



Clinical study on risk factors related to postoperative recurrence or metastasis of rectal cancer: a retrospective cohort study

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Background: Rectal cancer is usually treated by surgery, but recurrence or metastasis seriously affect the quality of life and survival of patients. Identifying the risk factors for postoperative recurrence or metastasis of rectal cancer has important guiding value for the treatment of rectal cancer. However, the research on risk factors of postoperative recurrence or metastasis of rectal cancer has not been unified.

Methods: The data of all patients undergoing rectal cancer surgery in The Fifth People's Hospital of Shanghai, Fudan University, from 2016 to 2020 were collected and analyzed. A total of 185 patients were included for statistical analysis and were divided into a recurrence or metastasis group and a non-recurrence or metastasis group. Patients were followed up according to National Comprehensive Cancer Network (NCCN) guidelines by enhanced CT or MRI, and colonoscopy. The cut-off of the research was recurrence, metastasis, or death. Logistic regression analysis and Cox regression analysis were used to analyze the risk factors related to postoperative recurrence or metastasis of rectal cancer, and the survival curve was drawn.

Results: Multiple logistic regression analysis showed involvement of the mesorectal fascia (MRF) [OR (odds ratio) =2.9, 95% confidence interval (CI): 1.16–7.29, P=0.023], nerve and vascular invasion (OR =1.7, 95% CI: 1.08–2.59, P=0.022), intraoperative blood transfusion (OR =3.7, 95% CI: 1.45–9.40, P=0.006), and Dukes staging (OR =2.3, 95% CI: 1.26–4.35, P=0.007) were independent risk factors for postoperative recurrence or metastasis of rectal cancer. Involvement of mesenteric fascia infiltration (OR =11.5, 95% CI: 1.49–88.79, P=0.019) and Dukes stage (OR =3.0, 95% CI: 1.46–6.26, P=0.003) were independent risk factors for liver metastasis, while nerve and vascular invasion (OR =2.4, 95% CI: 1.19–5.00, P=0.015) was an independent risk factor for pulmonary metastasis.

Conclusions: Postoperative recurrence or metastasis of rectal cancer is related to many factors. These findings have clinical guiding value and significance for the follow up and prognosis of patients with rectal cancer after surgery. Large-scale prospective clinical studies are needed.

Keywords: Rectal cancer; recurrence; metastasis; risk factors; liver metastasis

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Introduction

Rectal cancer is a life-threatening malignancy, the incidence and mortality of which are gradually increasing. According to the statistics of the International Agency for Research on Cancer (IARC), the number of newly diagnosed global

rectal cancer patients in 2020 was 1,331,600, accounting for 10% of the total number of new cancers and ranking third in the incidence of malignant tumors (1,2). At present, rectal cancer is mainly treated by surgery, combined with chemotherapy, radiotherapy, and molecular targeted

therapy after surgery. However, studies have shown the postoperative recurrence or metastasis rate of stage I–III rectal cancer is still about 30%. Once recurrence or metastasis occurs, the five-year survival rate is less than 5%, and the average survival time is only about 7 months (3–5). Even under the premise of total mesorectomy (TME) and neoadjuvant chemotherapy, rectal cancer still has a recurrence rate of 5.6–17.6% (6–8). Therefore, postoperative recurrence or metastasis resulting in death remain a significant clinical problem and have a serious impact on the quality of life and lifetime of patients. Relevant risk factors related to postoperative recurrence or metastasis of rectal cancer have been proposed. However, some studies have shown that local recurrence or liver metastasis after rectal cancer surgery is associated with tumor location, while others have shown that tumor location is only associated with postoperative pelvic wall recurrence, but not with rectal cancer metastasis or other sites of metastasis (9,10). In addition, the research methods, inclusion criteria and research perspectives of these studies are different, resulting in numerous risk factors for postoperative recurrence or metastasis of rectal cancer, but no specificity. Five years of rectal cancer data were analyzed, and closed follow-up of the patients. Postoperative recurrence or metastasis of rectal cancer patients for the single factor analysis and multifactor variables, and prospective validation would proceed in a follow-up study. This could establish high specificity risk factors for rectal cancer of postoperative recurrence or metastasis, which was for clinical treatment. We present the following article in accordance with the STROBE reporting checklist (available at <https://jgo.amegroups.com/article/view/10.21037/jgo-22-942/rc>).

Methods

Participants and trial design

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Ethics Committee of The Fifth People's Hospital of Shanghai, Fudan University (No. 2021-237) and individual consent for this retrospective analysis was waived.

The clinical records of 321 patients who underwent rectal cancer surgery in the hospital between 2016.1–2020.12 were retrospectively collected, and the number of patients determined the sample size. According to the principle of TME, laparoscopic or open surgery was performed

directly after evaluation of cT1–cT2 rectal cancer. For cT3 and some cT4 rectal cancer patients, preoperative evaluation was followed by neoadjuvant radiotherapy or chemotherapy, followed by re-evaluation 6–8 weeks later, when surgery was performed. Postoperative adjuvant chemotherapy and follow-up were routinely performed according to NCCN guidelines. Patients were followed up in hospital or as outpatients every 3 months during the first 2 years, every 6 months in the third year, and once a year in the fourth year. Follow-up included routine blood and biochemical examinations, tumor markers, and imaging examinations, such as lung CT, abdominal enhanced CT or enhanced MRI, and colonoscopy. The inclusion criteria were: Preoperative pathological diagnosis of ct1–cT3 and part of cT4 rectal malignant tumor; and preoperative CT/MRI examination showed no distant metastasis. The exclusion criteria were: Rectal cancer patients with distant metastasis confirmed before surgery; patients who had palliative surgery or could not tolerate surgery; patients with multiple tumors or other tumors; and familial adenomatous polyposis. A total of 185 rectal cancer patients were included for statistical analysis, and the screening procedures are shown in *Figure 1*.

Intervention and study setting

Patients were followed up in our hospital and through outpatient records, telephone follow-up, and other ways, to record whether recurrence or metastasis had occurred after surgery, and the survival status. The cut-off of the research was recurrence, metastasis, or death. Recurrence refers to the occurrence of malignant tumors related to the primary tumor after rectal cancer surgery, including local recurrence of anastomosis, and recurrence of pelvic and perineum tissues and organs around the surgical site. Metastasis refers to organ metastasis outside the surgical site, such as the lung, liver, or other sites. Recurrence or metastasis was confirmed by lung CT, enhanced CT or MRI, and other imaging examinations during the patient's visit, combined with surgery, puncture, biopsy or cytopathology. According to the data reported in relevant research literatures at home and abroad, as well as the clinical experience and observation results of our hospital, the following relevant clinical risk factors were included. Tumor distance to the anal margin (preoperative colonoscopy localization, measurement of tumor distance to the anal margin, digital examination of rectum, and intraoperative judgment), preoperative bowel preparation (emptying colon contents

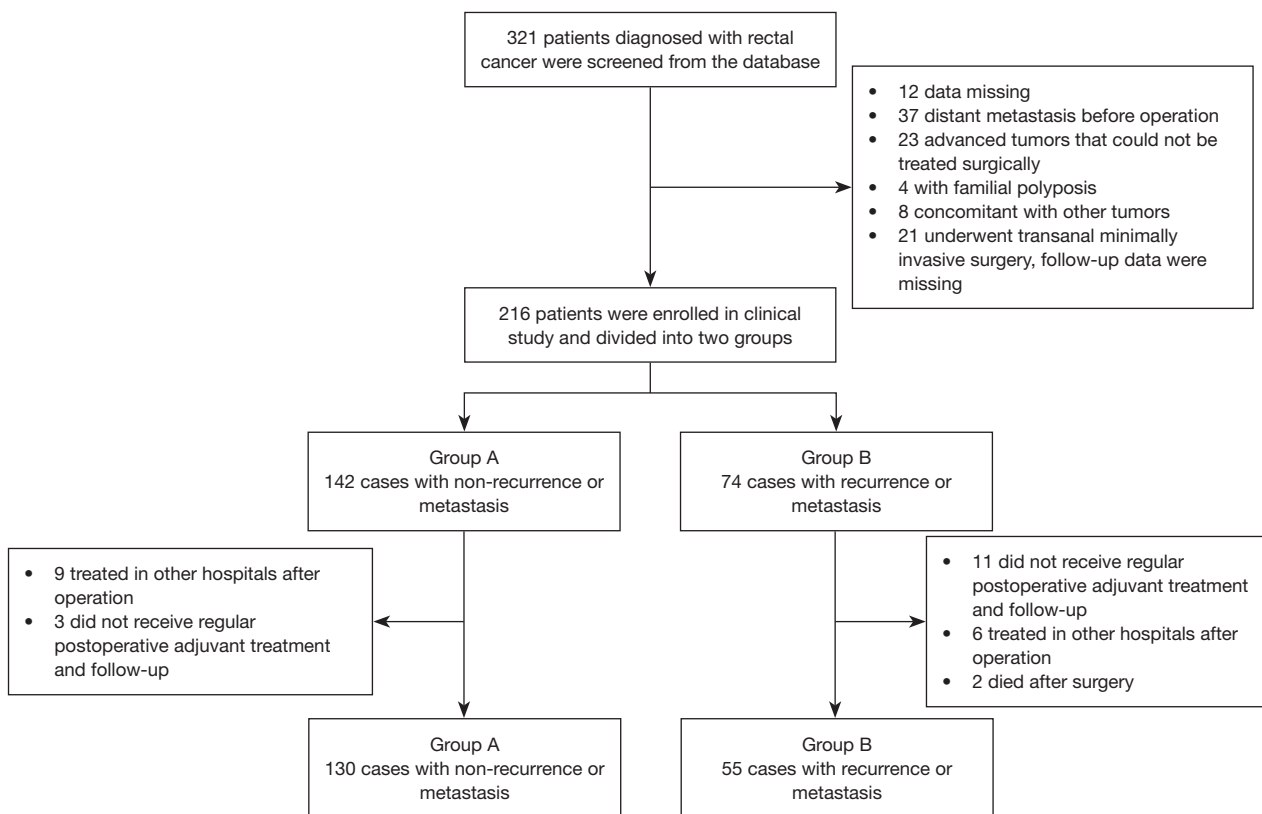


Figure 1 Patient flow through the trial.

preoperative by oral polyethylene glycol electrolyte), preoperative antibiotics (three days of oral cephalosporins antibiotics and metronidazole were given), involvement of the mesorectal fascia (MRF) (preoperative pelvic CT or MRI evaluation of the rectal fascia around the infiltrating tumor), operation type (laparoscopic or open surgery), operation time, intraoperative perfusion chemotherapy (platinum chemotherapy drugs 50 mg/m² for preoperative irrigation), intraoperative blood transfusion, sphincter-preservation, colostomy, left colic artery preservation, postoperative complications (bleeding, infection, intestinal obstruction, deep vein thrombosis, pulmonary infection, abdominal infection, or wound infection), anastomosis leakage, postoperative retained catheter time, hospital stay, tumor size, distance of distal tumor incisional margin (the tumor was cut and measured after surgery), T staging of tumor, nerve, and/or vascular invasion, circumferential resection margin (CRM), total number of lymph nodes, number of metastasis lymph nodes, Dukes staging, and other relevant factors.

Statistical analysis

As for the lost follow-up and censored data, it was deleted because there were only 2 cases of lost follow-up data, which had little significant impact on this study. In addition, we conducted stratified statistical and comparative studies on the offset caused by different follow-up times. For measurement data conforming to normal distribution, the independent sample *t* test was used for comparison between groups, and χ^2 test or Fisher's exact probability method was used for comparison of count data. Univariate and multiple logistic regression were used for the risk factors analyzed. Cox regression and Kaplan-Meier method were used for establishing survival curves. A univariate COX regression model was applied followed by multivariate COX regression model in backward stepwise (Wald) that was used to provide an estimate of the hazard ratio (HR) and its confidence interval (CI) for investigating the association between the survival time of patients and one or more predictor variables. P values were two-sided, and P<0.05 were

considered statistically significant. Statistical analyses were performed using SPSS 26.0 (IBM Corporation, Armonk, NY, USA).

Results

Of the initial 321 patients counted, 12 had missing data, 37 had distant metastasis before operation, 23 had advanced tumors that could not be treated surgically, four had familial polyposis, eight had concomitant other tumors, and 21 underwent transanal minimally invasive surgery, leaving 216 patients. These were then divided into two groups: Group A as a recurrence or metastasis group, and group B as a non-recurrence or metastasis group. In group A, nine patients were treated in other hospitals after operation and three did not receive regular postoperative adjuvant treatment and follow-up, while in group B, 11 patients did not receive regular postoperative adjuvant treatment and follow-up, six were treated in other hospitals after operation, and two died after surgery. This left a total of 185 patients included in the final study. All patients were followed up between 20 to 60 months and the median time was 45 months. Their age ranged from 33 to 94 years, with a mean of 66.3 years, and included 125 males (67.6%) and 60 females (32.4%). There were 130 patients in Group A, with an average age of 65.36 years, including 87 males (66.9%) and 43 females (33.1%), and group B contained 55 patients, with an average age of 68.53 years, including 38 males (69.1%) and 17 females (30.9%). Recurrence or metastasis occurred in 55 patients, accounting for 29.7%, with an average time of 10.8 months. Detailed data and other indicators are shown in *Table 1*.

Univariate logistic regression analysis showed the risk factors associated with recurrence or metastasis were involvement of the MRF (OR =5.6, 95% CI: 2.01–10.48, P=0.000), without preoperative antibiotics (OR =2.1, 95% CI: 1.07–4.32, P=0.032), nerve and vascular invasion (OR =2.30, 95% CI: 1.61–3.29, P=0.000), nerve or vascular invasion (OR =3.90, 95% CI: 1.97–7.70, P=0.000), ileostomy (OR =5.6, 95% CI: 2.01–10.48, P=0.000), operative time (OR =1.0, 95% CI: 1.00–1.01, P=0.015), intraoperative blood transfusion (OR =2.5, 95% CI: 1.14–5.45, P=0.022), tumor T stage (OR =2.6, 95% CI: 1.34–4.91, P=0.005), positive CRM (OR =5.2, 95% CI: 1.25–21.54, P=0.024), number of metastatic lymph nodes (OR =1.25, 95% CI: 1.12–1.41, P=0.000), and Dukes stage (OR =3.7, 95% CI: 2.19–6.16, P=0.000), as shown in *Table 1*. According to the area under ROC curve analysis of the number of metastatic lymph nodes, the critical value was calculated as 1.5, being

the number of metastatic lymph nodes found in pathological specimens was more than 1.5, which was a risk factor for postoperative recurrence or metastasis. Multivariate logistic regression analysis of statistically significant risk factors in univariate analysis showed MRF involvement (OR =2.9, 95% CI: 1.16–7.29, P=0.023), nerve and vascular invasion (OR =1.7, 95% CI: 1.08–2.59, P=0.022), intraoperative blood transfusion (OR =3.7, 95% CI: 1.45–9.40, P=0.006), and Dukes staging (OR =2.3, 95% CI: 1.26–4.35, P=0.007) were independent risk factors for postoperative recurrence or metastasis of rectal cancer with statistical significance, as shown in *Table 2*.

Among the 55 patients with recurrence or metastasis, three with postoperative recurrence involved the pelvic floor. Postoperative metastasis occurred in 52 patients, and included 27 (49.1%) with liver metastasis, 11 (20%) with lung metastasis, while others such as sacrococcygeal and peritoneal metastasis occurred in 14 patients (25.45%). The mean time of liver metastasis was 7.2 months, lung metastasis was 8.6 months, and other sites metastasis was 18.1 months. Among patients with T stage, recurrence, or metastasis, 1 patient (1.8%) was T1 stage, none were T2 stage, 6 (10.9%) were T3 stage, and 48 (87.3%) were T4 stage. Dukes stages included 3 patients (5.5%) in stage A, 12 (21.8%) in stage B, 37 cases (67.3%) in stage C, and 3 patients (5.5%) in stage D. Univariate logistic regression analysis showed that in patients with liver metastasis low rectal cancer (OR =0.3, 95% CI: 0.12–0.95, P=0.040), nerve and vascular invasion (OR =1.8, 95% CI: 1.21–2.81, P=0.005), nerve or vascular invasion (OR =2.5, 95% CI: 1.04–5.79, P=0.041), tumor T stage (OR =4.7, 95% CI: 1.22–18.18, P=0.025), lymph node metastasis (OR =1.1, 95% CI: 1.03–1.24, P=0.007), Dukes stage (OR =3.7, 95% CI: 1.83–7.30, P=0.000), and MRF involvement (OR =17.7, 95% CI: 2.34–133.77, P=0.005) were risk factors. Multivariate logistic regression analysis showed MRF involvement (OR =11.5, 95% CI: 1.49–88.79, P=0.019) and Dukes stage (OR =3.0, 95% CI: 1.46–6.26, P=0.003) were independent risk factors for liver metastasis, as shown in *Table 3*. For patients with lung metastasis, univariate logistic regression analysis showed nerve and vascular invasion (OR =2.8, 95% CI: 1.39–5.65, P=0.004), intraoperative nonperfusion chemotherapy (OR =4.0, 95% CI: 1.07–14.68, P=0.039), ileostomy (OR =8.1, 95% CI: 1.01–65.46, P=0.049), lymph node metastasis (OR =1.2, 95% CI: 1.05–1.30, P=0.005), and Dukes stage (OR =3.9, 95% CI: 1.33–11.65, P=0.013) were risk factors, and multivariate logistic regression analysis showed nerve and vascular invasion (OR

Table 1 Demographic and clinical characteristics and univariate logistic regression of recurrence or metastasis

Factors of research	No recurrence or metastasis, n (%)	Recurrence or metastasis, n (%)	β	OR (95% CI)	P value
Sex					
Male	87 (66.9)	38 (69.1)	-0.10	0.9 (0.46-1.78)	0.773
Female	43 (33.1)	17 (30.9)			
Age(years)					
≤50	14 (10.8)	1 (1.8)	1.87	6.5 (0.83-50.8)	0.074
51-60	25 (19.2)	8 (14.5)	-0.33	0.7 (0.30-1.70)	0.448
61-70	48 (36.9)	23 (41.8)	0.21	1.2 (0.64-2.33)	0.532
71-80	30 (23.1)	16 (29.1)	0.31	1.4 (0.67-2.78)	0.388
>80	13 (10.0)	7 (12.7)	0.27	1.3 (0.49-3.49)	0.586
BMI (kg/m ²)					
<18.5	9 (7.0)	5 (9.1)	-0.29	0.7 (0.24-2.33)	0.611
18.5-24.9	93 (71.5)	34 (61.8)	-0.44	0.6 (0.33-1.25)	0.194
25-29.9	26 (20.0)	14 (25.5)	0.31	1.4 (0.65-2.87)	0.411
≥30	2 (1.5)	2 (3.6)	0.88	2.4 (0.33-17.59)	0.384
Medical history					
Diabetes	15 (11.5)	7 (12.7)	0.11	1.1 (0.43-2.92)	0.819
Cardiovascular disease	59 (45.4)	21 (38.2)	-0.30	0.7 (0.39-1.42)	0.367
Pulmonary disease	3 (2.3)	0 (0.0)	-20.37	0.0 (0.00-0.00)	0.999
Other major disease	9 (7.0)	3 (5.5)	-0.13	0.9 (0.22-3.45)	0.854
Distance from anal verge (cm)					
≤5	46 (35.4)	22 (40.0)	-0.20	0.8 (0.43-1.57)	0.552
5-10	54 (41.5)	18 (32.7)	-0.38	0.7 (0.35-1.33)	0.262
>10	30 (23.1)	15 (27.3)	0.22	1.3 (0.61-2.57)	0.544
Preoperation bowel preparation					
Yes	125 (96.2)	51 (92.7)	-0.67	0.5 (0.13-1.98)	0.330
No	5 (3.8)	4 (7.3)			
Preoperative antibiotic					
Yes	75 (57.7)	14 (25.5)	0.76	2.1 (1.07-4.32)	0.032
No	55 (42.3)	41 (74.5)			
Involvement of mesorectal fascia					
Yes	73 (56.2)	47 (85.5)	1.52	5.6 (2.01-10.48)	0.000
No	57 (43.8)	8 (14.5)			
Operation type					
Laparoscopic	106 (81.5)	43 (78.2)	0.21	1.2 (0.57-2.68)	0.059
Open	24 (18.5)	12 (21.8)			
Operation time (mean)	213.4	246.4	0.01	1.0 (1.00-1.01)	0.015

Table 1 (Continued)

Table 1 (Continued)

Factors of research	No recurrence or metastasis, n (%)	Recurrence or metastasis, n (%)	β	OR (95% CI)	P value
Intraoperative chemotherapy					
Yes	37 (28.5)	17 (30.9)	0.12	1.1 (0.57–2.24)	0.738
No	93 (71.5)	38 (69.1)			
Intraoperative blood transfusion					
Yes	17 (13.1)	40 (72.7)	0.91	2.5 (1.14–5.45)	0.022
No	113 (86.9)	15 (27.3)			
Sphincter preservation					
Yes	117 (90.0)	45 (81.8)	–0.69	0.5 (0.21–1.22)	0.128
No	13 (10.0)	10 (18.2)			
Ileostomy					
Yes	64 (49.2)	37 (67.3)	0.75	2.1 (1.10–4.10)	0.026
No	66 (50.8)	18 (32.7)			
Left colonic artery preservation					
Yes	59 (45.4)	24 (43.6)	–0.07	0.9 (0.49–1.76)	0.827
No	71 (54.6)	31 (56.4)			
Anastomotic leakage					
Yes	4 (3.1)	4 (7.3)	0.90	2.5 (0.59–10.26)	0.213
No	126 (96.9)	51 (92.7)			
Postoperative complications					
Yes	14 (10.8)	6 (10.9)	0.01	1.0 (0.37–2.79)	0.978
No	116 (89.2)	49 (89.1)			
Postoperative catheter retention time (mean)	7.1	8.5	0.08	1.1 (1.00–1.16)	0.051
Length of stay (mean)	25.3	26.8	0.01	1.0 (0.98–1.04)	0.455
Tumor volume (mean)	22.52	24.37	0.00	1.0 (0.99–1.01)	0.722
Distal margin distance (mean)	2.04	2.25	0.08	1.1 (0.89–1.33)	0.428
T stage of tumor					
T1	5 (3.8)	1 (1.8)	0.77	2.2 (0.25–18.93)	0.487
T2	13 (10.0)	0 (0.0)	–20.45	0.0 (0.00–0.00)	0.999
T3	29 (22.3)	6 (10.9)	–0.85	0.4 (0.17–1.10)	0.076
T4	83 (63.8)	48 (87.3)	1.36	3.9 (1.63–9.27)	0.002
Nerve or vascular invasion					
Yes	50 (38.5)	39 (70.9)	1.36	3.9 (1.97–7.70)	0.000
No	80 (61.5)	16 (29.1)			
Nerve and vascular invasion					
Yes	20 (15.4)	27 (49.1)	0.83	2.3 (1.61–3.29)	0.000
No	110 (84.6)	28 (50.9)			

Table 1 (Continued)

Table 1 (Continued)

Factors of research	No recurrence or metastasis, n (%)	Recurrence or metastasis, n (%)	β	OR (95% CI)	P value
Nerve invasion					
Yes	11 (8.5)	9 (16.4)	0.75	2.1 (0.82–5.44)	0.120
No	119 (91.5)	46 (83.6)			
Vascular invasion					
Yes	19 (14.6)	3 (5.5)	–1.09	0.3 (0.10–1.19)	0.091
No	111 (85.4)	52 (94.5)			
CRM					
Positive	3 (2.3)	6 (10.9)	1.65	5.2 (1.25–21.54)	0.024
Negative	127 (97.7)	49 (89.1)			
Total lymph nodes (mean)	17.33	15.8	–0.02	1.0 (0.94–1.02)	0.267
No. of lymph node metastasis (mean)	1.15	4	0.23	1.3 (1.12–1.41)	0.000
Dukes stage					
Dukes A	38 (29.2)	3 (5.5)	–1.97	0.1 (0.04–0.48)	0.002
Dukes B	52 (40.0)	12 (21.8)	–0.87	0.4 (0.20–0.87)	0.019
Dukes C	39 (30.0)	37 (67.3)	1.57	4.8 (2.44–9.44)	0.000
Dukes D	1 (0.8)	3 (5.5)	2.01	7.4 (0.76–73.20)	0.085

OR, odds ratio; CI, confidence interval; BMI, body mass index; CRM, circumferential resection margin.

Table 2 Multiple logistic regression model and weighted point assignment of recurrence or metastasis.

Factors of research	No recurrence or metastasis, n (%)	Recurrence or metastasis, n (%)	β	OR (95% CI)	P value
Involvement of mesorectal fascia					
Yes	73 (56.2)	47 (85.5)	1.07	2.9 (1.16–7.29)	0.023
No	57 (43.8)	8 (14.5)			
Nerve and vascular invasion					
Yes	20 (15.4)	27 (49.1)	0.51	1.7 (1.08–2.59)	0.022
No	110 (84.6)	28 (50.9)			
Intraoperative blood transfusion					
Yes	17 (13.1)	40 (72.7)	1.31	3.7 (1.45–9.40)	0.006
No	113 (86.9)	15 (27.3)			
Dukes stage					
Dukes A	38 (29.2)	3 (5.5)	0.85	2.3 (1.26–4.35)	0.007
Dukes B	52 (40.0)	12 (21.8)			
Dukes C	39 (30.0)	37 (67.3)			
Dukes D	1 (0.8)	3 (5.5)			

OR, odds ratio; CI, confidence interval.

Table 3 Univariate and multiple logistic regression model and weighted point assignment of liver metastasis

Logistic regression	No Liver metastasis, n (%)	Liver metastasis, n (%)	β	OR (95% CI)	P value
Univariate logistic regression					
Distance from anal verge (cm)					
≤5	63 (39.9)	5 (18.5)	-0.07	0.3 (0.12–0.95)	0.040
>5	95 (60.1)	22 (81.5)			
Nerve and vascular invasion					
Yes	34 (21.5)	13 (48.1)	0.61	1.8 (1.21–2.81)	0.005
No	124 (78.5)	14 (51.9)			
Nerve or vascular invasion					
Yes	71 (44.9)	18 (66.7)	0.89	2.5 (1.04–5.79)	0.041
No	87 (55.1)	9 (33.3)			
T stage of tumor					
T3	33 (20.9)	2 (7.4)	-1.19	0.3 (0.07–1.35)	0.116
T4	106 (67.1)	25 (92.6)	1.18	6.1 (1.40–26.88)	0.016
No. of lymph node metastasis					
>0.5	60 (38.0)	21 (77.8)	0.12	1.1 (1.03–1.24)	0.007
≤0.5	98 (62.0)	6 (22.2)			
Dukes stage					
Dukes A	40 (25.3)	1 (3.7)	-2.18	0.1 (0.02–0.86)	0.036
Dukes B	59 (37.3)	5 (18.5)	-0.96	0.4 (0.14–1.06)	0.065
Dukes C	57 (36.1)	19 (70.4)	1.44	4.2 (1.73–10.22)	0.002
Dukes D	2 (1.3)	2 (7.4)	1.83	6.2 (0.84–46.34)	0.073
Involvement of mesorectal fascia					
Yes	94 (59.5)	26 (96.3)	2.87	17.7 (2.34–133.8)	0.005
No	64 (40.5)	1 (3.7)			
Multiple logistic regression					
Involvement of mesorectal fascia					
Yes	94 (59.5)	26 (96.3)	2.4	11.5 (1.49–88.79)	0.019
No	64 (40.5)	1 (3.7)			
Dukes stage					
Dukes A	40 (25.3)	1 (3.7)	1.1	3.0 (1.46–6.26)	0.003
Dukes B	59 (37.3)	5 (18.5)			
Dukes C	57 (36.1)	19 (70.4)			
Dukes D	2 (1.3)	2 (7.4)			

OR, odds ratio; CI, confidence interval; T stage, tumor stage.

Table 4 Univariate and multiple logistic regression model and weighted point assignment of pulmonary metastasis

Factors of research	No pulmonary metastasis, n (%)	Pulmonary metastasis, n (%)	β	OR (95% CI)	P value
Univariate logistic regression					
Nerve and vascular invasion					
Yes	40 (23.0)	7 (63.6)	1.03	2.8 (1.39–5.65)	0.004
No	134 (77.0)	4 (36.4)			
Intraoperative chemotherapy					
Yes	48 (27.6)	6 (54.5)	1.38	3.9 (1.07–14.68)	0.039
No	126 (72.4)	5 (45.5)			
Ileostomy					
Yes	92 (52.9)	9 (81.8)	2.09	8.1 (1.01–65.46)	0.049
No	82 (47.1)	2 (18.2)			
No. of lymph node metastasis					
≤ 2.5	137 (78.7)	2 (18.2)	0.16	1.2 (1.05–1.31)	0.005
> 2.5	37 (21.3)	9 (81.8)			
Dukes stage					
Dukes A	40 (23.0)	1 (9.1)	-0.98	0.4 (0.05–3.05)	0.359
Dukes B	64 (36.8)	0 (0.0)	-18.80	0.0 (0.00–0.00)	0.997
Dukes C	67 (38.5)	9 (81.8)	1.84	6.3 (1.30–30.53)	0.022
Dukes D	3 (1.7)	1 (9.1)	1.85	6.4 (0.60–67.49)	0.124
Multiple logistic regression					
Nerve and vascular invasion					
Yes	40 (23.0)	7 (63.6)	1.6	2.4 (1.19–5.00)	0.015
No	134 (77.0)	4 (36.4)			

OR, odds ratio; CI, confidence interval.

=2.4, 95% CI: 1.19–5.00, $P=0.015$) was an independent risk factor, as shown in *Table 4*.

The median follow-up time was 45 months, and 28 (15.1%) of the 185 patients died. Univariate logistic regression analysis showed recurrence or metastasis (OR =22.3, 95% CI: 6.26–79.77, $P=0.000$), liver metastasis (OR =15.4, 95% CI: 5.59–42.26, $P=0.000$), MRF involvement (OR =3.9, 95% CI: 1.11–13.68, $P=0.034$), intraoperative blood transfusion (OR =3.3, 95% CI: 1.26–8.74, $P=0.016$), no left colon artery preservation (OR =0.3, 95% CI: 0.11–0.93, $P=0.033$), total number of lymph nodes (OR =0.9, 95% CI: 0.88–0.99, $P=0.028$), and Dukes stage (OR =3.5, 95% CI: 1.67–7.35, $P=0.001$) were risk factors for death, as shown in *Table 5*. Multivariate logistic regression analysis showed recurrence or metastasis (OR =7.6, 95% CI: 1.59–

36.59, $P=0.011$), liver metastasis (OR =4.7, 95% CI: 1.17–18.57, $P=0.029$), total number of lymph nodes (OR =0.9, 95% CI: 0.78–0.98, $P=0.016$) and left colon artery without preservation (OR =0.2, 95% CI: 0.06–0.74, $P=0.016$) were independent risk factors for death, as shown in *Table 6*. In addition, the ROC curve analysis showed involvement of ≤ 6 lymph nodes was a risk factor for death.

During the follow-up, multiple factors were further stratified and analyzed, and among these, the recurrence or metastasis rate of low rectal cancer was 32.3%, middle rectal cancer was 25%, and high rectal cancer was 33.3%, and the rate of T1, T2, T3, and T4 was 16.7%, 0, 17.1%, and 36.6%, respectively. Dukes A stage was 7.3%, Dukes B stage 18.8%, Dukes C stage 48.7%, and Dukes D stage was 75%.

Multivariate Cox regression was used to analyze the

Table 5 Univariate logistic regression model and weighted of death

Factors of research	No death, n (%)	Death, n (%)	β	OR (95% CI)	P value
Recurrence or metastasis					
Yes	30 (19.1)	25 (89.3)	3.11	22.3 (6.26–79.77)	0
No	127 (80.9)	3 (10.7)			
Pulmonary metastasis					
Yes	8 (5.1)	3 (10.7)	–0.21	0.8 (0.10–6.76)	0.85
No	149 (94.9)	25 (89.3)			
Liver metastasis					
Yes	11 (7.0)	16 (57.1)	2.73	15.4 (5.59–42.26)	0
No	146 (93.0)	12 (42.9)			
Involvement of mesorectal fascia					
Yes	96 (61.1)	24 (85.7)	1.36	3.9 (1.11–13.68)	0.034
No	61 (38.9)	4 (14.3)			
Intraoperative blood transfusion					
Yes	22 (14.0)	10 (35.7)	1.2	3.3 (1.25–8.74)	0.016
No	135 (86.0)	18 (64.3)			
Sphincter preservation					
Yes	140 (89.2)	22 (78.6)	–0.86	0.4 (0.14–1.28)	0.128
No	17 (10.8)	6 (21.4)			
Left colonic artery preservation					
Yes	76 (48.4)	7 (25.0)	–1.14	0.3 (0.11–0.93)	0.033
No	81 (51.6)	21 (75.0)			
T stage of tumor					
T1	6 (3.8)	0 (0.0)	–19.24	0.0 (0.00–0.00)	0.999
T2	12 (7.6)	1 (3.6)	–0.51	0.6 (0.07–4.85)	0.631
T3	31 (19.7)	4 (14.3)	–0.93	0.4 (0.09–1.77)	0.224
T4	108 (68.8)	23 (82.1)	1.06	2.9 (0.82–10.19)	0.1
CRM					
Positive	6 (3.8)	3 (10.7)	1.42	4.1 (0.95–17.89)	0.058
Negative	151 (96.2)	25 (89.3)			
Total lymph nodes (mean)	17.5	13.5	–0.07	0.9 (0.88–0.99)	0.028
No. of lymph node metastasis (mean)	1.9	2.5	0.05	1.1 (0.95–1.17)	0.312
Dukes stage					
Dukes A	40 (25.5)	1 (3.6)	–19.49	0.0 (0.00–0.00)	0.998
Dukes B	58 (36.9)	6 (21.4)	–0.39	0.7 (0.25–1.83)	0.444
Dukes C	57 (36.3)	19 (67.9)	1.05	2.9 (1.13–7.19)	0.026
Dukes D	2 (1.3)	2 (7.1)	2.09	8.1 (1.07–60.34)	0.042

OR, odds ratio; CI, confidence interval; CRM, circumferential resection margin.

Table 6 Multiple Cox regression model and weighted point assignment of death

Factors of research	No death, n (%)	Death, n (%)	β	OR (95% CI)	P value
Recurrence or metastasis					
Yes	30 (19.1)	25 (89.3)	-2.18	0.1 (0.03–0.46)	0.002
No	127 (80.9)	3 (10.7)			
Liver metastasis					
Yes	11 (7.0)	16 (57.1)	-1.54	0.2 (0.08–0.61)	0.004
No	146 (93.0)	12 (42.9)			
Dukes D	2 (1.3)	2 (7.1)	-2.10	0.1 (0.02–0.80)	0.028
Intraoperative blood transfusion					
Yes	22 (14.0)	10 (35.7)	-0.99	0.4 (0.15–0.94)	0.036
No	135 (86.0)	18 (64.3)			
Left colonic artery preservation					
Yes	76 (48.4)	7 (25.0)	1.82	6.1 (1.80–20.95)	0.004
No	81 (51.6)	21 (75.0)			
Total lymph nodes (mean)	17.5	13.5	-0.11	0.9 (0.82–0.99)	0.024

OR, odds ratio; CI, confidence interval.

survival of postoperative death from rectal cancer, and showed intraoperative blood transfusion (HR =0.4, 95% CI: 0.15–0.94, P=0.036), recurrence or metastasis (HR =0.1, 95% CI: 0.03–0.46, P=0.002), liver metastasis (HR =0.2, 95% CI: 0.08–0.61, P=0.004), left colic artery preservation (HR =6.1, 95% CI: 1.80–20.95, P=0.004), number of lymph nodes (HR =0.9, 95% CI: 0.82–0.99, P=0.024) and Dukes D stage (HR =0.1, 95% CI: 0.02–0.80, P=0.028) were statistically significant, and were independent risk factors affecting patient death, as shown in *Figure 2*.

Kaplan-Meier was used to analyze the survival curve of postoperative death, and the results showed MRF involvement, recurrence or metastasis, liver metastasis, positive CRM, intraoperative blood transfusion, unreserved left colon artery, and Dukes stage were statistically significant risk factors, and the survival curve is shown in *Figure 3*. The Dukes stages were stratified, and the 2-year and 3-year survival rates were 92% and 78.1% for Dukes A, 78.1% and 60.9% for Dukes B, 78.9% and 46.1% for Dukes C, and 0% for Dukes D. The 2-year and 3-year survival rates were 65.5% and 34.5% in patients with recurrence or metastasis, 86.2% and 64.6% in patients with non-recurrence or metastasis, 48.1% and 29.6% in patients with liver metastasis, and 85.4% and 62% in patients with non-liver metastasis.

Discussion

Rectal cancer is comprehensive treated by surgery, and both TME (total mesorectum excision) standards and neoadjuvant chemoradiation have greatly improved the quality of surgery and the cure rate, bringing a significant improvement in the quality of life of patients. However, the rectal cancer postoperative survival rate remains variable, mainly because of recurrence or metastasis. At the time of initial diagnosis, about 25% of stage IV patients have liver metastasis and about 50% have metastasis to other sites (11,12). For locally advanced or advanced rectal cancer, distant metastasis is the most common cause of death, and the lung is the most likely site, followed by the liver (13,14). However, if local recurrence occurs without surgery, the 5-year overall survival is about 4% (15-20).

Studies on postoperative recurrence or metastasis of rectal cancer exist, but varying inclusion criteria, methods, and research sites mean a unified conclusion has not been reached. A study on factors related to the local recurrence in 497 patients with T3 rectal cancer with tumor located within 12 cm of the anal margin by laparoscopic surgery without preoperative chemoradiotherapy in four Asian countries found gender, tumor location, lymph node metastasis, and tumor perforation were independent

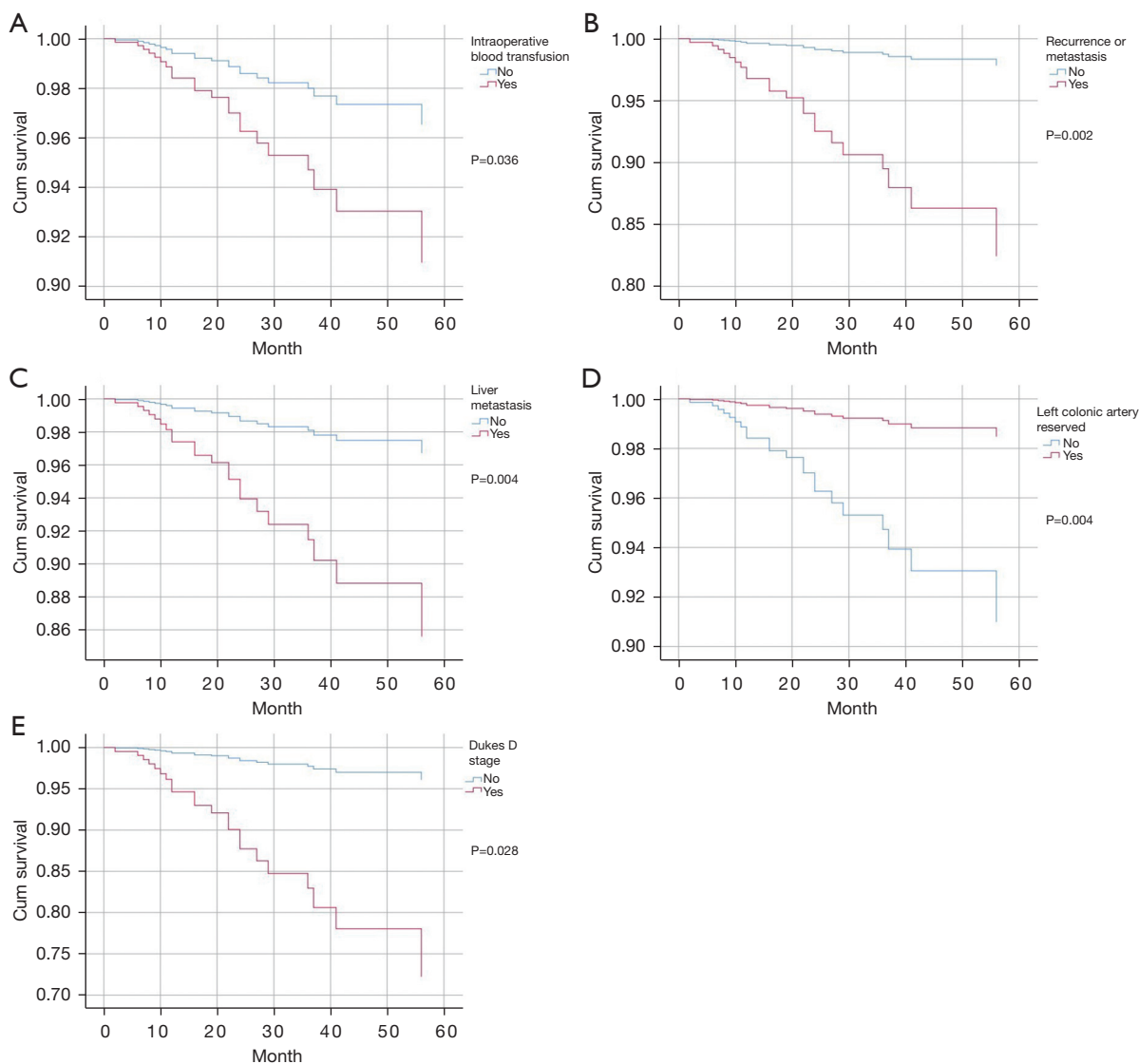


Figure 2 Multivariate COX analysis of mortality risk factors survival curve. (A) intraoperative blood transfusion, HR =0.4, 95% CI: 0.15–0.94, P=0.036; (B) recurrence or metastasis, HR =0.1, 95% CI: 0.03–0.46, P=0.002; (C) liver metastasis, HR =0.2, 95% CI: 0.08–0.61, P=0.004; (D) retention of left colonic artery, HR =6.1, 95% CI: 1.80–20.95, P=0.004; (E) Dukes D stage, HR =0.1, 95% CI: 0.02–0.80, P=0.028.

factors for local recurrence (21). In our study, recurrence or metastasis was found in 29.7% of patients after surgery. There are many risk factors associated with recurrence or metastasis, such as MRF involvement, no preoperative antibiotics use, nerve and/or vascular invasion, stoma, operative time, intraoperative blood transfusion, T stage of tumor, positive CRM, number of metastatic lymph nodes, and Dukes stage of tumor. Multivariate logistic regression analysis showed MRF involvement (P=0.023), nerve and vascular invasion (P=0.022), intraoperative blood transfusion

(P=0.006), and Dukes stage (P=0.007) were independent risk factors for postoperative recurrence or metastasis.

MRF involvement, diagnosed by preoperative MRI, is a risk factor for poor prognosis in rectal cancer. In a univariate analysis, poorly differentiated tumors, tumors larger than 5cm, and MRF involvement were associated with poorer 3-year disease-free survival and overall survival, and patients with early distant metastasis were more likely to develop MRF involvement than those without distant metastasis (P=0.002) (22), which is consistent with

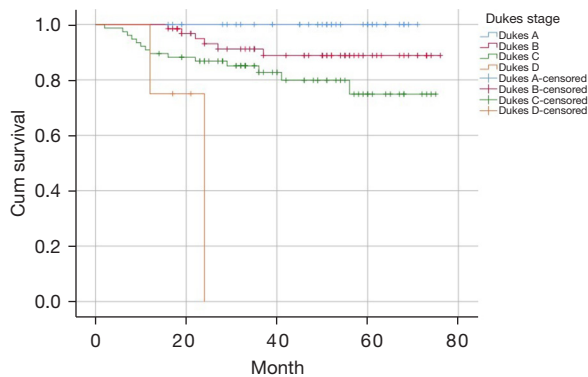


Figure 3 Kaplan-Meier survival analysis of Dukes stage, inter-group comparison: Dukes A vs. B, $P=0.038$; Dukes A vs. C, $P=0.002$; Dukes A vs. D, $P=0.000$; Dukes B vs. C, $P=0.099$; Dukes B vs. D, $P=0.000$; Dukes C vs. D, $P=0.044$.

our research conclusions. Therefore, preoperative MRI evaluation of rectal cancer is crucial. However, there is no consensus on whether preoperative radiotherapy and chemotherapy reduce the rate of postoperative recurrence or metastasis if the MRF is involved, although this may suggest a more rigorous treatment and follow-up plan be implemented.

Multifactorial analysis showed venous invasion was an independent adverse prognostic factor and was associated with an increased risk of liver metastases. In a study specifically focused on pT1 and superficial pT2 rectal cancer, the involvement of small vessels at any tumor site was significantly correlated with regional nodular metastasis (23,24). Lee *et al.* (25) found lymphatic vascular invasion was an independent risk factor for disease-free survival after radical resection of colorectal cancer, and postoperative recurrence or metastasis were more likely. Additionally, a meta-analysis showed lymphatic vascular invasion was an independent risk factor for lymph node metastasis (26). Lymphatic vascular invasion plays an important role in the prognosis of rectal cancer, and its value can be fully utilized clinically to provide a better surgical plan and follow-up treatment. Intraoperative blood transfusion affects postoperative recurrence or metastasis of rectal cancer, and the possible reason is that during surgery, due to factors such as late tumor stage, tumor invasion of peripheral blood vessels, and low tumor location, the operation time is long and the injury is large, leading to more intraoperative blood loss.

Postoperative pathological staging has long been considered the most powerful prognostic indicator of rectal

cancer and often determines the selectivity of systemic adjuvant therapy. In pT3 tumors, the degree of extraneous invasion has been reported to be an important prognostic feature regardless of regional lymph node metastasis. Many studies suggest extramural infiltration of more than 5mm may have a serious adverse effect on prognosis (27,28). The pathologic assessment of serous tumor invasion is only relevant to the upper rectum, which importantly, is frontally covered by visceral peritoneum. For pT4 tumors penetrating the visceral peritoneum, the median survival time after surgical resection was significantly reduced compared with patients without serous membrane involvement. Kim *et al.* (29) conducted a retrospective study on 714 patients with locally advanced rectal cancer who received TME surgery after preoperative neoadjuvant chemotherapy. Among them, 139 patients (19.5%) relapsed, and of these, 49 recurred within 1 year after operation, and 90 patients recurred over 1 year after. Multivariate analysis showed that positive ypN stage and grade 3 or above tumor stage were statistically significant and were independent risk factors for postoperative local recurrence. Therefore, tumor stage is one of the important factors affecting the prognosis of rectal cancer.

Liver metastasis of colorectal cancer is a common clinical problem. According to statistics, about 25% of patients have liver metastasis when first diagnosed, about 50% have liver metastasis during the whole course of disease, and the liver is the only metastatic site in 20–30% of patients. In a study on the correlation of preoperative liver metastasis in rectal cancer, univariate analysis showed the level of carcinoembryonic antigen, N stage, MRF invasion, and mesenteric vascular lesion (MVL) grade were correlated with liver metastasis ($P<0.05$), and multivariate analysis showed rectal MVL grading and MRF invasion were independent factors (30–32). The characteristics of rectal reflux blood circulation are also closely related to the liver. The capillaries in the mucosal layer of the rectal wall pass through the submucosa and muscle layer and enter the subserous membrane. If the tumor infiltrates to this point, tumor cells could enter the blood circulation and enter the liver.

The lung is a common site of postoperative lung metastasis. The influence of pelvic lymph node size before and after radiotherapy and chemotherapy on postoperative lung metastasis was studied, and the results showed the cumulative lung metastasis rate in 5 years was 15.2%. Mean lateral lymph nodes were larger in patients with lung metastasis than in those without and multivariate analysis

showed lung metastasis correlated with lateral lymph node size, tumor T stage, and tumor location after radiotherapy and chemotherapy (33). Tumor location, lymph node metastasis, tumor stage, and positive CRM were independent risk factors for lung metastasis in a study of patients with postoperative lung metastasis for rectal cancer. Therefore, in view of the risk factors related to postoperative lung metastasis of rectal cancer, a more intensive monitoring program is required timely intervention, and treatment (34). Although there are many studies on the risk factors related to lung metastasis, there is still no clear specific risk factor, and the metastasis mechanism remains to be further studied.

There are many other risk factors associated with postoperative recurrence or metastasis of rectal cancer. For example, studies have found that a distal resection margin less than 0.9 cm and lymph node dissection less than 14 are independent risk factors for postoperative distant metastasis of middle and low rectal cancer (35). A prospective study of three Italian medical institutions showed that age less than 63 years, CEA greater than 3 ng/dL, and tumor location below 5 cm in the anal margin were adverse risk factors for early postoperative recurrence or metastasis of rectal cancer (36). Local recurrence after R0 resection is not uncommon. There is a correlation between the pathological features of rectal cancer and postoperative recurrence or metastasis. It was found that venous invasion of primary lesions and tumor progression pattern (bulge type, invasion type, mixed type) were independent predictors of local recurrence (37). It is still controversial whether neoadjuvant radiotherapy should be performed before surgery, and new Dutch guidelines reject radiotherapy in low-risk patients. There were 407 cases of primary rectal cancer surgery without synchronous metastasis, including 225 under the old guidelines and 182 under the new guidelines. The new group had lower tumor stage and lymph node stage, and no differences in pathological tumor stage were found. There was no significant difference in 1-year local recurrence rate and mortality (38). Therefore, radiotherapy does not have a high clinical value for patients with low-risk rectal cancer.

The effectiveness of different surveillance regimens for recurrence or metastasis after radical rectal cancer surgery has not been well established. One study using different surveillance protocols for assessment found the proportion of recurrences detected during regular follow-up was, on average, earlier than during additional follow-up (39). Therefore, for rectal cancer patients with high risk factors, individualized follow-up programs should be established to better conduct early intervention and treatment, and

effectively improve the prognosis of patients.

Limitations

This was a retrospective clinical study with limited research conditions and limited quantity of patients. In the statistical process of factors related to postoperative recurrence or metastasis of rectal cancer, some factors could not be included due to a lack of data.

Conclusions

The results of multivariate analysis showed MRF involvement, nerve and vascular invasion, intraoperative blood transfusion, and Dukes stage were independent risk factors for postoperative recurrence or metastasis of rectal cancer. MRF involvement and Dukes stage were independent risk factors for liver metastasis, and nerve and vascular invasion were independent risk factor for lung metastasis. These risk factors can be combined to establish a risk prediction model, to provide a more personalized and effective follow-up and treatment plan for each patient with rectal cancer.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at <https://jgo.amegroups.com/article/view/10.21037/jgo-22-942/rc>

Data Sharing Statement: Available at <https://jgo.amegroups.com/article/view/10.21037/jgo-22-942/dss>

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://jgo.amegroups.com/article/view/10.21037/jgo-22-942/coif>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was

conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Ethics Committee of The Fifth People's Hospital of Shanghai, Fudan University (*No. 2021-237*) and individual consent for this retrospective analysis was waived.

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