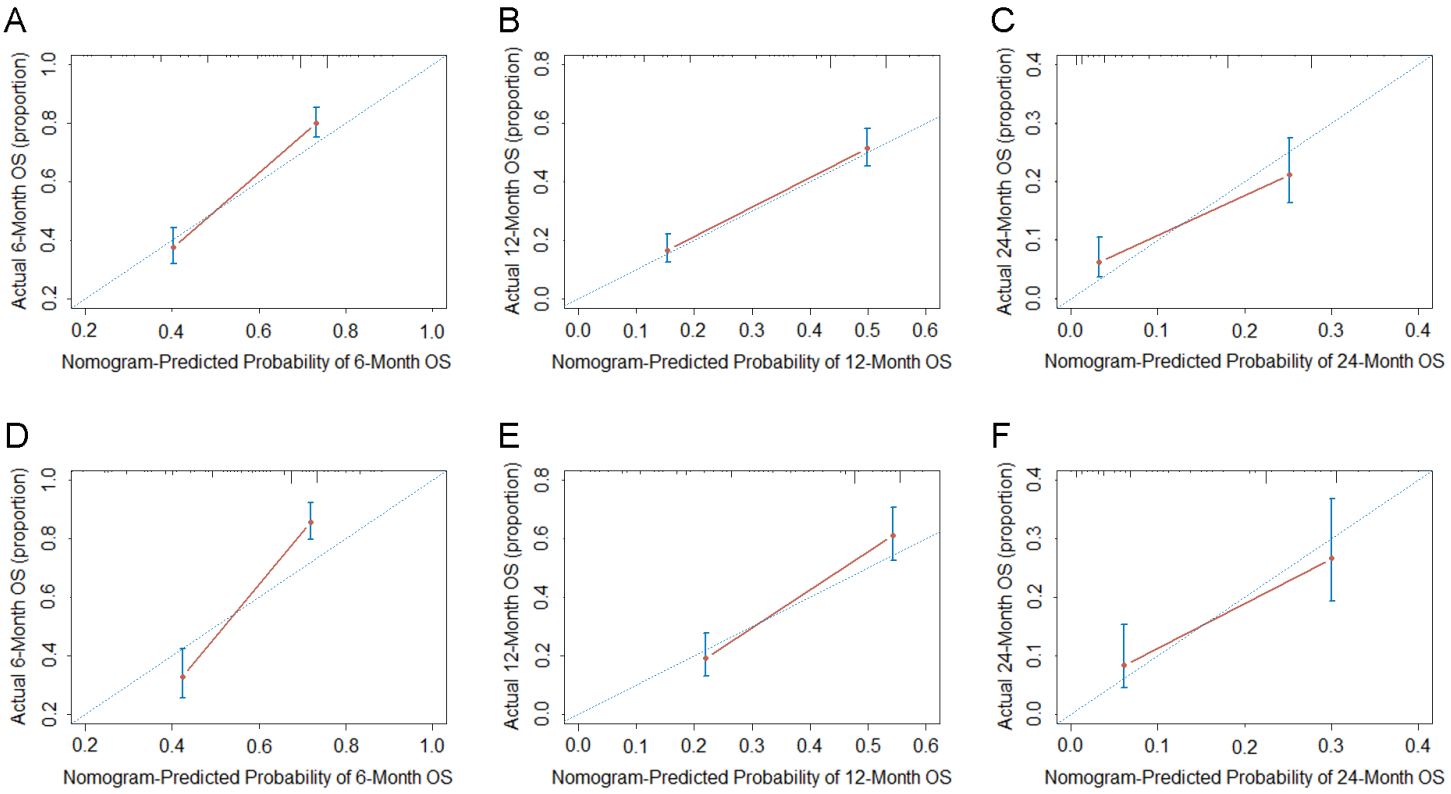

Figure 8

The calibration curve for predicting survival probability at (A) 6months, (B) 12 months, and (C) 24months in the training group and at (D) 6months, (E) 12months, (F) 24 months in the validation cohort.

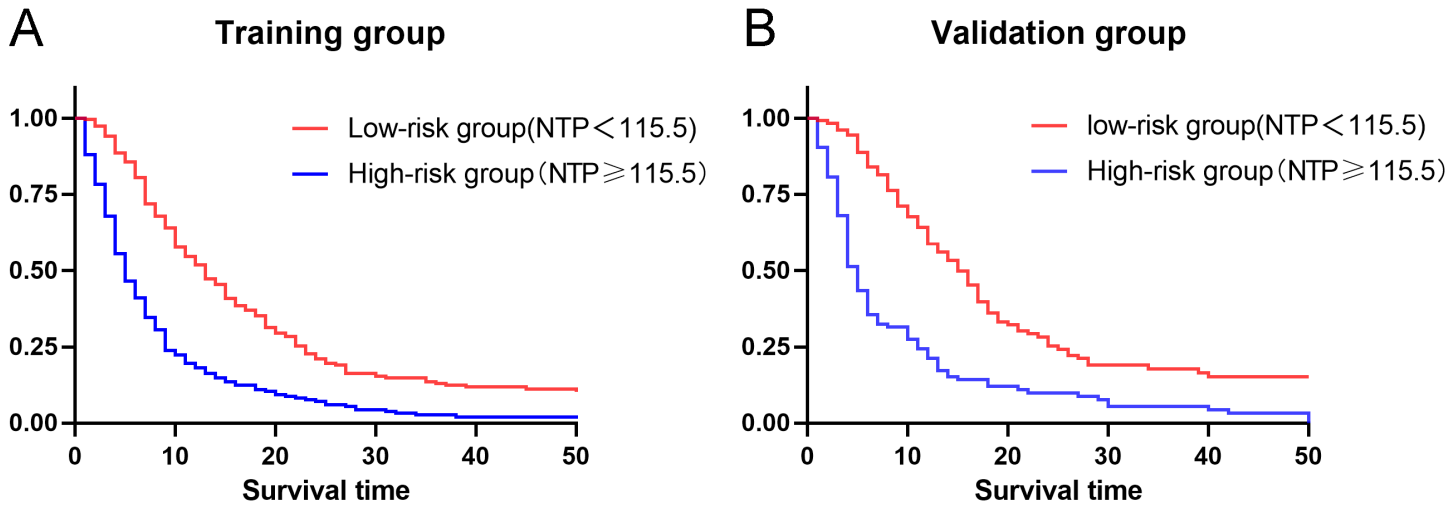

Figure 10

Kaplan-Meier analysis based on NTP(nomogram total points) in the training group(A) and validation group(B).