Case Analysis

Results and Predictive Factors of Surgery for Locally Recurrent Rectal Cancer

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Key Words Curative surgery; Locally recurrent rectal cancer; Predictive factors *Purpose.* This study aimed to evaluate surgical results for locally recurrent rectal cancer and to compare median post-operative survival and analyze predictive factors for achieving curative surgery.

Methods. Thirty patients who received surgery between January 1994 and December 2005 for locally recurrent rectal cancer were enrolled. All patients had previously undergone radical surgical resection of primary rectal cancer. Age, gender, place of primary surgery, date and type of initial operation, stage of rectal cancer, and administration of adjuvant therapy were retrospectively analyzed. Date of detection, presenting symptoms and diagnostic work-up, location and fixity of recurrent tumor, type of surgery, and pre- and post-operative carcinoembryonic antigen levels were analyzed.

Results. The median survival of the 30 included patients was 16.7 months. Curative surgery was achieved in 15 patients and palliative surgery was performed in 15. Median survival was 28.6 months after curative surgery and 11.9 months after palliative surgery (p = 0.014). Data showed predictive factors of curative surgery to be rectal symptoms or asymptomatic patients (p = 0.014), anastomosis location (p = 0.001), and tumor fixity (p < 0.001).

Conclusions. Curative surgery proved to be the only significant prognostic factor of survival. Predictive factors of curative surgery can therefore be used in the selection of surgical candidates and establishment of appropriate treatment plans.

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S ince Miles introduced abdominoperineal resection in 1908 as a radical surgery for rectal cancer, treatment of rectal cancer has undergone a remarkable evolution and revolution.¹ With the application of total mesorectal excision (TME) in radical surgery for rectal cancer, the rate of local recurrence after treatment for primary rectal cancer has decreased.^{2,3} Furthermore, preoperative radiotherapy has become the standard treatment since it was proven to reduce local recurrence of rectal cancer.⁴ Despite the use of TME and preoperative radiotherapy, the rate of local recurrence ranges from 2.6 to 32%.^{5,6} Recurrent rectal cancer carries a high morbidity and poor prognosis, and leads to poor quality of life in the absence of further treatment.⁷ Treatment options for locally recurrent rectal cancer (LRRC) include surgery, radiotherapy, chemotherapy, or a combination of these modalities. Fiveyear survival rates reported in the literature range from

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19 to 82% in patients treated surgery for LRRC.⁸ This variability is related primarily to the selection of patients as candidates for surgery, since only a portion of surgeries achieve complete excision of LRRC with a negative surgical margin. While curative surgery provides the only chance for long-term survival.⁸ However, curative resections usually require extensive resection of adjacent pelvic organs, often accompanied by morbidity that may diminish the desired benefit of improving patients' quality of life, and may actually be hazardous for some patients, especially those for whom complete resection has failed. As a result, the selection of appropriate candidates for potential curative surgery or the proposal of appropriate treatment plans are major concerns in the treatment of LRRC. The purpose of this study was three fold: to evaluate the results of surgery for LRRC; compare median survival after surgery, and; analyze factors that might predict the possibility of achieving curative surgery.

Materials and Methods

Between January 1994 and December 2005, 626 patients underwent curative surgery for primary rectal cancer at the Division of Colon and Rectal Surgery, Tri-Service General Hospital. These patients were followed at three-month intervals during the first two years, six-month intervals during the third to fifth years, and then annually thereafter. Local recurrence was defined as cancer recurrence within the pelvis. In this period, local recurrence occurred in 22 patients. Three patients were ineligible for surgical treatment due to concomitant distant metastases diagnosed via diagnostic imaging work-ups. The remaining 19 patients underwent surgical treatment for recurrent tumors. In addition, 11 patients with local recurrence after initial surgery performed at a different hospital were referred to our hospital for surgical treatment resulting in a series of 30 patients who underwent surgery for LRRC. The medical records of these 30 patients were retrospectively reviewed. Age, gender, place of initial operation, date and type of initial operation, stage of rectal cancer, and adjuvant therapy for the rectal cancer were recorded. Data concerning detection of the local recurrence such as date of detection, presenting symptoms of local recurrence, and diagnostic work-up were also collected. All local recurrences of rectal cancer were confirmed histologically. Location and fixity of recurrent tumor, type of surgery for LRRC, carcinoembryonic antigen (CEA) levels before and after surgery for LRRC were analyzed. Complications and days of hospitalization were also recorded.

Curative surgery was defined as complete surgical resection of LRRC with negative margin involvement (R0 resection). Palliative surgery was defined as surgical management of LRRC with microscopic margin involvement (R1 resection) or with gross residual disease (R2 resection).

Statistical analysis was performed with the Statistical Package for Social Sciences (SPSS) version 14.0 (SPSS Inc., Chicago, IL). Cumulative survival curves were constructed using the Kaplan-Meier method and were calculated from the time of resection of LRRC until the last follow-up visit or death. Comparisons of median survival times of curative and palliative surgery were made using a log-rank test. The chi-square test was used to compare categorical variables of curative and palliative surgery. A *p* value < 0.05 was considered statistically significant.

Results

Between January 1994 and December 2005, 30 patients received surgery for LRRC at the Tri-Service General Hospital. Patient demographics, treatment and tumor characteristics have been summarized in Table 1. All patients had previously undergone curative resection for primary rectal cancer. Among surgical procedures performed for rectal cancer in these patients, low anterior resection (LAR) was performed in 17, transanal wide excision in 2, abdominoperineal resection (APR) in 10, and total proctocolectomy with ileal J pouch-anal anastomosis (IPAA) in one patient with malignant transformation of familial adenomatous polyposis. There was one case classified as UICC stage IV due to primary cancer at rectum with solitary liver metastases. The patient underwent concomitant low anterior resection of rectal cancer and wedge resection of liver metastases. The pathological report

 Table 1. Patient demographics, treatment details, and tumor characteristics and factors affecting type of surgery for local recurrence

		Curative	Palliative	_
Characteristics (Factors)	n	n (%)	n (%)	p-value
Gender				
Male	13	6 (40.0)	7 (46.7)	1.000
Female	17	9 (60.0)	8 (53.3)	
Age				
> 60-year	14	7 (46.7)	7 (46.7)	1.000
< 60-year	16	8 (53.3)	8 (53.3)	
Median age in years	59 (26-81)			
Place of initial operation				
TSGH	19	8 (53.3)	11 (73.3)	0.449
Other hospitals	11	7 (46.7)	4 (26.7)	
Type of initial operation				
Sphincter preserving surgery	20	12 (80.0)	8 (53.3)	0.245
APR	10	3 (20.0)	7 (46.7)	
Stage of rectal cancer				
I	5	3 (20.0)	2 (13.3)	0.269
II	7	5 (33.3)	2 (13.3)	
III	17	6 (40.0)	11 (73.3)	
IV	1	1 (6.7)	0 (0)	
nvasion depth of rectal cancer		· /	~ /	
T1	1	0 (0)	1 (6.7)	1.000
T2	5	3 (20.0)	2 (13.3)	
Т3	21	11 (73.3)	10 (66.7)	
T4	3	1 (6.7)	2 (13.3)	
Lymph node metastasis of rectal cancer				
N0	12	8 (53.3)	4 (26.6)	0.877
N1	5	2 (13.3)	3 (20.0)	01077
N2	13	5 (33.3)	8 (53.3)	
Disease-free interval			- ()	
< 12 months	13	8 (53.3)	5 (33.3)	0.649
$12 \sim 24$ months	9	4 (26.7)	5 (33.3)	0.015
> 24 months	8	3 (20.0)	5 (33.3)	
Median disease free interval (months)	14 (4-72)	5 (20.0)	5 (55.5)	
Symptoms of recurrence	11(172)			
Asymptomatic	3	3 (20.0)	0 (0)	0.014
Rectal symptoms	9	7 (46.7)	2 (13.3)	0.014
Pain	15	3 (20.0)	12 (80.0)	
Hydronephrosis	3	2 (13.3)	12 (80.0) 1 (6.7)	
Recurrent tumor location	5	2 (15.5)	1 (0.7)	
Central (anastomosis)	15	13 (86.7)	2 (13.3)	0.001
Lateral (sidewall)	11	2 (13.3)	2 (13.3) 9 (60.0)	0.001
Posterior (sacral)	2	2(13.3) 0(0)	2 (13.3)	
Perineal	$\frac{2}{2}$	0(0) 0(0)	2(13.3) 2(13.3)	
Sixity	4	0 (0)	2 (15.5)	
FO	8	8 (53.3)	0 (0)	< 0.001
F0 F1	8 8	6 (40.0)	2(13.3)	< 0.001
F1 F2	° 14	1 (6.7)	13 (86.7)	
	17	1 (0.7)	15 (00.7)	
Pre-operative CEA	20	10 (66 7)	10(667)	1 000
High(> 5 ng/ml)	20	10 (66.7)	10(66.7)	1.000
Normal (< 5 ng/ml)	10	5 (33.3)	5 (33.3)	
Post-operative CEA				
High (> 5 ng/ml)	13	1 (6.7)	12 (80.0)	< 0.001
Normal (< 5 ng/ml)	17	14 (93.3)	3 (20.0)	
Median survival (months)	16.7	28.6	11.9	0.014

TSGH = Tri-Service General Hospital; APR = abdominoperineal resection; F0 = not fixed; F1 = fixed to one site; F2 = fixed to two or more sites; CEA = carcinoembryonic antigen.

showed complete resection of both the primary and metastatic lesion. Since only locally pelvic recurrence was found during the period of follow-up, this case was included in this study.

Since the concept of neoadjuvant therapy had only recently been introduced at the time of this retrospective study period, preoperative chemoradiation was performed in only two patients. Adjuvant radiotherapy was used in six patients and chemotherapy was administered to 18 patients. Twelve of the 30 patients did not receive postoperative adjuvant therapy for their rectal cancer.

Characters of LRRC

The median interval between resection of rectal cancer and detection of local recurrence was 14 months (range = 4 to 72 months). Pain in the pelvis or peripheral limbs was the primary presenting symptom of local recurrence which occurred in 15 of the 30 patients. Changes in bowel habits and/or bloody stool (rectal symptoms) occurred in nine patients, and hydronephrosis occurred in three. The remaining three asymptomatic patients were diagnosed with LRRC on digital rectal examination, endoscopic biopsy, and identification of elevated CEA levels during follow-up. The location of the recurrent tumor was central (anastomosis of rectum or neorectum) in 15 of 30 patients, lateral (pelvic sidewall) in 11, posterior (sacral) in two, and perineal in two. Recurrent tumors were classified as not fixed (F0) in 8 of 30 patients, fixed at one site (F1) in 8 patients, and fixed to two or more sites (F2) in 14 patients.

Surgical procedures for LRRC

As described in Table 2, complete surgical resection of recurrent tumors with negative margin involvement (curative surgery) was confirmed histologically in 15 of 30 patients and the remaining 15 patients were positive for surgical margin involvement or gross residual disease (palliative surgery). Surgical resection of the recurrent tumor with rectum or neorectum included LAR performed in 3 patients, APR in 5, Hartmann's procedure in 2, and pelvic exenteration in 2. The surgical resection of recurrent tumor without the rectum or neorectum comprised removal of pelvic tumors in 13 patients, perineal excision in 2 and enterostomy in 2. Extended resection involving resection of one or more adjacent organs was required in 10 patients. Concurrent resection of the uterus and ovaries was performed in 4 patients and resection of small bowel was needed in 2 patients. Three patients received segmental resection of the ureter, and one patient underwent concomitant total cystectomy with construction of an ileal conduit. The median duration of hospitalization was 18 days (range = 3-42 days) for patients undergoing curative surgery and 12 days (range = 4-60 days) for patients treated palliatively.

Operative mortality and morbidity

All 30 patients recovered from their surgeries. Post-operatively, 11 complications occurred in 10 patients, which primarily affected the urinary system. These included urinary tract infections, bladder injury, urethral injury and leakage of ureteral anastomosis (n = 7). Deep vein thrombosis of the lower leg, abdominal wound dehiscence, leakage of chylous ascites, and vaginal laceration occurred in four patients and 1 patient sustained concomitant vaginal injury and bladder injury. Three patients required surgical management for their post-operative complications, including repair of urethra, bladder, vagina, and closure of an abdominal wound. Post-operative complications were described and listed in Table 3.

Survival after curative and palliative surgery

At the time of the last follow-up, 17 of the 30 patients had died and the median survival was 16.7 months. The opportunity to perform curative surgery was identified as a significant determinant of survival

Table 2. Types of surgery performed for locall	y
recurrent rectal cancer	

Type of surgery	n
Low anterior resection	3
Abdominoperineal resection	5
Hartmann's procedure	2
Pelvic exenteration	3
Removal of pelvic tumor	13
Perineal excision	2
Enterostomy	2
Total	30

Type of complications	n	Operative correction
Urologic complication	7	2
Urinary tract infection	(4)	(0)
Bladder injury	(1)	(1)*
Urethral injury	(1)	(1)
Leakage of ureteral anastomosis	(1)	(0)
Deep vein thrombosis	1	0
Abdominal wound dehiscence	1	1
Leakage of chylous ascites	1	0
Vaginal laceration	1	1*
Total	11	4

Table 3. Post-operative complications for locally recurrent rectal cancer

*Coexisting vaginal injury and bladder injury occurred in one patient receiving surgery for locally recurrent rectal cancer. Repair of bladder and vagina were performed concomitantly.

(p = 0.014). Median survival times for curative and palliative surgery were 28.6 and 11.9 months, respectively. The cumulative survival curves for both curative and palliative surgery are shown in Fig. 1. Only two patients received preoperative neoadjvant chemoradiation for LRRC. Curative resection was achieved in 1 while the other underwent palliative surgery. Ten patients received post-operative adjuvant radiotherapy for LRRC while 18 of 30 patients did not receive radiotherapy at any time for LRRC.

Predictive factors of curative surgery

Of the 30 included patients, 15 patients received curative surgery and 15 received palliative surgery. The characteristics of these two groups of patients have been compared as described in Table 1. Rectal symptoms or asymptomatic patients (p = 0.014), anastomosis location (p = 0.001), fixity (F0) of tumor (p < 0.001), and normal post-operative CEA levels (p < 0.001) had significant effects on the possibility of achieving curative surgery. In contrast, gender, age, place of initial operation, type of initial operation, stage of rectal cancer, disease free interval, and pre-operative CEA level had no effect on the possibility of achieving curative surgery.

Discussion

LRRC and prognosis

Despite worldwide use of TME and preoperative

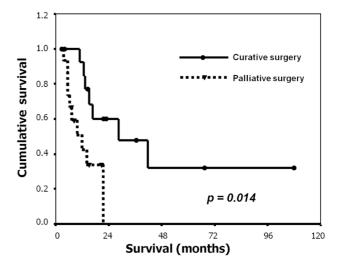


Fig. 1. Comparison of survival of patients who underwent curative or palliative surgery for locally recurrent rectal cancer (p = 0.014).

radiotherapy, local recurrence remains the Gordian knot after initial curative surgery for rectal cancer. Recurrence rates range from 2.6 to 32%.⁶ Patient survival is adversely affected by the presence of local recurrence and median survival ranges from 3.5 to 13 months in the absence of further treatment.⁹ At least half of LRRCs are isolated without distant metastasis, and represent potential chance of cure given appropriate treatment. Nonetheless, despite of subsequent treatment, 25% of patients still die of recurrent rectal cancer in the absence of distant metastasis.⁹ Development of local recurrence is responsible not only for significant mortality and morbidity, but also for an impairment in quality of life. Therefore, treatment of local recurrence should be directed at the physical, psychological, and social aspects of the affected patient.⁷

Treatment of LRRC

Treatment options for LRRC include surgery, radiotherapy, chemotherapy, or a combination of these modalities. Radiotherapy and chemotherapy can palliate the symptoms resulting from LRRC, but do not prolong survival.^{10,11} Surgery is thought to offer the best chance of long-term disease-free survival and local control. Indeed, five-year survival rates reported in the literature range from 19 to 82% in patients treated surgically.8 This marked variability in survival is thought to be primarily related to patient selection for surgery since complete excision of LRRC with negative surgical margins is only accomplished in a portion of patients. On the other hand, palliative surgery does not appear to improve long-term survival, but in some cases this may be the only management option to relieve the intractable symptoms of LRRC (especially pain).

Neoadjuvant chemoradiation plays an important role in the treatment of primary rectal cancer and apparently decreases the opportunity for local recurrence;⁴ however, the role of neoadjuvant chemoradiation in the treatment of LRRC is not well recognized. In our study, only two patients received neoadjuvant chemoradiation for LRRC before surgery. In these two patients, one surgery was curative resection and the other was palliative surgery. Further evaluation of neoadjuvant chemoradiation for LRRC is needed to determine its value in the management of patients with LRRC.

Previous surgery and surgery for LRRC

Ten of 30 the patients with LRRC included in this study were previously treated with APR. In these cases, the recurrent tumors generally presented in the pelvic cavity either with or without pelvic organ involvement. Since there was no rectum left, only resection of pelvic tumor could be performed in these patients. A curative resection was achieved in 3 of the 10 cases based on the pathology results.

In the curative surgery group, 3 cases were treated

with LAR, 5 with APR, 3 cases with pelvic exenteration, 1 case with Hartmann's procedure, and 3 cases with removal of pelvic tumor. In contrast, the surgeries performed in the palliative surgery group included 10 cases with removal of pelvic tumor, 2 cases with perineal excision, and 2 cases with enterostomy. For cases undergoing a primary surgery involving a sphincter-preserving surgery, 8 of 20 patients underwent palliative surgery. Difference in primary surgery did not influence the ability to achieve curative surgery (p = 0.245).

Post-operative complications

The majority of complications affected the urinary tract (7 out of 11). Urologic organs, particularly the left ureter and the urinary bladder, were commonly invaded by the recurrent tumor and injury to those organs was sometimes inevitable at the time of surgery. In addition, anatomic changes of the pelvis and the formation of extensive adhesions affecting the pelvic organs due to prior surgery may also explain these post-operative complications. With appropriate management, these complications did not influence the quality of life or survival of the patients included in this study. It is therefore important to identify which cases are amenable to complete resection of LRRC without resulting in the massive destruction of pelvic organs. The selection of optimal treatment for LRRC is not only based on improving patient survival, but also at maintaining an acceptable quality of life postoperatively.

While pelvic abscess is a common post-operative complication in patients with LRRC, this complication was not recorded in this study. This might be a result of adequate drainage of pelvic discharge after surgery in the cases included in this study.

Survival and influencing factors

The reported median survival for patients with LRRC varies from 17 to 36 months after curative surgery.⁹ In our study, the median survival of patients receiving curative surgery was 28.6 months and 11.9 months for those receiving palliative surgery. The opportunity to perform curative surgery is a significant

factor in long-term survival. Some studies have speculated about other influencing factors of survival such as gender,⁹ symptoms,¹² CEA level doubling time before salvage operation,¹³ and surgery for primary rectal cancer.¹⁴ In the large series review of Caricato et al,⁸ these factors were associated with a significant curative resection rate but did not impact survival. Further, Caricato and colleagues concluded that the only reliable prognostic factor for survival is a microscopically negative margin after surgery (R0 resection).

Predictive factors for curative surgery

Curative surgery is defined as complete surgical resection of LRRC with negative margin involvement (R0 resection). In the published literature, curative surgery can be achieved in about 45% of cases (range = 10%-67%).¹⁴⁻¹⁷ In this study, a curative surgery was achieved in 50% of LRRC patients. Since curative resection requires the extensive resection of adjacent pelvic organs (accompanied with marked morbidity), identifying factors that can predict the likelihood of achieving a curative surgery may assist in patient selection and ultimately increase the potential of achieving curative surgery.

Some reports show that female gender may be a predictive factor for curative resection, as the difference in the female pelvis is presumed to allow easier surgical access and earlier identification of recurrence from the anterior spread of the tumor to the vaginal wall and uterus.^{9,18} Female gender was not significant in our study. Age is not considered a significant predictor for curative surgery, except for the study by Garcia-Aguilar et al.¹⁷ This group found that younger age at time of diagnosis of recurrence is a predictor of curative surgery. In our analysis, age at time of LRRC diagnosis was not a significant factor.

Regarding the characteristics of the rectal cancer and initial surgery, no association between prediction of curative surgery and the following factors was identified: place of initial operation, stage of rectal cancer, type of initial operation, and disease-free interval. Several studies have demonstrated that sphincter-preserving surgery did increase the potential for a curative resection compared to APR.^{17,19-22} LRRC is usually diagnosed earlier after a primary sphincter-preserving surgery because there symptoms of recurrence, such as rectal bleeding or changes in bowel habits, are identified earlier and the tumor is detected more easily by rectal digital examination and endoscopic evaluation. In contrast, LRRC after primary APR tends to rely on elevated CEA levels or the presentation of pelvic pain, which usually develop late in cases of LRRC compared to patients treated with a sphincter-preserving surgery. When the rectum is excised during primary tumor resection, recurrence of disease is more likely to invade adjacent organs.²³ In our study, a higher number of sphincter-preserving surgeries (12/20) achieved curative surgery more frequently than APR did (only 3/10 were curative), but this difference was not statistically significant (p = 0.245).

In our study, rectal symptoms such as rectal bleeding or changes in bowel habits were predictive factors of curative surgery, and were related to an early detection of LRRC. Asymptomatic patients are also eligible for curative surgery since their LRRCs are detected relatively early as well via digital rectal examination, endoscopic biopsy, or a slight elevation in CEA levels during follow-up visits. Our data indicate that location and fixity of recurrent cancer are significantly associated with the probability of curative surgery, which confirms the findings of other studies.^{20,24} Centrally located tumors are usually less fixed to adjacent organs whereas lateral and posterior locations are fixed in one or more sites. An increased number of fixed sites are indicative of a more advanced LRRC and make surgical resection more difficult.²³ In addition, higher morbidity rates are observed in patients with one or more sites of fixation and with a lateral or posterior location of tumors.¹⁹ Thus, central location and fixity (F0) of the tumor are significant predictive factors of curative surgery. Finally, post-operative CEA levels for LRRC are not predictors of curative surgery. Nonetheless, we found that CEA levels after surgery for LRRC were markedly decreased in patients with a curative surgery, whereas CEA levels in patients treated with a palliative surgery were usually elevated. Since CEA levels usually reflect the extent of tumor progression,¹³ post-operative CEA levels may be useful in estimating achievement of curative surgery.

Palliative treatment for LRRC

Without treatment, the survival of patients with LRRCs range from 3.5 to 13 months.⁹ In our study, the palliative surgery group had a median survival of 11.9 months indicating that there is no survival benefit for patient receiving palliative surgery. Palliative treatment for LRRC included radiotherapy, chemotherapy, chemoradiation, endoscopically-placed stents, and surgery. Surgical resection for palliation is usually inappropriate due to the associated morbidity; however, surgical resection is sometimes the only way to palliate the symptoms of LRRCs. In our opinion, radiotherapy, chemotherapy or chemoradiation is the primary modality for palliation in the treatment of unresectable LRRCs. Palliative surgery should be preserved for intractable cases and should be performed with minimal destruction of adjacent tissues as possible and should be aimed at symptomatic relief.

Conclusions

Curative surgery (R0 resection) for the management of LRRC is the only prognostic factor of longterm survival and can be performed in approximately 50% of affected patients. Based on the data collected in this study, curative surgery is more likely to be achieved in patients with rectal symptoms, central location and F0 fixation of tumor. These factors provide valid evidence for the selection of surgical candidates and appropriate treatment plans.

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病例分析

手術治療局部復發直腸癌的結果及預測因子

歐金俊 饒樹文 吳昌杰 李才宇 陳家輝 陳莊偉 王良財 蕭正文

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目的 評估手術治療局部復發直腸癌的結果,比較手術後存活時間及分析可能達成根治 手術的預測因子。

方法 從 1994 年 1 月到 2005 年 12 月間,共 30 位病患接受手術治療局部復發直腸癌。 所有病患均曾接受過手術切除原發直腸癌而後局部復發。年齡,性別,手術切除直腸癌 之醫院、日期、手術方式及輔助治療,局部復發直腸癌之發現日期、表現症狀、及診斷 方法,復發腫瘤之位置及鄰近組織侵犯情形,手術前後癌胚抗原濃度等均加以分析。

結果 30 位病患之存活時間中位數為 16.7 個月。有 15 位病患達成根治手術,另外 15 位病患則接受緩和手術。根治手術病患之存活時間中位數為 28.6 個月,緩和手術病患 之存活時間中位數為 11.9 個月。能夠達成根治手術的患者確實能延長存活時間 (*p* = 0.014)。比較兩組病患的相關影響因子後,達成根治手術的預測因子如下:有便血等直 腸症狀者或無症狀者,復發腫瘤位置在直腸吻合處,及未侵犯鄰近組織者。

結論 治療局部復發直腸癌時,達成根治手術是唯一能延長存活時間的預後因素。達成 根治手術的預測因子則提供我們在治療局部復發直腸癌時,作為手術病患選擇及提供適 當治療計劃之參考。

關鍵詞 根治手術、局部復發直腸癌、預測因子。