

Original Article

Minimally Invasive Surgery for Patients with Metachronous Colorectal Cancer

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Key Words

Colorectal cancer;

Metachronous;

Minimally invasive surgery

Purpose. To investigate the clinical outcomes of metachronous colorectal cancer (CRC) patients who underwent minimally invasive surgery.

Methods. From May 2010 to December 2020, we recruited surgical patients with clinical diagnoses of metachronous CRC, defined as a second primary colorectal cancer developing 1-year apart from the primary index cancer. We analyzed the characteristics of the patients, complications, and the following clinical variables: 30-day mortality rate and overall survival. The surgical outcomes of the patients were analyzed using the intention-to-treat principle.

Results. The treatment outcomes of 20 patients were analyzed. Eighteen patients received laparoscopic surgery, and 2 patients underwent robotic surgery. The clinicopathological features were as follows: male/female (15/5), mean age (71.2 years), tumor site (right colon: 12; left colon: 8), stage (adenoma/0/I/II/III/IV: 2/3/5/4/5/1), and time interval between the index and metachronous cancers (range, 1.1-22.6 years; mean, 9.7 years). The surgical outcomes were operation length (mean, 314 minutes; range, 188-541 minutes), blood loss (mean, 237.5 mL; range, 50-500 mL), and the complication rate (Clavien-Dindo classification grades: 2, 20%; 3, 5%). The 30-day mortality was 0%. The estimated 5-year survival rate was 90%.

Conclusions. The present study showed that a minimally invasive approach is feasible for patients with metachronous CRC, without any increases in surgical morbidity and mortality rates. Because metachronous CRC developed an average of 9.7 years after resection of the primary CRC, we recommend further screening for a second primary cancer, even for patients whose CRC has been considered cured after a 5-year follow-up.

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Metachronous colorectal cancer (CRC) is defined as a second primary CRC that develops 6-12 months after colorectal surgery for the primary cancer.¹ Patients with past histories of CRC are at risk of developing metachronous CRC.² Despite the low incidence of metachronous colorectal tumors compared with local recurrence and metachronous metastasis, they remain a problem for CRC patient man-

agement. In recent years, minimally invasive surgical approaches have become the gold standard for CRC surgery because they create smaller wound sizes, produce less wound-site pain, and allow for faster recovery. However, the minimally invasive approach is less used in the treatment of metachronous CRC because the second surgery might be more difficult and riskier, and may encounter problems including adhe-

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sion and distortion of anatomy. Currently, little is known whether minimally invasive surgery provides benefits without increasing complications.

Also, early detection and treatment of the secondary tumor before distant metastasis could reduce disease-related mortality.³⁻⁵ Currently, there is no consensus about screening intervals and surveillance end points for metachronous CRC. The follow-up end point for CRC patients in our hospital is 5 years after curative treatment if there is no evidence of recurrence or a *de novo* neoplasm, but whether this is long enough is still being debated.

Thus, we analyzed the patient characteristics, intraoperative and postoperative variables, intensive care unit (ICU) stays, hospital stays, intervals between the index and metachronous cancers, complication rates, 30-day mortality rates, and the survival outcomes. The aims of our study were to investigate whether minimally invasive surgery is safe and feasible for patients with clinical diagnoses of metachronous CRC, and whether further screening for a second primary cancer after a 5-year follow-up is needed.

Materials and Methods

Patients with clinical diagnoses of metachronous CRC undergoing surgery at the National Taiwan University Hospital (NTUH) from May 2010 to December 2020 were recruited. Metachronous CRC is defined as a second primary colorectal cancer developing one year apart from the primary index cancer. Patients and family members with familial adenomatous polyposis (FAP) were excluded. NTUH patients receive their first post-surgical colonoscopy within 6 months of their index colorectal surgery. Then an annual colonoscopy is arranged, combined with an annual CT scan. Twenty-three patients were recruited for this study. Three patients who underwent traditional open surgery were excluded; therefore, the treatment outcomes of the remaining 20 patients were analyzed.

We analyzed patient characteristics, intraoperative and postoperative variables, intensive care unit (ICU) stays, hospital stays, intervals between the in-

dex and secondary cancers, morbidity during admission, 30-day mortality rates, and survival outcomes.

SPSS software ver. 12 (IBM, Armonk, NY, USA) was used for statistical analyses. The survival outcome is described using the Kaplan-Meier method.

Results

During the 10-year period, a total of 20 patients with clinical diagnoses of metachronous CRC underwent minimally invasive surgery. The patient characteristics are listed in Table 1, and the treatment algorithm for the patients is presented in Fig. 1.

Of the 20 patients, 15 were male (75%). The mean age at the clinical diagnosis of the metachronous cancer was 71.2 years old. We defined the right-sided colon as the cecum, ascending colon, hepatic flexure, and proximal transverse colon and the left-sided colon as the distal transverse colon, descending colon, sigmoid colon, rectosigmoid junction, and rectum. The metachronous cancer was more commonly located in the right-sided colon ($n = 12$, 60%). The time intervals between the index and clinically diagnosed metachronous cancers ranged from 1.1 to 22.6 years (mean, 9.7 years). Seven occurred within 5 years of the index cancers, and 9 occurred more than 10 years after the index cancers (Fig. 2).

The mean intraoperative blood loss volume was 237.5 mL, the mean operation time was 314 minutes, and the mean ICU stay was 0.8 days. Patients started oral water intake on post-operative day 1 and started clear liquid intake after flatus passage; they then advanced to a low-residue diet if they had no discomfort. The mean hospital stay was 22.1 days. For uneventful patients, the mean hospital stay was 16 days. The mean hospital stay for patients with complications was 39 days. Using the Clavien-Dindo classification for complication analysis, 4 patients were class II, and 1 patient was class III. Two patients experienced postoperative ileus, and 3 patients experienced minor leakage. The 30-day mortality rate was 0%.

In our study, final pathology showed 2 patients had adenomas, 3 patients had adenomas with focal high-grade dysplasia (stage 0), and 5, 4, 5, and 1 pa-

Table 1. Patient characteristics

| | |
|---|-----------------------|
| Total No. of patients | 20 |
| Gender | |
| Male (n (%)) | 15 (75%) |
| Female (n (%)) | 5 (25%) |
| Age at index cancer (years, mean ± SD) | |
| ≤ 50 (n (%)) | 6 (30%) |
| > 50 (n (%)) | 14 (70%) |
| Location of index cancer | |
| Right (n (%)) | 2 (10%) |
| Left (n (%)) | 17 (85%) |
| Synchronous (n (%)) | 1 (5%) |
| Age at clinically diagnosed metachronous cancer (years, mean ± SD) | |
| ≤ 50 (n (%)) | 0 (0%) |
| > 50 (n (%)) | 20 (100%) |
| Location of clinically diagnosed metachronous cancer | |
| Right (n (%)) | 12 (60%) |
| Left (n (%)) | 8 (40%) |
| Pathological TMN staging | |
| Adenoma (n (%)) | 2 (10%) |
| Stage 0 (n (%)) | 3 (15%) |
| Stage I (n (%)) | 5 (25%) |
| Stage II (n (%)) | 4 (20%) |
| Stage III (n (%)) | 5 (25%) |
| Stage IV (n (%)) | 1 (5%) |
| Interval between index and clinically diagnosed metachronous cancer (years, mean ± SD) | |
| | 9.7 ± 7.2 |
| Surgery for clinically diagnosed metachronous cancer | |
| Laparoscopic (n (%)) | 18 (90%) |
| Robotic (n (%)) | 2 (10%) |
| Blood loss (mean, range) | 237.5 mL (50-500) |
| Operation time (mean, range) | 314 minutes (188-541) |
| ICU stay | 0.8 days (0-6) |
| Hospital stay (mean, range) | 22.1 days (9-55) |
| Hospital stay of uneventful patients (mean, range) | 16 days (9-38) |
| Hospital stay of patients with complications (mean, range) | 39 days (28-55) |
| Complication | |
| Clavien-Dindo classification = 2 (n (%)) | 4 (20%) |
| Clavien-Dindo classification > 2 (n (%)) | 1 (5%) |

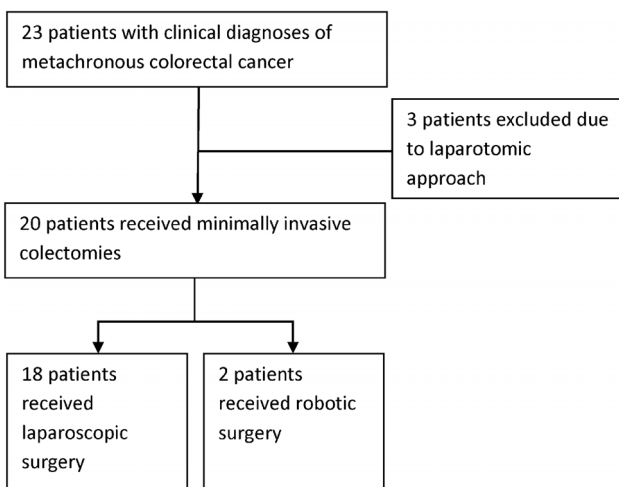


Fig. 1. Patient recruitment algorithm.

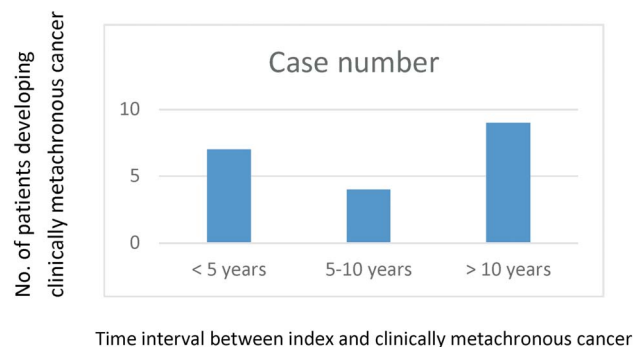


Fig. 2. Time intervals between index and clinically metachronous cancers.

tient had stage I, stage II, stage III, and stage IV cancers (liver metastasis), respectively.

The 5-year overall survival was 90% (Fig. 3). One patient died of aspiration pneumonia 58 days after surgery, and another patient died of pneumonia 73 days after surgery.

Discussion

Surgical intervention for resectable metachronous CRC has been the mainstay of treatment modalities. Surgical intervention includes traditional open and minimally invasive approaches, and the latter features smaller wound sizes, reduced wound pain, shorter hospital stays, and faster recoveries. However, some surgeons may question the advantage of minimally invasive approach for metachronous CRC, and may concern about the complication. Because the inevitable adhesiolysis procedure may be technically tedious and time-consuming when using a laparoscope, especially for patients whose anatomical structures have been distorted by a previous surgery for an index cancer. Generally, traditional open surgery approach is preferred for patients who need second surgeries. In our study, the mean operation time was much longer for minimally invasive surgery for metachronous CRC, with a mean blood loss of 237.5 mL. Only 2 (10%) patients had blood losses reaching 500 mL and required blood transfusions. No patients required conversion to open surgery. Anastomotic leakage, which occurred in 3 patients, remained the most common complication after the surgery; only 1 of these 3 patients required ileostomy creation, and another 2 patients only received conservative treatment. Based on our data, the minimally invasive approach is feasible, even for patients with clinical diagnoses of metachronous CRC.

We observed that 7 patients were clinically diagnosed with metachronous CRC within 5 years of the index cancer (short-interval group). Among these 7 patients, one patient had tubulovillous adenoma according to the pathology report. The pathological staging of the other 6 patients were as following: 2 were stage I, 2 were stage II, 2 were stage III. We also observed that 9 patients were clinically diagnosed with metachronous cancer more than 10 years apart from their index cancers (long-interval group). One of these

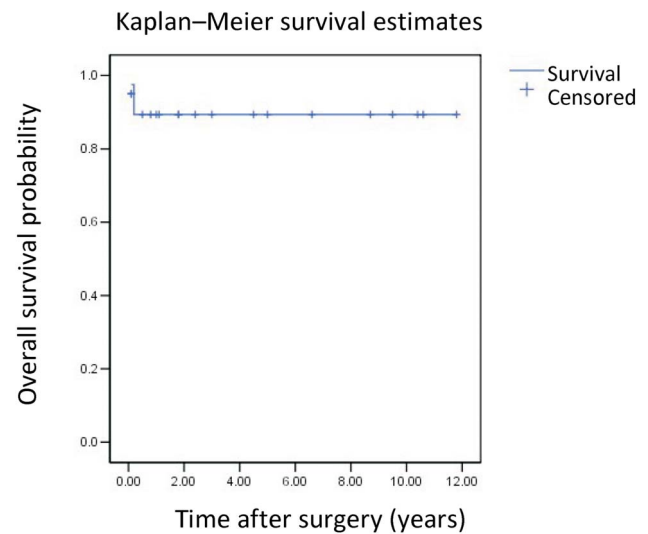


Fig. 3. Survival curve determined by the Kaplan-Meier method.

nine patient had tubulovillous adenoma according to the pathology report. The pathological staging of the other 8 patients were as following: 3 were stage I, 2 were stage II, 2 were stage III, 1 was stage IV. By comparing these two groups, although patients in the short-interval group received annual colonoscopies and CT scans, there was no significant reduction in advanced stage metachronous cancer.

According to the data reported by Park et al. in 2005, about 66.7% of the metachronous CRC were developed within 5 years after the diagnosis of the index cancer, 33% were developed 5 years after the index cancer.⁶ Our data showed that only 35% of the metachronous CRC were developed within 5 years, 65% were developed 5 years after the index cancer. One possible explanation is that the risk of development of metachronous cancer increased continuously according to time after diagnosis of index cancer.⁶ Due to longer follow up time, our data have more patients with longer interval (1.1 to 22.6 years, mean 9.7 years) compared to the data from Park et al. (0.5 to 17.9 years, mean 3.25 years).⁶

For patients no longer receiving annual colonoscopies who developed metachronous cancer more than 5 years after the index cancer, most were diagnosed with metachronous cancer at the time of symptom development. If annual surveillance could be maintained, early diagnosis of metachronous cancer could be achieved.

Postoperative colonoscopies and image studies are probably the most important keys to early detection of metachronous cancer.⁷ An appropriate surveillance end point for metachronous CRC is still under debate. Colon polypectomy may lower the risk of metachronous CRC development in patients with classic adenoma-carcinoma sequences.³⁻⁵ Thus, a surveillance period of up to 8-9 years has been suggested.⁸ Although the risk of developing metachronous cancer does not decrease 5 years after the index cancer, annual colonoscopies for longer than 5 years may be difficult to achieve due to poor patient compliance.⁶ The use of screening tools other than colonoscopies, such as annual fecal occult blood tests, may be an alternative.

The limitations of our study are the small sample size, lack of colonoscopy data 5 years after the index surgery for some of the patients, and a lack of mismatch repair status data for some patients. We also lacked sufficient control group patients who received open surgery. An additional study with a larger sample size and a control group (open surgery for metachronous CRC) is needed.

Conclusion

Despite a longer operation time, minimally invasive surgery is safe and feasible for patients with clinical diagnoses of metachronous CRC. Good overall survival was achieved for patients with metachronous

CRC. For patients at risk of developing metachronous CRC, colonoscopy surveillance longer than 5 years after the index cancer is still required.

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None reported.

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原 著

微創手術治療異時性大腸直腸癌之探討

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目的 藉由本研究呈現微創手術使用於異時性大腸直腸癌之治療成效。

方法 我們回溯性蒐集臨床診斷異時性大腸直腸癌（與第一次大腸直腸癌手術後相隔一年以上新診斷之大腸直腸癌），於 2010 年 5 月至 2020 年 12 月間接受微創手術（腹腔鏡或機器人手臂輔助手術）之病患。病患之臨床資訊、術中及術後臨床資料與併發症比例、加護病房住院日數、總住院日數、三十日內死亡率、五年存活率等皆蒐集並加以分析。

結果 共計二十名病患被納入此篇研究。十八位病人接受腹腔鏡手術，兩位病人接受機器人手臂輔助手術。男女比為 3:1，平均年齡 71.2 歲。十二位病人其腫瘤位置位於右側大腸，八位位於左側大腸。距離第一次手術平均為 9.7 年。平均手術耗時 314 分鐘，術中出血 237.5 毫升。手術後出現併發症共五人 (25%)，其中兩位病患為術後腸阻塞，皆經保守治療後順利出院。其他三位出現腸滲漏，僅一人須接受小腸造口術。手術相關三十天內死亡率為 0%，五年存活率為 90%。

結論 本研究顯示以微創手術治療異時性大腸直腸癌，其手術併發症發生機率與死亡率為可接受的。本研究中異時性大腸直腸癌的發生距離第一次手術平均為 9.7 年，建議對於大腸直腸癌術後已追蹤五年無復發之病人，應繼續保持追蹤計畫。

關鍵詞 大腸直腸癌、異時性、微創手術。