Original Article

Simultaneous Resection for Patient with Resectable Synchronous Colorectal Cancer and Liver Metastasis, Comparing the Result between Laparotomy and Laparoscopic Groups: Our Experience at Chi-Mei Hospital

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Key Words
Colorectal cancer;
Colorectal liver metastasis;
Surgical resection

Purpose. This study aimed to determine the trend and changes demonstrated through our experience with surgical treatment and short-term results of resectable synchronous colorectal cancer with liver metastasis.
Methods. This retrospective study enrolled 37 patients with primary colorectal cancer and associated liver metastasis who underwent simultaneous colorectal and liver resection at Chi Mei Hospital between 2011 and 2017. Twenty-three patients underwent colorectal and liver resection using the open method, and 14 patients underwent laparoscopic surgery. Patients' demographic and clinical data, including operative details, tumor-related parameters, and postoperative outcomes, were analyzed retrospectively.
Results. Demographic features and pathologic results were similar between groups, except for primary tumor location. Although mean operative time was similar between groups (open group 417.39 ± 126.42 minutes vs. laparoscopic group 423.86 ± 146.60 minutes, $p = 0.8922$), mean operative blood loss was greater in the open group (976.09 ± 765.87 ml vs. laparoscopic 546.43 ± 495.54 ml, $p = 0.0458$). Open group patients had significantly more intraoperative blood transfusions than laparoscopic group patients (86.96% versus 35.71%, $p = 0.0028$). No statistically significant differences were found in protective ostomy, post-operative ICU admissions, days of ventilator weaning, duration of ICU stay and post-operative complications. No significant differences were found between groups in postoperative recurrence and overall, disease-free, and cancer-specific survival.
Conclusion. The laparoscopic surgical approach for primary colorectal cancer and liver metastasis is the mainstream approach and the trend at Chi-Mei Hospital. With careful evaluation and patient selection, laparoscopic surgery provides a feasible and safe treatment choice for these patients.
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In Taiwan, colorectal cancer (CRC) is the most common cancer and the third most frequent cause of cancer-related death, accounting for an estimated 5722 deaths in 2016.[1] The liver is the most common site of CRC metastasis, and synchronous liver metastases are found in up to 25% of CRC patients.[2] For these patients, a curative resection (R0) is the only therapeutic chance of long-term survival, although the problem of how to optimally schedule colorectal and liver surgery plus neoadjuvant and/or adjuvant chemotherapy is still debated.[3-7] Results of some studies have also shown that simultaneous resections are not associated with increased hepatic (perihepatic abscess due to translocation of intestinal bacteria or decreased hepatocyte regeneration) or colonic (increased incidence of anastomotic leakage) complications when compared with staged procedures.[8-10] However, despite the increasing use of laparoscopy in colorectal and liver resections, combined minimally invasive resection of the primary colorectal tumor and synchronous liver metastasis is rarely performed. Few studies have directly compared one-stage laparoscopic colorectal resection and liver resection with one-stage open surgery.[11] The aim of this study was to determine the trend and changes demonstrated through our experience with simultaneous surgical treatment and short-term results of resectable synchronous colorectal cancer with liver metastasis.

Materials and Methods

Study sample

Between January 2010 and December 2017, 2854 patients were diagnosed with colorectal cancer at Chi Mei Medical Center. Among them, 525 patients were diagnosed as clinical stage IV (518 patients were single primary colon cancer, 7 patients were multiple primary colon cancer). Of these 525 patients, 383 patients were diagnosed as having CLM, and details of their cases were reviewed retrospectively, as shown below.

Patient selection and definitions

For the purpose of this study, the primary tumor location was divided into three groups: right-side colon, left-side colon, and rectum. The right-side colon includes the cecum, ascending colon, liver flexure, and proximal two thirds of the transverse colon; and the left colon includes the splenic flexure, distal third of the transverse colon, descending colon and sigmoid colon. The diagnosis of liver metastasis was based on the results of imaging studies such as ultrasonography and enhanced computed tomography, or magnetic resonance imaging with/without needle biopsy. Needle aspiration biopsy was performed before treatment only in patients with atypical hepatic mass enhancement. Liver metastases were defined as synchronous whenever they were diagnosed before colorectal resection. Resectability was defined by experienced hepatobiliary surgeons and a radiologist as the ability to immediately achieve complete resection (R0) with an adequate future remnant liver. The estimated liver volume following hepatic resection was > 20% of the total estimated liver volume. The safety limit for the liver parenchymal resection rate was estimated using ICG-R15 and Makuuchi criteria to select patients for hepatectomy. Hepatobiliary surgeons determined the appropriate surgical procedure. Since 2005, a weekly colorectal multidisciplinary team meeting has been held at Chi-Mei Hospital, during which cases of all newly diagnosed patients are discussed. During 2011 and 2017, 48 patients underwent simultaneous surgical procedures for colorectal cancer and liver. Perioperative staging, operative records, and final pathology reports were reviewed for all 48 patients. Exclusion criteria included: 1. patient did not undergo the same open or laparoscopic procedure (e.g., patient who received laparoscopic colectomy + open hepatectomy); 2. Final liver pathology showed benign liver lesion, primary liver tumor, or colon cancer with direct liver invasion (T4 lesion). Finally, 37 patients were enrolled in this study (Fig. 1), among whom 14 cases of simultaneous laparoscopic colorectal and hepatic resection were identified and 23 cases received a totally open procedure.

Main measures

Demographic and clinical characteristics of the

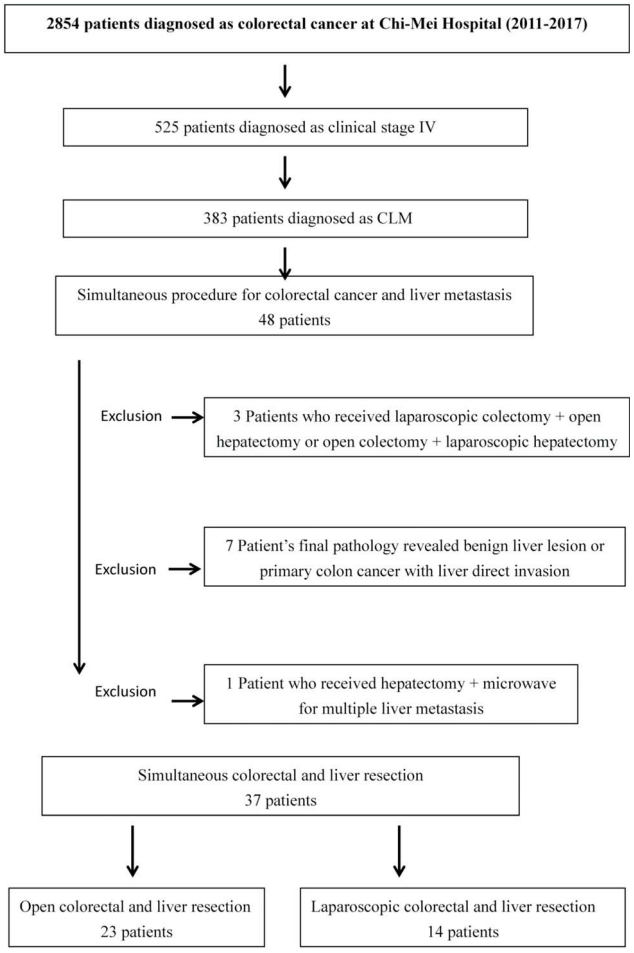

Fig. 1. Diagram of study flow.

included 37 patients are listed Table 1. The follow-up period ended on December 31, 2018. The clinicopathologic characteristics, surgical features, perioperative outcomes, and oncologic outcomes of all patients in these two surgical groups were analyzed.

Statistical analysis

Continuous variables are presented as means with standard deviation (Mean ± SD) with analysis of variance (ANOVA) to compare the differences between the four treatment groups. Categorical variables are presented as frequency with percentage using Pearson's chi-square test or Fisher's exact test to examine the differences. The survival curves are presented using the Kaplan-Meier method, and the log-rank test was used for comparing the differences between the three treatment groups. All data were analyzed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA). The Kaplan-Meier curves were plotted using STATA (version 12; Stata Corp., College Station, TX, USA). Statistical significance was set as $p < 0.05$.

Results

Patients' demographic and clinical data

A total of 37 patients receiving simultaneous resection for colorectal and liver metastasis were enrolled in this study. Twenty-three patients received conventional open-method surgical intervention (open group) and the other 14 patients received laparoscopic surgery (laparoscopic group). The demographic and clinicopathological characteristics for all 37 patients are listed in Table 1. The laparoscopic group had predominant left-sided tumor location ($p = 0.0012$). No significant differences were found between the two groups in the other observed parameters, including mean age, gender, pre-OP CEA level, number of liver metastasis, pathology T/N status, number of lymph nodes harvested, percentage of pathological liver margin involved, percentage of neoadjuvant chemotherapy and adjuvant chemotherapy (Table 1).

Operative features

Operative features focus on the perioperative procedure and post-operative complications, as shown in Table 2. Mean operative blood loss and blood transfusion during surgery were significantly different between the open and laparoscopic groups. The laparoscopic group had significantly less intraoperative blood loss and percentage of blood transfusion than the open group ($p = 0.0458$ and $p = 0.0028$, respectively). No significant differences were found between the two groups in operative time ($p = 0.8922$), method of hepatectomy ($p > 0.999$), creation of protective ileostomy ($p > 0.9999$). Postoperatively, the percentage of ICU admission ($p = 0.5154$), days of ventilator weaning ($p = 0.0966$), duration of ICU stay ($p = 0.1756$), postoperative complication rate ($p > 0.9999$) and surgical mortality were similar between the two groups.

Table 1. Characteristics of 37 CRC patients with resectable liver metastasis compared by surgical group

	Open (N = 23), N (%)	Laparoscopic (N = 14), N (%)	*p*-value*
Age			0.4418
Means ± SD	62.04 ± 8.87	59.36 ± 10.82	
Gender			0.3035
Male	16 (69.57)	7 (50.00)	
Female	7 (30.43)	7 (50.00)	
Pre-op CEA (ng/ml)			0.1589
Means ± SD	115.21 ± 258.01	34.51 ± 51.97	
Tumor location			0.0012
Right side	12 (52.17)	0 (0.00)	
Left side	7 (30.43)	11 (78.57)	
Rectum	4 (17.39)	3 (21.43)	
Number of liver metastases			0.1894
≤ 1	12 (52.17)	10 (71.43)	
1-3	6 (26.09)	4 (28.57)	
> 3	5 (21.74)	0 (0.00)	
Pathology T stage			0.3346
0	0 (0.00)	1 (7.14)	
1	0 (0.00)	0 (0.00)	
2	0 (0.00)	1 (7.14)	
3	14 (60.87)	8 (57.14)	
4	9 (39.13)	4 (28.57)	
Pathology N stage			0.7261
0	3 (13.04)	2 (14.29)	
1	10 (43.48)	4 (28.57)	
2	10 (43.48)	8 (57.14)	
Number of LN harvested			0.0605
Means ± SD	24.04 ± 12.45	18.07 ± 6.17	
Liver margin involved	5 (21.74)	1 (7.14)	0.3761
Neoadjuvant C/T	3 (13.04)	4 (28.57)	0.3895
Post-OP chemotherapy	20 (86.96)	12 (85.71)	> 0.9999

* *p* value was calculated by Fisher exact test. † *p* value was calculated by two sample t Test. # *p* value was calculated by Wilcoxon Rank Sum Test.

Table 2. Operative features by surgical groups

	Open (N = 23), N (%)	Laparoscopic (N = 14), N (%)	*p*-value
Operative time (minutes)			0.8922
Means ± SD	417.39 ± 126.42	423.86 ± 146.60	
Hepatectomy			> 0.9999
Wedge resection	20 (86.96)	13 (92.86)	
Lobectomy	3 (13.04)	1 (7.14)	
Blood loss (ml)			0.0458
Means ± SD	976.09 ± 765.87	546.43 ± 495.54	
Transfusion during operation	20 (86.96)	5 (35.71)	0.0028
Protective ostomy	5 (21.74)	3 (21.43)	> 0.9999
ICU admission	11 (47.83)	5 (35.71)	0.5154
Days of ventilator weaning			0.0966
Means ± SD	2.61 ± 5.76	0.5 ± 0.76	
Duration of ICU stay (days)			0.1756
Means ± SD	3.13 ± 4.38	1.57 ± 2.47	
Complications	11 (47.83)	7 (50.00)	> 0.9999
Intraabdominal infection	4 (17.39)	5 (35.71)	0.2546
Minor bile leakage	4 (17.39)	1 (7.14)	0.6303
Chyle leakage	0 (0.00)	1 (7.14)	0.3784
Pancreatic injury	0 (0.00)	1 (7.14)	0.3784
Wound infection	4 (17.39)	2 (14.29)	> 0.9999
Pneumonia	2 (8.70)	0 (0.00)	0.5165
Ileus	1 (4.35)	0 (0.00)	> 0.9999
Liver abscess	0 (0.00)	1 (7.14)	0.3784
Anastomosis leakage	2 (8.70)	2 (14.29)	0.6246
Post-op stroke	1 (4.35)	0 (0.00)	> 0.9999
Surgical mortality (within 30 days)	0 (0.00)	0 (0.00)	-

* *p* value was calculated by Fisher exact test. † *p* value was calculated by two sample t Test. # *p* value was calculated by Wilcoxon Rank Sum Test.

Recurrence and survival

Median follow-up of all patients was 34.87 months (range 5.67-102.17 months), 30.17 months in the open group, and 37.50 months in the laparoscopic group (Table 3). In total, 15 patients (15/23, 65.22%) in the open group and 10 patients (10/14, 71.43%) in the laparoscopic group developed liver recurrence ($p > 0.9999$). The open group had a respective 3-year overall, disease-free and cancer-specific survival rate of 47.43%, 40.42%, and 54.81%, whereas these respective rates were 77.55%, 35.71%, and 77.55% in the laparoscopic group (Table 3, Figs. 2-4). As shown in Table 3, no statistically significant differences were found in 3-year overall survival, disease-free survival and cancer-specific survival between the two groups ($p = 0.0689$, $p = 0.7866$, $p = 0.1667$, respectively).

Discussion

Simultaneous laparoscopic resection of the primary CRC and associated liver lesions was first performed in our center in September 2014. Within these years, improvement of surgical instruments (endoscopic fluorescence imaging) plus increase of laparoscopic surgical experience, the simultaneous laparoscopic colorectal and hepatic resection became more and more. Since 2014, we had performed 14 cases of simultaneous laparoscopic colorectal and hepatic resection. We show the trends of the simultaneous procedure for colorectal cancer and liver metastasis in Fig. 5. In our series, no significant differences were found in operative times, method of hepatectomy, protective ileostomy, ICU admission, days of ventilator weaning, duration of ICU stay, perioperative complication, surgical mortality, and pathological liver margin involvement between these two groups.

The optimal strategy for resectable synchronous colorectal liver metastasis remains controversial. Although combined resections have been associated with an increase in complications and mortality rates,[12] re-

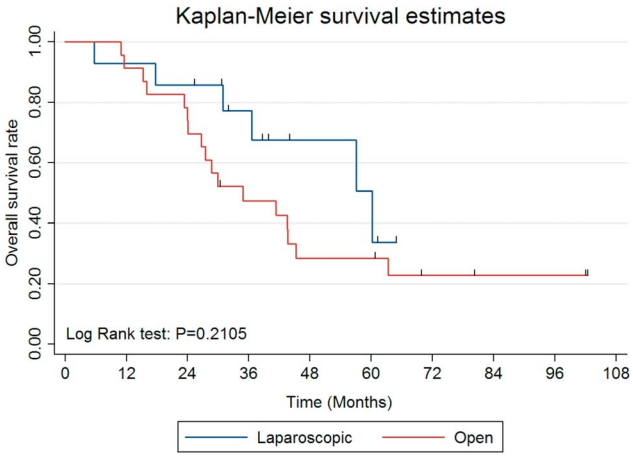

Fig. 2. Kaplan-Meier estimates of overall survival between surgical groups.

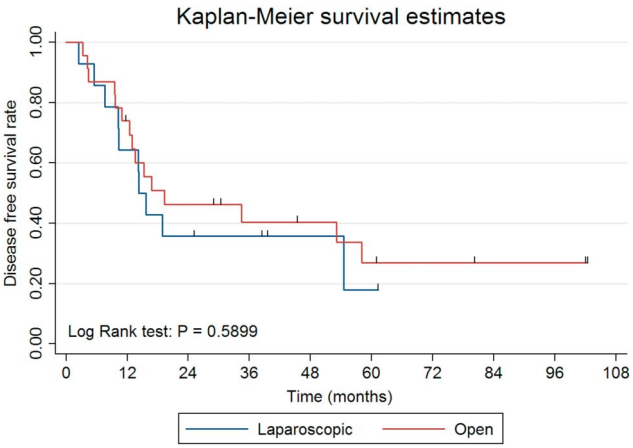

Fig. 3. Kaplan-Meier estimates of disease-free survival between surgical groups.

Table 3. Recurrence and survival between surgical groups

	Open (N = 23)	Laparoscopic (N = 14)	*p*-value*
Median follow-up (months), (Q1, Q3)	30.17, (24.02, 52.97)	37.50, (30.77, 53.74)	0.7222
Recurrence	15 (65.22%)	10 (71.43%)	> 0.9999
3-year overall survival rate	47.43%	77.55%	0.0689
3-year disease-free survival rate	40.42%	35.71%	0.7866
3-year cancer-specific survival rate	54.81%	77.55%	0.1667

* *p* value was calculated by Fisher exact test.

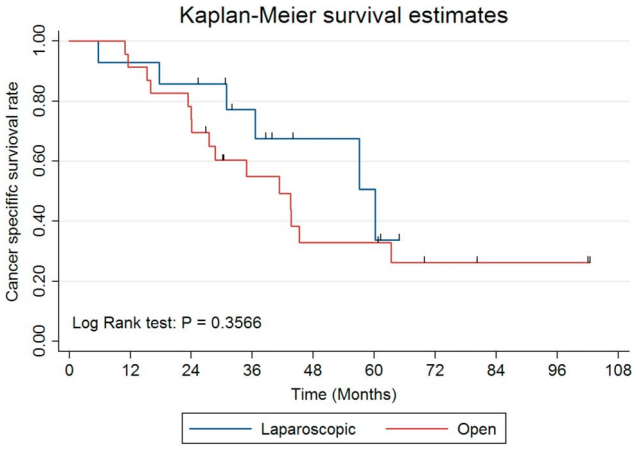

Fig. 4. Kaplan-Meier estimates of cancer-specific survival between surgical groups.

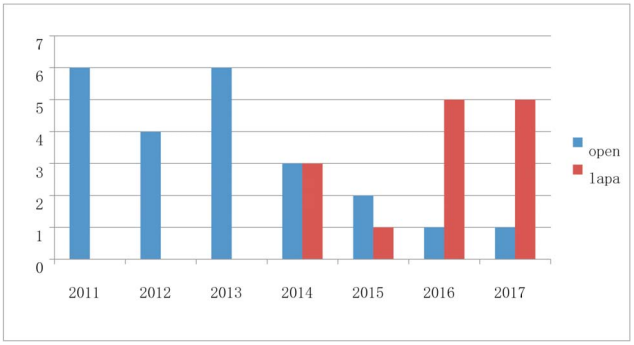

Fig. 5. The trends for simultaneous surgical procedure for colorectal cancer and liver metastasis at Chi-Mei Hospital.

cent studies have confirmed its safety and benefits even when major hepatectomies must be performed.[9,13] One recent multicenter international study that compared simultaneous versus staged approaches showed no differences in morbidity and mortality rates as well as long-term outcomes between the two approaches.[14] Studies of thousands of cases of laparoscopic liver resections concluded that laparoscopy was associated with lower morbidity, less pain, a faster recovery, and a shorter hospital stay than open procedures, without compromising oncologic clearance.[15-19] Initially, we performed simultaneous resection of primary colorectal cancer and liver metastasis using the open method. Subsequently, some surgeons combined a laparoscopic colorectal resection with an open procedure for the liver metastasis. In open hepatectomy, surgical access to the liver involves a lengthy subcostal or bisubcostal incision and fixed costal margin retraction. This incision is required regardless of whether a major or minor liver resection is undertaken. However, this technique leaves a large operative wound in the upper abdomen, which does not allow the advantage of laparoscopy surgery to be presented fully.

The consideration between simultaneous open approach and simultaneous laparoscopic approach toward the resectable synchronous colorectal cancer with liver metastasis is case by case and it was discussed between the colorectal and liver team doctors. If liver tumor locating at liver dome, posterior side of S6, S7, or too many liver tumors, the open approach liver tumor resection is more favored to prevent blood loss and to save operative time. In colonrectal surgical field, most cases could be complete by using laparoscopic approach except severe adhesion, locally advanced tumor invasion.

Parenchymal-sparing resections achieve similar oncologic outcomes to those of anatomic resections while preserving greater hepatic reserve, which potentially increases salvageability in case of hepatic recurrence. Liver parenchymal-sparing with wedge resection is the principle by which CLM is treated in our hospital. The blood loss is less in the laparoscopic groups, which recognizes the importance of hemostasis. The operative principle for laparoscopic surgery is dissection in bloodless planes, and any bleeding encountered must be stopped immediately to prevent loss of the visual field. Hepatic parenchymal transection during laparoscopic hepatectomy can be undertaken using the ultrasonic suction aspirator (CUSA excel, ValleyLab, Boulder, CO, USA) or using an energy device coupled with vascular staplers. This approach permits control of the major hepatic veins within the liver parenchyma. Pneumo-peritoneum may also facilitate hemostasis. In our surgery practice, we advise performing laparoscopic colectomy prior to hepatectomy, for two main reasons. First, hepatectomy sometimes needs hilum control. If the Pringle maneuver is performed, the venous return of the small bowel to the portal vein will be blocked. If hepatectomy takes a long time, swelling of the small bowel is predictable, which make mobilization of the small bowel especially difficult during colectomy. Second,

hepatectomy sometimes has massive blood loss, which means that blood transfusion is required during surgery. Too many fluid supplements or blood transfusions will also result in small bowel swelling.

Limitations

The present study has a few limitations. Because of the retrospective nature of the study, we could not exclude the possibility of selection bias. Moreover, as with many reported studies using this approach, the number of patients in the laparoscopic group was small. Nevertheless, although limited, our experience suggests that simultaneous laparoscopic colorectal and hepatic resection is safe and feasible with acceptable pathology parameters and short-term oncological outcomes.

Conclusion

The laparoscopic approach for primary colorectal cancer and liver metastasis is the mainstream approach and the trend at Chi-Mei Hospital. With careful evaluation and selection of patients, laparoscopic surgery provides a feasible and safe choice of treatment. It may provide an alternative to open procedures when performed by an expert surgical team composed of experienced colorectal and hepatobiliary surgeons. However, further long-term follow-up studies and large-scale studies are still needed to confirm the safety of simultaneous laparoscopic colorectal and hepatic resection.

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原　著

同時切除針對可手術切除的大腸癌合併肝轉移的患者，比較剖腹手術及腹腔鏡手術的成果：奇美醫院的經驗

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目的　該回顧性研究目的，是要分析大腸癌同時合併肝轉移的患者在奇美醫院接受手術治療上的趨勢及改變。

方法　從 2011 年 1 月至 2017 年 12 月，在奇美醫學中心有 2854 位新診斷的大腸直腸癌患者，其中有 37 位大腸癌同時合併肝轉移的患者接受同時性大腸及肝臟切除手術。這些人分成兩組：23 人接受開腹式同時大腸及肝臟切除術，另外 14 人接受腹腔鏡同時大腸及肝臟切除術。病人臨床統計資料，手術細項，術後結果進行分析。

結果　病人個別特徵及腫瘤期別在這兩組是相似的，除了原發腫瘤位置。平均手術時間在此兩組是類似的 (開腹組 417.39 ± 126.42 對比腹腔鏡組 423.86 ± 146.60 分鐘；p = 0.8922)，但平均的失血量在開腹組在統計上是較多 (976.09 ± 765.87 對比 546.43 ± 495.54 mL，p = 0.0458)。因此，在開腹組中手術時輸血的機率對比腹腔鏡組要來的高 (開腹組 86.96% 對比腹腔鏡組 35.71%，p = 0.0028)。而在保護性造口的施作、術後有無入住加護病房、拔管所需天數、加護病房的住院天數、術後併發症等，兩組在統計學上沒有明顯差異的。在術後短期的腫瘤復發率、短期總體生存率、短期無病存活率、短期大腸癌特定存活期等，在此兩組也是沒有統計學上差異的。

結論　腹腔鏡下同時執行大腸及肝臟切除術，在奇美醫院已經是此類患者的手術主流。在小心篩選病人的情況下，腹腔鏡方式是相當安全且可行的手術選擇。

關鍵詞　大腸直腸癌、大腸直腸癌併肝轉移、手術切除。