Original Article

Prognosis of Resecting Local Recurrence for the Cases with Synchronous Distant Metastasis of Rectal Cancer

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Key Words
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Purpose. In recent years, surgery has been believed to provide better prognosis for local recurrence of rectal cancer (LRRC). This study aimed to investigate the role of surgical local control for patients with simultaneous LRRC and distant metastasis.
Methods. Thirty patients with LRRC and distant metastasis following curative resection of primary rectal cancer were retrospectively identified from the database at the Taipei Veterans General Hospital from 1999 to 2013. All prognostic factors, including patient information, tumor characteristics, treatment, recurrence and metastasis, were collected and analyzed statistically.
Results. Among 30 patients, ten cases underwent surgical resection (SR) for local recurrence, and 20 cases received non-surgical treatment (NST). Surgical indication included intestinal obstruction, tumor bleeding, or ureter invasion with infection. In SR group, only three cases had microscopically negative margins (R0 resection). Overall, the mean interval from the curative resection of the primary cancer to the local recurrence diagnosis was 18.9 months. There were no differences in age, gender, primary tumor stage, tumor histology, local recurrence sites, distant metastatic sites and treatment for distant metastases between these two groups. However, surgery for local recurrences provided no difference in the survival analysis ($p = 0.829$), while the presence of liver metastasis was the only significant prognostic factor for survival ($p = 0.009$).
Conclusions. Surgery for LRRC alone did not improve the survival of patients who had LRRC with distant metastasis, and liver metastasis was the only significant prognostic factor in these patients.
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Local recurrence of rectal cancer (LRRC) following curative surgery occurs in approximately 4%-10% of patients who underwent total mesorectal excision.[1-4] The median survival ranges from 3.5 to 13 months for patients without treatment.[1] Treatment of LRRC has been a difficult problem, and the controversy between operative and non-operative treatment has also been discussed for decades.[2,5] Although LRRC surgeries are complex, they have been contraindicated in the early years because of high morbidity

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and mortality;[6] however, non-operative treatments, such as radiotherapy and chemotherapy, could prolong life expectancy.[7] In contrast, many recent studies have revealed a better survival rate with operative treatment compared with non-operative treatment in selected patients[2,8-10] since Lowy had reported an acceptable mortality after LRRC with multimodal therapy, including surgery, in 1996.[9] According to these studies, one of the most important prognostic factors in the selection of patients for LRRC surgery was a microscopically negative resection margin (R0 resection).[1,11]

Since margin-negative surgery had indicated a relatively good prognosis, many articles had focused on the results of different surgeries.[2,12,13] However, coexisting local and distant recurrences could also present. Although, current guidelines have recommended surgery and chemotherapy for cases with primary cancer and distant metastases, there has been less information on cases with coexisting local and distal recurrences.[14,15] Overall, the role of surgery for local control in cases with both local and distant recurrences simultaneously is still not clear.

As a result, the purpose of this study was to investigate the role of surgery for cases with simultaneous local and distant recurrences.

Methods

Patients

Cases were selected from our rectal cancer database, which is maintained at the Department of Colorectal Surgery, Taipei Veteran General Hospital, Taiwan. Rectal cancer was defined as a tumor located 15 cm from the anal verge. LRRC was defined as the presence of a soft tissue mass that was limited to the pelvic cavity. There is pathological report or image evidence plus elevated serum carcinoembryonic antigen (CEA) level. Distal recurrence was defined as a metastatic tumor outside the pelvic cavity, such as in the lungs, liver, bone, brain or abdominal lymph nodes. However, cases of peritoneal dissemination were excluded because it was difficult to define the metastasis as either local or distant in the peritoneal cavity. Overall, 2,613 cases underwent curative or palliative surgery for primary rectal cancer from July 1999 to December 2013, and 132 (5.1%) cases were identified as having local recurrences. Among these cases, 39 (1.5%) were excluded because they were stage IV at the initial diagnosis and 63 (2.9%) were excluded due to the presence of only local recurrence initially. As a result, 30 (1.2%) cases were recruited for this study (Fig. 1).

Collected data

All data were collected retrospectively. Demographic data included gender, age, initial primary rectal cancer stage, initial operative type, initial pathological features, the interval between primary surgery and diagnosis of recurrence, recurrent sites and serum CEA levels at the diagnosis of recurrence. Any surgical resection (SR) for LRRC was recorded and could have involved an abdominoperitoneal resection, low anterior resection, sacrectomy, pelvic exenteration or sole excision. Non-surgical treatments for LRRC included receiving chemotherapy, radiotherapy or concurrent chemoradiotherapy. However, the SR group might have also received these treatments. The pathological resection margin statuses were defined as follows: R0 meant no cancer cells can be seen microscopically over the resection margin; R1 meant no

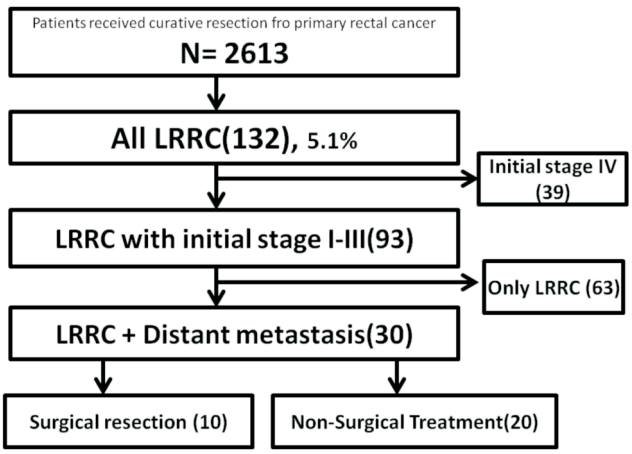

Fig. 1. Overview of patients with local and distant recurrence according to initial cancer stage and recurrent sites.

cancer cells can be seen macroscopically over the resection margin and R2 meant positive cancer cells can be seen by the naked eye over the resection margin.[16] Local recurrences were simply classified as intraluminal or extraluminal.[17]

Statistical analysis

Statistical analysis was conducted using IBM SPSS Statistics for Windows, version 22 (IBM Corp, Armonk, NY). We used the Chi-squared test (χ^2 test) to compare category variables. We used the T-test and one-way analysis of variance for continuous variables. We used the Kaplan-Meier method for cumulative survival curves since the LRRC diagnosis and used the log-rank test to compare the factors affecting survival. Statistical significance was defined as a *p*-value of < 0.05.

Results

The demographics are shown in Table 1. Ten cases underwent resection for LRRC, whereas 20 pa-

Table 1. Patients baseline demographic

	Total (30)	SR (10)	NST (20)	*p*-value
Age	64.7 +/- 14.9	65.4 +/- 12.8	64.4 +/- 16.1	0.866
Gender				0.548
Male	22	7	15	
Female	8	3	5	
Interval (months)	22.0 +/- 19.4	25.4 +/- 28.5	20.3 +/- 13.4	0.507
Primary surgery type				
Sphincter preserving	19	6	13	
Non-sphincter preserving	11	4	7	
Initial TNM stage				0.584
I	17	6	11	
II	11	4	7	
III	2	0	2	
Histological differentiation				0.563
Well/moderate	28	9	19	
Poor	2	1	1	
Recurrent location				0.44
Intraluminal	10	4	6	
Extraluminal	20	6	14	
CEA level at recurrence				0.656
< 5.0 mg/dl	8	2	6	
> 5.0 mg/dl	13	3	10	
Distant metastasis site				
Liver	9	4	5	0.331
Lung	16	5	11	0.55
Bone	9	1	8	0.1
Lymph nodes (outside pelvis)	7	4	3	0.143
Others	1	0	1	0.667
Treatment for distant metastasis				
Surgery	0	0	0	
Non-surgery	30	10	20	
Other treatment except operation				
Chemotherapy	27	9	18	0.719
Radiotherapy	6	4	2	0.076
Chemotherapy +/- target therapy	7	1	6	0.228
Palliative	3	1	2	0.749
Resection margin status				
R0		3		
R1		2		
R2		5		
Mean survival time (months)	18.9 +/- 16.3	17.3 +/- 7.8	19.7 +/- 19.4	0.712

tients did not. There were no differences in age, gender, interval since the initial tumor resection, presence of initial sphincter surgery, initial tumor stage, differentiation, CEA level at recurrence, and neoadjuvant radiotherapy or other multi-modality treatments for distant recurrences. None of these thirty cases received surgery for distant metastasis. Of SR group, only three cases had R0 resection, two cases had R1 resection and five cases had R2 resection. Among the 21 cases with collectable CEA levels, only 13 cases (61.9%) had levels > 5 mg/dL.

In SR group, every case received operation after multidisciplinary meeting conference, and these surgical indications included intestinal obstruction, ureter invasion with infection, tumor bleeding, and simply anastomosis site recurrence (Table 2). Among SR group, 9 patients, except one, enabled to receive further chemotherapy, radiotherapy, or target therapy for distant metastasis after SR. However, nine cases had local re-recurrences, and only a case was free of re-recurrence after SR.

The 3-, and 5-year survival rates for the 30 patients were 12.2%, and 4.1% respectively. The survival rates for the SR group were both 0%; while the rates for NST were 15.1% and 5.1%. There was no difference between the two groups by survival analysis (p = 0.829) (Fig. 2). Univariate survival analyses revealed that the presence of liver metastasis was the only significant prognostic factor (p = 0.009) among all the analyzed factors (Table 3). The cases with liver metastasis had poorer prognosis than those without metastasis (Fig. 3).

Discussion

This retrospective study did not reveal a survival benefit of SR for the treatment of LRRC in cases with distant metastasis. The only significant factor for these cases was the presence of liver metastasis. This posed a negative effect on survival. The local control rate for the LRRC operation was low.

Although the inclusion criteria of stages I-III were different from those of other series,[1,2,7] the LRRC rate of 5.1% was similar to those studies.[1-4] The main reasons to exclude stage IV cases were that it was difficult to evaluate the correlation between the initial metastasis and LRRC and that multi-modality therapies

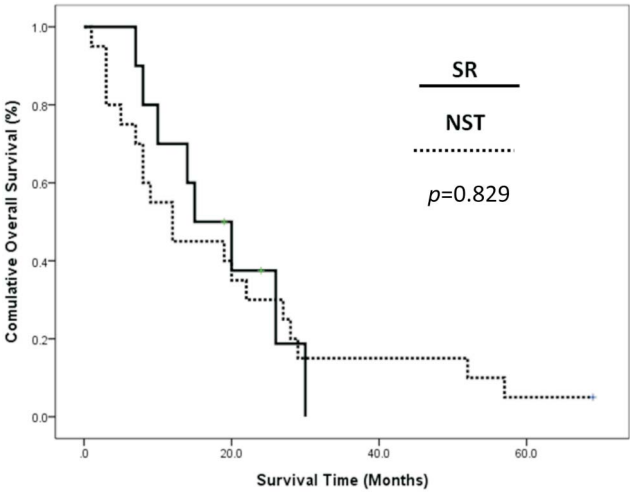

Fig. 2. Comparison of the cumulative survival of non-surgical therapy (NST) group (solid line), and surgical resection (SR) group (dotted line) for local recurrence (p = 0.829).

Table 2. Data of surgical resection group

Case	Operation indication	Margin status	Survival time (months)	Distant metastasis	Further treatment
1	Intestinal obstruction	R2	26	Intraabdominal LNs	C/T + R/T
2	Tumor bleeding	R0	30	Lung	C/T
3	Ureter invasion with infection	R1	24	Intraabdominal LNs	C/T
4	Only anastomosis recurrence	R0	14	Bone	C/T + R/T
5	Intestinal obstruction	R1	20	Liver, lung	C/T
6	Ureter invasion with infection	R0	19	Intraabdominal LNs	C/T + R/T
7	Intestinal obstruction	R2	8	Liver, lung	C/T + R/T
8	Intestinal obstruction	R2	10	Liver, lung	C/T
9	Intestinal obstruction	R2	7	Liver, lung	Palliative care
10	Intestinal obstruction	R2	15	Intraabdominal LNs	C/T + target Tx

C/T: chemotherapy, R/T: radiotherapy, Tx: treatment, LNs: lymph nodes.

Table 3. Univariate survival analysis

Prognostic factors	*p*-value
Age (65)	0.761
Gender	0.712
Primary surgery sphincter preserving (Yes vs. No)	0.961
Initial TNM stage (I vs. II vs. III)	0.57
Histological differentiation (Well/moderate vs. poor)	0.322
Recurrent location (Iintraluminal vs. extraluminal)	0.448
Treatment for local recurrence (SR vs. NST)	0.829
Distant metastasis site	
Liver	0.009
Lung	0.412
Bone	0.993
Lymph nodes (outside pelvis)	0.765
Treatment for distant metastasis (surgery vs. non-surgery)	0.829
CEA level at recurrent (< 5.0 vs. > 5.0 mg/dl)	0.67
Other treatment except operation	
Chemotherapy	0.828
Radiotherapy	0.96
Palliative care	0.828
Chemotherapy + target therapy	0.248
Resection margin status (R0 vs. R1 vs. R2)	0.467

SR: surgical resection, NST: non-surgical treatment.

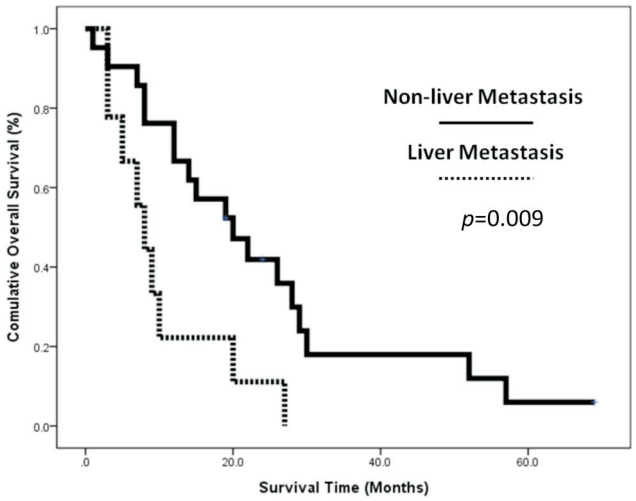

Fig. 3. Comparison of the cumulative survival of No liver metastasis group (solid line) and Liver metastasis group (dotted line) ($p = 0.009$).

might complicate the nature of LRRC.

The reasons for LRRC surgeries might be resolving local symptoms or the potential for staged removal of local and distant tumors. However, the benefit was limited, although 9 of 10 cases in the SR group were enabled to receive further systemic chemotherapy or target therapy. The fact that only 2 patients (20%) had R0 resection means that LRRC is much more complicated to remove than the preoperative planning according the images.

As shown in this study, debulking surgery for local control did not improve survival, while distant metastasis did matter, especially liver metastasis. Uncontrolled growth of hepatic metastases significantly affects survival.[18] Most metastases not resected die within 5 years.[18,19]

Serum CEA levels had been used to diagnose and evaluate the efficacy of treatment in colorectal cancer. In a previous study from our hospital,[20] we found that postoperative CEA level could also be a prognostic factor for recurrence. However, in this series, even with local recurrences and distant metastases, the CEA levels did not appear to be sensitive enough (38%). Serum CEA was not a prognostic factor in this series.

Future aspects to improve the poor prognosis of this group should be focused on systemic therapy for distant metastases. Surgery for LRRC should not be considered until definite control of distant metastasis has been obtained. Liver metastasis should also be

closely controlled so that this group's prognoses can be improved.

To our knowledge, this was the first study that explored the outcomes of LRRC operations for cases with distant metastasis. There were several limitations of our study. First, there were a small number of cases because of the natural rarity of the condition. Second, it was a retrospective, single-center study and could have been associated with unavoidable biases. Third, SR for LRRC depended on so many non-standardized indications.

Conclusions

The grim prognosis of cases with LRRC and distant metastases has been shown in this series. To operate for LRRC alone does not improve survival, and the local re-recurrence rate remains high. The presence of liver metastasis was the only prognostic factor found in these cases. Thus, we believe that better systemic control will be required for better survival, and the concept of LRRC debulking may not currently be helpful.

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Disclosure Statement

There is no conflict of interest or funding to disclose.

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原　著

直腸癌局部復發併遠端轉移病人接受局部切除之預後

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目的 近年來，研究顯示手術治療對於有直腸癌併局部復發的病人有較好的存活率。而此研究目的在探討直腸癌局部復發並遠端轉移病人接受局部切除之預後。

方法 自 1999 至 2013 年間，自台北榮民總醫院資料庫中回溯性地找出 30 名診斷有直腸癌合併局部復發和遠端轉移的病人。我們收集並分析所有的預後因子，如病人基本資料、腫瘤特性、治療方法、復發特質及遠端轉移型態等。

結果 在 30 名病人中，依據對於局部復發的治療可分成手術切除組 (SR) 及非手術治療組 (NST)。開刀的適應症包括腸阻塞、腫瘤出血、輸尿管侵犯併感染等。在 SR 組中，只有 3 名病人達到顯微鏡下邊緣無腫瘤侵犯 (R0 切除)。整體來說，平均復發時間是 18.9 個月。兩組病人在年齡、性別、初始腫瘤期別、腫瘤細胞型態、治療方法、復發位置、及遠端轉移之治療皆沒有統計上差別。然而，採取局部切除的病人的存活時間在統計上並無顯著差別 (p 值 = 0.829)；而是否有肝臟轉移反倒是唯一有達到統計上顯著差異的預後因子 (p 值 = 0.009)。

結論 對於有直腸癌合併有局部復發及遠端轉移病人而言，只採取局部手術切除並無法改善存活時間。在本研究中，是否有肝臟轉是最重要的預後因子。

關鍵詞 直腸癌、局部復發、遠端轉移、手術治療、預後。