Predictors and Risk Factors of Pathologic Complete Response Following Neoadjuvant Chemoradiotherapy for Rectal Cancer: A Population-Based Analysis

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Background: Patients with rectal cancer who achieve pathologic complete response (pCR) after neoadjuvant chemoradiotherapy (nCRT) may have a better prognosis and may be eligible for non-operative management. The aim of this research was to identify variables for predicting pCR in rectal cancer patients after nCRT and to define clinical risk factors for poor outcome after pCR to nCRT and radical resection in rectal cancer patients.

Methods: A retrospective review was performed using the Surveillance, Epidemiology, and End Results (SEER) database from 2004 to 2013. Non-metastatic rectal cancer patients who received radical resection after neoadjuvant chemoradiotherapy were included in this study. Multivariate analysis of the association between clinicopathological characteristics and pCR was performed, and a logistic regression model was used to identify independent predictors for pCR. A nomogram based on the multivariate logistics regression was built with decision curve analyses to evaluate the clinical usefulness.

Results: A total of 6,555 patients were included in this study. The proportion of patients with pCR was 20.5% ($n = 1,342$). The nomogram based on multivariate logistic regression analysis showed that clinical T4 and N2 stages were the most significant independent clinical predictors for not achieving pCR, followed by mucinous adenocarcinoma and positive pre-treatment serum CEA results. The 3-year overall survival rate was 92.4% for those with pCR and 88.2% for those without pCR. Among all the pCR patients, mucinous adenocarcinoma patients had the worst survival, with a 3-year overall survival rate of 67.5%, whereas patients with common adenocarcinoma had an overall survival rate of 93.8% ($P < 0.001$). Univariate and multivariate analyses showed that histology and clinical N2 stage were independent risk factors.

Conclusion: Mucinous adenocarcinoma, positive pre-treatment serum CEA results, and clinical T4 and N2 stages may impart difficulty for patients to achieve pCR. Mucinous adenocarcinoma and clinical N2 stage might be indicative of a prognostically unfavorable biological tumor profile with a greater propensity for local or distant recurrence and decreased survival.

Keywords: rectal cancer, pathologic complete response, neoadjuvant chemoradiotherapy, mucinous adenocarcinoma, SEER

INTRODUCTION

Colorectal cancer is the third leading cause of cancer death worldwide (1, 2). Recent studies suggest that 1.2 million new patients are diagnosed annually worldwide, among whom approximately half a million would die of this disease (3). Neoadjuvant chemoradiotherapy (nCRT), followed by radical surgical resection, is the most recommended routine management for locally advanced rectal cancer (4–6). nCRT has been proven to downstage tumors and improve surgical outcomes, which would eventually turn out to be a long-term oncologic outcome (5, 6). Some rectal cancer patients who received nCRT achieve a pathologic complete response (pCR), which is always associated with a better outcome than that of patients who had residual tumor after nCRT. Total mesorectal excision (TME) is a standard surgery for rectal cancer (6), and it may lead to a risk of morbidity, including bowel, urinary and sexual function impairment, and a temporary or permanent ostomy (7). More and more research is focused on the "watchful waiting" approach as an alternative to radical resection, which means that those who achieved clinical complete response (cCR) following nCRT are monitored closely instead of receiving surgery (4, 8, 9). Patients with low-recurrence-risk tumors or those who achieve pCR may be more suitable for this strategy (8, 10). Thus, the ability to predict factors for pCR or factors associated with a high risk of recurrence is needed, which may help clinicians select patients who may be more suitable for the "watchful waiting" approach after nCRT. The aim of this research was to identify clinicopathological factors that predict pCR and overall outcome after nCRT and TME surgery.

PATIENTS AND METHODS

Patient Selection

The data in this study were extracted from the SEER database as previously reported (11, 12). The SEER database is a National Cancer Institute-based authoritative source of cancer data in the United States. It collects and publishes cancer incidence and survival data from 18 population-based cancer registries that cover ∼28% of the US population (1). SEER*Stat is an online program provided by SEER to obtain patient information. This study was approved by the ethics committee of the Second

FIGURE 1 | Filtering process of patient data from the SEER database.
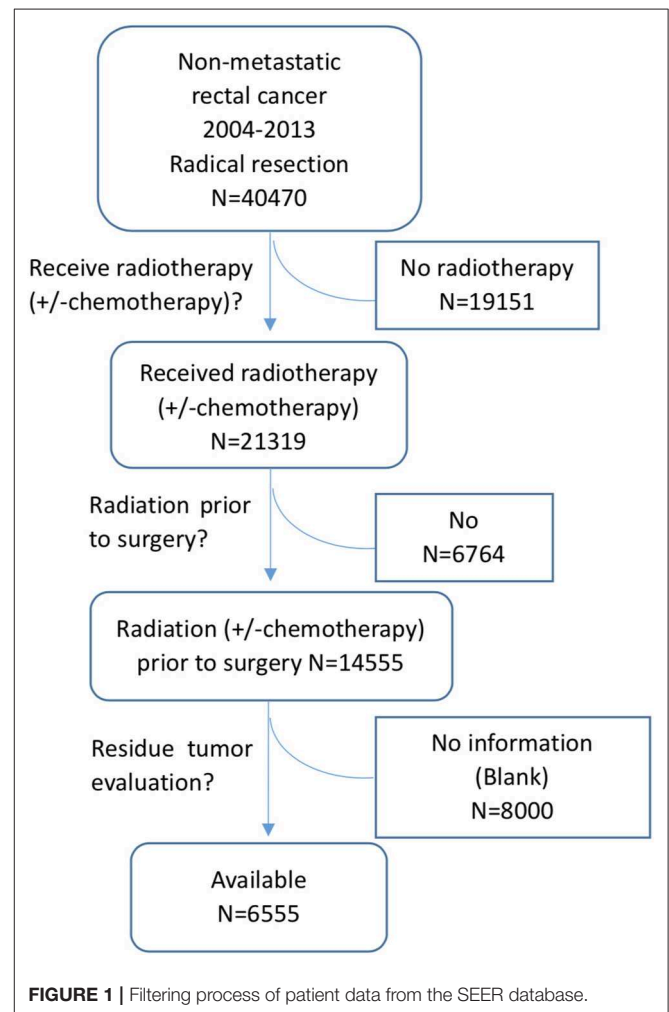
Affiliated Hospital of Zhejiang University College of Medicine. Patients were eligible for inclusion if they had histologically confirmed, primary, non-metastatic rectal adenocarcinoma and received curative resection after nCRT. Patients were excluded if they had a lifetime history of another primary malignancy, had *in situ* cancer, or died within 1 month after the operation. Patients without residual tumor information were also excluded. The detailed selection process is shown in **Figure 1**. As we don't know whether chemotherapy was administered together with radiation, all the patients received radiotherapy with or without chemotherapy were included in the selection process, noted as radiotherapy (± chemotherapy).

Clinicopathological Data

The patient demographics (age, gender, race, and marital status), tumor characteristics (differentiation, clinical T and N stage, tumor histology, and pre-treatment CEA level) and survival data were acquired from the SEER database.

For the univariate and multivariate analyses, the variables were analyzed as discrete categorical variables. A median age of 50 was chosen as the cut-off value. Patients with a survival time of less than 1 month were excluded because such patients may have died of surgical complications.

Statistical Analysis

Univariate and multivariate logistic regression models were used to identify factors predicting pCR. A nomogram was constructed based on statistically significant factors identified by the multivariate analysis from the logistic regression model to predict the possibility of pCR. Decision curve analysis (DCA) was used to assess the clinical usefulness and net benefits of the prediction model for achieving pCR. The primary endpoint of this study, colorecal cancer cancer-specific survival (CSS), was calculated from the date of diagnosis to the date of cause-specific death. Clinicopathological variables were tested for independence by Pearson χ^2 tests. CSS was analyzed using Kaplan-Meier survival methods, and the 3-year CSS was estimated by Kaplan-Meier survival curves. Log-rank tests were employed to assess statistical significance. Multivariate analyses using Cox proportional hazards models were used to identify independent prognostic factors for cause-specific survival. Statistical analyses were performed and graphics were created using IBM SPSS Statistics software version 22.0 (IBM Corporation, Armonk, NY, USA). The nomogram analysis and DCA were conducted using R version 3.5.1 (https://www.r-project.org/). Statistical significance was set at a two-sided P-value < 0.05.

RESULTS

A total of 6,555 patients were included in our study. The proportion of patients with pCR was 20.5% ($n = 1,342$). The clinical and pathological features of all patients are shown in **Table 1**. Among the variables, no significant differences were found in age, gender, marital status or race between the pCR and non-pCR groups, but there were differences in histology ($P < 0.001$), pre-treatment serum CEA results ($P = 0.006$), clinical T stage ($P < 0.001$) and N stage ($P < 0.001$).

Predictors of pCR

The proportion of patients who received pCR was ~20.47% (1,342/6,555). Patients with clinical T4 tumors (12%, 70/585) were significantly less likely to reach pCR ($P < 0.001$) than were those with lower T stage tumors (T1, 27%, 104/382; T2, 23%, 193/845; T3, 21%, 975/4,743). Patients with clinical N2 tumors (13%, 100/764) were significantly less likely to reach pCR ($P < 0.001$) than were those with lower N stage tumors (N0, 23%, 729/3,206; N1, 20%, 513/2,585).

Additionally, patients whose pathological diagnosis was common adenocarcinoma (21%, 1,283/6,192) were significantly

TABLE 1 | Patient demographics and tumor characteristics.

Variable	non-pCR (%)	pCR(%)	P-value
Age			0.197
≤50 years	1,201 (81%)	287 (19%)	
>50 years	4,012 (79%)	1,055 (21%)	
Gender			0.545
Male	1,973 (79%)	520 (21%)	
Female	3,240 (80%)	822 (20%)	
Marital status			0.094
Married	3,073 (79%)	804 (21%)	
Single	912 (82%)	206 (18%)	
Divorced	1,003 (80%)	258 (20%)	
Unknown	225 (75%)	74 (25%)	
Race			0.313
White	4,198 (79%)	1,087 (21%)	
Black	437 (82%)	95 (18%)	
Other	560 (79%)	153 (21%)	
Unknown	18 (72%)	7 (28%)	
Histology			<0.001
Common adenocarcinoma	4,846 (79%)	1,283 (21%)	
Mucinous adenocarcinoma	367 (86%)	59 (14%)	
Differentiation		<0.001	
Well	327 (80%)	83 (20%)	
Moderate	3,753 (81%)	908 (19%)	
Poor	511 (81%)	121 (19%)	
Undifferentiated	67 (86%)	11 (14%)	
Unknown	555 (72%)	219 (28%)	
CEA			0.006
Negative	1,928 (78%)	543 (22%)	
Positive	1,576 (82%)	348 (18%)	
Unknown	1,709 (79%)	451 (21%)	
cT stage			<0.001
1	278 (73%)	104 (27%)	
2	652 (77%)	193 (23%)	
3	3,768 (79%)	975 (21%)	
4	515 (88%)	70 (12%)	
cN stage			
0	2,477 (77%)	729 (23%)	0.000
1	2,072 (80%)	513 (20%)	
2	664 (87%)	100 (13%)	
Total	5,213 (80%)	1,342 (20%)	

more likely to achieve pCR ($P < 0.001$) than were those diagnosed with mucinous adenocarcinoma (14%, 59/426). Moreover, patients with positive pre-treatment serum CEA results (18%, 348/1,924) were significantly less likely to reach pCR ($P = 0.006$) than were negative pre-treatment serum CEA patients (22%, 543/2,471).

The details about the univariate analyses and multivariate analyses of predictors with logistic regression models for pCR are shown in **Table 2**. It appears to be significantly harder for patients who were diagnosed with mucinous adenocarcinoma to reach pCR [odds ratio (OR) = 0.61, (P =0.001)]. The patients with positive pre-treatment serum CEA results (OR = 0.78, $P =$

TABLE 2 | Univariate analyses and multivariate analyses of predictors for pCR using logistic regression models.

Variable	Univariate analyses		Multivariate analyses	
	Odds Ratio (95% CI)	P-value	Odds ratio (95% CI)	P-value
AGE				
≤ 50 years	1		1	
>50 years	1.1 (0.95–1.27)	0.198	1.05 (0.91–1.22)	0.511
GENDER				
Male	1		1	
Female	0.96 (0.85–1.09)	0.545	0.96 (0.84–1.09)	0.500
MARRIAGE STATUS				
Married	1		1	
Single	0.86 (0.73–1.02)	0.090	0.93 (0.78–1.1)	0.402
Divorced	0.98 (0.84–1.15)	0.832	1.02 (0.87–1.2)	0.814
Unknown	1.26 (0.96–1.65)	0.102	1.22 (0.92–1.61)	0.161
RACE				
White	1		1	
Black	0.84 (0.67–1.06)	0.139	0.83 (0.66–1.06)	0.132
Other	1.06 (0.87–1.28)	0.581	1.06 (0.88–1.29)	0.532
Unknown	1.5 (0.63–3.6)	0.363	1.47 (0.6–3.56)	0.397
HISTOLOGY				
Common adenocarcinoma	1		1	
Mucinous adenocarcinoma	0.61 (0.46–0.8)	0.001	0.68 (0.51–0.9)	0.008
DIFFERENTIATION				
Well	1		1	
Moderate	0.95 (0.74–1.23)	0.709	0.96 (0.74–1.23)	0.733
Poor	0.93 (0.68–1.27)	0.663	1.08 (0.79–1.48)	0.626
Undifferentiated	0.65 (0.33–1.28)	0.21	0.81 (0.41–1.61)	0.544
Unknown	1.55 (1.17–2.07)	0.003	1.58 (1.18–2.11)	0.002
CEA				
Negative	1		1	
Positive	0.78 (0.67–0.91)	0.001	0.83 (0.71–0.97)	0.016
Unknown	0.94 (0.81–1.08)	0.365	0.92 (0.8–1.06)	0.244
cT STAGE				
1	1		1	
2	0.79 (0.6–1.04)	0.097	0.86 (0.65–1.13)	0.278
3	0.69 (0.55–0.88)	0.002	0.79 (0.62–1)	0.050
4	0.36 (0.26–0.51)	<0.001	0.44 (0.31–0.61)	<0.001
cN STAGE				
0	1		1	
1	0.84 (0.74–0.96)	0.008	0.88 (0.77–1)	0.052
2	0.51 (0.41–0.64)	<0.001	0.57 (0.45–0.72)	<0.001

0.001), clinical T4 stage (OR = 0.36, $P < 0.001$) and N2 stage (OR = 0.51, $P < 0.001$) were also included.

A nomogram was constructed based on statistically significant factors identified by multivariate logistic regression to predict the possibility of achieving pCR. T4 was the most predominant prognostic factor, followed by N2, poor differentiation grade, and positive pre-surgery CEA results (**Figure 2**). A vertical line was drawn from the factor to the point scale to determine the

scores of all risk factors (detailed in **Supplement Table 2**). We then summarized all the discrete values and drew a straight line from the total scale to lines estimating the possibility of achieving pCR to obtain the individual's possibility.

Decision curve analysis to inform clinical decisions was better than a scenario in which all patients or no patients are treated across a wide range of thresholds between 0.10 and 0.34 (**Figure 3**). The calibration curve for predicting probability of achieving pCR was shown in **Supplement Figure 1**.
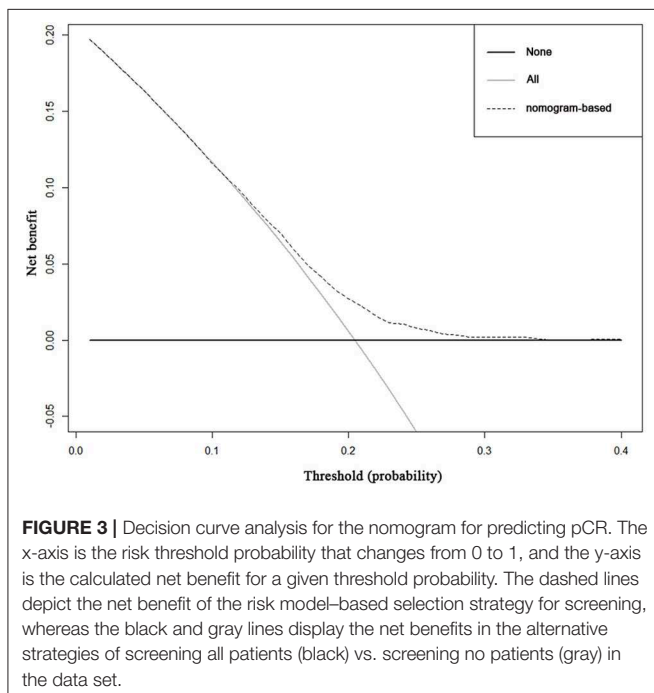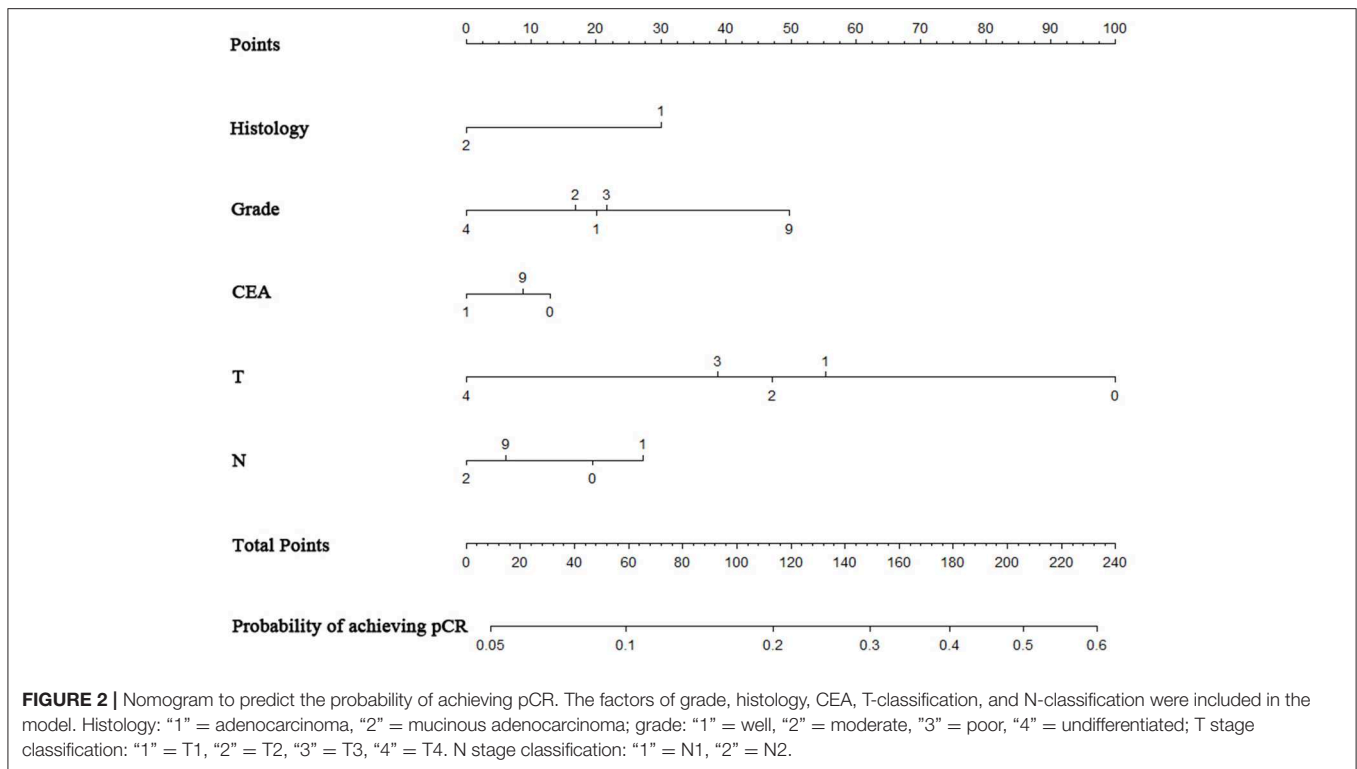
Risk Factors Among pCR Patients

Among the 6,555 rectal cancer patients, the 3-year overall survival rate was 92.4% for those with pCR and 88.2% for those without pCR. The clinical and pathological characteristics of pCR patients was shown in **Supplement Table 1**. Among all the pCR patients, mucinous adenocarcinoma patients had the worst survival, with a 3-year overall survival rate of 67.5%, while those with common adenocarcinomas had a rate of 93.8% ($P < 0.001$). Kaplan-Meier survival curves for patients with and without pCR are shown in **Figure 4**. Kaplan-Meier survival curves for patients with mucinous adenocarcinoma and common adenocarcinoma are shown in **Figure 5**.

The results of the univariate and multivariate analysis using the Cox regression model among patients who achieved pCR are demonstrated in **Table 3**. The adjusted HR from the univariate analyses indicates that patients with mucinous adenocarcinoma had a significantly poorer survival rate than did those with common adenocarcinoma (HR 5.04, 95% CI 2.74–9.26; $P < 0.001$). Similarly, the adjusted HR for clinical N stage indicates that patients with N2 stage tumors had a worse prognosis than that of patients with lower N stage tumors (HR 4.19, 95% CI 2.17–8.1; $P < 0.001$).

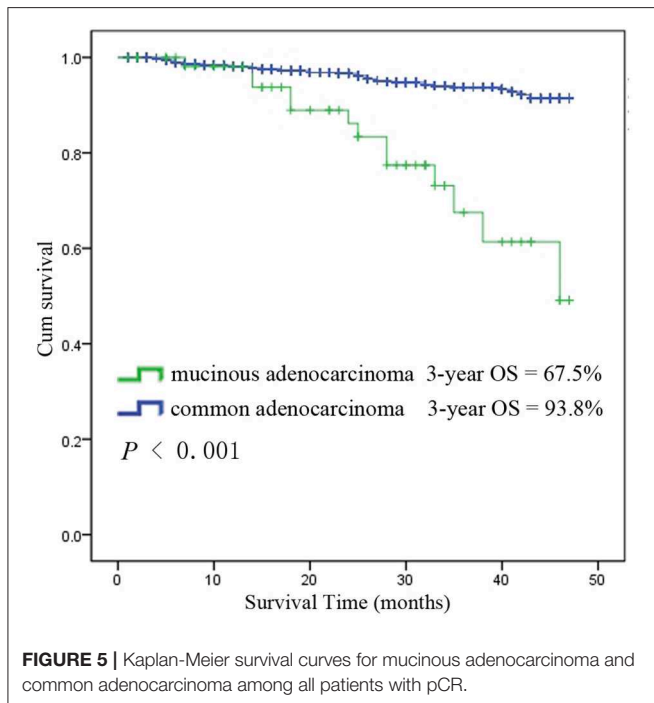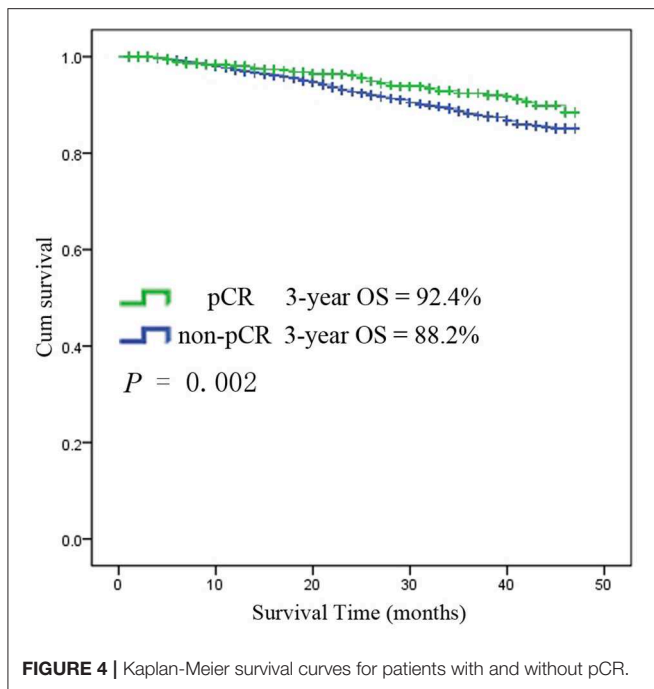## DISCUSSION AND CONCLUSIONS

Predictors of pCR

The rates of pCR after nCRT for rectal cancer vary from 10 to 25% or higher in the literature.(5, 13–29) In our study using the SEER database, the rate of non-metastatic rectal cancer patients who achieved pCR between 2004 and 2013 was 20.5%, ranging from 13 to 28% among different subgroups. Several clinicopathologic factors were identified in our study to be associated with pCR, including non-mucinous adenocarcinoma, negative pre-treatment serum CEA, and non-T4 clinical and non-N2 clinical stages. Numerous retrospective cohort studies have previously identified a variety of disease-related and treatment-related variables as potential predictors of pCR, including tumor differentiation, tumor size, pre-treatment CEA, clinical T and N stages, circumferential tumor extent, whether the CEA decrease reaches 75%, radiation dose, and the interval from the end of radiation to surgery (5, 10, 16, 18, 21–25, 28, 30–40). In recent years, the watch and wait approach has been increasingly mentioned, as the survival rate among patients who received watch and wait care after initial cancer treatment is comparable to those who received radical resection (8, 9, 41). However, the risks, recovery period, and long-term impact on the function and quality of life of rectal cancer patients receiving surgery

FIGURE 2 | Nomogram to predict the probability of achieving pCR. The factors of grade, histology, CEA, T-classification, and N-classification were included in the model. Histology: "1" = adenocarcinoma, "2" = mucinous adenocarcinoma; grade: "1" = well, "2" = moderate, "3" = poor, "4" = undifferentiated; T stage classification: "1" = T1, "2" = T2, "3" = T3, "4" = T4. N stage classification: "1" = N1, "2" = N2.

FIGURE 3 | Decision curve analysis for the nomogram for predicting pCR. The x-axis is the risk threshold probability that changes from 0 to 1, and the y-axis is the calculated net benefit for a given threshold probability. The dashed lines depict the net benefit of the risk model–based selection strategy for screening, whereas the black and gray lines display the net benefits in the alternative strategies of screening all patients (black) vs. screening no patients (gray) in the data set.

are important considerations for both surgeons and patients, especially among the elderly (41–44). Awareness of these factors may help to predict which patients are more likely to achieve pCR after nCRT, and this information may be used to counsel patients more accurately regarding treatment options.

In this study, our univariate analysis implies that mucinous adenocarcinoma, positive pre-treatment serum CEA, and higher clinical T and N stages are associated with lower odds of pCR. Our logistic regression analysis more convincingly identifies mucinous adenocarcinoma, positive pre-treatment serum CEA, and clinical T4 and N2 stages as independent clinical predictors for not achieving pCR. These results are in line with the studies mentioned above and offer additional variables that can help identify those patients who are most likely to respond to treatment, and these findings suggest which clinicopathological factors may be used for predicting pCR. Serum CEA levels are primarily used in long-term follow-up of colorectal cancer patients (14, 39), and clinicians should be alerted of the possibility of local and distant recurrence while CEA is progressively elevated. In the present study, 22% of patients with negative pre-treatment CEA levels achieved pCR, while 18% achieved pCR in the positive CEA group, and the association persisted in the regression analyses, which is consistent with the results of previous studies. This result reminds us again that CEA is not only an indicator of more advanced tumors but also an indicator of treatment response.

Mucinous adenocarcinoma of the rectum was reported to be a poor indicator for nCRT in terms of larger residual tumors, higher incidence of margin positivity, and greater residual nodal disease, but the patient population was small in reported studies (45–49). Our study included a large population number to test for the low pCR rate among mucinous adenocarcinoma patients, and the conclusion persisted in the regression analyses. Thus, in clinical practice, the watch and wait approach should be applied

FIGURE 4 | Kaplan-Meier survival curves for patients with and without pCR.

FIGURE 5 | Kaplan-Meier survival curves for mucinous adenocarcinoma and common adenocarcinoma among all patients with pCR.

prudently in mucinous adenocarcinoma patients due to the low pCR rate.

Risk Factors Among pCR Patients

Rectal cancer patients with pCR after nCRT and radical resection have better long-term outcomes than do those without pCR (4, 5). Nevertheless, there are still patients with pCR suffering from local recurrence and distant metastasis, of which the risk factors

TABLE 3 | Univariate and multivariate analyses using Cox models among patients who achieved pCR.

Variable	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value
AGE				
≤50 years	1.00		1.00	
>50 years	1.93 (0.92–4.04)	0.082	1.04 (1.01–1.06)	0.001
GENDER				
Male	1.00		1.00	
Female	1.48 (0.87–2.53)	0.148	1.66 (0.94–2.94)	0.080
RACE				
White	1.00		1.00	
Black	0.58 (0.18–1.87)	0.365	0.71 (0.22–2.31)	0.572
Other	0.76 (0.33–1.77)	0.529	0.94 (0.4–2.21)	0.883
MARRIAGE STATUS				
Married	1.00		1.00	
Single	0.65 (0.27–1.54)	0.325	0.78 (0.32–1.89)	0.583
Divorced	1.19 (0.64–2.2)	0.583	1.35 (0.7–2.6)	0.369
HISTOLOGY				
Common adenocarcinoma	1.00		1.00	
Mucinous adenocarcinoma	5.04 (2.74–9.26)	<0.001	2.92 (1.48–5.74)	0.002
DIFFERENTIATION				
Well	1.00		1.00	
Moderate	0.79 (0.28–2.22)	0.651	0.77 (0.27–2.2)	0.628
Poor	3.08 (1.03–9.23)	0.044	1.9 (0.61–5.94)	0.268
Undifferentiated	4.82 (0.88–26.46)	0.070	3.79 (0.63–22.97)	0.147
CEA				
Negative	1.00		1.00	
Positive	1.15 (0.62–2.14)	0.663	1.13 (0.6–2.14)	0.712
cT STAGE				
1	1.00		1.00	
2	0.84 (0.24–2.98)	0.788	0.78 (0.21–2.81)	0.701
3	1.4 (0.51–3.89)	0.515	1 (0.35–2.87)	1.000
4	3.2 (0.94–10.95)	0.063	2.68 (0.74-9.76)	0.135
cN STAGE				
0	1.00		1.00	
1	1.26 (0.73–2.17)	0.407	1.16 (0.66–2.03)	0.602
2	4.19 (2.17–8.1)	<0.001	3.3 (1.61–6.75)	0.001

remain unrevealed. In our study, univariate and multivariate analyses using the Cox regression model imply that mucinous adenocarcinoma and clinical N2 stage might be indicative of a prognostically unfavorable biological tumor profile with a higher propensity for local or distant recurrence and decreased survival, which is consistent with the results of earlier studies (21, 25).

It has been widely reported that mucinous adenocarcinoma is a distinct pathological entity associated with poor outcome, which accounts for 5–10% of all adenocarcinomas of the rectum (50). Some researchers believe that mucinous adenocarcinomas are always associated with advanced stage at presentation and that the advanced stage of the tumor rather than its

histology is responsible for the worse outcome (51, 52). The guidelines of the National Comprehensive Cancer Network (NCCN) have not ascribed mucinous histology as a risk factor that should influence therapeutic decision making. In current clinical practice, non-mucinous, and mucinous tumors are considered similar, and histology does not affect treatment decision making. However, many studies have demonstrated that mucinous histology is an independent prognostic factor (53, 54), which may have different oncogenic and molecular pathways (55). In our study, mucinous adenocarcinoma patients showed a significantly poorer outcome after nCRT and radical resection than did common adenocarcinoma patients. After Cox regression analysis, mucinous histology was still an independent risk factor, and similar reports focused on nCRT response and the prognosis of patients with mucinous adenocarcinomas are rare. Some researchers reported that mucinous tumors are always less sensitive than common adenocarcinomas are to radiation or chemotherapy (50), and mucinous tumors are more likely to relapse after radiation or chemotherapy (52). Our study also showed a worse overall outcome of mucinous rectal cancer patients after nCRT and radical resection, so the watch and wait approach should be applied more prudently in mucinous adenocarcinoma patients not only because of their low pCR rate but also because of the high relapse rate and poor overall outcome. The genetic variations of mucinous rectal cancer have been reported to affect survival, and further investigation of the relationships between genetic factors and chemoradiotherapy efficacy in mucinous adenocarcinoma is needed in the future.

Strengths and Limitations of the Study

This study represents the largest published data set to date identify predictors of pCR and to recognize risk factors among pCR rectal cancer patients. These data were derived from the Surveillance, Epidemiology, and End Results database. SEER currently collects and publishes cancer incidence and survival data from population-based cancer registries covering ∼28%of the US population.

Limitations of this study include patient selection bias and unavailable variables that may potentially be related to pCR, including information on radiation dose, chemotherapy regimens, the interval from the end of radiation to surgery, and distance from the anal verge. As the watch and wait approach for patients with a complete clinical response to nCRT has been increasingly mentioned and was attempted in some hospitals, some cCR patients may not be included in our study, causing a selection bias of patients. In our patient selection process, we found that residual tumor evaluation information in the SEER database was not available in 55% (8,000/14,555) of rectal cancer patients after nCRT, and only 45% (6,555/14,555) had available residual tumor data. The reason for residual tumor evaluation information unavailable was unknown, but it may somehow

cause selection bias. With respect to the prognostic analysis of pCR patients, local and distant recurrence information was not available in the SEER database, which is also a limitation of this study. Additionally, retrospective analysis cannot offer a relationship as strong as causality. Thus, further prospective analysis is recommended for risk factor assessment.

CONCLUSION

Among rectal cancer patients undergoing surgical resection after nCRT, 20.5% achieved pCR. Factors predicting a lower likelihood of pCR were mucinous adenocarcinoma, positive pre-treatment serum CEA, and clinical T4 and N2 stages. In addition, mucinous adenocarcinoma and clinical N2 stage might indicate poor prognosis. Awareness of these factors can be valuable in counseling rectal cancer patients regarding prognosis, treatment options, and follow-up plans.

ETHICS STATEMENT

This study was approved by the ethics committee of the Second Affiliated Hospital of Zhejiang University School of Medicine.

AUTHOR CONTRIBUTIONS

YT and DF: designed the study. YT, DF, DL, XK, KJ, LC, YY, and KD: performed all experiments. YT, DF, DL, YY, and KD: performed the data analysis and drafted the manuscript. XK, KJ, and YY: critically revised the manuscript. All authors reviewed the 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.2019.00497/full#supplementary-material

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