

Case Analysis

## Clinical Outcome of Salvage Surgery for Stage III Patients with Recurrent Colorectal Cancer

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### Key Words

Salvage surgery;  
Recurrent colorectal cancer

**Purpose.** The aim of this study is to evaluate the survival benefits of salvage surgery as a treatment for recurrent colorectal cancer in stage III patients.

**Methods.** We reviewed 568 cases (treated in Chang Gung Memorial Hospital between 1996 and 2001) of stage III colorectal cancer with recurrence (including metastasis) and analyzed the survival outcomes associated with salvage surgery.

**Results.** The rate of salvage surgery was 30.3%. The 8-year overall and cancer-specific survival rates were higher in patients who had undergone salvage surgery than in those who had not (14.4% and 16.5% v.s. 5.0% and 5.1% respectively,  $p < 0.01$ ). The resection of tumors resulted in long-term survival. The 8-year overall and cancer-specific survival rates were 57.0% and 57.0%, respectively in patients who had undergone lung metastectomy, 30.9% and 35.0%, respectively in those who had undergone liver metastectomy, and 5.0% and 7.1%, respectively in those who had undergone resection of intra-abdominal and pelvic tumor. No long-term survival was noted in patients who had undergone palliative procedures without tumor resection. Although the patients who underwent salvage surgery of lung metastectomy had the best long-term survival outcomes, followed by those who underwent liver metastectomy, however, the observed difference in survival rates between the two types of salvage surgery was not statistically significant.

**Conclusion.** Salvage surgery improved the survival prospects of recurrent colorectal cancer patients. In fact, some patients were cured by salvage surgery. Early detection of tumor recurrence and the appropriate identification of patients requiring salvage surgery are predicted to improve the survival rate of stage III patients with recurrent colorectal cancer.

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Colorectal cancer is a major cause of cancer-related deaths. Approximately half of the patients who are initially treated by surgical resection of their tumors, develop relapses and eventually die of

the disease. Chemotherapy is the mainstay of treatment for recurrent cancer. However, some patients in our study underwent secondary operations in a bid to prevent recurrence of the disease. Indeed some stage

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IV colorectal cancer patients were cured after intensive chemotherapy and salvage surgery. In a previous study salvage surgery was performed on 41% patients with recurrent colon cancer. In half of the patients, the surgery was of curative intent and resulted in a 5-year disease-free survival rate of 23%.<sup>1</sup> After salvage surgery for solitary recurrent rectal cancer, the 5-year overall survival rate was 27%.<sup>2</sup> In contrast, long-term survival is rare in patients with recurrent colorectal cancer who do not undergo surgical resection. In this study, we reviewed the patients with recurrent colorectal cancer and evaluated the survival benefits of salvage surgery.

## Patients and Methods

We reviewed the registered cases of the patients with stage III primary colorectal cancer who had been treated and received regular follow-up in Chang Gung Memorial Hospital from 1996 to 2001. The follow-up schedules included serial serum CEA measurement every three months at least for three years, then every four to six months later; abdominal sonography or CT scan, chest X-ray and colonoscopy every twelve months. Of these patients, 568 were found to have developed recurrent colorectal cancer (including metastasis) during the follow-up periods. The clinicopathologic characteristics, form of recurrent cancer and kind of salvage surgery of these patients with recurrence were recorded for further analysis of survival outcomes. The classification of tumor stage was according to the fourth edition AJCC cancer staging manual published in 1992.

The types of salvage surgery were classified into several categories: liver metastectomy, lung metastectomy, resection of intra-abdominal and pelvic tumors, local excision, palliative procedures without tumor resection and other procedures for metastasis to the brain, bone or organs. The resection of intra-abdominal and pelvic tumor included the operation types of segmental bowel resection, omentum resection, oophorectomy, hysterectomy, cystectomy, low anterior resection, abdomino-perineal resection, intra-abdominal or intrapelvic tumor or metastatic lymph node resection and multiple tumor site resection. The local excision included transanal, perineal local excision and subcutaneous or inguinal nodes resection.

The palliative procedures included the stoma creation, by-pass, laparotomy and other procedures without resection of tumor for relief of patient's symptoms. In colon cancer group, one case received both lung and liver metastectomy was classified into other procedures. Statistical analyses were performed with the SPSS software package for Windows (Version 12.0, SPSS Inc. Chicago, IL, USA). The Kaplan-Meier method and Log-rank test were used to analyze survival and prognostic factors. All *p* values were two-sided; *p* values of less than 0.05 were considered to indicate statistical significance.

## Results

The age of the 568 patients with recurrent colorectal cancer (including metastasis) ranged from 16 to 87 years (mean 61.2 years). These cases included 218 and 350 cases of recurrent colon and rectal cancer, respectively. In total, 172 patients received salvage surgery: 66 for recurrent colon cancer, and 106 for recurrent rectal cancer. The rate of salvage surgery was 30.3% and did not differ between the colon and rectal cancer groups. The recurrent type is shown in Table 1. In recurrent colon cancer, liver metastasis is the most common form of metastasis, followed by lung metastasis, pelvic organ metastasis, bone metastasis and intra-abdominal metastasis. In recurrent rectal cancer,

**Table 1. Types of recurrent tumors in patients with colorectal cancer**

Recurrent type	Colon	Rectum
	Number of cases (%)	Number of cases (%)
Total	218	315
Anastomosis	13 (6.0)	69 (19.7)
Pelvic organ	41 (18.8)	60 (17.1)
Intra-abdominal	27 (12.4)	26 (7.4)
Perineum	0 (0)	7 (2.0)
Inguinal nodes	2 (0.9)	6 (1.7)
Other nodes	12 (5.5)	20 (5.7)
Kidney	0 (0)	4 (1.1)
Lung	80 (36.7)	161 (46.0)
Liver	118 (54.1)	148 (42.3)
Bone	29 (13.3)	78 (22.3)
Brain	15 (6.9)	30 (8.6)
Retroperitoneum	31 (13.8)	25 (7.1)
Others	18 (9.3)	34 (9.8)

Some patients had multiple sites of recurrence.

lung metastasis is the most common type, followed by liver metastasis, bone metastasis, anastomosis recurrence, pelvic recurrence, and intra-abdominal metastasis. The types of salvage surgery for recurrent colon and rectal cancer are shown in Table 2. Resection of metastasis in the intra-abdominal and pelvic organs had the highest incidence, followed by resection of metastasis in the lungs and liver. There was no significant difference between the colon and rectal cancer groups in terms of the rates of surgical procedures carried out. The 8-year overall and cancer-specific survival rates were 14.4 % and 16.5 % respectively in patients managed with salvage surgery of which were significantly higher than the 5.0% and 5.1% , respectively for those who did not receive surgical intervention ( $p < 0.01$ ) (Fig. 1). The survival rates, mean and median survival months according to the specific type of surgery are shown in Table 3. Resection of lung tumors resulted in the highest survival rate, followed by resection of liver and intra-abdominal and pelvic tumors. The 8-year overall and cancer-specific survival rates were 57.0% and 57.0% in patients with lung metasectomy, 30.9% and 35.0% in patients with liver metasectomy, respectively. Both were significantly higher than 5.0% and 7.1% in patients with resection of intra-abdominal and pelvic tumor ( $p < 0.01$ ). Although the survival rates of lung metasectomy were higher than those of liver metasectomy, there was no statistically significant difference. No long-term survival was noted for patients treated with a palliative operation.

### Discussion

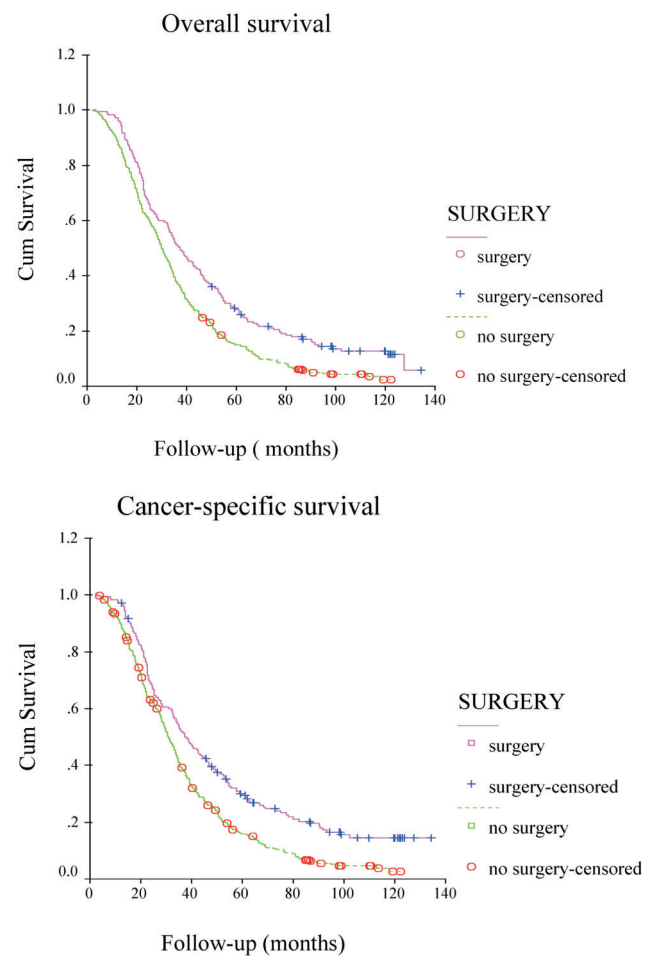
Despite recent advances in systemic chemother-

**Table 2. Types of salvage surgery**

Surgery type	Colon No. of cases (%)	Rectum No. of cases (%)
Total	66	106
Liver metasectomy	9 (14.1)	17 (16.8)
Lung metasectomy	10 (15.6)	9 (8.9)
Intra-abdominal pelvic resection	25 (37.5)	41 (40.6)
Local excision	1 (1.6)	4 (4.0)
Palliative, no resection	13 (20.3)	17 (14.9)
Others	8 (9.4)	18 (14.9)

apy, there is rarely a case of stage IV colorectal cancer being cured by systemic chemotherapy alone. Data from past studies indicate that the complete response (CR) rate achieved with first-line FU/LV (or capecitabine) alone is 1% or lower; that achieved with irinotecan-FU combinations, 2% to 3%; and that achieved with oxaliplatin-FU combinations, 1.5% to 4.5%. The results from the intergroup N7941 study revealed that only 62 (4%) of 1,508 patients achieved a CR with chemotherapy alone, but 84% of these patients developed disease progression during the follow-up periods.<sup>3</sup> Therefore, salvage surgery is vital for improving the long-term survival chances of patients with recurrent colorectal cancer.

In our studies, we found that patients who received lung or liver metasectomy had higher survival



**Fig. 1.** The overall and cancer-specific survival of patients with or without salvage surgery for recurrent colorectal cancer ( $p < 0.01$ ).

**Table 3. The 8-year overall and cancer-specific survival rates (mean/median months) relative to surgical procedures**

Surgical types	Overall (mean/median)	Cancer-specific (mean/median)
Liver metasectomy	30.9 (76.3/57.8)*	35.0 (80.5/86.4)*
Lung metasectomy	57.0 (99.2/98.8)*	57.0 (99.2/98.8)*
Intra-abdominal pelvic resection	5.0 (42.4/34.2)	7.1 (44.7/37.2)
Local excision	0.0 (26.3/19.8)	0.0 (28.4/20.4)
Palliative, no resection	0.0 (28.4/20.4)	0.0 (32.9/28.2)
Others	0.0 (32.9/28.2)	0.0 (38.9/38.9)

\*:  $p < 0.01$  compared to the groups of intra-abdominal pelvic resection, local excision, palliative resection and others.

rates than those who received resection of intra-abdominal or pelvic tumors. This indicates that organ-specific metastasis maybe an important prognostic factor for salvage surgery. In lung metastasis, the five-year survival rates ranged from 32.4% to 60.0% after resection of lung metastasis.<sup>4-7</sup> Following curative resection of lung metastasis, the overall 5-year survival rate was 67.8%. The 5- and 7-year survival rates of patients with a prethoracotomy carcinoembryonic antigen (CEA) level below 5 ng/ml and no lymphatic invasion by a pulmonary tumor were 94% and 79%, respectively. A prethoracotomy CEA level below 5 ng/ml and no lymphatic invasion by a pulmonary tumor in the absence of pathological features of the primary colorectal cancer and previous hepatectomy for liver metastasis and repeated thoracotomy had a positive impact on the survival prognosis.<sup>8</sup> In addition to an elevated CEA level, the number of lung metastasis is a significant prognostic factor for overall survival after the resection of lung metastases originating from colorectal cancer.<sup>9</sup> In our series, the higher survival rates of patients with lung metasectomy than those of liver metasectomy might be resulted from highly selective patients for lung metasectomy.

In liver metastasis, 5-year survival rates ranged from 25% to 40% after resection of liver metastasis.<sup>10-13</sup> The data from the largest retrospective multicentric trial available, which assessed the results of hepatic resections in 1818 patients showed that the 5-year overall survival rates were 26% in all patients, 28% in 1588 patients who underwent resection of isolated colorectal liver metastases and 15% in 250 patients who underwent resection for liver and extrahepatic metastases. None of the 77 patients who had undergone palliative resection survived for 5 years.<sup>14</sup>

In a series study of 350 patients, after potentially curative resection of liver metastasis, the actual 5-, 10- and 20-year survival rates were calculated at 39%, 23% and 17% respectively, with a 33.6% tumor-free survival rate at 5 years.<sup>15</sup> A recent study, using multivariate analysis, revealed 7 risk factors – > 3 hepatic metastases, a node-positive primary tumor, a poorly differentiated primary tumor, extrahepatic disease, tumor diameter  $\geq 5$  cm, CEA level  $> 60$ ng/ml, and positive resection margins – as independent predictors of poor survival after liver metasectomy.<sup>16</sup>

For local recurrent rectal cancer, the survival rate of patients who underwent salvage surgery was higher than that of patients who received conservative treatment. A recent study reported that 44 (75.9%) of 58 patients underwent surgical resection. The overall 5-year survival rate of patients after surgery was 54.2% against 0% for patients who did not undergo surgery ( $p < 0.001$ ). Patients with R0 resection showed a statistically higher 5-year overall survival and local control rates (72.4% and 70.2%, respectively) compared to R1 patients (37.5% and 31.2%, respectively).<sup>17</sup> The feasibility of a surgical resection and radical excision were proved to be independent positive prognostic factors in a multivariate survival analysis. Another study reports that the predictors of survival after salvage surgery include tumor differentiation (well and moderately differentiated), negative lymph node status at the time of the initial operation (pN0), and a perianastomotic pattern of recurrence.<sup>18</sup> In carcinomatosis or other unresectable metastasis as brain or bone, cases of long-term survival were rare.

Salvage surgery can indeed cure some patients with recurrent colorectal cancer. The early detection of tumor recurrence especially locally or in the liver or lungs, and the appropriate selection of patients for

curative-intent salvage surgery and intensive adjuvant chemotherapy are the keystones of survival improvement. The next challenge is to improve intensive post-operative survey after primary tumor resection, so that tumor recurrence is detected as early as possible.

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## 病例分析

# 第三期大腸直腸癌復發的病患進行 拯救性手術的臨床結果

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**目的** 評估拯救性手術對於第三期大腸直腸癌復發病患的存活利益。

**方法** 以回溯性之方法從 1996 年至 2001 年，將在長庚紀念醫院共有 568 位第三期大腸直腸癌復發的病患作存活與拯救性手術之間的相關分析。

**結果** 進行拯救性手術的比例是 30.3%，8 年的整體存活率與癌症相關存活率明顯在有接受拯救性手術這一組比較高 (14.4% 與 16.5% v.s. 5% 與 5.1%)，只有切除復發的腫瘤才能得到比較長的存活期。8 年的整體存活率與癌症相關存活率在切除肺腫瘤這一組是 57.0% 與 57.0%，在切除肝腫瘤這一組是 30.9% 與 35.0%，而在切除腹腔與骨盆腔其他腫瘤這一組則只有 5% 與 7.1%，至於只有進行姑息手術而無腫瘤切除這一組則沒有長期的存活。雖然病人在接受拯救性手術切除肺腫瘤這一組得到最好的存活利益，其次是肝腫瘤這一組，但兩組間並無統計學上的差異。

**結論** 拯救性手術改善大腸直腸癌復發病患的存活，確實有些病患經由拯救性手術而痊癒。早期偵測到腫瘤的復發和適當的選擇病患，拯救性手術將會改善第三期大腸直腸癌復發病患的存活。

**關鍵詞** 拯救性手術、大腸直腸癌復發。