

Do the Locally Advanced Rectal Cancer Patients Enjoy Long-term Survival Benefit From the Radiation-based Neoadjuvant Treatments in the Total Mesorectal Excision Era: a Population-based Analysis

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Abstract

Background: Radiation-based neoadjuvant therapy followed by radical surgery is the standard treatment for locally advanced rectal cancer (LARC), but things might have changed with the advent of total mesorectal excision (TME). This study re-evaluated the clinical efficacy of preoperative radiotherapy for LARC patients in the TME era by population-based analysis to identify any long-term survival benefits.

Methods: LARC patients receiving preoperative radiotherapy or not followed by surgery between 2011 and 2015 were extracted from the Surveillance, Epidemiology, and End Results (SEER) database. Overall survival (OS) was analyzed by Kaplan-Meier curves, and potential candidates for preoperative radiotherapy were identified by nomogram.

Results: There were 7582 eligible patients; 6066 received preoperative radiotherapy, and 1516 received non-preoperative radiotherapy. The initial result showed that the pooled hazard ratio (HR) for OS was in favor of preoperative radiotherapy compared with non-preoperative radiotherapy group (HR = 0.86, 95% confidence interval (CI) = 0.75-0.98, $P < 0.05$). The cases were randomly divided into training and validation datasets, and multivariate Cox regression analysis of the training set determined that age, sex, carcinoembryonic antigen level, tumor stage, node stage, tumor differentiation, perineural invasion, and the number of dissected lymph nodes were independent risk factors for OS in the training set (all $P < 0.05$). A nomogram was established based on the risk factors to predict the OS (concordance index, training set: 0.70, validation set: 0.67). Further analysis showed that the long-term survival of high-risk patients was better with preoperative radiotherapy (HR = 0.71, 95% CI = 0.56-0.91, $P < 0.05$).

Conclusions: Preoperative radiotherapy has long-term survival benefits for LARC patients, especially those with high risk.

Background

Colorectal cancer is one of the most common malignant cancers worldwide and the second leading cause of cancer mortality globally [1]. In the United States, 43 340 new patients were diagnosed with rectal cancer, including 25 960 men and 17 380 women in 2020 [2]. Nonetheless, rectal cancer has steadily decreased in recent decades [2, 3], and the mortality rate is down by approximately 50% from the peak, perhaps owing to earlier diagnoses by screening and comprehensive treatment [4].

Radiation-based neoadjuvant therapy following radical surgery has been the standard treatment for locally advanced rectal cancer (LARC) [5, 6], but the long-term survival benefit has never been established [7, 8]. The advent of the total mesorectal excision (TME) has decreased the local recurrence rate to approximately 9%, even lower if intensified radiotherapy is applied [9–14]. Currently, treatment failure primarily presents as distant metastasis rather than local recurrence [7, 8, 15, 16].

In 2019, a retrospective study based on the Surveillance, Epidemiology, and End Results (SEER) database verified the preoperative radiotherapy survival benefit in 49 439 patients, but the study had a critical

limitation. The study span, ranging from 1988–2011, was too long to avoid confounding factors. The surgical technique evolved (from local excision to TME), radiation therapy progressed (from convention radiotherapy to intensity-modulated radiation therapy), and the timeframe of intensive chemotherapy shifted (from postoperative to preoperative) [17]. Therefore, the effects of preoperative radiotherapy on the long-term survival benefits are still unclear.

This study analyzed patients from the SEER database diagnosed between 2011 and 2015 to re-evaluate the clinical value of radiation-based neoadjuvant therapies in the TME era and identify candidates who may benefit from radiation-based neoadjuvant therapy in long-term survival. This study also summarized phase III randomized clinical trials (RCTs) to elucidate long-term survival failure reasons.

Methods

Data source and patient selection

The SEER database was screened for patients diagnosed with rectal cancer between 2011 and 2015 using SEER*Stat software (version 8.3.8) with the International Classification of Diseases for Oncology 3rd Edition (ICD-O-3) code: C20.9 Rectum, NOS. Rectal cancer cases were retrieved based on the following: adenocarcinoma (ICD-O-3 codes: 8140/3, 8144/3, 8210/3, 8221/3, 8255/3, 8263/3, and 8572/3) ; stage T3-4 or N+ and M0 tumors (derived from derived AJCC T, 7th ed (2010-2015), derived AJCC N, 7th ed (2010-2015) and derived AJCC M, 7th ed (2010-2015)); received surgery, including lymphadenectomy (derived from reason no cancer-directed surgery, and regional nodes examined examination (1988+)); and underwent chemotherapy (derived from chemotherapy recode). Cases were excluded if there were multiple primary tumors or no preoperative radiotherapy records. All patients underwent active follow-ups. The T/N classification was re-staged according to the 8th edition of the American Joint Committee on Cancer (AJCC) staging system with the following codes: derived AJCC T, 7th ed. (2010-2015); derived AJCC N, 7th ed. (2010-2015); CS extension (2004-2015); CS lymph nodes (2004-2015); and CS site-specific factor 4 (2004+ varying by schema). The endpoint was overall survival (OS), which was extracted directly from the database as months.

Variable definitions and stratification

The data were collected and re-categorized as follows: age at diagnosis (≤ 65 years, >65 years), sex (male, female), insurance (no, yes), serum carcinoembryonic antigen (CEA) level (≤ 5 ng/mL, >5 ng/mL), stage (II, III), T stage (T0/T1/T2, T3, T4), N stage (N0, N1, N2), tumor differentiation (I/II, III/IV), tumor size (≤ 3 cm, 3-5 cm, >5 cm), tumor deposits (negative, positive), perineural invasion status (absent, present), number of dissected lymph nodes (LND) (<12 , ≥ 12), preoperative radiotherapy (no, yes), and survival (months).

Statistical analyses

Continuous variables were re-defined as categorical variables and presented as n (%). Kaplan-Meier curves were plotted to compare the survival difference between patients who received preoperative radiotherapy and those who did not (presented with hazard ratios [HR] and 95% confidence intervals [CI]). Subgroup analysis among patients who received or did not receive preoperative radiotherapy were further stratified by variable and plotted using a forest map.

The entire data set was randomly divided into training and validation sets at a 6:4 ratio and compared using the chi-square test or Fisher's test. A nomogram was established based on the multivariate analysis results, which integrated all of the independent prognostic factors. A calibration plot was constructed to evaluate the calibration of the nomogram. Harrell's concordance index (C-index) and the area under the receiver operating characteristic curve (AUC) were used to assess the predictive outcome performance of the nomogram and the outcomes. The clinical utility of the nomogram was also evaluated using decision curve analysis (DCA), which included the continuous risk of the probability threshold (x-axis) and the net benefit (y-axis). The nomogram was also compared with the 8th AJCC staging system.

Statistical tests were conducted using RStudio (version 1.3.1073), including the `xlsx`, `table1`, `survminer`, `survival`, `forestplot`, `rms`, `nomogramFormula`, `timeROC`, `stdca`, and `survcomp` packages. All statistical tests were two-tailed, and statistical significance was set to $P < 0.05$.

Results

Patient characteristics

There were 7582 eligible patients according to the predesigned flow chart (Additional File 1: Figure S1), and their baseline characteristics are presented in Table 1; 6066 patients (80.0%) received preoperative radiotherapy, and 1516 patients (20.0%) did not. There were 2752 patients (36.3%) at stage II and 4817 (63.5%) at stage III according to the 8th AJCC staging system. In addition, 73.5% of patients had ≥ 12 LND.

The effect of preoperative radiotherapy on LARC patients' long-term survival

For the entire dataset (training and validation), the Kaplan-Meier survival curve showed that the pooled HR for the median OS favored preoperative radiotherapy instead of surgery without preoperative radiotherapy (HR = 0.86, 95% CI = 0.75-0.98, $P = 0.028$, Figure 1). The 3- and 5-year survival rates with or without preoperative radiotherapy were all over 70% (with: 3-year, 86.9%, 5-year: 84.8%; without: 3-year, 74.9%, 5-year, 72.5%). Univariate and multivariate Cox regression analysis showed that preoperative radiotherapy was not an independent risk factor for OS (HR = 0.97, 95% CI = 0.80-1.17, $P = 0.728$).

Subgroup analysis of OS stratified by risk factor

Using the entire dataset, stratified subgroup analysis showed that patients with the following risk factors benefited from preoperative radiotherapy regarding OS (Figure 2): aged >65 years (HR = 0.75, 95% CI =

0.61-0.92, $P = 0.005$), stage III (HR = 0.83, 95% CI = 0.71-0.97, $P = 0.020$), T3 (HR = 0.81, 95% CI = 0.69-0.95, $P = 0.010$), T4 (HR = 0.70, 95% CI = 0.51-0.95, $P = 0.020$), N2 (HR = 0.62, 95% CI = 0.48-0.80, $P < 0.001$), tumor size >5 cm (HR = 0.71, 95% CI = 0.57-0.88, $P = 0.002$), tumor deposits (HR = 0.77, 95% CI = 0.59-0.99, $P = 0.042$), and LND ≥ 12 (HR = 0.81, 95% CI = 0.69-0.95, $P = 0.008$).

Nomogram construction for LARC prognosis

The entire dataset was randomly divided into training and validation sets (6:4 ratio, Additional File 2, Table S1). The univariate and multivariate Cox regression results for the training set are presented in Table 2. Age >65 years, CEA >5 ng/mL, T3, T4, N2, tumor differentiation III/IV, and perineural invasion were independent risk factors for OS (all $P < 0.05$), while female and LND ≥ 12 were independent protective factors for OS (both $P < 0.05$). A prognostic nomogram was developed based on the multivariate Cox regression results to predict the 1-, 3-, and 5-year survival rates (Figure 3).

Nomogram predictive performance

The C-index of the nomogram was 0.70 in the training set (95% CI = 0.67-0.72) and 0.67 in the validation set (95% CI = 0.63-0.71), which were higher than the 8th AJCC staging system (training set: 0.63, 95% CI = 0.60-0.67, $P < 0.001$; validation set: 0.61, 95% CI = 0.56-0.66, $P = 0.005$; Table 3). The nomogram also had better discrimination compared to the 8th AJCC staging system using time-dependent AUC analysis. The 1-, 3-, and 5-year AUC with 95% CIs for different models are presented in Table 3. Additionally, there was good consistency between the observed and the predicted outcomes of the nomogram regarding 3- and 5-year OS in the training and validation sets using calibration plots (Figure 4). DCA also showed that the nomogram had better net benefits at the 5-year mark than the 8th AJCC staging system in the training (Figure 5A) and validation sets (Figure 5B).

Clinical application of the nomogram

Each patient's total score was determined based on the nomogram. The median total score for the entire dataset was 129 (range: 24-296). A score of 158 was set as the cut-off value to divide patients into high- and low-risk groups. There were 1224 patients in the high-risk group, which had a shorter median OS than the low-risk group (HR = 2.62, 95% CI = 2.25-3.04, $P < 0.001$, Figure 6A). Further analysis showed that there were no differences between the low-risk groups with and without preoperative radiotherapy (HR = 1.19, 95% CI = 0.92-1.54, $P = 0.180$, Figure 6B), but significantly prolonged median OS in the high-risk group who received preoperative radiotherapy (HR = 0.71, 95% CI = 0.56-0.91, $P = 0.006$, Figure 6C).

Discussion

This is the first retrospective population-based study to evaluate the effect of radiation-based neoadjuvant treatments on the long-term prognosis of LARC patients in the TME era. Patients who received preoperative radiotherapy had a significantly prolonged OS and a slightly higher 5-year survival rate compared to those without. The nomogram, constructed based on the multivariate Cox regression

analysis, predicted the prognosis better than the 8th AJCC staging system and showed that high-risk patients are more likely to benefit from preoperative radiotherapy, as indicated by their OS.

Radiotherapy was initially introduced as an adjuvant treatment to prevent local rectal cancer recurrence [18, 19]. Later on, radiotherapy was tested as a preoperative treatment, resulting in stronger anti-recurrence efficacies, higher R0 resection rate, increased sphincter-preserving, and less radiation toxicity [7, 13, 20, 21]. Generally, radiation based neoadjuvant therapies, including long-course radiotherapy (LCRT) combined with concurrent chemotherapy and short-course radiotherapy (SCRT), followed by instant or delayed surgery, have been the standard treatment for patients with LARC [13, 22, 23]. Numerous single-center and multi-center trials have laid the foundation for radiation-based neoadjuvant treatment for LARC management, which is now used in clinics worldwide. In this study, 80.0% of LARC patients received radiation-based neoadjuvant treatment.

However, there has always been controversy regarding preoperative radiotherapy. First, the pathological complete response (pCR) rate following radiation-based neoadjuvant treatments varies different from different modalities (LCRT: 2.2 to 33.8%; SCRT: 0.3 to 28.0%) [15, 22, 24–27]. Second, acute radiation-induced injury, such as radiation colitis, decreases treatment compliance and quality of life [28–30]. Third, late radiation-induced injury, such as fibrosis, increases the surgical dissection difficulty and the risk for postoperative complications [31, 32]. Ultimately, the long-term survival benefit (e.g., disease-free survival [DFS] and OS) of radiation-based neoadjuvant treatments (regardless of the modality) is not clear. Since the start of TME, the primary treatment failure indicator is distant metastasis rather than local recurrence, suggesting that the clinical value of preoperative radiotherapy for LARC management needs re-evaluation.

The key to correctly evaluate the clinical efficacy of a treatment modality is endpoint selection. pCR is the most widely used endpoint to evaluate neoadjuvant treatments, but using pCR as an optimal surrogate endpoint remains controversial [33]. This may be because the correlation between pCR and long-term survival is not definite [34–37], and pCR is influenced by other non-treatment factors (e.g., the interval between radiotherapy completion and surgery) [38, 39]. DFS is the time from randomization to recurrence or death from any cause [40], which was found to be a stronger predictor of OS than pCR among 2795 patients receiving neoadjuvant treatment [41]. However, DFS is also not an ideal surrogate endpoint because the DFS starting time varies, especially regarding surgery. OS is a hard endpoint for any treatment, although it has been confounded by salvage treatments (in recurrence cases) and potential causes of non-cancer-related mortality. OS also often requires a larger sample size, longer follow-up, and higher costs. Radiation-based neoadjuvant treatment advantages on the OS were rarely observed among phase III RCTs (Table 4) [8, 10, 42–49], but advantages were identified in a meta-analysis including 6426 trial patients in 2000 and a population-based analysis including 49 439 patients in 2019 [17, 50]. The most likely reason for this divergence was the sample size.

In the TME era, local recurrence is no more than a primary cause of treatment failure. Intensified neoadjuvant chemotherapy was also found to be comparable to radiation-based neoadjuvant treatments

in terms of OS, and even had a weak DFS advantage [51, 52]. Both of above have caused the necessity of preoperative radiotherapy to be questioned. In this study, 7582 patients between 2011 and 2015 from the SEER database were eligible for survival analysis, and the pooled HR for the median OS favored the preoperative radiotherapy group compared to the group without preoperative radiotherapy. In addition, a nomogram was developed to predict the long-term prognosis of LARC patients with better calibration than the 8th AJCC staging system and a significantly higher C-index. The nomogram also indicated that high-risk patients would benefit from preoperative radiotherapy more than low-risk patients regarding long-term survival. Therefore, we concluded that radiation-based neoadjuvant treatments should be conducted in the management of LARC patients in the era of TME and intensified chemotherapy.

From the other hand, watch and wait strategy has been pouring new vigor into the application of preoperative radiotherapy. Although radical surgery followed by neoadjuvant treatment is the standard treatment for LARC patients, there are two kinds of particular cases. Some patients are reluctant to undergo surgery, and some are not tolerant to surgery. A retrospective study analyzed 71 patients with a complete clinical response using the “watch and wait” strategy and 21 patients with an incomplete clinical response but a complete pathologic response post-TME [53]. The 5-year OS and DFS rates were 100% and 92% in the “watch and wait” group, and 88% and 83% in the surgery group, respectively. The “watch and wait” advantage was also confirmed in a study by three neighboring UK regional cancer centers that used a propensity score-matched cohort to analyze the 3-year rates of non-regrowth DFS (wait: 88%, surgery: 78%), OS (wait: 96%, surgery: 87%), and colostomy-free survival (wait: 74%, surgery: 47%) [54]. In a retrospective study of 3298 patients receiving neoadjuvant chemoradiotherapy, pCR was found to be significantly associated with the radiotherapy dose [55]. A prospective single-arm study including 55 patients reported that the clinical complete response rate was up to 73% using high-dose chemoradiotherapy (60 Gy/30 fractions) [56]. Hence, multidisciplinary management combined with patient willingness is strongly recommended to make decision for LARC patients, and intensified curative chemoradiotherapy may be an alternative for select patients.

This study has several limitations. First, this was a retrospective study. Second, preoperative radiotherapy data, including modality, gross tumor volume, clinical target volume, dose, and combination with chemotherapy, were not available. Third, chemotherapy administration before or after surgery is unknown. Although, LCRT is preferred in the USA, and chemotherapy is increasingly suggested. Finally, the TME technique has been popular worldwide since 2002 [57–60] and we only enrolled patients after 2010, but data on surgery in the SEER database were unavailable.

Conclusion

Preoperative radiotherapy may bring long-term survival benefits for LARC patients, but further validation with a larger sample size and multi-center RCTs with well-designed outcome measurements is required.

Abbreviations

LARC: locally advanced rectal cancer

TME: total mesorectal excision

SEER: Surveillance, Epidemiology, and End Results

RCT: randomized clinical trials

AJCC: American Joint Committee on Cancer

T: primary tumor

N: Regional Lymph Nodes

OS: overall survival

CEA: carcinoembryonic antigen

LND: dissected lymph nodes

HR: hazard ratio

CI: confidence interval

C-index: Harrell's concordance index

AUC: area under the receiver operating characteristic curve

DCA: decision curve analysis

LCRT: long-course radiotherapy

SCRT: short-course radiotherapy

pCR: pathological complete response

DFS: disease-free survival

Declarations

Ethics approval and consent to participate:

The ethical committee waved away the informed consent, due to that all the data was derived from public database and individual information was anonymous.

Consent for publication:

Not applicable.

Availability of data and materials:

The datasets analyzed in this study are obtained from SEER database and can be obtained from: <https://seer.cancer.gov/data/>. The data are also available by contacting the corresponding author on reasonable request.

Competing interests:

The authors declare that they have no competing interests.

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Authors' contributions:

LW, XHZ, HQL contributed to conception and design. XHZ, HQL conducted data collection and analyzed the data. LW drafted the manuscript. XQZ, LDS, JXW contributed critical revision of the manuscript. All authors read and approved the final manuscript.

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Tables

Table 1
Demographic and tumor characteristics of
7582 rectal cancer patients

Character	n	%
Sample size	7582	100.0
Age		
≤ 65 years	5421	71.5
> 65 years	2161	28.5
Sex		
Male	4649	61.3
Female	2933	38.7
Insurance		
No	299	3.9
Yes	7200	95.0
Unknown	83	1.1
CEA		
≤ 5 ng/mL	3047	40.2
> 5 ng/mL	2300	30.3
Unknown	2235	29.5
Stage		
II	2752	36.3
III	4817	63.5
Unknown	13	0.2
T stage		
T0/T1/T2	670	8.8
T3	6065	80.0
T4	804	10.6
Unknown	43	0.6
N stage		

Character	n	%
N0	2671	35.2
N1	3787	49.9
N2	1111	14.7
Unknown	13	0.2
Tumor differentiation		
Grade I/II	5961	78.6
Grade III/IV	827	10.9
Unknown	794	10.5
Tumor size		
≤ 3 cm	1811	23.9
3–5 cm	2570	33.9
> 5 cm	2220	29.3
Unknown	981	12.9
Tumor deposits		
Negative	6094	80.3
Positive	961	12.7
Unknown	527	7.0

Table 1
(Continued)

Character	n	%
Perineural invasion		
Absent	5876	77.5
Present	903	11.9
Unknown	803	10.6
Number of LND		
< 12	1992	26.3
≥ 12	5577	73.5
Unknown	13	0.2
Preoperative radiotherapy		
No	1516	20.0
Yes	6066	80.0
CEA, carcinoembryonic antigen; LND, dissected lymph nodes.		

Table 2

Univariate and multivariate analysis of prognostic factors associated with overall survival (Training set).

Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Age				
≤ 65 years	Reference	-	Reference	-
> 65 years	1.89(1.63,2.19)	0.000	2.25(1.82,2.78)	0.000
Sex				
Male	Reference	-	Reference	-
Female	0.73(0.63,0.85)	0.000	0.65(0.52,0.82)	0.000
Insurance				
No	Reference	-		
Yes	0.77(0.55,1.07)	0.116		
CEA				
≤ 5 ng/mL	Reference	-	Reference	-
> 5 ng/mL	1.65(1.38,1.97)	0.000	1.40(1.13,1.74)	0.002
T stage				
T0/T1/T2	Reference	-	Reference	-
T3	1.61(1.17,2.22)	0.004	1.80(1.05,3.09)	0.032
T4	3.51(2.46,5.02)	0.000	3.58(1.99,6.43)	0.000
N stage				
N0	Reference	-	Reference	-
N1	1.25(1.06,1.48)	0.008	1.16(0.89,1.51)	0.266
N2	1.87(1.52,2.30)	0.000	2.02(1.47,2.77)	0.000
Tumor differentiation				
Grade I/II	Reference	-	Reference	-
Grade III/IV	1.63(1.35,1.98)	0.000	1.45(1.11,1.88)	0.006
Tumor size				
≤ 3 cm	Reference	-	Reference	-

	Univariate analysis		Multivariate analysis	
3–5 cm	1.10(0.89,1.35)	0.375	0.90(0.68,1.18)	0.451
> 5 cm	1.53(1.25,1.86)	0.000	1.29(0.98,1.69)	0.066
Tumor deposits				
Negative	Reference	-	Reference	-
Positive	1.99(1.66,2.39)	0.000	1.30(0.98,1.71)	0.066
Perineural invasion				
Absent	Reference	-	Reference	-
Present	1.98(1.64,2.38)	0.000	1.35(1.03,1.78)	0.030
Number of LND				
< 12	Reference	-	Reference	-
≥ 12	0.79(0.68,0.93)	0.004	0.68(0.54,0.85)	0.001
Preoperative radiotherapy				
No	Reference	-	Reference	-
Yes	0.86(0.72,1.02)	0.081	1.00(0.77,1.28)	0.972
CEA, Carcinoembryonic antigen; LND, dissected lymph nodes; HR, hazard ratio; CI, confidence interval. Unknown data points were removed before performing statistical tests.				

Table 3

Comparison of time-dependent AUC and C-index between the nomogram and the 8th AJCC staging system.

	Training set			Validation set		
	Nomogram	8th AJCC	P-value	Nomogram	8th AJCC	P-value
1-year AUC (95% CI)	0.71(0.65,0.77)	0.57(0.50,0.64)	0.000	0.74(0.66,0.81)	0.58(0.49,0.66)	0.000
3-year AUC (95% CI)	0.71(0.68,0.75)	0.63(0.59,0.67)	0.000	0.67(0.63,0.71)	0.58(0.54,0.63)	0.000
5-year AUC (95% CI)	0.69(0.64,0.73)	0.61(0.56,0.65)	0.001	0.68(0.63,0.73)	0.61(0.56,0.66)	0.040
C-index (95% CI)	0.70(0.67,0.72)	0.63(0.60,0.67)	0.000	0.67(0.63,0.71)	0.61(0.56,0.66)	0.005
AUC, area under the receiver operating characteristic curve; CI, confidence interval; AJCC, American Joint Committee on Cancer						

Table 4

Overall survival in rectal cancer associated with neoadjuvant radiotherapy among phase III RCTs

study	Treatment arm (Sample size)	Total dose/Daily dose (Gy)	Treatment interval time (day)	5-year OS (%)	P- value
VASOG I	R + S (189)	20/2	14	43.4%*	0.042
(1975) [42]	S (187)			31.6%*	
VASOG II	R + S (126)	31.5/1.75	immediate	50.3%*	0.997
(1986) [43]	S (136)			49.6%*	
EORTC	R + S (166)	34.5/2.3	11	69.1%*	0.08
(1988) [44]	S (175)			59.1%*	
Stockholm I	R + S (331)	25/5	7	42.0%*	NA
(1990) [45]	S (348)			41.9%*	
Goldberg	R + S (146)	15/5	7	40.3%	0.92
(1994) [46]	S (134)			38.8%	
Marsh	R + S (143)	20/5	7	30.1%	0.21
(1994) [47]	S (141)			30.5%	
MRC II	R + S (139)	40/2	45	31%	0.1
(1996) [48]	S (140)			38%	
Swedish rectal cancer trial	R + S (573)	25/5	7	58%	0.004
(1997) [49]	S (574)			48%	
Dutch TME trial	R + TME (924)	25/5	< 10 (87%)	62.2%	NA
(2001) [8, 10]	TME (937)			61.9%	
R, radiotherapy; S, surgery; TME, total mesorectal excision; RCTs, randomized clinical trials					
*Analysis of the results of patients undergoing radical surgery					

Figures

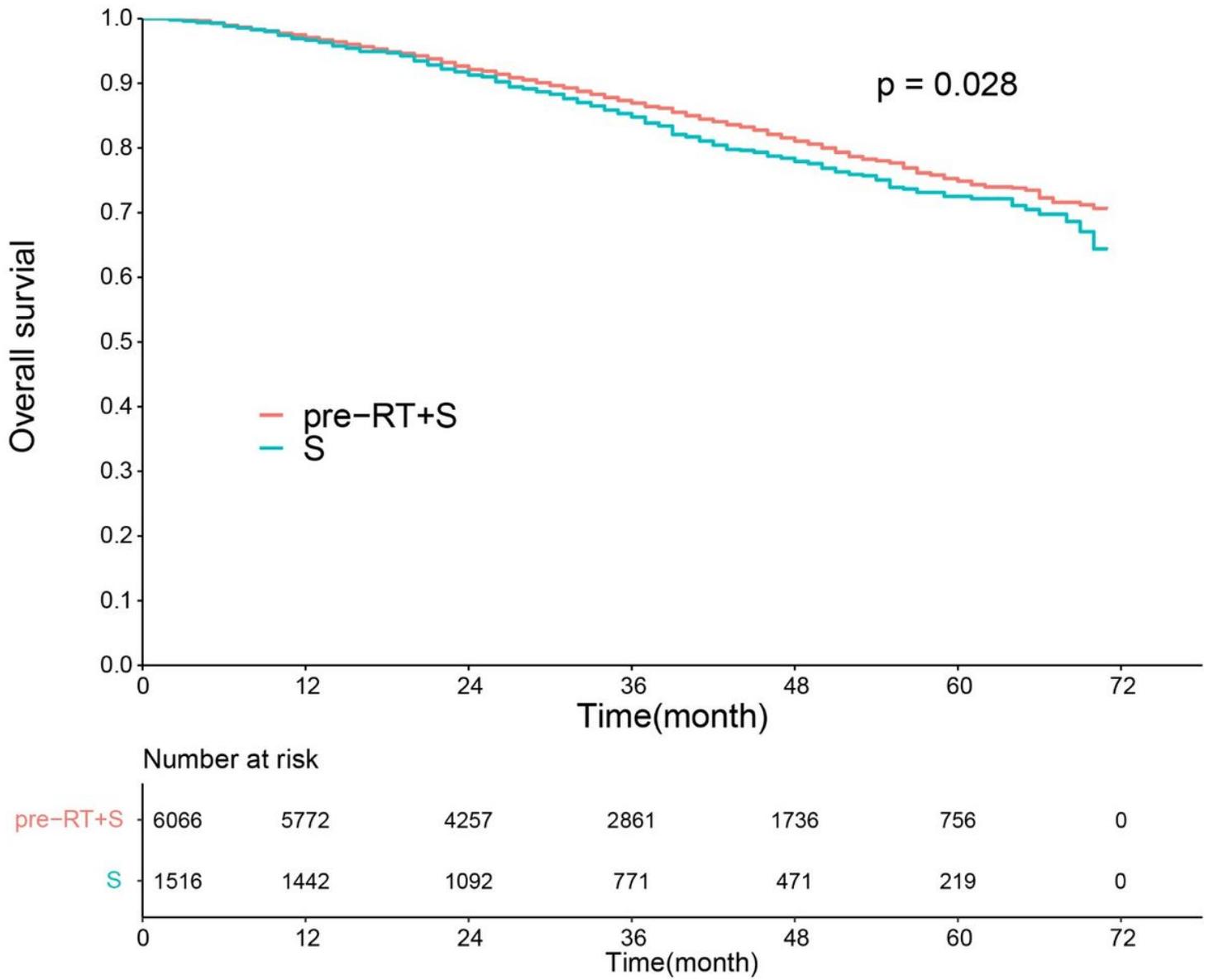


Figure 1

Kaplan-Meier analysis of overall survival according to preoperative radiotherapy (pre-RT). S, surgery without pre-RT.

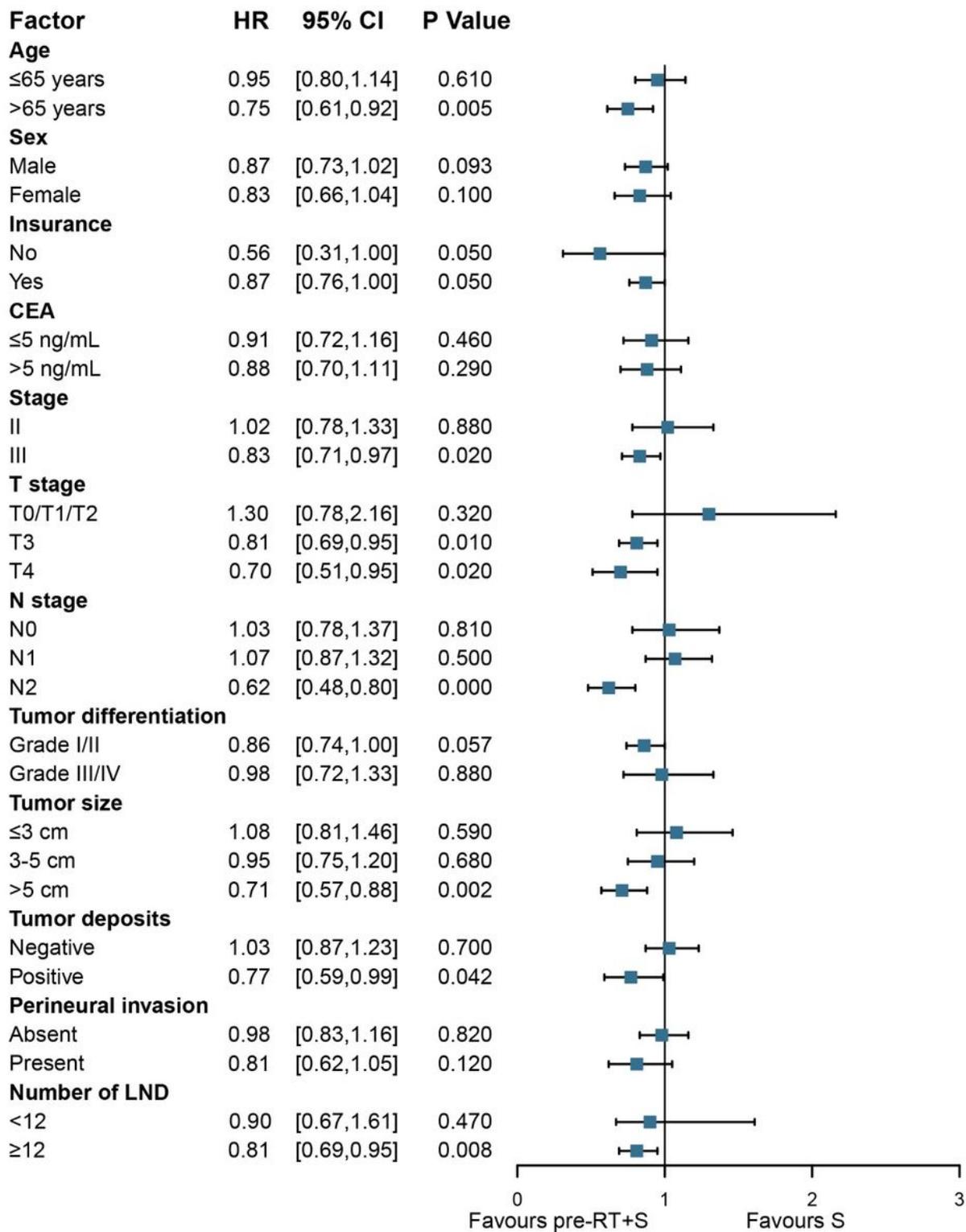


Figure 2

Subgroup analysis of OS stratified by risk factor. CEA, carcinoembryonic antigen; LND, dissected lymph nodes; pre-RT, preoperative radiotherapy; S, surgery without pre-RT; HR, hazard ratio; CI, confidence interval.

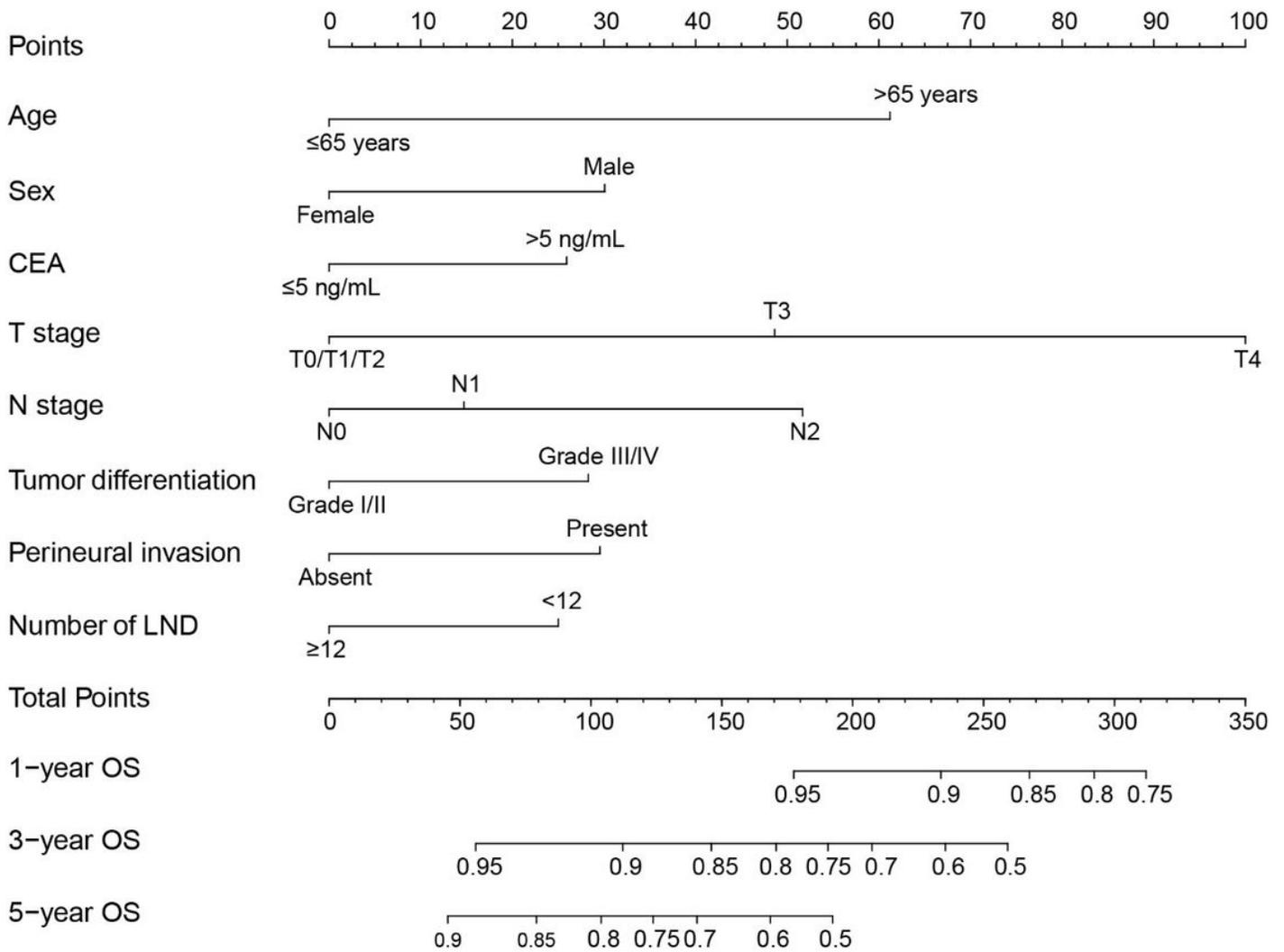


Figure 3

Locally advanced rectal cancer survival nomogram. (To use the nomogram, an individual patient’s value is located on each variable axis, and a line is drawn upward to determine the number of points received for each variable value. The sum of these numbers is located on the Total Points axis, and a line is drawn downward to the OS axes to determine the likelihood of 1-, 3- or 5-year OS). OS, overall survival; CEA, carcinoembryonic antigen; LND, dissected lymph nodes.

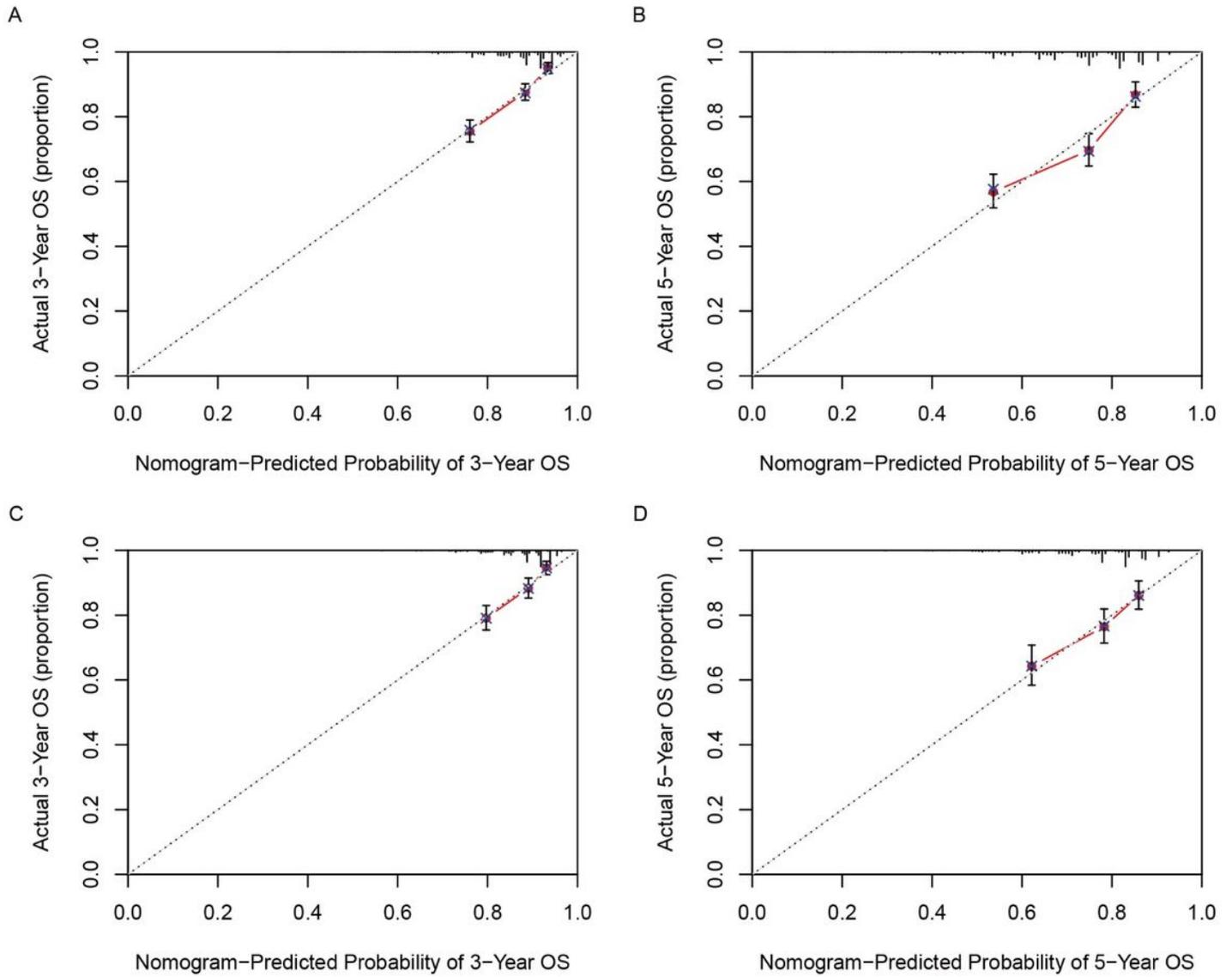


Figure 4

Calibrations of the nomogram for predicting survival rates. (A) 3-year, (B) 5-year in the training set and (C) 3-year, (D) 5-year in the validation set. Nomogram predicted probability of OS is plotted on the x-axis; actual overall survival is plotted on the y-axis.

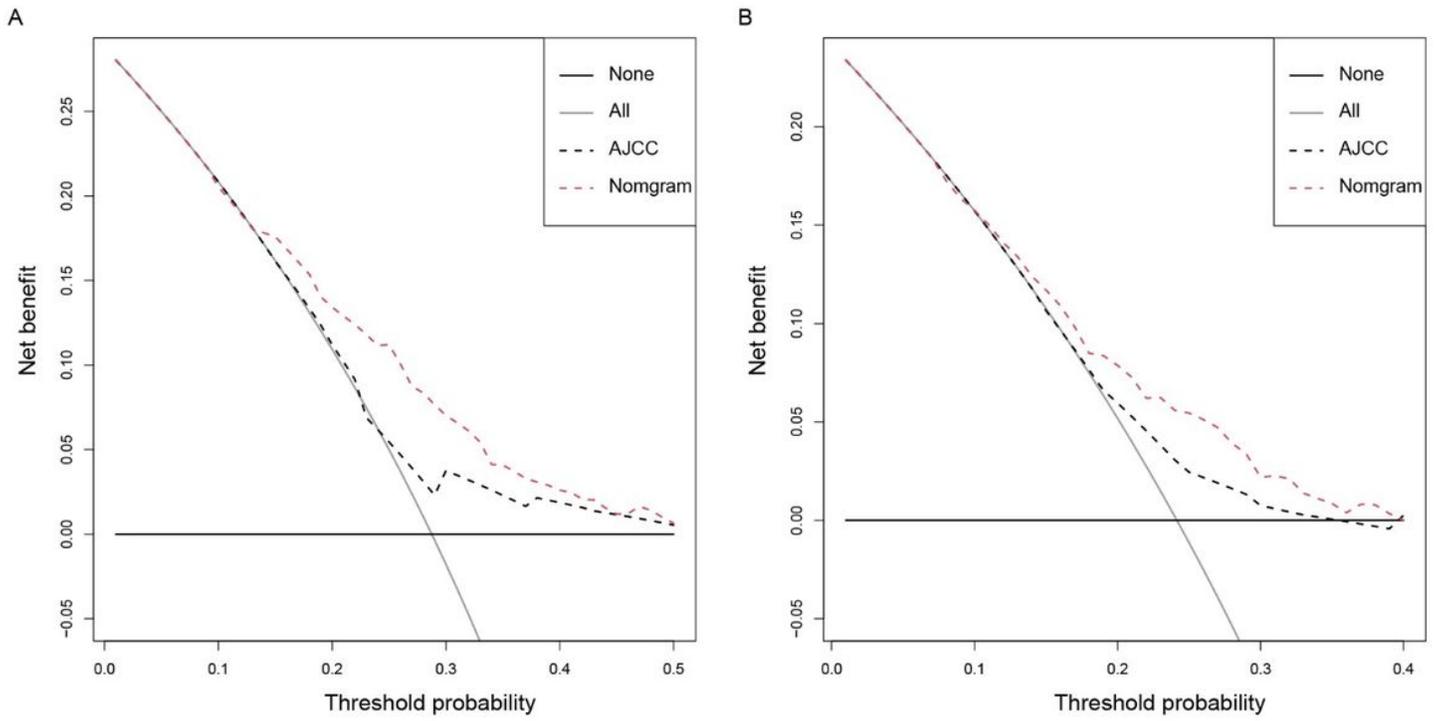


Figure 5

Decision curve analysis (DCA) of overall survival using nomogram and the 8th AJCC staging system. (A) DCA of 5-year OS in the training set; (B) DCA of 5-year OS in the validation set. The x-axis represents the threshold probability. The y-axis measures the net benefit. The threshold probability is where the expected benefit of treatment balances the expected benefit of avoiding treatment. The nomogram resulted in a superior net benefit to the 8th AJCC staging system, with a wide range of threshold probabilities.

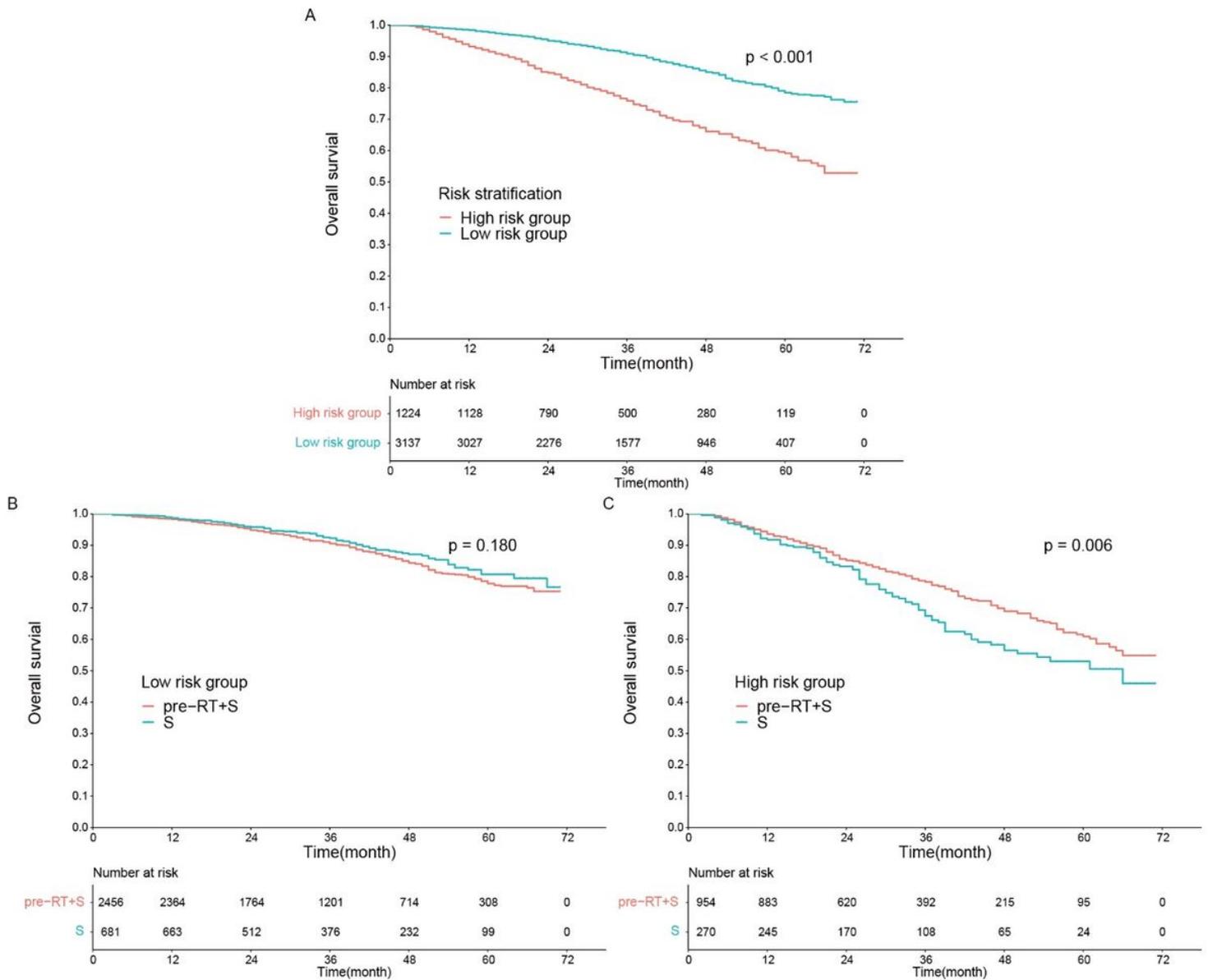


Figure 6

Kaplan-Meier analysis of overall survival according to (A) risk stratification (high risk group vs low risk group); (B) preoperative radiotherapy (pre-RT) for low-risk patients (pre-RT + S vs S) and (C) preoperative radiotherapy for high-risk patients (pre-RT+S vs S). S, surgery without pre-RT.

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