THERAPEUTIC ADVANCES in
Medical Oncology

Original Research

Age-related differences in progression patterns, follow-up strategies, and postoperative outcomes in locally advanced rectal cancer: insights from a large-scale validated study

Ther Adv Med Oncol

2024, Vol. 16: 1–15

DOI: 10.1177/17588359241290129

© The Author(s), 2024.
Article reuse guidelines: sagepub.com/journals-permissions

Yilin Yu*, Haixia Wu*, Jianjian Qiu*, Liang Hong, Shiji Wu, Lingdong Shao, Cheng Lin, Zhiping Wang and Junxin Wu

Abstract

Background: Locally advanced rectal cancer (LARC) presents significant treatment challenges, particularly as patient age may influence disease progression and treatment response. Understanding the differences in progression patterns and treatment outcomes between older patient (OP) and non-older patient (NOP) is essential for tailoring effective management strategies.

Objectives: We aimed to explore the differences of progression pattern, postoperative treatment, and survival outcome between OP and NOP groups in LARC.

Design/Methods: The random survival forest model was used to determine the probability of time-to-event occurrence every 3 months. Patients in the NOP and OP group were both categorized into three risk groups based on progression-free survival nomogram scores. We employed inverse probability of treatment weighting (IPTW) analysis and the Surveillance, Epidemiology, and End Results (SEER) database to verify our findings.

Results: Our results revealed that Groups 1, 2, and 3 experienced peaks in progression within the first 24 months in NOP group. As for OP group, Group 4 reached a progression peak at the 18th month, Group 5 at the 12th month, and Group 6 at the 9th month. In NOP group, high-risk patients who underwent postoperative chemotherapy had significantly improved overall survival compared to those who did not. Additionally, postoperative chemotherapy did not significantly improve prognosis for patients in low-, moderate-, or high-risk groups of OP group. Finally, the validation results of IPTW analysis and SEER database showed compliance with our findings.

Conclusion: For NOP group, we recommended close follow-up during the first 2 years. As for OP group, it was suggested to conduct close follow-up at the 18th, 12th, and 9th month for low-, moderate-, and high-risk groups, respectively. Furthermore, postoperative chemotherapy can provide survival benefits for patients in high-risk group of NOP group. However, OP group patients should be informed that the potential benefits of postoperative chemotherapy may be minimal.

Keywords: inverse probability of treatment weighting analysis, locally advanced rectal cancer, older patient, progression patterns, postoperative chemotherapy

Received: 8 July 2024; revised manuscript accepted: 23 September 2024.

Correspondence to:
Junxin Wu
Zhiping Wang
Cheng Lin
Department of Radiation Oncology, Clinical Oncology School of Fujian Medical University, Fujian Cancer Hospital, No. 420, Fuma Road, Fuzhou, Fujian 350014, China
junxinwufj@aliyun.com
707770685@qq.com
chenglin1988@yeah.net

Yilin Yu
Jianjian Qiu
Liang Hong
Shiji Wu
Lingdong Shao
Department of Radiation Oncology, Clinical Oncology School of Fujian Medical University, Fujian Cancer Hospital, Fuzhou, Fujian, China

Haixia Wu
Shengli Clinical Medical College of Fujian Medical University, Fuzhou, Fujian, China

*These authors contributed equally as first authors

Creative Commons Non Commercial CC BY-NC: This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 License (https://creativecommons.org/licenses/by-nc/4.0/) which permits non-commercial use, reproduction and distribution of the work without further permission provided the original work is attributed as specified on the Sage and Open Access pages (https://us.sagepub.com/en-us/nam/open-access-at-sage).

Introduction

Cancer cases are steadily increasing worldwide, making it the second most common cause of death.[1] Rectal cancer (RC) ranks as the world's eighth most prevalent cancer, resulting in around 730,000 new cases and 340,000 fatalities annually.[2] The global burden of cancer is staggering, with RC being a major contributor. It is anticipated that there will be a greater proportion of older patients (OPs) in the future as a result of both the general population's increasing age and the rising rate of the occurrence of RC.[3] The existing guidelines lack comprehensive treatment suggestions for the aged population and inadequately address the multifaceted issues encountered in this demographic.[4] Thus, it remains uncertain if older RC patients are experiencing similar treatment benefits as younger counterparts from newer strategies.

The treatment strategy for locally advanced rectal cancer (LARC) encompasses a multimodal approach that combines various therapeutic modalities.[5] Based on the guidelines, the primary approach for RC treatment is surgery, and additional adjuvant chemoradiotherapy may be recommended for individuals with a higher risk of recurrence. In recent years, advances such as total neoadjuvant therapy and the use of immunotherapy based on mismatch repair (MMR) status have emerged as new standards of care, offering improved treatment outcomes.[6] Diffusion-weighted magnetic resonance imaging (DW-MRI) has also gained attention as a tool for treatment response assessment in LARC. A study[7] analyzing the role of DW-MRI in patients undergoing neoadjuvant chemoradiotherapy found that apparent diffusion coefficient values could help distinguish between patients who achieve pathologic complete response and those who do not, highlighting the potential of DW-MRI in optimizing treatment strategies.

The selection of treatment is influenced by factors such as tumor features, expected survival time, patient tolerance for chemotherapy, and personal preferences. Over the past two decades, there has been a significant improvement in the survival rates of RC patients, primarily attributed to the increased utilization of chemotherapy. Nevertheless, the enhanced survival rates and the heightened adoption of chemotherapy were less pronounced among OPs as compared to their younger counterparts.[8,9] Moreover, the potential advantages of incorporating adjuvant chemotherapy to enhance local control and survival remain uncertain, particularly among older individuals. There is limited research available regarding the effectiveness of incorporating adjuvant chemotherapy in the older population.

The biological characteristics of cancer often exhibit variations in younger RC patients.[10] Hence, it is not advisable to use younger RC patients as suitable models or reference points when considering therapeutic options for OPs. There is an urgent need to prioritize the development of personalized cancer care tailored to each individual patient.[11] The current study aimed to explore the differences in progression and prognosis between non-older patients (NOPs) and OPs with LARC. Additionally, we investigated the benefits of adjuvant chemotherapy for both groups. Finally, we employed the inverse probability of treatment weighting (IPTW) analysis method and the Surveillance, Epidemiology, and End Results (SEER) database to validate our findings.

Materials and methods

Study design and population

From January 2014 to May 2020, a total of 932 consecutive patients with LARC who underwent surgery at the Fujian Provincial Cancer Hospital (Fuzhou, China) were retrospectively analyzed in this study. The inclusion criteria were as follows: (1) aged ⩾18 years old; (2) histopathologically confirmed RC; (3) patients with postoperative pathology of II–III stage; (4) Karnofsky performance status point ⩾70 points; and (5) patients underwent radical surgery. The exclusion criteria were as follows: (1) patients with multiple primary cancers; (2) patients with incomplete clinical data; and (3) patient without follow-up information. The pathological stage of RC was determined according to the 8th edition guidelines from the American Joint Committee on Cancer. All treatments in our study were administered according to the National Comprehensive Cancer Network (NCCN) guidelines of the respective year. Additionally, treatment plans were formulated collaboratively by two senior oncologists with associate professor or higher qualifications. After taking into account the aforementioned criteria, a cohort of 932 LARC patients were enrolled in the current study. Patients were divided into OP group (⩾60 years) and NOP

group (<60 years). The reporting of this study conforms to the Reporting recommendations for tumor MARKer prognostic studies guidelines.[12] The checklist has been included in the Supplemental Material 1.

Age cut-off selection

The decision to use 60 years as the threshold for defining OP was based on several considerations. Epidemiological data indicate that the median age of onset for RC is approximately 63 years, and colorectal cancer is the second leading cause of cancer-related mortality among individuals aged 60–79 years.[13] Additionally, there is an observable trend toward younger diagnoses in RC cases, further supporting the need to encompass a wider range of the elderly population. The World Health Organization (WHO) defines elderly individuals as those aged 60 years and above, which is consistent with our selected cut-off.[14] Moreover, a review of relevant literature revealed that 60 years is a commonly used age threshold in study,[15] thereby allowing our findings to align with existing research. This rationale guided the selection of 60 years as the dividing line between OP and NOP groups in this study.

Data collected

The primary patient demographic characteristics, including gender, carcinoembryonic antigen (CEA), mesorectal fascia involvement, extra-mural vascular invasion, pathological T stage, pathological N stage, postoperative chemotherapy, postoperative radiotherapy, vascular cancer embolus, perineural invasion, and tumor deposit, were collected from the electronic medical record.

End point and case follow-up

This study's primary endpoint was progression-free survival (PFS), which has been defined as the interval between diagnosis and progression, death, or the end of follow-up. Overall survival (OS), defined as survival from the time of diagnosis until death or the end of follow-up, was the secondary endpoint. The postoperative surveillance protocol entailed regular assessments at 3-month intervals for the initial 2-year period, followed by 6-month evaluations for the subsequent 3 years, and annual evaluations thereafter. The last follow-up date ended on June 2023.

SEER database verification

The study population consisted of individuals who received a diagnosis of RC throughout the period from 2011 to 2015. Identification of these patients was conducted via the WHO's International Classification of Diseases, 3rd edition, with specific codes including 8140, 8144, 8210, 8211, 8213, 8221, 8255, 8261, and 8263. The study included SEER data from 2171 patients. Official authorization was received to access the research data from the SEER database, and all analyses undertaken in this study adhered to the regulations set forth by the database.

Statistical analysis

All statistical analyses were performed using SPSS software (version 26.0) and R software (version 4.2.2). We have obtained a copyright license of SPSS statistical software. The analysis of survival outcomes was conducted using the Kaplan–Meier method, and the comparison between groups was performed using the log-rank test. The random survival forest model was used to determine the probability of time-to-event occurrence every 3 months. Besides, predictors of PFS and OS were identified through univariate and multivariate analyses employing Cox proportional hazards regression. Factors meet a significance threshold of $p < 0.05$ in the univariate analysis were eligible for inclusion in the multivariate analysis. The PFS were predicted using the nomogram based on the independent prognostic variables. The concordance index (C-index) and calibration curve were used to evaluate the nomogram's performance and discriminative ability. Lastly, we performed IPTW analysis to verify the results and improve the reliability of our findings. A significance level of $p < 0.05$ was regarded as statistically significant in this study.

Results

Study cohort characteristics

Table 1 provided an overview of the demographic information as well as the characteristics of the tumor. The study included 932 patients diagnosed with LARC. There were 486 patients in NOP group and 446 patients in OP group. The median age of patients in NOP group and OP group was 52 (range 24–59) years and 66 (range 60–87) years, respectively. In OP group, the proportion of male was higher (65.2% vs 56.6%) compared to NOP group. Three hundred

Table 1. Distribution of clinicopathological features for all LARC patients stratified by age groups.

Clinicopathologic variable	Age <60	Age ⩾60
Total (*N*)	486	446
Gender		
Male	275	291
Female	211	155
CEA		
⩽5	338	270
>5	148	176
Mesorectal fascia involvement		
Yes	62	86
No	424	360
Extra-mural vascular invasion		
Yes	37	51
No	449	395
Pathological T stage		
T1–3	398	356
T4	88	90
Pathological N stage		
N0	169	182
N1–2	317	264
Postoperative chemotherapy		
Yes	364	245
No	122	201
Postoperative radiotherapy		
Yes	37	24
No	449	422
Vascular cancer embolus		
Yes	240	211
No	246	235
Perineural invasion		
Yes	132	107
No	354	339
Tumor deposit		
Yes	91	69
No	395	377

CEA, carcinoembryonic antigen; LARC, locally advanced rectal cancer.

Table 2. Univariate and multivariate analysis of PFS for NOP group in LARC.

Clinicopathologic parameters	Univariate analysis			Multivariate analysis		
	HR	95% CI	*p*	HR	95% CI	*p*
Gender						
Male vs Female	0.914	0.645–1.296	0.614			
CEA						
>5 vs ⩽5	2.308	1.628–3.272	<0.001	2.319	1.631–3.296	<0.001
Mesorectal fascia involvement						
Yes vs No	1.217	0.739–2.004	0.441			
Extra-mural vascular invasion						
Yes vs No	1.640	0.923–2.911	0.091			
Pathological T stage						
T4 vs T1–3	1.523	1.011–2.294	0.044	1.514	1.000–2.293	0.050
Pathological N stage						
N1–2 vs N0	3.091	1.935–4.937	<0.001	2.666	1.576–4.509	<0.001
Postoperative chemotherapy						
No vs Yes	0.908	0.603–1.368	0.646			
Postoperative radiotherapy						
No vs Yes	1.022	0.536–1.949	0.948			
Vascular cancer embolus						
Yes vs No	1.843	1.289–2.635	0.001	1.215	0.821–1.798	0.330
Perineural invasion						
Yes vs No	1.150	0.787–1.681	0.471			
Tumor deposit						
Yes vs No	1.769	1.198–2.612	0.004	1.135	0.756–1.703	0.542

CEA, carcinoembryonic antigen; CI, confidence interval; HR, hazard ratio; LARC, locally advanced rectal cancer; NOP, non-older patient; PFS, progression-free survival.

sixty-four (74.9%) of patients in NOP group and 245 (54.9%) of patients in OP group received postoperative chemotherapy. In addition, 37 (7.6%) NOPs underwent postoperative radiotherapy compared to 24 (5.4%) OPs.

Prognostic factors of PFS for NOP group and OP group

For NOP group, univariate analyses for PFS showed CEA level ($p < 0.001$), pathological T stage ($p = 0.044$), pathological N stage ($p < 0.001$), vascular cancer embolus ($p = 0.001$), and tumor deposit ($p = 0.004$) to be significant predictors. CEA level (hazard ratio (HR): 2.319; 95% confidence interval (CI): 1.631–3.296; $p < 0.001$), pathological T stage (HR: 1.514; 95% CI: 1.000–2.293; $p = 0.050$), and pathological N stage (HR: 2.666; 95% CI: 1.576–4.509; $p < 0.001$) remained significant in multivariate analyses (Table 2). Besides, univariate Cox survival analyses revealed that PFS

Table 3. Cox regression model of PFS for OP group in LARC.

Clinicopathologic parameters	Univariate analysis			Multivariate analysis		
	HR	95% CI	*p*	HR	95% CI	*p*
Gender						
Male vs Female	1.551	0.983–2.447	0.059			
CEA						
>5 vs ⩽5	1.249	0.835–1.867	0.279			
Mesorectal fascia involvement						
Yes vs No	1.463	0.922–2.322	0.107			
Extra-mural vascular invasion						
Yes vs No	1.536	0.885–2.666	0.127			
Pathological T stage						
T4 vs T1–3	1.756	1.131–2.727	0.012	1.724	1.108–2.682	0.016
Pathological N stage						
N1–2 vs N0	1.814	1.168–2.818	0.008	1.425	0.880–2.305	0.150
Postoperative chemotherapy						
No vs Yes	0.759	0.504–1.142	0.186			
Postoperative radiotherapy						
No vs Yes	0.655	0.303–1.415	0.282			
Vascular cancer embolus						
Yes vs No	1.467	0.981–2.193	0.062			
Perineural invasion						
Yes vs No	2.064	1.362–3.128	0.001	1.759	1.146–2.699	0.010
Tumor deposit						
Yes vs No	2.230	1.422–3.499	<0.001	1.711	1.049–2.792	0.032

CEA, carcinoembryonic antigen; CI, confidence interval; HR, hazard ratio; LARC, locally advanced rectal cancer; OP, older patient; PFS, progression-free survival.

was significantly associated with pathological T stage ($p = 0.012$), pathological N stage ($p = 0.008$), perineural invasion ($p = 0.001$), and tumor deposit ($p < 0.001$) in OP group. Multivariate analyses revealed that pathological T stage (HR: 1.724; 95% CI: 1.108–2.682; $p = 0.016$), perineural invasion (HR: 1.759; 95% CI: 1.146–2.699; $p = 0.010$), and tumor deposit (HR: 1.711; 95% CI: 1.049–2.792; $p = 0.032$) were independent poor prognostic factors of PFS (Table 3).

The development and verification of nomograms to predict PFS in NOP group and OP group

We constructed nomogram models for the NOP group and OP group based on independent prognostic factors identified in the multivariate analysis. The C-index for the NOP group model was 0.68, while the C-index for the OP group model was 0.62. Additionally, calibration curves demonstrated good consistency between observed and predicted outcomes of the models (Supplemental Material 2 Fig. S1).

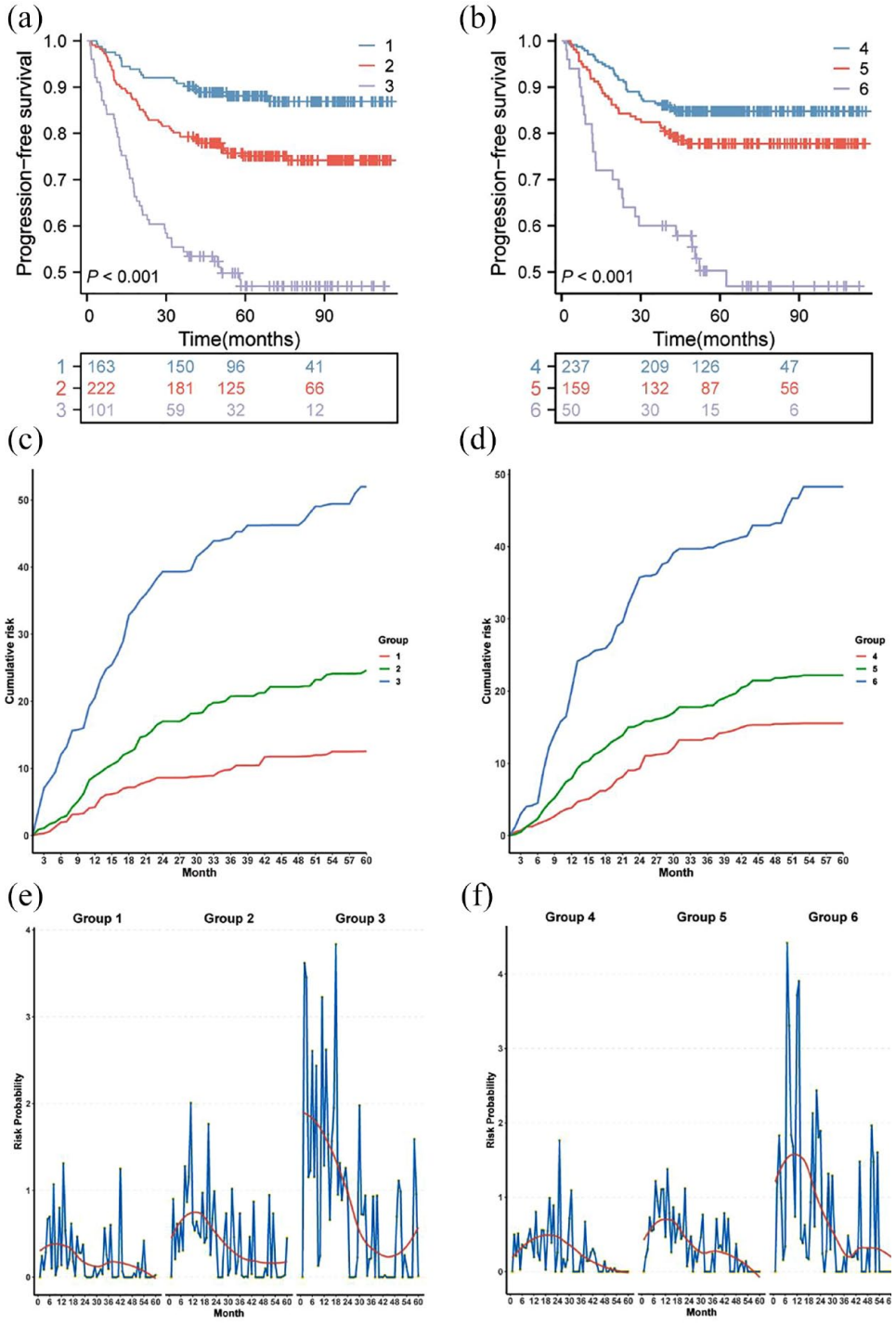

Figure 1. Kaplan–Meier curves for PFS and time-specific progression probabilities were generated for different risk groups in both NOP and OP groups. (a) Kaplan–Meier curve for PFS in NOP group. (b) Kaplan–Meier curve for PFS in OP group. (c) The cumulative progression risk probability for NOP group. (d) The cumulative progression risk probability for OP group. (e) The risk probability of progression at specific time points for patients in NOP group. (f) The risk probability of progression at specific time points for patients in OP group.

NOP, non-older patient; OP, older patient; PFS, progression-free survival.

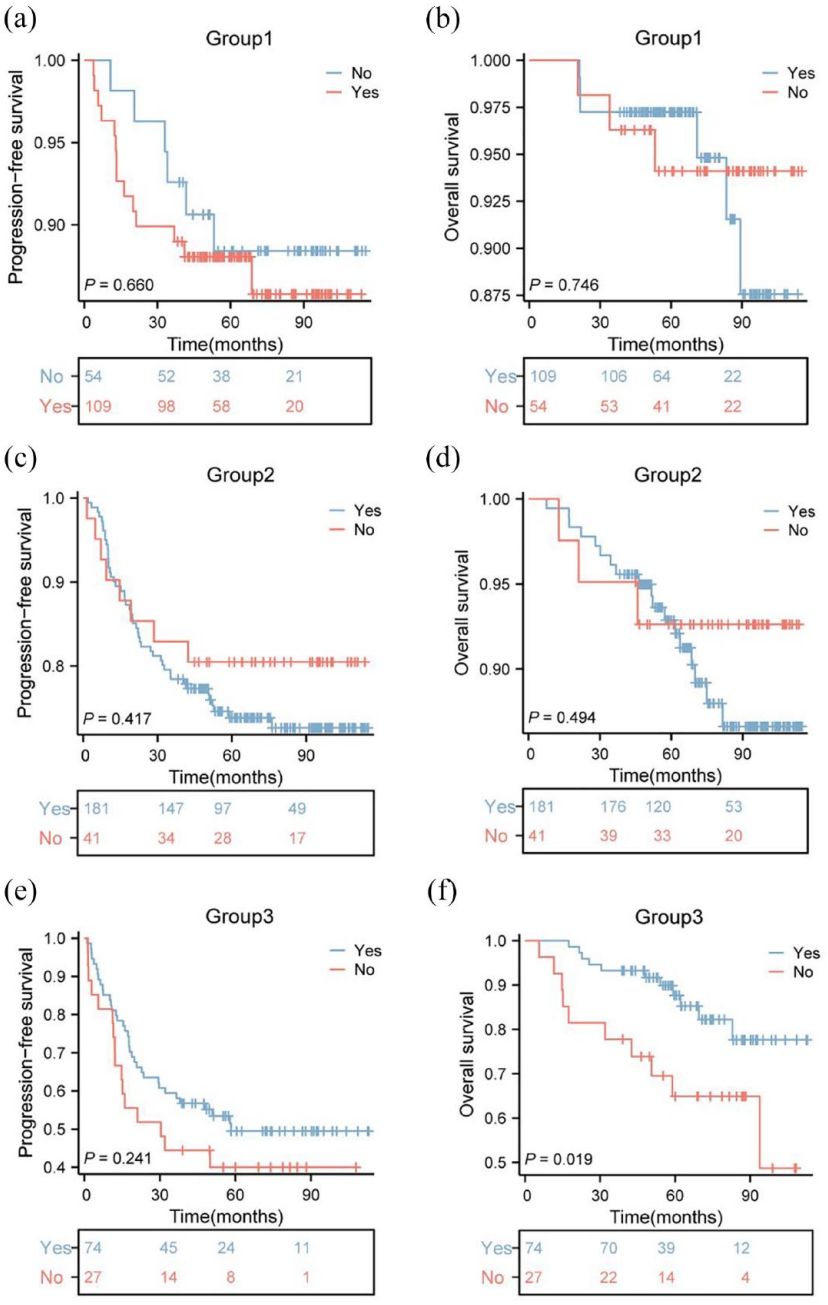

Figure 2. Risk stratification and survival analysis of PFS and OS for postoperative chemotherapy in NOP group. (a) and (b) Kaplan–Meier curves of PFS and OS for postoperative chemotherapy in Group 1. (c) and (d) Kaplan–Meier curves of PFS and OS for postoperative chemotherapy in Group 2. (e) and (f) Kaplan–Meier curves of PFS and OS for postoperative chemotherapy in Group 3.
NOP, non-older patient; OS, overall survival; PFS, progression-free survival.

Risk stratification for progression and time-specific follow-up strategies in NOP group and OP group

The PFS nomogram was utilized to calculate a total score for each patient in NOP group (ranging from 0 to 213.93). Patients were categorized into three groups according to their scores: Group 1 (low-risk, score $\leqslant$ 76.91), Group 2 (moderate-risk, 76.91 $<$ score $\leqslant$ 137.02), and Group 3 (high-risk, 137.02 $<$ score $\leqslant$ 213.93). To summarize, the study consisted of 163 out of 486 patients (33.5%) in Group 1, 222 out of 486 patients (45.7%) in Group 2, and 101 out of 486 patients (20.8%) in Group 3. Furthermore, OP group

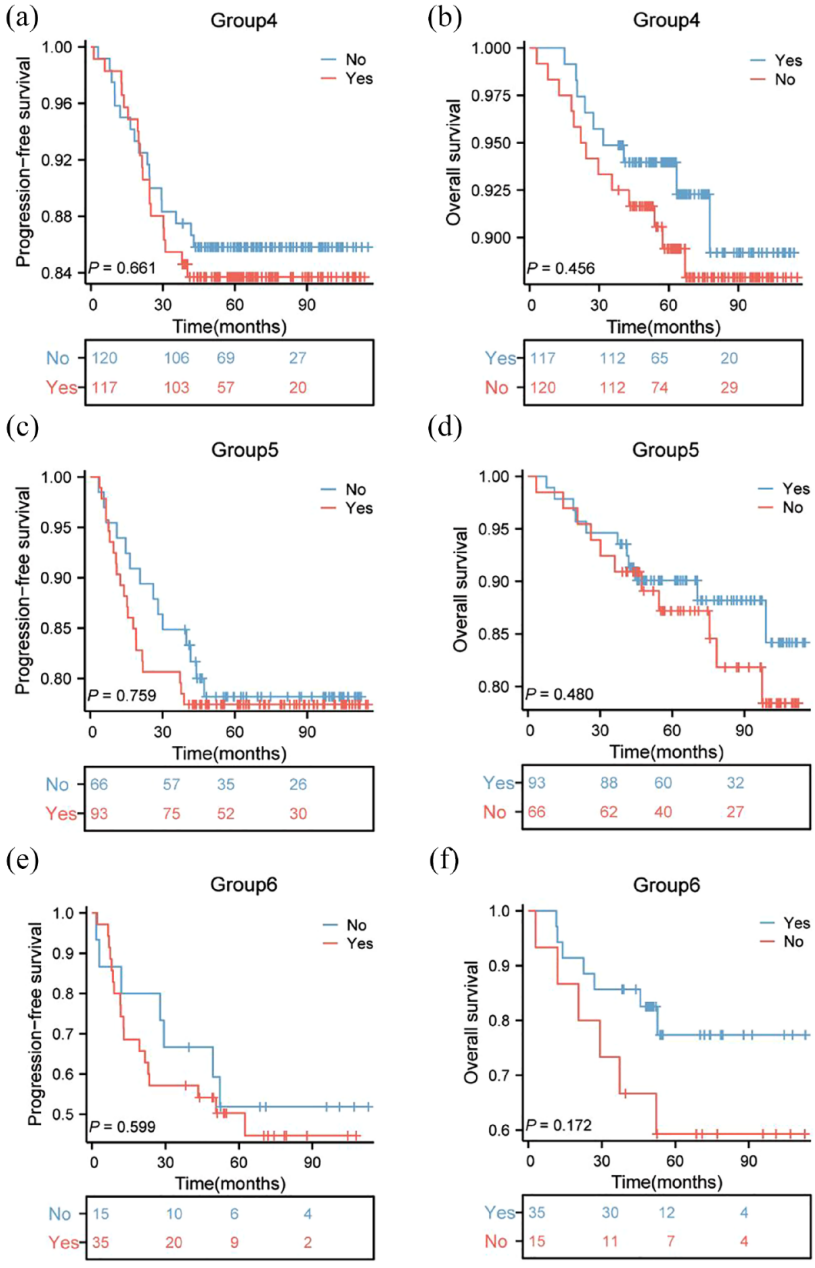

Figure 3. Risk stratification and survival analysis of PFS and OS for postoperative chemotherapy in OP group. (a) and (b) Kaplan–Meier curves of PFS and OS for postoperative chemotherapy in Group 4. (c) and (d) Kaplan–Meier curves of PFS and OS for postoperative chemotherapy in Group 5. (e) and (f) Kaplan–Meier curves of PFS and OS for postoperative chemotherapy in Group 6.
OP, older patient; OS, overall survival; PFS, progression-free survival.

patients were assigned individual total scores (ranging from 0 to 268.59) using the generated PFS nomogram. The patients were also categorized into three groups: Group 4 (low-risk, score $\leqslant$0), Group 5 (moderate-risk, 0 $<$ score $\leqslant$ 100), and Group 6 (high-risk, 100 $<$ score $\leqslant$ 268.59). The study consisted of 237 out of 446 patients (53.1%) in Group 4, 159 out of 446 patients (35.7%) in Group 5, and 50 out of 446 patients (11.2%) in Group 6. Figure 1(a) and (b) presents the differences in PFS among different risk groups in NOP and OP groups, demonstrating significant separation of survival curves among the different risk groups in both groups. Figure 1(c) and (d) reveals the probability of progression over time among different risk groups in NOP and OP

groups. It can be observed that patients in the high-risk group have the fastest increase in progression probability, followed by the moderate-risk group and low-risk group. Lastly, Figure 1(e) and (f) illustrates the progression probabilities at specific time points for patients in different risk groups within NOP and OP groups. In NOP group, Groups 1, 2, and 3 experienced peaks in progression within the first 24 months. As for OP group, Group 4 reached a progression peak at the 18th month, Group 5 at the 12th month, and Group 6 at the 9th month.

Risk stratification and survival analysis of PFS and OS for postoperative chemotherapy

We further performed corresponding prognosis analysis for different risk groups among patients in NOP group and OP group based on the patients' postoperative chemotherapy status. The results showed that in the NOP group, patients in the high-risk group who received postoperative chemotherapy had significantly better OS than those who did not receive postoperative chemotherapy. However, there was no significant difference in PFS of high-risk group. For patients in the low- and moderate-risk groups, there was no significant difference in either PFS or OS, regardless of whether they received postoperative chemotherapy or not (Figure 2). Additionally, postoperative chemotherapy did not significantly improve PFS or OS for patients in the low-, moderate-, or high-risk groups in OP group (Figure 3).

Prognostic factors of OS for NOP group and OP group

In NOP group, univariate Cox analysis revealed CEA level, pathological T stage, and pathological N stage were associated with OS (all $p < 0.05$). Multivariate Cox regression analysis showed that CEA level (HR: 2.300; 95% CI: 1.324–3.995; $p = 0.003$), pathological T stage (HR: 1.986; 95% CI: 1.096–3.599; $p = 0.024$), and pathological N stage (HR: 2.480; 95% CI: 1.206–5.098; $p = 0.014$) were independent predictors of OS (Supplemental Material 2 Table s1). On univariate analysis, pathological N stage ($p = 0.007$) and tumor deposit ($p = 0.001$) were potential prognostic factors for the OS in OP group. While a multivariate Cox regression analysis showed that tumor deposit (HR: 2.115; 95% CI: 1.154–3.877; $p = 0.015$) was independently correlated with the OS (Supplemental Material 2 Table s2).

Validation of IPTW analysis

To enhance the accuracy of evaluating the independent prognostic indicators for each patient group, we utilized IPTW analysis to mitigate the influence of confounding bias in both NOP and OP groups. Supplemental Material 2 Figure s2A and B presents the standardized mean difference (SMD) values of each factor in NOP and OP groups, respectively, after IPTW analysis. It can be observed that the SMD values after IPTW are significantly lower than those before IPTW, with all factors being less than 0.05. This indicated that the influence of confounding factors between groups has been greatly reduced after the use of IPTW. Supplemental Material 2 Figure s2C–E validates the prognostic significance of independent prognostic factors in NOP group, while Supplemental Material 2 Figure s2F validates the prognostic significance of independent prognostic factor in OP group.

Verification of the SEER database

Finally, to increase the reliability of our research findings, we conducted a validation of our results by utilizing existing data from the SEER database. Supplemental Material 2 Figure s3A–C verifies the prognostic significance of independent prognostic factors in NOP group, while Supplemental Material 2 Figure s3D validates the prognostic significance of independent prognostic factor in OP group. These findings further reinforced the credibility of our research results.

Discussion

As the global population's life expectancy continues to rise, the aging of the population becomes an inevitable consequence. RC is a disease that is highly associated with advancing age, making it a notable example of age-related illnesses.[16] RC patients should have their treatment plans tailored to their specific tumor characteristics, such as T-stage, lymph node involvement, and the occurrence of distant metastases.[17] The management of LARC presents significant challenges and necessitates the implementation of a multidisciplinary approach. Moreover, it is worth noting that clinical trials, which have played a crucial role in shaping current practice standards, have historically exhibited a notable lack of representation of OPs.[18] Since most clinical trials do not include OPs, the available evidence primarily relies on studies conducted with younger patients.[19] With the rising incidence of RC among

the older, it is crucial to assess the safety and efficacy of employing current treatment strategies, including multimodality approaches recommended for the general population, in OPs.

Treatment approaches in OPs are generally comparable to those used in younger patients, as there are no specific recommendations to direct the management of advanced age patients.[20] Nevertheless, it should be noted that younger individuals exhibit a higher prevalence of impacted lymph nodes, more progressed stages of tumor, and tumors that are less differentiated.[21] This variation may be attributed to the heterogeneity of the OP population. There is also evidence indicating that OPs may possess distinct biological characteristics compared to younger patients. OPs exhibited a decreased probability of experiencing distant metastases[22] and presented with less advanced stages of RC.[23] In the absence of objective evidence from clinical trials, it poses a challenge to offer older adult patients a comprehensive understanding of the potential advantages and disadvantages associated with specific treatment regimens. As a result, our understanding of the effectiveness of suitable therapeutic approaches in OPs is often significantly constrained. Given the ambiguity in the existing literature, our objective was to investigate the progression patterns and treatment outcomes of both NOPs and OPs with LARC.

In our study, the results showed that CEA level, pathological T stage, and pathological N stage were independent predictors of PFS in NOP group. Besides, pathological T stage, perineural invasion, and tumor deposit were independent poor prognostic factors of PFS in OP group. Based on the models, we also performed analysis of risk stratification for progression and time-specific follow-up strategies in NOP group and OP group. The result revealed that patients in the high-risk group have the fastest increase in progression probability, followed by the moderate-risk group and low-risk group. In NOP group, Groups 1, 2, and 3 experienced peaks in progression within the first 24 months. As for the OP group, Group 4 reached a progression peak at the 18th month, Group 5 at the 12th month, and Group 6 at the 9th month. In the age of personalized medicine, the approach to postoperative surveillance is becoming more individualized, taking into account the unique characteristics of both the patient and the tumor. Hence, it is necessary to establish a personalized follow-up plan for patients with LARC. For NOP group, we recommended close follow-up and examinations for all patients during the first 2 years after surgery. As for OP group, it was advised to conduct close follow-up at the 18th, 12th, and 9th month for low-, moderate-, and high-risk groups, respectively. In RC, the time to tumor progression is a substantial predictor of survival after progression.[24] These follow-up strategies aimed to identify patients with progression at an early stage and provide substantial guidance for treatment decisions.

Furthermore, we conducted a specific assessment on the influence of age on the comparative efficacy of postoperative chemotherapy methods. The results showed that in NOP group, patients in the high-risk group who received postoperative chemotherapy had significantly better OS than those who did not receive postoperative chemotherapy. Additionally, postoperative chemotherapy did not significantly improve PFS or OS for patients in the low-, moderate-, or high-risk groups in OP group. According to the results of our analysis, patients in the high-risk group of NOP group can benefit in terms of OS by undergoing postoperative chemotherapy. Nonetheless, postoperative chemotherapy may not be recommended for patients in OP group, either in the low-, moderate-, or high-risk groups. Given the heterogeneity in ages and performance status among the patients in this category, it is essential to consider a personalized and customized approach to ensure the optimal treatment selection for achieving a curative outcome.

Systemic chemotherapy has the potential to cause toxic effects, which may reduce the physical reserve capacity, especially in older individuals. As age increases, the risk of chemotherapy toxicities also increases due to the presence of comorbidities and general effects of aging. According to the guidelines provided by the European Society for Medical Oncology and International Society of Geriatric Oncology, it is suggested that OPs who are deemed unsuitable for conventional combination treatment should be prescribed a less intensive therapy protocol. Recent research indicated that OPs with colon cancer may not experience the same benefits from chemotherapy as younger patients.[25] Additionally, the potential reduction in mortality from postoperative chemotherapy seems to diminish as patients get older.[26] These results were consistent with our findings. Therefore, the decision regarding postoperative

chemotherapy should be made collaboratively between the patient and the clinician, taking into consideration the predicted toxicity for the patient and the potential survival benefits. It should be a risk-balanced approach.[5] A similar approach of careful consideration and shared decision-making should also be implemented when dealing with OPs diagnosed with LARC.

Our result also showed that CEA level, pathological T stage, and pathological N stage were independent predictors of OS in NOP group. Furthermore, tumor deposit was independently correlated with the OS in OP group. CEA is a crucial biomarker for predicting outcomes in RC. It is commonly employed to forecast treatment outcome and evaluate tumor response following surgery.[27] An elevated level of CEA is associated with an increased risk of disease recurrence and a less favorable prognosis in cases of RC.[28] In addition, the presence of tumor deposits is regarded as one of the most critical factors in determining appropriate treatment options for personalized patients.[29] Ueno et al. discovered that tumor deposit was an independent unfavorable prognostic factor, regardless of the tumor pathological T stage and pathological N stage.[30,31] Recent research on RC demonstrated that tumor deposit was found to be linked with a higher likelihood of local recurrence, distant metastasis, and reduced OS.[32] Finally, to strengthen the reliability of our results, we also validated our results with IPTW analysis and SEER database. The validation results showed compliance with our results.

It is important to note that our study specifically focused on patients with LARC, which includes those with stages II and III. We excluded patients with stages 0–I, who typically present with early-stage disease and have different clinical characteristics and treatment paradigms. The exclusion of stage 0–I patients ensures that our findings are specifically relevant to the management of LARC and not confounded by the more favorable outcomes associated with early-stage disease. Patients with LARC face a significant risk of disease progression.[33] A considerable proportion, ranging from 30% to 50%, of patients with LARC are expected to experience tumor progression, which ultimately results in an unfavorable prognosis.[34] Gaining insights into the risk factors associated with tumor progression after surgery can assist in making informed decisions regarding postoperative chemotherapy, surveillance, and potentially enhance the survival outcomes for patients.[35] There is limited research available regarding the factors associated with the time to progression in both non-older and OPs. The task force of the International Society of Geriatric Oncology has determined that personalized treatment is crucial, and guidelines are necessary to assist clinicians in the comprehensive treatment of OPs.[36] In the future, to enhance the care provided to OPs with cancer, it is imperative to develop and optimize medical decision-making models that incorporate molecular phenotypes capable of predicting disease progression and survival outcomes.

Our study was strengthened by its large sample size and rigorous analysis, including Cox regression and IPTW, validated through the SEER database. We offered comprehensive risk stratification and assessed the impact of age on postoperative chemotherapy efficacy, providing valuable insights into personalized treatment strategies. The validity was further supported by rigorous statistical methods and consideration of biological variations, enhancing the reliability of our findings. However, it is important to acknowledge several limitations associated with the current study. First, despite the inclusion of a large sample size in our study, it is crucial to acknowledge that our findings were constrained by the retrospective design of our analyses. Nonetheless, we employed Cox regression analysis and IPTW analysis to minimize confounding factors between groups, and validated our findings using the SEER database. Second, due to a lack of relevant data, the impact of other factors on tumor progression and prognosis could not be evaluated. Third, it is unclear whether our findings are representative of the general population. Finally, future well-designed multicenter prospective studies with larger sample sizes are necessary to validate our findings.

Conclusion

For NOP group, we recommended close follow-up during the first 2 years. As for OP group, it was suggested to conduct close follow-up at the 18th, 12th, and 9th month for low-, moderate-, and high-risk groups, respectively. Furthermore, postoperative chemotherapy can provide survival benefits for patients in the high-risk group of NOP group. Finally, OP group patients should be informed that the potential benefits of postoperative chemotherapy may be minimal, and treatment decisions should take into consideration

individual risks and preferences. In the future, we plan to conduct more in-depth research in age to uncover some unresolved issues, which may provide evidence-based data on how to best manage both non-older and OPs with LARC.

Declarations

Ethics approval and consent to participate

The current study was approved by the ethics committee of Fujian Medical University Cancer Hospital (No. K2021-050-01), Fuzhou, China and conducted in accordance with the principles of the Declaration of Helsinki and its amendment. Due to the retrospective nature of this study, the requirement for obtaining informed consent from patients was waived.

Consent for publication

Not applicable.

Author contributions

Yilin Yu: Data curation; Formal analysis; Methodology; Software; Writing – original draft.

Haixia Wu: Data curation; Formal analysis; Methodology; Software; Writing – original draft.

Jianjian Qiu: Data curation; Formal analysis; Writing – original draft.

Liang Hong: Data curation; Formal analysis; Methodology.

Shiji Wu: Formal analysis; Software.

Lingdong Shao: Methodology; Software.

Cheng Lin: Conceptualization; Funding acquisition; Investigation; Project administration; Supervision; Validation; Visualization; Writing – review & editing.

Zhiping Wang: Conceptualization; Investigation; Project administration; Visualization; Writing – review & editing.

Junxin Wu: Conceptualization; Funding acquisition; Investigation; Project administration; Supervision; Visualization; Writing – review & editing.

Acknowledgements

We thank all the investigators and patients who participated in the present study.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by the Joint Funds for the National Clinical Key Specialty Construction Program (Grant No. 2021), the High-level Talent Development Program (Grant No. 2024YNG11), the Fujian Provincial Clinical Research Center for Cancer Radiotherapy and Immunotherapy (Grant No. 2020Y2012), and Fujian Clinical Research Center for Radiation and Therapy of Digestive, Respiratory and Genitourinary Malignancies (Grant No. 2021Y2014).

Competing interests

The authors declare that there is no conflict of interest.

Availability of data and materials

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID iD

Cheng Lin https://orcid.org/0009-0002-7912-2109

Supplemental material

Supplemental material for this article is available online.

References

1. Global Burden of Disease Cancer Collaboration, Fitzmaurice C, Abate D, et al. Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 29 cancer groups, 1990 to 2017: a systematic analysis for the Global Burden of Disease Study. *JAMA Oncol* 2019; 5: 1749–1768.
2. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2021; 71: 209–249.
3. Claassen YHM, Vermeer NCA, Iversen LH, et al. Treatment and survival of rectal cancer patients over the age of 80 years: a EURECCA international comparison. *Br J Cancer* 2018; 119: 517–522.
4. Podda M, Sylla P, Baiocchi G, et al. Multidisciplinary management of elderly patients with rectal cancer: recommendations from the SICG (Italian Society of Geriatric Surgery), SIFIPAC (Italian Society of Surgical Pathophysiology), SICE (Italian Society of

Endoscopic Surgery and new technologies), and the WSES (World Society of Emergency Surgery) International Consensus Project. *World J Emerg Surg* 2021; 16: 35.

5. Glynne-Jones R, Wyrwicz L, Tiret E, et al. Rectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2017; 28: iv22–iv40.
6. Benson AB, Venook AP, Al-Hawary MM, et al. Rectal Cancer, Version 2.2022, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Cancer Netw* 2022; 20: 1139–1167.
7. De Felice F, Magnante AL, Musio D, et al. Diffusion-weighted magnetic resonance imaging in locally advanced rectal cancer treated with neoadjuvant chemoradiotherapy. *Eur J Surg Oncol* 2017; 43: 1324–1329.
8. Brenner H, Bouvier AM, Foschi R, et al. Progress in colorectal cancer survival in Europe from the late 1980s to the early 21st century: the EUROCARE study. *Int J Cancer* 2012; 131: 1649–1658.
9. Elferink MA, van Steenbergen LN, Krijnen P, et al. Marked improvements in survival of patients with rectal cancer in the Netherlands following changes in therapy, 1989–2006. *Eur J Cancer* 2010; 46: 1421–1429.
10. Goldvaser H, Purim O, Kundel Y, et al. Colorectal cancer in young patients: is it a distinct clinical entity? *Int J Clin Oncol* 2016; 21: 684–695.
11. Korc-Grodzicki B, Downey RJ, Shahrokni A, et al. Surgical considerations in older adults with cancer. *J Clin Oncol* 2014; 32: 2647–2653.
12. McShane LM, Altman DG, Sauerbrei W, et al. REporting recommendations for tumour MARKer prognostic studies (REMARK). *Br J Cancer* 2005; 93: 387–391.
13. Hathout L, Maloney-Patel N, Malhotra U, et al. Management of locally advanced rectal cancer in the elderly: a critical review and algorithm. *J Gastrointest Oncol* 2018; 9: 363–376.
14. Mathers CD, Stevens GA, Boerma T, et al. Causes of international increases in older age life expectancy. *Lancet* 2015; 385: 540–548.
15. Shahir MA, Lemmens VE, van de Poll-Franse LV, et al. Elderly patients with rectal cancer have a higher risk of treatment-related complications and a poorer prognosis than younger patients: a population-based study. *Eur J Cancer* 2006; 42: 3015–3021.
16. Braendegaard Winther S, Baatrup G, Pfeiffer P, et al. Trends in colorectal cancer in the elderly in Denmark, 1980–2012. *Acta Oncol* 2016; 55(Suppl. 1): 29–39.
17. Hagemans JAW, Alberda WJ, Verstegen M, et al. Hospital volume and outcome in rectal cancer patients; results of a population-based study in the Netherlands. *Eur J Surg Oncol* 2019; 45: 613–619.
18. Vitale C, Fini M, Spoletini I, et al. Under-representation of elderly and women in clinical trials. *Int J Cardiol* 2017; 232: 216–221.
19. Montroni I, Ugolini G, Saur NM, et al. Personalized management of elderly patients with rectal cancer: expert recommendations of the European Society of Surgical Oncology, European Society of Coloproctology, International Society of Geriatric Oncology, and American College of Surgeons Commission on Cancer. *Eur J Surg Oncol* 2018; 44: 1685–1702.
20. Nitsche U, Stoss C and Friess H. Effect of adjuvant chemotherapy on elderly colorectal cancer patients: lack of evidence. *Gastrointest Tumors* 2017; 4: 11–19.
21. Wang R, Wang MJ and Ping J. Clinicopathological features and survival outcomes of colorectal cancer in young versus elderly: a population-based cohort study of SEER 9 Registries Data (1988–2011). *Medicine (Baltimore)* 2015; 94: e1402.
22. Jung B, Pahlman L, Johansson R, et al. Rectal cancer treatment and outcome in the elderly: an audit based on the Swedish Rectal Cancer Registry 1995–2004. *BMC Cancer* 2009; 9: 68.
23. Chang GJ, Skibber JM, Feig BW, et al. Are we undertreating rectal cancer in the elderly? An epidemiologic study. *Ann Surg* 2007; 246: 215–221.
24. Furuke H, Arita T, Kuriu Y, et al. The survival after recurrence of colorectal cancer: a retrospective study focused on time to recurrence after curative resection. *Surg Today* 2022; 52: 239–250.
25. McCleary NJ, Meyerhardt JA, Green E, et al. Impact of age on the efficacy of newer adjuvant therapies in patients with stage II/III colon cancer: findings from the ACCENT database. *J Clin Oncol* 2013; 31: 2600–2606.
26. Lund JL, Sturmer T and Sanoff HK. Comparative effectiveness of postoperative chemotherapy among older patients with non-metastatic rectal cancer treated with preoperative chemoradiotherapy. *J Geriatr Oncol* 2016; 7: 176–186.
27. Wu S and Gu W. Association of T stage and serum CEA levels in determining survival of rectal cancer. *Front Med (Lausanne)* 2019; 6: 270.

28. Pu H, Xie P, Chen Y, et al. Relationship between preoperative and postoperative serum carcinoembryonic antigen and prognosis of patients with stage I–III rectal cancer: a retrospective study of a multicentre cohort of 1022 rectal cancer patients. *Cancer Manag Res* 2021; 13: 2643–2651.

29. Chinese Society of Clinical Oncology Csco Diagnosis and Treatment Guidelines for Colorectal Cancer Working Group. Chinese Society of Clinical Oncology (CSCO) diagnosis and treatment guidelines for colorectal cancer 2018 (English version). *Chin J Cancer Res* 2019; 31: 117–134.

30. Ueno H, Hashiguchi Y, Shimazaki H, et al. Peritumoral deposits as an adverse prognostic indicator of colorectal cancer. *Am J Surg* 2014; 207: 70–77.

31. Ueno H, Mochizuki H, Shirouzu K, et al. Multicenter study for optimal categorization of extramural tumor deposits for colorectal cancer staging. *Ann Surg* 2012; 255: 739–746.

32. Agger E, Jorgren F, Joud A, et al. Negative prognostic impact of tumor deposits in rectal cancer: a national study cohort. *Ann Surg* 2023; 278: e526–e533.

33. Sun Y, Lin H, Lu X, et al. A nomogram to predict distant metastasis after neoadjuvant chemoradiotherapy and radical surgery in patients with locally advanced rectal cancer. *J Surg Oncol* 2017; 115: 462–469.

34. Guraya SY. Pattern, stage, and time of recurrent colorectal cancer after curative surgery. *Clin Colorectal Cancer* 2019; 18: e223–e228.

35. National Guideline Alliance. *Follow-up to detect recurrence after treatment for non-metastatic colorectal cancer: colorectal cancer (update): evidence review E1*. London, 2020.

36. Papamichael D, Audisio RA, Glimelius B, et al. Treatment of colorectal cancer in older patients: International Society of Geriatric Oncology (SIOG) consensus recommendations 2013. *Ann Oncol* 2015; 26: 463–476.

Visit Sage journals online journals.sagepub.com/home/tam

Sage journals