

Original Article

## Infrequent Metastatic Site in Diffuse Metastatic Colorectal Cancer – A Review from a Tertiary Referral Center

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### Key Words

Colorectal carcinoma;  
Infrequent metastasis site

**Background.** Approximately 50% of patients with colorectal cancer (CRC) will develop metastasis eventually. The liver is the most common metastatic site followed by the lungs. CRC metastases to other sites are less frequently reported, even in diffuse metastatic cases. The aim of this study was to determine the incidence and tumor characteristics of infrequent metastases site in CRC.

**Patients and Methods.** A total of 7198 patients with CRC were reviewed from a prospectively maintained database and 25 patients (0.35%) with diffuse metastatic CRC were found to have infrequent metastases site. The general data of the patients, characteristics of the primary tumor, metastatic sites, treatment strategy, and outcomes were reviewed and analyzed.

**Results.** There were 13 male patients and the median age was 64 years. The median survival time after presentation of an infrequent metastasis was 12 months (range 0-56 months). Twenty cases had uncommon metastases from colon cancers. All of the patients had concurrent metastases. The most common infrequent metastasis site was the adrenal gland (n = 11), followed by the spleen (n = 6), kidneys, colon, uterus, and skin (n = 1 each). A survival benefit was observed in patients who underwent combined therapy (surgery with chemotherapy ± radiotherapy).

**Conclusions.** CRC patients might develop infrequent site metastasis. Its occurrence was part of widely disseminated disease, and the prognosis was poor. Combined therapy provided a better survival outcome for these patients.

[J Soc Colon Rectal Surgeon (Taiwan) 2017;28:119-124]

Colorectal cancer (CRC) is the most frequently encountered cancer and the third among the top 10 causes of tumor-related deaths in Taiwan.<sup>1</sup> Patient survival of CRC for all stages has improved in recent decades, which may be related to detection and removal of colonic polyps, detection of CRC at an earlier stage, and more effective treatments.<sup>2</sup> Nonethe-

less, approximately 20% of patients with CRC present with metastasis at diagnosis (i.e., stage IV disease),<sup>3</sup> while approximately 30% of stage I-III CRC patients developed distant metastases during their lifetime. Metastasis is the most common cause of CRC mortality. Metastatic CRC occurs through lymphatic, hematogenous, contiguous, or transperitoneal routes.

Received: July 23, 2016.

Accepted: October 21, 2016.

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Common sites of metastasis included the liver, lungs, peritoneum, bones, brain, and ovaries, while metastasis to other organs, e.g., the adrenal glands, kidneys, spleen, or skin, are very rare and are presented in the literature only as case reports, even in diffuse metastatic CRC.

In this study, based on the computerized database of Taipei Veterans General Hospital, a retrospective review of patients with infrequent metastases secondary to CRC was conducted. Our aim was to determine the incidence and characteristics of the tumors, and additionally, the strategies for management and the outcomes of these patients were reported.

## Patients and Methods

Data were collected from a prospectively maintained database. A total of 7198 consecutive cases of CRC were registered between January 2002 and December 2013. Of the 7198 cases, 1263 patients were identified with metastatic disease. An infrequent metastasis was defined as metastasis to an organ other than the liver, lungs, brain, bones, ovaries, or peritoneum. Twenty-five cases were identified with infrequent metastases, which accounts for 2.0% of all metastatic cases. Patients with anal malignancy and colorectal malignancies other than adenocarcinoma were excluded from this study. Information regarding the general data of the patients, characteristics of the primary tumors and metastases, treatment strategy, and survival of the patients were recorded.

## Statistical analysis

All statistical analyses were performed with the Statistical Package for the Social Sciences (SPSS version 16.0, SPSS Inc. Chicago, IL). Statistical analysis was performed using Student's *t*-test and analysis of variance for comparison of the means. Qualitative parameters were compared with the chi-squared test. Overall survival was computed using the Kaplan-Meier method. Values with  $p \leq 0.05$  were considered significant.

## Results

Demographic data of the patients with infrequent metastases are shown in Table 1. There were 13 men and 12 women. The primary lesions were 20 colon cancers and 5 rectal cancers. The incidence of unusual metastasis was 2.0% among all metastatic cases. The incidence of infrequent metastasis from colon cancer was 2.0% among all colon cancer cases with metastasis and 1.5% for rectal cancer. The primary tumor tended to be advanced (all patients were T3 or 4 and 18 were N-positive cases), and all of the infrequent metastases presented with concurrent metastases.

Table 2 demonstrates the sites of infrequent metastases. The adrenal gland was the most common site

**Table 1.** Demographics of patients with infrequent metastasis

Demographics	
Gender (M:F)	13:12
Age (years old)	64 (range: 36-93)
Location	
Colon	20
Rectum	5
T stage	
T1-2	0
T3	15
T4	10
N stage	
N0	7
N1	1
N2	17
Metastasis pattern	
Solitary	0
With concurrent metastasis	25
Overall survival (months)	20 (range: 0-56)
Overall survival after unusual metastasis (months)	12 (range: 0-56)

Figures were median (range).

**Table 2.** Infrequent metastatic sites

Infrequent metastatic site	No. of patients (%)
Adrenal gland	11 (44.0%)
Kidney	3 (12.0%)
Spleen	6 (24.0%)
Abdominal wall	2 (8.0%)
Colon	1 (4.0%)
Uterus	1 (4.0%)
Skin	1 (4.0%)
Total	25

of infrequent metastasis ( $n = 11$ , 46%), followed by the spleen ( $n = 6$ , 25%) and kidneys ( $n = 3$ , 12.5%). One unusual case developed a colon-to-colon metastasis. A 1.0-cm submucosal tumor was found at the cecum incidentally during exploratory laparotomy for an obstructive sigmoid colon cancer. There was no direct invasion of the tumor, and no peritoneal cancerous seeding was found. A similar morphology to the primary tumor was reported by the pathologist, and a metastatic adenocarcinoma was confirmed. To the best of our knowledge, this is the first colon-to-colon metastasis reported in the literature.

Nine cases developed infrequent metastases during the treatment of metastatic CRC, while 16 cases presented with concurrent metastasis. The liver was the most common site of concurrent metastasis ( $n = 17$ ), followed by the lungs ( $n = 12$ ) (Table 3).

The median overall survival was 20 months (range: 0-56 months) and median survival after presentation of the infrequent metastasis was 12 months (range: 0-56 months) (Table 1). Univariate analysis for overall survival after diagnosis of infrequent metastasis revealed no significant difference between sexes or the location of the primary tumor (Table 4). However, a significant difference in survival was observed between combined treatment (surgery followed by chemotherapy  $\pm$  radiotherapy) and surgery alone (Table 4, Fig. 1). We then compared overall survival for multiple metastases with or without an infrequent metastasis and there was no significant survival difference between the two groups ( $17.8 \pm 1.3$  vs.  $13.1 \pm 13$  months,  $p = 0.248$ ) (Table 5).

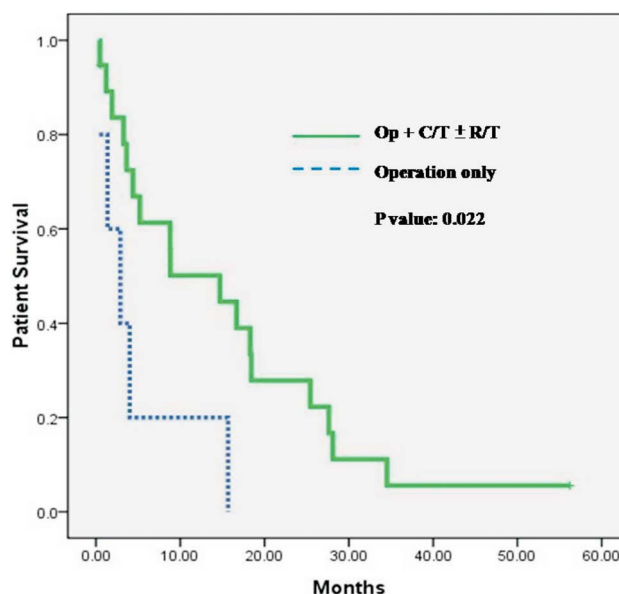
## Discussion

Approximately 50% of patients with CRC eventu-

ally develop distant metastasis.<sup>3,4</sup> Metastatic CRC occurs through lymphatic, hematogenous, contiguous, or transperitoneal routes. The most common metastatic site is the liver, followed by the lungs. The ova-

**Table 4.** Univariate analysis of overall survival after discovery of infrequent metastasis

Variable	No. of patients	Mean survival time $\pm$ SD (months)	<i>p</i> value
Gender			0.159
Male	13	$3.6 \pm 0.6$	
Female	12	$15.6 \pm 6.2$	
Location of primary lesion			0.97
Colon	20	$8.8 \pm 4.6$	
Rectum	5	$5.2 \pm 2.5$	
Treatment			0.022
Operation only	5	$2.9 \pm 1.6$	
Combined (OP + C/T $\pm$ R/T)	20	$14.7 \pm 6.2$	



**Fig. 1.** Overall survival curve between combined treatment and surgery alone.

**Table 5.** Comparison of overall survival between multiple metastases with and without infrequent metastasis

Variable	No. of patients	Mean overall survival $\pm$ S.D. (months)	<i>p</i> value
Metastases			0.248
With infrequent metastasis	25	$17.8 \pm 1.3$	
Without infrequent metastasis	154	$13.1 \pm 2.8$	

**Table 3.** Concurrent metastatic sites

Concurrent metastatic site	No. of patients
Liver	17
Lung	12
Ovary	4
Peritoneum	4
Bone	1

ries, bones, brain, and peritoneum are less common sites of metastasis. In a literature review, approximately 10-25% of patients have liver metastasis at their initial presentation,<sup>5,6</sup> and approximately 10% of patients develop lung metastasis at diagnosis.<sup>7,8</sup> The incidences of bone, ovary, and brain metastasis are 6%, 3-7%, and 3%, respectively.<sup>9-11</sup> Eight percent of CRC patients are diagnosed with synchronous peritoneal seeding.<sup>12</sup>

CRC with metastasis to the adrenal gland, spleen, kidney, or abdominal wall occurs infrequently, and these cases usually presented as disseminated disease. Isolated metastasis to infrequent sites is very rare.<sup>13,14</sup> Similarly, in our study, all infrequent metastasis cases had concurrent metastases. Sixteen cases (64%) presented with concurrent metastasis, while 9 cases developed infrequent metastasis during the treatment of metastatic CRC. The incidence of adrenal metastasis was reported to be between 1.9% and 17.4%.<sup>15,16</sup> Bracken et al. reported the incidence of kidney metastasis from CRC was 2.7% in 11328 patients at autopsy. Cutaneous metastasis secondary to CRC is very rare, with a large series from south Taiwan reporting an incidence of 0.81%. In this study, the incidences of adrenal, kidney, and skin metastasis were 0.15%, 0.04%, and 0.01%, respectively, which are lower than that reported in the previous literature. One of the possible reasons could be that, in our database, only patients who underwent surgery were collected, and thus, patients who presented with disseminated disease and then underwent chemotherapy only were not enrolled in the current study.

Colon cancer and rectal cancer are thought to be heterogeneous disease entities. Colon cancer patients tend to develop more intra-abdominal metastasis, such as peritoneal seeding, omental seeding, or ovarian metastases, while rectal cancer patients frequently develop extra-abdominal metastases, such as lung and brain metastases.<sup>17</sup> The proposed mechanisms are the different venous drainage and anatomic location of the primary CRC. Because colon cancer is located in the peritoneal cavity, metastasis through the transperitoneal route can result in peritoneal seeding and/or ovarian metastases. Rectal cancer can spread hematogenously through the iliac vein and central vein,

which results in distant lung or brain metastases.

However, there was no significant difference in the incidence of infrequent metastases between colon cancer and rectal cancer in our study. We believe that infrequent metastasis is part of disseminated disease and most of our cases had concurrent metastases; meanwhile, their incidence was very low, and therefore, no significant difference was observed between colon and rectal cancer.

The treatment strategy for patients with infrequent metastases may be a topic of interest. Some studies reported that resection of isolated infrequent metastasis could prolong survival.<sup>18,19</sup> However, surgical resection of concurrent infrequent metastases remains controversial because they are usually considered as a systemic disease.<sup>20</sup> In this study, when we compared combined therapy (operation for the primary tumor, followed by chemotherapy  $\pm$  radiotherapy) and operation alone (for the primary tumor), we found a significantly better survival among patients who underwent combined therapy. All of our infrequent metastasis cases had concurrent metastases, and therefore, systemic therapy could contribute to a better survival. On the other hand, in the survival analysis, there was no significant difference between patients with multiple metastases with and without infrequent metastases.

Cases of infrequent metastasis from CRC are rare and most of the literature is in the form of case reports or small case series; therefore, discussions regarding treatment strategy and survival analysis are limited. Our report is by far the largest series demonstrating infrequent metastasis from diffuse metastatic CRC in one single institute; we also addressed treatment strategy and survival outcome. We demonstrated that the incidence of infrequent metastasis of CRC is low. Its occurrence is part of wide disseminated disease and the survival outcomes are dismal. Combined therapy offered better survival outcomes for these patients. Nonetheless, this study was limited by its retrospective nature and low patient numbers.

## Sources of Support

None.

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原 著

## 瀰漫型轉移大腸直腸癌合併少見器官轉移 —— 一個三級轉診中心經驗之回顧

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**背景及目的** 大約 50% 的大腸直腸癌病人最終都會發生遠端轉移的情況。最常見的是肝及肺的轉移。大腸直腸癌轉移到其他器官則很少被報告，即使是在瀰漫性轉移大腸直腸癌的病例中。本篇研究是希望能藉由一個台灣的三級轉診中心之瀰漫性轉移大腸直腸癌合併少見器官轉移的病例來了解瀰漫性轉移大腸直腸癌合併罕見器官轉移的發生率以及腫瘤之型態。

**方法** 共有 7198 個大腸直腸癌病例被回溯分析，其中 25 個瀰漫性轉移大腸直腸癌病人 (0.35%) 發現有少見器官轉移。我們針對病患的一般資料，原發及轉移腫瘤的特性，同時合併的其他轉移部位，治療的方式及結果，作一回顧整理與分析。

**結果** 共有 13 位男性病人，平均年齡是 64 歲。發現少見器官轉移後的平均存活時間為 12 個月 (範圍從 0 到 56 個月)。原發腫瘤的位置，20 位在大腸。所有病人都有合併其他器官轉移。最多的少見器官轉移部位是腎上腺 (11 位病人)，然後是脾臟 (6 位病人)，再來是腎、大腸、子宮以及皮膚 (各 1 位病人)。在接受手術加上化學治療的病人能夠觀察到較好的存活率。

**結論** 臨床上瀰漫性轉移大腸直腸癌併發少見器官轉移的情形並不常見。它是末期腫瘤的一部分且有差的預後，但手術合併化學治療可以提供病人較好的存活率。淋巴結數目及淋巴結摘取數目比率，無法對第三期大腸直腸癌預後，提供精準的預測。

**關鍵詞** 大腸直腸癌、少見器官轉移。