Am J Cancer Res 2022;12(11):5095-5104
www.ajcr.us /ISSN:2156-6976/ajcr0144593

Original Article

Defining early recurrence of locally recurrent rectal cancer

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Received June 6, 2022; Accepted October 12, 2022; Epub November 15, 2022; Published November 30, 2022

Abstract: Despite advances in rectal cancer treatments, its local recurrence rate is still 4-10 percent. And an evidence-based definition of early recurrence is lacking. Our study hopes to establish a clear threshold to distinguish early and late recurrence, and analyze risk and prognostic factors for them. Rectal cancer patients who underwent proctectomy from 2009 to 2019 were included. Patients who received neoadjuvant treatment and with incomplete records were excluded. The optimal interval was obtained using the minimum *P* value approach. Risk factors for early recurrence were analyzed by logistic regression models, and prognostic factors associated with additional surgery were assessed by Cox proportional hazards models. The optimal interval for the definition of early recurrence was 26 months based on the subsequent prognosis ($P < 0.001$). The 5-year survival rate of early and late recurrence cohort was 32.5% and 57.1%, respectively ($P < 0.001$). Adjuvant radiotherapy was the independent protective factor for early recurrence. And the presence of lymphovascular invasion, positive surgical margin, and no re-neoadjuvant radiotherapy were independent prognostic factors for the survival of LRRC patients under additional surgery.

Keywords: Locally recurrent rectal cancer, early recurrence, late recurrence, survival

Introduction

Despite the advances in surgical techniques and multimodal treatments of rectal cancer, the incidence of locoregional relapse after operation is still 4-10 percent [1-3]. Locally recurrent rectal cancer (LRRC) is characterized by isolated pelvic/anastomotic recurrence of disease and without distant metastases. It was reported that only approximately 40 percent of patients with locally recurrent rectal cancer are candidates for potentially curative treatment [4]. Surgery with complete radical resection is the only curative method for this relapse, even if it requires an extensive operative procedure [5-7]. Without treatment, these patients will have a short survival complicated with ongoing pelvic pain, bleeding, and fistula to bladder or vagina, which significantly impairs quality of life [8].

Previous studies have shown that cancer patients who underwent radical resection with shorter recurrence-free interval than others were related to worse prognosis, including lung cancer, liver cancer, gastric cancer, and pancreatic cancer [9-12]. And "early recurrence (ER)" was used to represent this situation. Although ER of LRRC is regularly used in both the clinical and academic setting, a clear definition is lacking, with arbitrary threshold varying between 1 and 5 years found in the reported literatures [13-16]. Stratification of early and late recurrence (LR) according to the optimal recurrence-free interval may contribute to the treatment of recurrence. Therefore, our study objective was to find an evidence-based cut-off value to differentiate ER and LR in locally recurrent rectal cancer patients, and to identify prognostic risk factors for early recurrence after surgery.

Methods

Patients and data sources

A total of 145 patients with LRRC who underwent surgery between 2009 and 2019 were included in our study (**Figure 1**). Exclusive criteria were synchronous distant metastasis, administration of neoadjuvant therapy, loss of

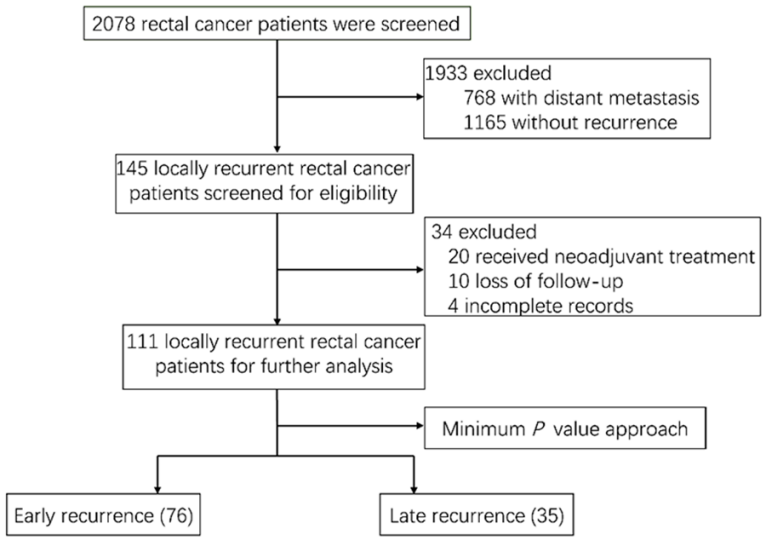

Figure 1. Flow chart of the research.

follow-up, incomplete records, and short-time postoperative mortality. Patients with short-time postoperative mortality refer to who dead from surgery for recurrence in on month, which is mostly due to surgical complications. Finally, 111 patients were further analyzed.

Treatment

All patients underwent initial surgery by gastrointestinal specialists. The treatments, tumor staging, and surveillance complied with National Comprehensive Cancer Network (NCCN) guidelines and the American Joint Committee on Cancer (AJCC) 8th edition as appropriate. Colonoscopy and abdominal and pelvic computed tomography (CT) were carried out for a surveillance program. When the local recurrence was suspected, pelvic magnetic resonance (MR) and positron emission tomography (PET) were administrated to determine the location of recurrence and the presence of distant metastasis. If imaging findings accorded with local recurrence, treatments would be discussed by the multidisciplinary team (MDT) containing surgeons, radiologists, oncologists, and pathologists. All patients who suffered from recurrence were encouraged to receive chemoradiotherapy. And surgery will be projected by at least two experienced surgeons when the tumor is resectable with curative intention.

In our study, we adopted the most used classification of recurrence pattern, which was proposed by the Leeds group in 2005 (**Table 1**) [17]. This pattern provides a systemic approach to surgical management based upon the location of the recurrence. And the survival was analyzed by three outcomes, overall survival (OS), recurrence-free survival (RFS), and post-recurrence survival (PRS). OS refers to the time from initial surgery to either last follow-up or death. RFS refers to the time from initial surgery to the date of recurrence or last follow-up if recurrence did not occur. And PRS was calculated from the time of recurrence to death or last follow-up.

Statistical analysis

Survival of potential early and late recurrence cohorts were compared using the log-rank test. The optimal threshold to differentiate ER from LR was evaluated by the minimum *P*-value approach. Parameters between ER and LR cohorts were compared using the chi-square test or t-test as appropriate. Risk factors associated with ER were determined by logistic regression models. Prognostic factors for survival of recurrence patients after surgery were analyzed by the log-rank test, and factors with a *P* value less than 0.1 were subsequently sent to the multivariable model for further analysis. A two-tailed $P < 0.05$ was considered statistically significant. And statistical analysis was performed by SPSS version 27.0 (SPSS Inc., Chicago, IL).

Results

Defining early and late recurrence

Cut-off values that divide the early and late cohort and related outcomes are shown in **Table 2**. Based on the present study, the optimal interval to distinguish early from late recurrence was 26 months ($P < 0.001$, **Table 2**; **Figure 2A**). In ER cohort, the median RFS was 14.1 months, and PRS was 23.7 months. The median RFS of LR patients was 33.4 months, while the median PRS was 35.8 months ($P = 0.04$, **Table 2**; **Figure 2B**). The median PRS of ER group was significantly shorter than LR group ($P = 0.027$). The 5-year survival rate of ER and LR groups were 32.5% and 57.1%, respectively.

Table 1. Patterns of invasion for locally recurrent rectal cancer

Central	Tumor confined to pelvic organs or connective tissue without contact onto or invasion into bone
Sacral	Tumor present in the presacral space and abuts onto or invades into the sacrum
Sidewall	Tumor involving the structures on the lateral pelvic sidewall, including the greater sciatic foramen and sciatic nerve through to piriformis and the gluteal region
Composite	Sacral and sidewall recurrence combined

Table 2. Subsequent cut-off thresholds for defining ER based on the prognosis

Subsequent cut-off values	*P* value	Potential ER cohort				Potential LR cohort			
		N	RFS (mo)	PRS (mo)	OS (mo)	N	RFS (mo)	PRS (mo)	OS (mo)
8	1.28×10^{-11}	19	3.5	18.0	22.7	92	16.3	31.2	62.7
9	1.40×10^{-12}	23	4.7	18.2	32.0	88	17.5	31.4	62.7
10	1.35×10^{-12}	25	4.7	18.7	32.3	86	18.6	31.7	63.4
11	1.02×10^{-12}	27	5.8	19.2	32.8	84	19.2	31.7	63.4
12	4.02×10^{-13}	32	5.9	19.5	34.2	79	19.7	32.1	64.2
13	2.68×10^{-13}	34	6.2	19.9	35.0	77	20.6	32.4	64.2
14	2.00×10^{-13}	37	7.9	20.1	35.8	74	21.3	32.6	68.4
15	1.54×10^{-13}	40	9.3	20.6	37.3	71	22.8	32.9	76.0
16	1.34×10^{-13}	42	9.7	20.7	37.3	69	23.0	33.2	77.5
17	1.04×10^{-14}	50	10.3	21.0	38.2	61	23.5	33.5	78.2
18	6.15×10^{-15}	52	10.7	21.4	39.6	59	24.2	33.8	78.7
19	4.37×10^{-15}	54	11.3	21.7	41.2	57	26.8	34.2	81.5
20	6.89×10^{-16}	58	11.6	21.9	41.5	53	27.4	34.6	83.7
21	4.18×10^{-16}	60	12.4	22.2	41.7	51	28.3	35.0	84.7
22	5.64×10^{-17}	64	12.9	22.4	42.4	47	29.5	35.1	83.7
23	9.64×10^{-17}	67	13.2	22.7	42.2	44	30.6	35.3	85.4
24	7.92×10^{-18}	71	13.5	23.0	42.9	40	31.2	35.3	82.7
25	2.05×10^{-18}	75	13.8	23.5	42.9	36	32.3	35.5	84.2
26	4.89×10^{-19}	76	14.1	23.7	43.7	35	33.4	35.8	83.7
27	4.93×10^{-19}	79	14.7	24.1	45.6	32	35.6	36.5	85.4
28	5.17×10^{-19}	81	15.3	24.2	47.3	30	36.7	37.3	86.1
29	7.99×10^{-19}	83	15.8	24.7	48.5	28	37.9	38.5	87.7
30	6.48×10^{-19}	84	16.2	25.3	47.9	27	40.3	39.2	89.2
31	1.09×10^{-18}	87	16.7	25.7	48.7	24	41.6	39.6	94.1
34	1.24×10^{-18}	88	17.0	25.9	49.1	23	42.7	40.0	96.6
36	1.96×10^{-18}	90	17.4	26.1	49.5	21	44.6	40.8	101.1
44	2.13×10^{-18}	92	17.9	26.5	50.5	19	45.8	40.9	117.2
45	3.86×10^{-17}	94	18.3	26.8	49.5	17	47.2	41.0	126.7
47	8.13×10^{-17}	95	18.6	27.0	49.5	16	48.5	41.3	143.5
48	8.33×10^{-17}	96	19.1	27.3	50.5	15	49.3	42.5	160.2
53	8.86×10^{-17}	98	19.7	28.2	51.7	13	50.7	57.8	179.5
56	1.96×10^{-16}	99	20.3	28.9	52.0	12	51.2	58.4	193.2
77	2.24×10^{-16}	101	20.5	30.2	52.2	10	53.6	58.4	206.9
100	2.66×10^{-14}	103	20.8	31.9	52.4	8	54.8	59.9	219.0

Clinicopathological characteristics of recurrent patients are shown in **Table 3**. ER patients were more frequently to have tumors with poorly histological differentiation, positive lymph nodes, and lymphovascular invasion. Furthermore, LR patients more often received adjuvant radio-

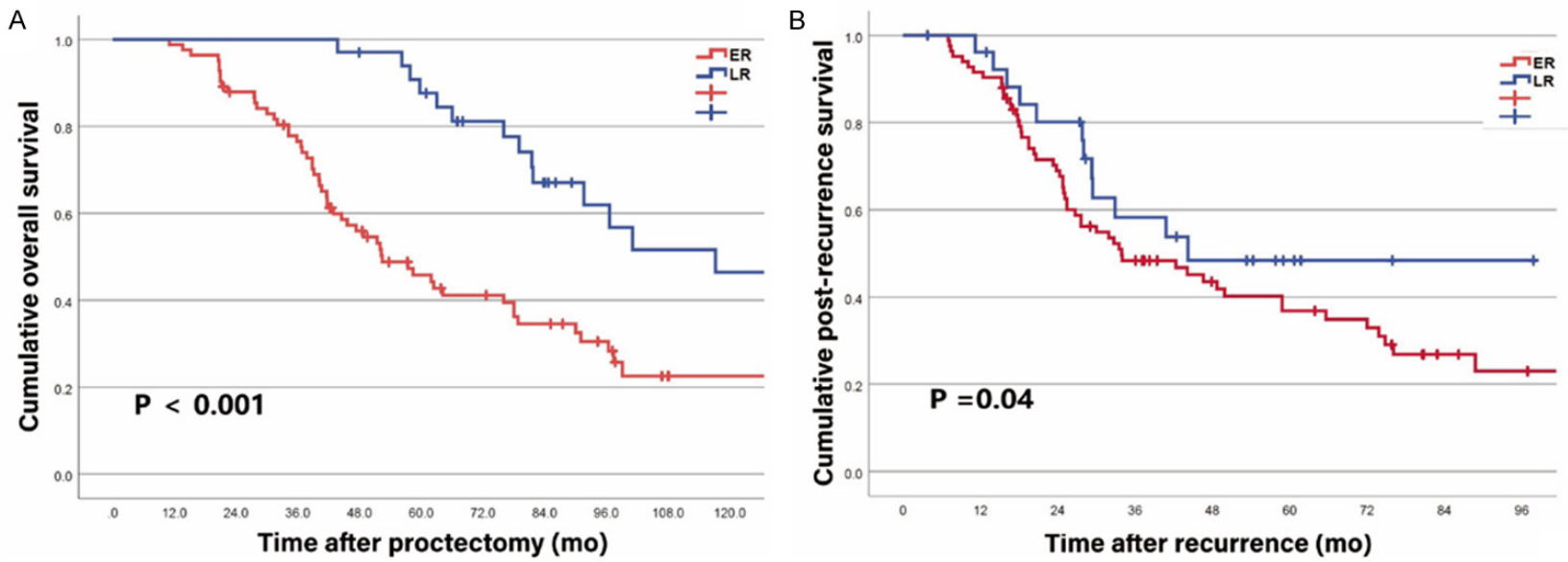

Figure 2. A. The overall survival curves between the early recurrence and late recurrence groups ($P < 0.001$); B. The post-recurrence survival curves between the early and late recurrence groups ($P = 0.04$).

Table 3. Clinicopathological characteristics of LRRC patients

Variable	ER (n = 76)	LR (n = 35)	*P* value
Age			0.42
≥ 65	21	5	
< 65	62	23	
Gender			0.55
Female	38	11	
Male	45	17	
Differentiation			0.003
Well-moderate	48	10	
Poor	14	6	
pT stage			0.72
T1	6	2	
T2	7	3	
T3	19	3	
T4	31	9	
Lymph nodes			0.006
Positive	53	9	
Negative	26	16	
Stage			
I	10	4	0.38
II	15	2	
III	53	9	
Lymphovascular invasion			0.03
Positive	31	4	
Negative	29	14	
Adjuvant chemotherapy			0.72
Yes	62	18	
No	14	5	
Adjuvant radiotherapy			< 0.001
Yes	10	14	
No	66	9	
Recurrence pattern			0.56
Central	61	23	
Sacral	17	3	
Sidewall	4	1	
Composite	1	1	

therapy, but there was no significant difference between the two cohorts in the proportion of receiving adjuvant chemotherapy.

Characteristics associated with ER

Univariable and multivariable analysis of characteristics associated with ER are presented in **Table 4**. For univariable analysis, poorly differentiation (OR 1.34, 95% CI 0.03-1.50, *P* = 0.01), positive lymph nodes (OR 3.62, 95% CI 1.41-9.29, *P* = 0.007), presence of lymphovascular invasion (OR 3.74, 95% CI 1.10-12.63, *P* = 0.03), and without radiotherapy (OR 0.10, 95% CI 0.03-0.28, *P* < 0.001) enhanced the likelihood of early recurrence. Furthermore, only the administration of radiotherapy showed a significant difference in multivariable analysis (OR 0.17, 95% CI 0.01-0.58, *P* = 0.014).

Prognostic factors for survival

Pre- and postoperative clinicopathological variables associated with survival are presented in **Table 5**. For univariate analysis, the presence of lymphovascular invasion was a powerful prognostic factor, and it enhanced the risk of death 4.16 times (95% CI 2.22-7.79, *P* < 0.001). A positive surgical margin also increased the likelihood of early death (HR 2.01, 95% CI 0.56-2.80, *P* < 0.001). And re-neoadjuvant chemotherapy and radiotherapy were protective factors for survival (HR 0.60, 95% CI 0.36-0.97, *P* = 0.04; HR 0.33, 95% CI 0.04-1.16, *P* = 0.03, respectively). Furthermore, these factors were sent forward for multivariable analysis. Lymphovascular invasion (HR 0.28, 95% CI 0.14-0.58, *P* < 0.001), positive surgical margin (HR 1.97, 95% CI 0.68-3.57, *P* < 0.001), and re-neoadjuvant radiotherapy (HR 0.41, 95% CI 0.21-2.41, *P* = 0.04) remained statistical difference, which were independent prognostic factors for survival.

Discussion

Over the past decades, the survival of rectal cancer patients improved significantly because of advances in radiotherapy, chemotherapy, and especially in surgical management [18-20]. And following the introduction of preoperative radiotherapy and total mesorectal excision (TME) technique, the local recurrence rate has decreased dramatically. Despite of these, local recurrence still occurs in about 4-10% of rectal cancer patients [21-23]. And for patients who failed to receive preoperative treatment or operated by less experienced surgeons, this rate may be higher. The recurrence of rectal cancer had a significant effect on the quality of life. It was not only because of the aspect of the disease, but also for its psychological and social aspects [8]. We

Table 4. Risk factors associated with early recurrence

Variable	Univariable			Multivariable		
	Odds ratio	95% CI	*P* value	Odds ratio	95% CI	*P* value
Age						
< 65	Ref					
≥ 65	1.56	0.53-4.61	0.42			
Gender						
Female	Ref					
Male	1.31	0.55-3.12	0.55			
Differentiation						
Well-moderate	Ref			Ref		
Poor	1.34	0.03-1.50	0.01	1.06	0.01-1.19	0.07
pT stage						
T1	Ref					
T2	1.15	0.20-6.70	0.54			
T3	1.23	0.13-2.26	0.88			
T4	1.48	0.32-6.90	0.62			
Lymph nodes						
Negative	Ref			Ref		
Positive	3.62	1.41-9.29	0.007	1.38	0.11-17.21	0.80
Stage						
I	Ref					
II	0.79	0.15-4.03	0.77			
III	1.36	0.61-9.15	0.22			
Lymphovascular invasion						
Negative	Ref			Ref		
Positive	3.74	1.10-12.63	0.03	2.52	0.85-19.63	0.06
Adjuvant chemotherapy						
Yes	Ref					
No	1.23	0.39-3.87	0.72			
Adjuvant radiotherapy						
No	Ref			Ref		
Yes	0.10	0.03-0.28	< 0.001	0.17	0.01-0.58	0.014
Recurrence pattern						
Central	0.38	0.02-6.28	0.50			
Sacral	0.25	0.01-8.56	0.44			
Sidewall	0.176	0.01-3.65	0.27			
Composite	Ref					

commonly use the term “early recurrence” to describe the patients who suffered from recurrence with shorter recurrence-free survival than others, and these patients frequently have worse prognosis. But how to define ER is not clear yet. The present study found that the optimal interval is 26 months. And the administration of adjuvant radiotherapy was an independent protective factor associated with a reduced likelihood of ER. For the treatment of LRRC, lymphovascular invasion, positive surgical margin, and re-neoadjuvant radiotherapy were independent prognostic factors for survival after the additional surgery.

Although “early recurrence” is frequently used in clinical practice, the optimal interval from initial proctectomy to local recurrence is lacking. Some efforts have been made to define ER in published articles. Many investigators defined recurrence less than one year after the operation as ER [13, 14]. Mahdi et al. used two years

Table 5. Prognostic factors associated with LRRC patients received surgery

Variables	Univariable			Multivariable		
	Hazards ratio	95% CI	*P* value	Hazards ratio	95% CI	*P* value
Differentiation: poor *vs.* well/moderate	1.16	0.65-2.07	0.61			
Lymphovascular invasion: yes *vs.* no	4.15	2.22-7.79	< 0.001	3.55	1.72-7.35	< 0.001
Surgical margin: positive *vs.* negative	2.00	0.56-2.80	< 0.001	1.97	0.68-3.57	< 0.001
Re-neoadjuvant chemotherapy: yes *vs.* no	0.60	0.36-0.99	0.04	0.51	0.16-1.68	0.27
Re-neoadjuvant radiotherapy: yes *vs.* no	0.33	0.04-1.16	0.03	0.41	0.21-2.41	0.04
Adjuvant chemotherapy: Yes *vs.* no	0.89	0.49-1.63	0.71			
Adjuvant radiotherapy: Yes *vs.* no	0.87	0.34-2.22	0.77			

after surgery [24]. And Cho et al. defined less than two years, 2-5 years, and more than five years after the operation as ER, intermediate recurrence, and LR, respectively [15]. Lan et al. adopted three years as the cut-off point [25]. And Oh et al. defined ER as recurrence less than five years for pT1 patients who underwent transanal local excision [16]. All of these studies differentiate ER from LR with an arbitrary interval but not based on the prognosis. And most of them confused local recurrence with distant metastasis. Patients with distant metastasis usually suffer worse outcomes and are difficult to cure compared with LRRC patients. Furthermore, additional surgery for LRRC was rarely analyzed by these studies. And our study confirmed that the optimal cut-off interval of ER was 26 months, and this point was an evidence-based value that related to the prognosis of the two recurrence cohorts. Different from past researches, our study introduced "post-recurrence survival (PRS)". And we believed that the use of PRS could estimate survival more objective than OS, which avoids the disturbance of a more prolonged RFS of LR cohort. In addition, we avoided the deficiencies in the studies mentioned above.

Variables associated with recurrence were analyzed. For univariable analysis, poor differentiation, positive lymph nodes, and the presence of lymphovascular invasion increased the likelihood of early recurrence, while the administration of radiotherapy was a protective factor. And for further multivariable analysis, only radiotherapy remained statistical difference. It has been reported in other series that these variables were independent risk factors for local recurrence [13, 14, 26], which were consistent with our study. It's well known that positive circumferential resection margin (CRM) is significantly associated with local recurrence [18, 20]. But there were only two patients who performed with positive CRM, which was too small for statistical analysis. The invasion depth of tumor in the rectal wall and tumor stage seemed not associated with recurrence in our study. And we also did not discover positive findings of these in current studies.

For LRRC patients, complete surgical removal offers them the best chance of cure and provides significant improvement in prognosis. And surgical resection can be undertaken with acceptable postoperative morbidity and mortality. Pre- and postoperative clinical and pathologic characteristics were analyzed based on prognosis. Cox proportional hazards model was used in this section. And the presence of lymphovascular invasion, positive surgical margin, and no re-neoadjuvant radiotherapy were independent prognostic factors for the survival of LRRC patients. As mentioned above, the positive lymphovascular invasion was a risk factor for early recurrence, and we also confirmed its effect on prognosis after surgery. Some reported investigations hold the same opinion as our study [13, 27]. Possible explanation may be that tumor cells can invade the lymphatic and vascular system, which is hard to remove surgically. And the residual tumor cells will plant on the pelvic or form metastatic tumors. Quantities of studies have investigated the predominant function of the negative surgical margin on LRRC patients who underwent operations [13, 14, 25, 26]. In our study, we defined > 1 mm as a clear surgical margin. Contrary to most past studies, Koh et al. found that a microscopically narrow tumor-free margin can be accepted, and up to 1 mm or wider margin did not translate to an improved overall survival [28]. They believed that surgical dissection for recurrent rectal cancer was operated in an extra-anatomical plane, and deeper exploration may increase

the injury of major vessels and neuro. On the other hand, some recurrent tumors located on pre-sacral or bilateral pelvic areas, where wide margins are either unlikely or challenging to achieve, and narrow margins are common. How to define a safe margin may need further studies. Whether LRRC patients will benefit from the administration of neoadjuvant radiotherapy is still under debate.

It has been reported that reirradiation is associated with a higher risk of toxicity for LRRC patients who have received radiation previously, and these patients will not benefit from this treatment [29, 30]. Nevertheless, reirradiation is also reported to be safe [31]. And most studies have affirmed the active effect of neoadjuvant radiotherapy. It could increase the rate of resectability and prolong survival with acceptable complications [5, 32, 33]. And our study confirmed its function on prognosis. There are very few studies that concerning whether neoadjuvant chemotherapy is favorable to LRRC patients. And it was frequently reported accompanied with radiotherapy. And it did not reach statistical significance in our study. Impact of neoadjuvant chemotherapy deserves further study.

There was evidence that patterns of recurrence would affect prognosis. Some investigators found that the number of tumor fixation sites was inversely proportional to prognosis [34]. Others discovered that patients with local recurrence at a perianastomotic site have more prolonged survival than other sites [35]. But in our study, we did not find the association between type of recurrence and prognosis. Furthermore, there was also no difference in recurrence pattern between the two recurrence cohorts.

Our study established the evidence-based definition of early recurrence for LRRC patients. Furthermore, we analyzed the risk factors for early recurrence and prognostic variables for additional treatment. However, there are some limitations. Our research was a retrospective study, and the associated bias risks can't be avoided totally. In addition, some patients were excluded because of incomplete records, which may disturbance the extrapolation of our findings to the population of LRRC patients.

Conclusion

The present study found that the optimal interval for the definition of ER was 26 months based on the subsequent prognosis. Adjuvant radiotherapy was the independent protective factor for early recurrence. And the presence of lymphovascular invasion, positive surgical margin, and no re-neoadjuvant radiotherapy were independent prognostic factors for the survival of LRRC patients under additional surgery.

Acknowledgements

We thank Shanjun Huang for records collecting and surveillance of all patients included in our study.

Disclosure of conflict of interest

None.

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