Prognosis and risk factors for the development of pulmonary metastases after preoperative chemoradiotherapy and radical resection in patients with locally advanced rectal cancer

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Background: Although preoperative chemoradiotherapy (CRT) followed by total mesorectal excision (TME) is currently considered effective for treating locally advanced rectal cancer (LARC), a proportion of patients develop postoperative pulmonary metastases. The current study aimed to assess the prognostic characteristics and risk factors for the development of rectal cancer pulmonary metastases after CRT and radical resection.

Methods: We retrospectively analyzed data collected on 544 consecutive patients who were diagnosed with LARC and underwent preoperative CRT followed by tumor radical resection between December 2003 and June 2014. Overall survival (OS), disease-free survival (DFS), and pulmonary metastasis rates were calculated and compared among the subgroups, and risk factors for pulmonary metastases were identified by Cox models.

Results: A total of 61 (11.2%) patients developed pulmonary metastases postoperatively, 45 of whom (73.8%) developed the condition in the first 24 months. The 1-, 2-, and 3-year pulmonary metastasis rates were 6.7%, 10.4%, and 11.7%, respectively. Compared with the disease-free group, the pulmonary metastases group had a significantly lower proportion of downstaging and pathological complete regression (pCR) rate and a significantly higher proportion of low rectum tumor. In multivariate analysis, a distance of the tumor ≤5 cm from the anal verge [hazard ratio (HR), 1.394; 95% confidence interval (CI), 1.211–3.736; P=0.003] was identified as an independent negative predictor of the 3-year pulmonary metastasis rate, and N0 stage (HR, 0.490; 95% CI, 0.261–0.919; P=0.026) and TNM downstaging (HR, 0.514; 95% CI, 0.265–0.997; P=0.049) were identified as independent positive predictors of the 3-year pulmonary metastasis rate.

Conclusions: Pulmonary metastases warranted a more intensive follow-up in patients with low rectal cancer, lymph node metastases and poor response after preoperative CRT and radical tumor resection.

Keywords: Local advanced rectal cancer; pulmonary metastasis; preoperative chemoradiotherapy; risk factors; prognosis

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Introduction

Colorectal cancer (CRC) is the third most common cancer and one of the leading causes of cancer death and seriously decreases life expectancy worldwide and in China (1,2). The lungs are the most common extra-abdominal organ in which CRC metastasizes (3). In recent years, with the development of the increasing accuracy and widespread use of chest computed tomography (CT) at the initial diagnosis and follow-up, the proportion of CRC patients diagnosed with pulmonary metastasis is increasing, and is approximately 24.5% to 29.2% (1,4-10). Moreover, previous studies have reported that patients with rectal cancer are more likely to develop pulmonary metastasis than those with colon cancer (3,10). Therefore, the diagnosis and treatment of rectal cancer pulmonary metastases is an extremely important clinical problem.

Preoperative chemoradiotherapy (CRT) followed by total mesorectal excision (TME) is currently considered the standard treatment for locally advanced rectal cancer (LARC) (11-15). Oncological outcomes have been found to be satisfactory with this strategy, achieving a 66% to 75% 5-year overall survival (OS) rate with a low local recurrence rate between 6% and 8% (11,12,16). Moreover, 15% to 20% of affected patients were able to obtain a pathological complete response (pCR) (17-19). Nevertheless, we previously reported that approximately 20% of patients failed to benefit from preoperative CRT and developed postoperative distant metastasis, in which over 50% of metastatic organs were the lungs (20). Compared with liver or peritoneal metastasis, pulmonary metastasis has a relatively slower growth rate and a better overall prognosis (21), indicating different metastasis patterns warrant different treatment strategies. However, few studies have evaluated the characteristics of pulmonary metastasis after CRT followed by TME in LARC patients, and this issue therefore needs further description and study.

In this study, we aimed to assess the clinical and prognostic characteristics and risk factors for the development of rectal cancer pulmonary metastases after preoperative CRT and TME to determine the clinical implications of rectal pulmonary metastases among patients who undergo curative treatment.

Methods

Patient selection

This study included a total of 577 consecutive patients with rectal cancer who underwent preoperative CRT followed by TME from December 2003 through June 2014 at Sun Yat-sen University Cancer Center, China. The following inclusion criteria were used: (I) histologically confirmed rectal adenocarcinoma; (II) cT3-4 or N+ disease before CRT; (III) no other anti-tumor therapy was received before CRT; and (IV) no distant metastatic disease before TME. Thirty-one patients were excluded from this study due to distant metastatic disease before CRT, and an additional two patients who were confirmed to have adenosquamous carcinoma were also excluded. This left a total of 544 individuals who were included in the analysis. The patient demographics, tumor characteristics, neoadjuvant chemotherapy cycles, radiotherapy doses, surgery records and follow-up results were carefully reviewed. The present study was performed according to the ethical standards of the World Medical Association Declaration of Helsinki and approved by the Institutional Review Board and Independent Ethics Committees of Sun Yat-sen University Cancer Center. The informed consent requirement was waived based on the nature of this retrospective study, in which patient data were kept confidential.

Treatment

Neoadjuvant chemotherapy with XELOX (oxaliplatin 130 mg/m^2 administered intravenously on day 1 and capecitabine 1000 mg/m^2 administered orally twice daily on days 1–14 for a 3-week cycle) or a modified FOLFOX6 (oxaliplatin 85 mg/m^2 in a 2-h infusion, bolus fluorouracil 400 mg/m^2 on day 1, and a 46-h infusion of fluorouracil 2,400 mg/m^2) regimen. All patients received concurrent radiotherapy of 50 Gy delivered over 5 weeks in fractions of 2.0 Gy daily on 5 consecutive days per week. All patients underwent resection of the primary tumor with lymph node dissection based on the TME technique 6–8 weeks after the completion of preoperative radiotherapy. Lateral pelvic lymph node dissection was not routinely performed except in cases of valid imaging evidence. Adjuvant chemotherapy, including XELOX and modified FOLFOX6 regimens, was scheduled to begin within 3–6 weeks postoperatively. The treatment strategy and operability of pulmonary metastases for each patient were determined according to the final agreement of the multidisciplinary team (MDT).

Definition and measurements

Pathological assessments and staging of the resected specimens were confirmed according to tumor-node-

metastasis (TNM) classification by two independent pathologists. pCR was defined as the absence of viable tumor cells, with only fibrotic masses or acellular mucin pools present in proximity to the primary tumor and lymph nodes. Pulmonary metastasis diagnosis was mainly dependent on radiological evidence suggestive of pulmonary metastasis. Findings on CT were agreed upon by at least two independent radiologists. Pulmonary metastases group included the patients with only pulmonary metastases or concurrent extrathoracic metastases at the first disease progression after surgery. Other recurrence group included patients with other extrathoracic metastases or local recurrence without pulmonary metastases at the first disease progression after surgery. The response was defined according to response evaluation criteria in solid tumors (RECIST) standard 1.1.

Follow-up

Overall survival (OS) was defined as the interval from the date of surgery until death of any cause or the last follow-up; patients without any event (metastasis or death) at the last follow-up date were censored. Disease-free survival (DFS) was defined as the interval from surgery to disease recurrence, death, or the last follow-up. The pulmonary metastasis rate was defined as the cumulative incidence of pulmonary metastasis. All patients were observed through subsequent visits every 3 months for 2 years and then semiannually until 3 years after surgery. Physical examination, blood tests for carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) levels, abdominal ultrasonography, and chest X-rays were conducted every 3 months postoperatively. Chest/abdominal/pelvic computed tomography (CT) and colonoscopy were performed annually. The last follow-up visit was performed in December 2018.

Statistical analysis

All statistical analyses were performed using IBM SPSS statistics software, version 21.0 (IBM Corp., Armonk, NY, USA). Categorical variables were given as percentages and compared using the Chi-square or Fisher's exact test when appropriate. The OS, DFS and pulmonary metastasis rates were estimated with the Kaplan-Meier method, and the differences between groups were then assessed with the log-rank test. Parameters for which P<0.05 for the 3-year pulmonary metastasis rate in the univariate Cox models were further assessed in multivariate Cox models using a forward stepwise method. Hazard ratios (HRs) and 95% confidence intervals (CIs) were subsequently calculated. In addition, patients in other recurrence groups were excluded from the univariate and multivariate Cox models. All of the statistical tests were two-sided, and P<0.05 was considered significant.

Results

Characteristics of the whole study population

Among the total of 544 patients, 361 (66.4%) were males, and 183 (33.6%) were females, and they had a median age of 55 years old (range, 19–85 years old). With respect to postoperative pathological staging, 377 (69.3%) patients were identified as downstaging, of which 132 (24.3%) patients were identified as pCR. There were 442 patients who received adjuvant chemotherapy after surgery resection. The patients were followed for a median of 36.9 months (range, 8.0–130.0 months). Overall, 96 (17.6%) patients died from the disease, 27 (5.2%) were alive with recurrence, and 421 (77.4%) were disease-free at the end of follow-up. In total, 123 (22.6%) patients developed postoperative metastases or local recurrence during the study period, including 61 (52.0%) with pulmonary metastases, 31 (25.2%) with liver metastases, 11 (8.9%) with extensive dissemination of the abdominal cavity, 8 (6.5%) with bone metastases, 7 (5.7%) with brain metastases and 5 (4.1%) with local recurrence.

Survival analysis

As shown in *Figure 1A*, the 3-year OS and DFS rates were 91.5% and 89.3%, respectively, in the entire study population. As shown in *Figure 1B*, the 3-year OS rates were significantly lower in the pulmonary metastases group than in the disease-free group but similar between the pulmonary metastases group and other recurrence group (53.7% *vs.* 97.1%; P<0.001; 53.7% *vs.* 44.9%; P=0.93).

Characteristics of patients who developed pulmonary metastases

The median time to development of pulmonary metastases from surgery was 13.0 months (range, 3.0–52.0 months). Forty-five (80.3%) patients developed pulmonary only metastasis, while 12 (19.7%) patients developed concurrent

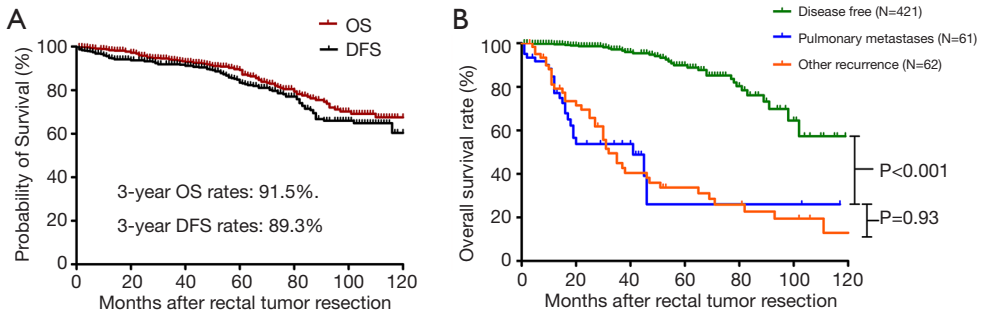

Figure 1 Kaplan-Meier curves of the patients with locally advanced rectal cancer (LARC) receiving preoperative chemoradiotherapy. (A) The whole study population; (B) comparison of overall survival (OS) among the disease free group, pulmonary metastases group and the other recurrence group.

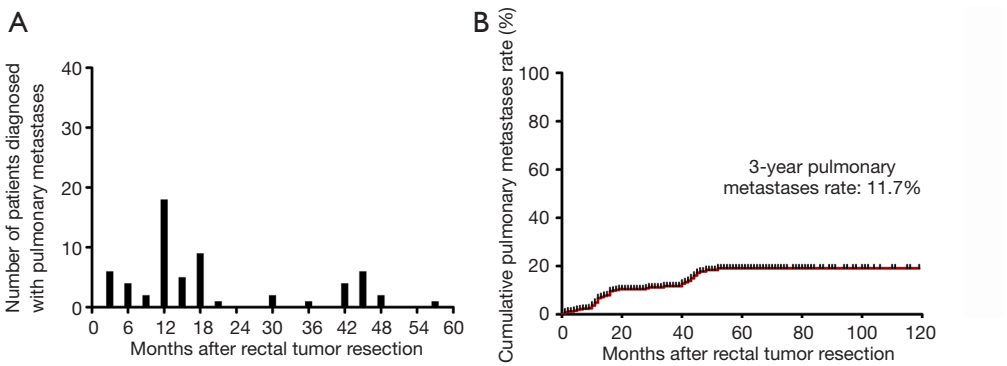

Figure 2 Description of the development of pulmonary metastases in the patients over time after rectal tumor resection. (A) The number of the patients diagnosed with pulmonary metastases after rectal tumor resection over time; (B) cumulative pulmonary metastases rate of the patients diagnosed with pulmonary metastases over time (patients developing other postoperative recurrence were excluded).

extrathoracic metastases or local recurrence, including 8 patients with liver metastases, 2 with brain metastases, and 2 with local recurrence. Among them, 25 patients (41.0%) presented unilateral pulmonary metastasis, while 36 patients (59.0%) had bilateral pulmonary metastases. Forty-two patients (68.9%) received chemotherapy as the treatment for pulmonary metastases and 11 patients (18.0%) received surgery or ablation. The association between number of patients diagnosed with pulmonary metastases and the time after surgery is shown in *Figure 2A*; we found that the highest peak was during 12 to 18 months and the second peak was during 42 to 48 months. Forty-five patients (73.8%) developed pulmonary metastases in the first 24 months. In *Figure 2B*, the 1-, 2-, 3-, and 5-year pulmonary metastasis rates were 6.7%, 10.4%, 11.7%, and 19.1%, respectively.

Relationships between the development of rectal cancer pulmonary metastases and clinicopathological characteristics

The clinicopathological and treatment information of all patients are summarized in *Tables 1,2*. The proportion of patients with tumors ≤5 cm from the anal verge was higher in patients in the pulmonary metastases group than in the disease-free group (78.7% *vs.* 52.3%; P=0.001) or the other recurrence group (78.7% *vs.* 59.7%; P=0.045). Patients in the pulmonary metastases group were less likely to have completed neoadjuvant chemotherapy (receiving only 1–2 cycles) than were those in the disease-free group (72.1% *vs.* 53.9%; P=0.026). TNM downstaging rate, response rate and pCR rate were lower in patients in the pulmonary metastases group than in those in the disease-

Table 1 Comparison of characteristics of the patients with disease free or with pulmonary metastases

Variables	Disease free (n=421) (%)	Pulmonary metastases (n=61) (%)	P value
Age at surgery (years)			1.000
≤60	280 (66.5)	40 (65.6)	
>60	141 (33.5)	21 (34.4)	
Gender			0.488
Male	285 (67.7)	38 (62.3)	
Female	136 (32.3)	23 (37.7)	
Post-CRT BMI (kg/m^2)			0.418
<18.5	46 (10.9)	10 (16.4)	
18.5–25.0	297 (70.5)	39 (63.9)	
>25.0	78 (18.6)	12 (19.7)	
Post-CRT tumor size (cm)			0.997
≤4	356 (84.6)	51 (83.6)	
>4	65 (15.4)	10 (16.4)	
Distance of the tumor from anal verge (cm)			0.001
≤5	220 (52.3)	48 (78.7)	
>5	201 (47.7)	13 (21.3)	
Tumor differentiation			0.323
Well/moderate	332 (78.9)	52 (85.2)	
Poor/undifferentiated	89 (21.1)	9 (14.8)	
Radiotherapy dose (Gy)			0.301
<50	194 (46.1)	33 (54.1)	
≥50	227 (53.9)	28 (45.9)	
Cycles of chemotherapy			0.026
≤2	227 (53.9)	44 (72.1)	
>2	194 (46.1)	17 (27.9)	
ypT stage			0.001
T0	125 (29.7)	6 (9.8)	
T1	16 (3.8)	1 (1.6)	
T2	95 (22.6)	11 (18.0)	
T3	128 (30.4)	27 (44.3)	
T4	57 (13.5)	16 (26.2)	
Numbers of resected lymph nodes			0.722
<12	340 (80.8)	51 (83.6)	
≥12	81 (19.2)	10 (16.4)	
ypN stage			<0.001
N0	348 (82.7)	31 (50.8)	
N1	59 (14.0)	23 (37.7)	
N2	14 (3.3)	7 (11.5)	

Table 1 (*Continued*)

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Variables	Disease free (n=421) (%)	Pulmonary metastases (n=61) (%)	P value
ypTNM stage			<0.001
0	120 (28.5)	6 (9.8)	
I	97 (23.0)	5 (8.2)	
II	131 (31.1)	20 (32.8)	
III	73 (17.4)	30 (49.2)	
TNM stage degrade			<0.001
Yes	322 (76.5)	24 (39.3)	
No	99 (23.5)	37 (60.7)	
Treatment evaluation			0.037
CR	19 (4.5)	3 (4.9)	
PR	240 (57.0)	23 (37.7)	
SD	159 (37.8)	34 (55.7)	
PD	3 (0.7)	1 (1.6)	
Interval between completion of CRT and surgery (weeks)			1.000
≤8	281 (66.7)	41 (67.2)	
>8	140 (33.3)	20 (32.8)	
Surgical procedure			0.784
LAR or CAA	257 (61.0)	35 (57.4)	
APR	144 (34.2)	22 (36.1)	
Hartmann	20 (4.8)	4 (6.6)	
Surgical complications[#]			0.528
Anastomotic leakage	18 (3.3)	1 (0.2)	
Delayed wound union	17 (3.1)	6 (1.1)	
Others*	18 (3.3)	8 (1.5)	
Preoperative (post-CRT) serum CEA (ng/mL)			<0.001
≤5	400 (95.0)	48 (78.7)	
>5	21 (5.0)	13 (21.3)	
Preoperative (post-CRT) serum CA19-9 (U/mL)			0.519
≤35	195 (46.3)	25 (41.0)	
>35	226 (53.7)	36 (59.0)	
Adjuvant chemotherapy			0.969
Yes	343 (81.5)	49 (80.3)	
No	78 (18.5)	12 (19.7)	

[#], there were totally 53 patients (9.7%) in disease free group and 15 patients (2.8%) in pulmonary metastases group developing surgical complications; *, other surgical complications include anastomotic bleeding, obstruction, perforation, sexual dysfunction, defecation disorder, Uropoiesis dysfunction. CRT, chemoradiotherapy; BMI, body mass index; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; LAR, low anterior resection; CAA, Coloanal Anastomosis; APR, Abdominoperineal Resection; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9.

Table 2 Comparison of characteristics of the patients grouped by different metastatic pattern

Variables	Pulmonary metastases (n=61) (%)	Other recurrence (n=62) (%)	P value
Age at surgery (years)			0.949
≤60	40 (65.6)	42 (67.7)	
>60	21 (34.4)	20 (32.3)	
Gender			1.000
Male	38 (62.3)	38 (61.3)	
Female	23 (37.7)	24 (38.7)	
Post-CRT BMI (kg/m^2)			0.998
<18.5	10 (16.4)	10 (16.1)	
18.5–25.0	39 (63.9)	40 (64.5)	
>25.0	12 (19.7)	12 (19.4)	
Post-CRT tumor size (cm)			0.395
≤4	51 (83.6)	47 (75.8)	
>4	10 (16.4)	15 (24.2)	
Distance of the tumor from anal verge (cm)			0.045
≤5	48 (78.7)	37 (59.7)	
>5	13 (21.3)	25 (40.3)	
Tumor differentiation			0.002
Well/moderate	52 (85.2)	36 (58.1)	
Poor/undifferentiated	9 (14.8)	26 (41.9)	
Radiotherapy dose (Gy)			0.794
<50	33 (54.1)	36 (58.1)	
≥50	28 (45.9)	26 (41.9)	
Cycles of chemotherapy			0.889
≤2	44 (72.1)	43 (69.4)	
>2	17 (27.9)	19 (30.6)	
ypT stage			0.167
T0	6 (9.8)	8 (12.9)	
T1	1 (1.6)	1 (1.6)	
T2	11 (18.0)	3 (4.8)	
T3	27 (44.3)	26 (42.0)	
T4	16 (26.3)	24 (38.7)	
Numbers of resected lymph nodes			0.847
<12	51 (83.6)	50 (83.9)	
≥12	10 (16.4)	12 (16.1)	
ypN stage			0.568
N0	31 (50.8)	37 (59.7)	
N1	23 (37.7)	18 (29.0)	
N2	7 (11.5)	7 (11.3)	

Table 2 (*Continued*)

Table 2 (*Continued*)

Variables	Pulmonary metastases (n=61) (%)	Other recurrence (n=62) (%)	P value
ypTNM stage			0.659
0	6 (9.8)	6 (9.7)	
I	5 (8.2)	4 (6.5)	
II	20 (32.8)	27 (43.5)	
III	30 (49.2)	25 (40.3)	
TNM stage degrade			0.235
Yes	24 (39.3)	31 (50.0)	
No	37 (60.7)	31 (50.0)	
Treatment evaluation			0.582
CR	3 (4.9)	1 (1.6)	
PR	23 (37.7)	28 (45.2)	
SD	34 (55.7)	31 (50.0)	
PD	1 (1.6)	2 (3.2)	
Interval between completion of CRT and surgery (weeks)			0.514
≤8	41 (67.2)	46 (74.2)	
>8	20 (32.8)	16 (25.8)	
Surgical procedure			0.208
LAR or CAA	35 (57.4)	26 (41.9)	
APR	22 (36.1)	30 (48.4)	
Hartmann	4 (6.6)	6 (9.7)	
Surgical complications[#]			0.326
Anastomotic leakage	1 (0.2)	4 (0.7)	
Delayed wound union	6 (1.1)	2 (0.3)	
Others*	8 (1.5)	3 (0.5)	
Preoperative (post-CRT) serum CEA (ng/mL)			0.613
≤5	48 (78.7)	52 (83.9)	
>5	13 (21.3)	10 (16.1)	
Preoperative (post-CRT) serum CA19-9 (U/mL)			0.916
≤35	25 (41.0)	27 (43.5)	
>35	36 (59.0)	35 (56.5)	
Adjuvant chemotherapy			1.000
Yes	49 (80.3)	50 (80.6)	
No	12 (19.7)	12 (19.4)	

Notes: other recurrence group includes patients with other extrathoracic metastases or local recurrence as the first disease progression after surgery. [#], there were totally 15 patients (2.8%) in pulmonary metastases group and 9 patients (1.5%) in other recurrence group developing surgical complications; *, other surgical complications include anastomotic bleeding, obstruction, perforation, sexual dysfunction, defecation disorder, Uropoiesis dysfunction. CRT, chemoradiotherapy; BMI, body mass index; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; LAR, low anterior resection; CAA, coloanal anastomosis; APR, abdominoperineal resection; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9.

Table 3 Uni- and multivariate analysis of risk factors for pulmonary metastases [3-year pulmonary metastasis rate (%)] after neoadjuvant chemoradiotherapy and R0 resection of locally advanced rectal cancer

Variables	3-year pulmonary metastasis rate (%)	Univariate analysis		Multivariate analysis	
		HR (95%CI)	P value	HR (95%CI)	P value
Age at surgery, year (>60 *vs.* ≤60)	12.5 *vs.* 12.9	0.939 (0.554–1.593)	0.817	–	–
Gender (male *vs.* female)	11.8 *vs.* 14.5	1.249 (0.744–2.096)	0.400	–	–
Post-CRT BMI, kg/m^2 (<18.5 *vs.* ≥18.5)	17.9 *vs.* 12.0	0.673 (0.342–1.325)	0.252	–	–
post-CRT tumor size, cm (>4 *vs.* ≤4)	12.5 *vs.* 13.0	0.916 (0.510–2.115)	0.916	–	–
Distance of the tumor from anal verge, cm (≤5 *vs.* >5)	17.9 *vs.* 6.1	*1.332 (1.180–3.613)*	*0.001*	1.394 (1.211–3.736)	0.003
Differentiation (poor *vs.* well/moderate)	13.5 *vs.* 9.2	0.654 (0.323–1.327)	0.239	–	–
Radiotherapy dose, Gy (<50 *vs.* ≥50)	14.5 *vs.* 11.0	0.982 (0.584–1.650)	0.945	–	–
Cycles of chemotherapy (0–2 *vs.* >2)	16.2 *vs.* 8.1	0.863 (0.445–1.673)	0.663	–	–
ypT stage (T0 *vs.* T1–4)	4.6 *vs.* 15.7	*0.277 (0.119–0.643)*	*0.003*	0.477 (0.194–1.172)	0.107
Numbers of resected lymph nodes (<12 *vs.* ≥12)	12.9 *vs.* 10.3	0.751 (0.369–1.527)	0.429	–	–
ypN stage (N0 *vs.* N1–2)	8.2 *vs.* 29.1	*0.243 (0.147–0.402)*	*0.001*	*0.490 (0.261–0.919)*	*0.026*
TNM stage degrade (yes *vs.* no)	6.9 *vs.* 27.2	*0.242 (0.145–0.404)*	*0.001*	*0.514 (0.265–0.997)*	*0.049*
Treatment reaction (CR + PR *vs.* SD + PD)	9.2 *vs.* 17.8	*0.541 (0.325–0.898)*	*0.018*	0.777 (0.456–1.323)	0.353
Anastomotic leakage (yes *vs.* no)	10.5 *vs.* 13.0	0.368 (0.051–2.658)	0.322	–	–
Delayed wound union (yes *vs.* no)	23.8 *vs.* 12.1	*2.409 (1.037–5.597)*	*0.041*	1.473 (0.618–1.473)	0.382
Interval between completion of CRT and surgery, weeks (≤8 *vs.* >8)	13.2 *vs.* 12.2	1.215 (0.708–2.085)	0.479	–	–
Preoperative serum CEA, ng/mL (>5 *vs.* ≤5)	12.2 *vs.* 14.4	0.807 (0.447–1.460)	0.487	–	–
Preoperative serum CA19-9, U/mL (>35 *vs.* ≤35)	16.9 *vs.* 11.9	1.549 (0.838–2.864)	0.162	–	–
Adjuvant chemotherapy (yes *vs.* no)	12.5 *vs.* 13.3	0.951 (0.506–1.788)	0.876	–	–

Notes: 62 patients with other extrathoracic metastases or local recurrence as the first disease progression after surgery (other recurrence group) were excluded. CRT, chemoradiotherapy; BMI, body mass index; CR, complete response; PR, partly response; SD, stable disease; PD, progressive disease CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; HR, hazard ratio; CI, confidence interval.

free group (39.3% *vs.* 76.5%; P<0.001; 42.6% *vs.* 61.5%; P=0.037; 9.8% *vs.* 28.5%; P<0.001), while the rates were similar between the pulmonary metastases group and other recurrence group. There were more patients in the pulmonary metastases group with a preoperative post-CRT serum CEA level >5 ng/mL than were found in the disease-free group (21.3% *vs.* 5.0%; P<0.001). Patients in the pulmonary metastases group had better tumor differentiation than was found in those in other recurrence group (85.2% *vs.* 58.1%; P=0.002). There were no significant differences in age, sex, post-CRT BMI, tumor size, the radiotherapy dose, the number of resected lymph nodes, the interval between CRT and surgery, the surgery procedure type, surgical complications, preoperative post-CRT serum CA19-9 levels, or the adjuvant chemotherapy rate.

Prognostic analysis of clinical factors

As shown in *Table 3*, univariate analysis revealed that the distance of the tumor from the anal verge, ypT stage, ypN stage, TNM downstaging, response, and wound delayed

union were significant risk factors for the 3-year pulmonary metastasis rate. In the multivariate analysis, a distance of the tumor from anal verge ≤5 cm (HR, 1.394; 95% CI, 1.211–3.736; P=0.003) was identified as an independent negative predictor of the 3-year pulmonary metastasis rate, and the N0 stage (HR, 0.490; 95% CI, 0.261–0.919; P=0.026) and TNM downstaging (HR, 0.514; 95% CI, 0.265–0.997; P=0.049) were identified as independent positive predictors of the 3-year pulmonary metastasis rate.

Discussion

In this retrospective study, we investigated risk factors for the development of rectal cancer pulmonary metastases after preoperative CRT and TME. We found that patients with low rectal cancer, lymph node metastases and a poor response to preoperative CRT were more likely to develop pulmonary metastasis.

The benefit of neoadjuvant CRT in decreasing local recurrence and distant metastases has been well-established and was reported by Sauer *et al.* (11). In the present study, significantly higher proportions of downstaging and pCR were found in the disease-free group than in the pulmonary metastases group. Moreover, downstaging was identified as an independent positive predictor of the 3-year pulmonary metastasis rate in the multivariate analysis, showing that the response to neoadjuvant CRT is associated with a reduced risk of developing pulmonary metastases after surgery. As reported by Lu *et al.* (22), the estimated 5-year OS was significantly better in responders than in non-responders (94% *vs.* 68%, P=0.001), and there was also a significant difference in the 3-year DFS between the two groups (93% *vs.* 68%, P=0.000). Most studies suggest that there are improved outcomes with tumor regression and complete remission to preoperative therapy (23-27). A randomized trial that compared patients with pCR to patients with non-pCR showed that the 5-year disease-specific survival increased from 78.0% to 95.8% (28). Chemoradiotherapy leads to microvascular damage and fibrosis of the tumor, blocking the pathway leading to pulmonary metastasis. One explanation for the good prognosis observed after pCR is that it is indicative of a prognostically favorable biological tumor profile with a lower propensity for local recurrence and distant metastases and better survival than is achieved in patients with a lesser response (29).

Patients with primary tumors located in the low rectum or lymph node metastases had a higher risk of developing pulmonary metastases in our study. A study of 10,398 CRC survivors found that the highest risk factors associated with recurrent CRC isolated pulmonary metastases were a low location of a rectal tumor and positive lymph nodes (30). Ding *et al.* showed that the tendency to develop pulmonary metastases was significantly higher for a low location of rectal tumors than for a higher location of rectal tumors (31). The reason that low rectal tumors are related to a higher pulmonary metastases rate is probably associated with the anatomical structure. The distal rectum drains into the inferior rectal vein, which drains directly into the inferior vena cava so that blood quickly reaches the lungs without passing the portal venous system. Several studies have reported the lymph node ratio (ratio of metastatic lymph nodes to resected lymph nodes) is a predictor of distant metastases after resection of rectal cancer with or without preoperative chemoradiotherapy (32-34). Interestingly, mediastinal lymph node metastases at the time of pulmonary metastasectomy have been shown to have an adverse effect on prognosis (35). Tumor cells may pass directly into lung tissue via the vena cava, and the lymphatic system is another potential route. Local tumor progression may directly affect the incidence of pulmonary metastases in rectal cancer. Therefore, preoperative CRT can effectively reduce the risk of pulmonary metastasis but does not change the pathways associated with and risk factors of pulmonary metastasis.

According to the most recent NCCN guidelines on rectal cancer, the standard follow-up protocol for patients with LARC is chest/abdominal/pelvic CT every 6–12 months for a total of 5 years. The current study found that the incidence of pulmonary metastases rose the fastest during the period from 12–18 months after surgery. Forty-five patients (73.8%) developed pulmonary metastases in the first 24 months. Onaitis and coworkers described a series of 378 patients with colorectal tumor pulmonary metastases whose median disease-free interval was 24 months from the time of the primary operation and demonstrated that a disease-free interval of less than 12 months was an independent negative prognostic factor (36). A retrospective analysis of 153 patients showed that 40 patients (28.4%) developed pulmonary metastases in the first 12 months, and 112 patients (79.4%) developed pulmonary metastases in the first 36 months (37). A review concluded that the median disease-free interval of patients without preoperative CRT ranged from 19 to 38 months and that earlier metastasis might indicate a more aggressive disease biology and tendency to spread (38). In our study, LARC patients with pulmonary metastases after preoperative CRT presented some characteristics, such as a shorter disease-free interval,

a high proportion (19.7%) of concurrent extrathoracic metastases or local recurrence and a high proportion (59.0%) of bilateral multiple pulmonary metastases, that indicated a prognostically unfavorable biological tumor profile. We suggest that follow-up protocols for LARC patients with a poor response to preoperative CRT should include 6-monthly chest CT examinations for at least 1–2 years after surgery, which is particularly important for patients with low tumors.

Several limitations should be acknowledged in the present study. First, this retrospective study included an uncontrolled methodology and a limited number of patients, especially for patients with pulmonary metastases, recruited from a single cohort. The findings need to be validated in future prospective clinical studies. Additionally, tumor molecular markers, such as microsatellite status, CpG island methylator phenotype (CIMP) status, BRAF mutations, and KRAS mutations, as well as tumor immune infiltration, have been linked to different recurrence risks and survival outcomes in patients with rectal cancer. Thus, it is necessary to include pathological, immunological and molecular prognostic markers for risk stratification in further studies.

In conclusion, pulmonary metastases are more likely to develop in patients with low rectal cancer, lymph node metastases and/or poor responses to preoperative CRT. Detailed preoperative comprehensive measurements might help stratify high-risk patients to identify those who warrant a more intensive follow-up within 2 years.

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Footnote

Conflicts of Interest: 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 present study was performed according to the ethical standards of the World Medical Association Declaration of Helsinki and approved by the Institutional Review Board and Independent Ethics Committees of Sun Yat-sen University Cancer Center. The informed consent requirement was waived based on the nature of this retrospective study, in which patient data were kept confidential.

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