

# Clinicopathology and Outcomes of Small Bowel Metastases: A Retrospective Study of 31 Consecutive Cases

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## Research

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# Abstract

## BACKGROUND

The small bowel (SB) is a rare site for distant metastasis. Few recent studies have systematically reported on the clinicopathology and outcomes of SB metastasis. This study aimed to describe the clinicopathology and outcomes of SB metastasis.

## METHODS

A retrospective study involving patients diagnosed with SB metastasis at a single medical center between January 2009 and December 2019 was conducted. Patients with secondary SB cancer with direct invasion or peritoneal carcinomatosis by a primary tumor were excluded. The demographic characteristics of the patients, clinical patterns of primary cancer and SB metastasis, and outcomes were analyzed.

## RESULTS

During the 10-year period, we identified 31 patients eligible for analysis. The female:male ratio was 8:24, and the median patient age was 63.5 years. Metastasis of lung cancer to the SB was noted most frequently. Most patients presented with abdominal pain, gastrointestinal bleeding, or abnormal imaging findings. The interval between primary cancer and SB metastasis was 19.2 months. Sole SB metastasis was noted in 20 patients (64.5%). Twenty-two (70.1%) patients underwent surgical intervention. The median survival was 6.6 months.

## Conclusions

Distant metastasis of other primary cancers to the SB is noted extremely rarely. The presence of SB metastasis indicated extremely poor prognosis. Surgery plays an important role in ameliorating critical symptoms. However, surgery does not confer survival benefits.

## Introduction

Although the small bowel (SB) is a major organ that occupies a large proportion of the abdominal space, it is rarely a site for distant metastasis from other primary cancers. Most cases of cancerous involvement of the SB occur through direct invasion or peritoneal carcinomatosis of a primary malignancy. However, the actual incidence of SB metastasis from all cancer types is unclear, and systemic descriptions of SB metastasis are limited[1, 2].

*Organ tropism* is a phenomenon describing a predilection of certain cancers to metastasize to specific organs. The mechanism of *organ tropism* may be associated with the route of spreading of primary cancers. Clinically, certain cancer types, such as lung cancers or melanomas, are more likely to metastasize to the SB[3, 4]. Other types of cancer metastasizing to the SB have only been described in case reports. Therefore, this study aimed to describe the clinicopathology and oncological outcomes of SB metastasis in a systemic manner by excluding the conditions of direct invasion and peritoneal carcinomatosis by primary tumors. It also aimed to further analyze the pattern of SB metastasis.

## Materials And Methods

### Patient selection

Between January 2009 and December 2019, a total of 31 patients who were diagnosed with SB metastasis at National Taiwan University Hospital were recruited for the study.

Secondary SB metastasis was defined as a malignancy that was found to grow on the SB (including the duodenum, jejunum, and ileum) but originated from another site as proven by the pathologist's report.

The inclusion criteria were: (1) diagnosis of secondary SB metastasis; and (2) primary malignancy diagnosed prior to or concomitant with secondary SB metastasis. Exclusion criteria were: (1) SB directly invaded by an adjacent cancer; (2) SB cancer was involved cancerous carcinomatosis; and (3) presence of hematological malignancy such as lymphoma or leukemia.

The clinical characteristics of the patients, including age, sex, site, and pathology of the primary cancer as well as the treatment of the primary cancer, were recorded. The symptoms and signs as well as the treatment of SB metastasis were recorded.

The date of the last follow-up was February 29, 2020. The date of the diagnosis of primary cancer was defined as the reported date of pathological analysis or surgery (if the date on which the pathology report was obtained was not available). As this was a retrospective study, some data were roughly documented and should be defined here. If only the month was recorded, we approximated the date base on the 15th day of the month. If only the year was recorded, we approximated the date base on the 15th day of the month.

The survival data of all patients were collected and updated by telephone interviews. The survival status of each patient was updated. If the actual date of death of the patient was not provided by the family, we used the last follow-up date as the date of death of the patient. The patients were followed up based on the clinical guidelines for the corresponding primary cancer.

### Statistical method

Continuous parameters are presented as mean  $\pm$  standard deviation, while categorical variables are presented as frequency and percentage. We used the Mann-Whitney U test for continuous variables and

Fisher's exact test for categorical variables to compare the clinical features of sole SB metastasis versus SB metastasis plus multiple distant metastases. Kaplan-Meier survival curves were used to calculate the overall survival. *P* values less than 0.05 were considered significant, and all statistical tests were two-sided. Small Stata 13.0 software (TX, USA) for Windows was used to perform the Kaplan-Meier survival curve analysis, while SAS 9.4 software for Windows was used to analyze the other data.

## Results

### Demographics and clinicopathology

A total of 31 patients were eligible for the study. The male:female ratio was 8:24, and the median patient age was 63.5 years. The most common primary tumor site was the lung (*n* = 11), followed by the liver (*n* = 3), melanoma (*n* = 2), and tongue (*n* = 2).

Abdominal pain was the most frequent clinical manifestation, affecting 12 patients (38.7%). Seven patients (22.6%) were asymptomatic and diagnosed with SB metastasis on imaging studies, including computed tomography or panendoscopy (Additional file 1). Surgical resection was the main treatment for primary cancer (*n* = 19). The mean interval between primary malignancy and SB metastasis was 19.2 months. The clinicopathological parameters are listed in Table 1.

Table 1  
Clinicopathological data

Variable	N (%)
Age (years) (median [range])	63.5 (39–82)
Gender (female/ male)	7/24
Primary cancer and its pathology	
Hepatocellular carcinoma	3
Lung cancer	
Squamous cell carcinoma (SCC)	1
Adenocarcinoma	5
Sarcomatoid carcinoma	1
Pleomorphic carcinoma	2
Non-small cell carcinoma	1
Melanoma	2
Tongue SCC	2
Hypopharyngeal SCC	1
Cervical cancer, adenocarcinoma	1
Endometrial cancer	
Endometroid adenocarcinoma	1
Bladder urothelial cell carcinoma	2
Renal cell carcinoma	1
Peripheral nerve sheath sarcoma	1
Heart, sarcoma	1
Colon cancer, adenocarcinoma	2
Breast cancer, adenocarcinoma	1
Pancreatic cancer, adenocarcinoma	1
Gastric cancer, adenocarcinoma	1
Unknown, adenocarcinoma	1
Treatment of primary cancer	

Variable	N (%)
Surgery	20
Chemotherapy/ radiotherapy	11
Initial clinical presentation of SB metastasis	
Abdominal pain	12
Abdominal fullness/nausea/vomiting	4
GI bleeding	8
Abnormal image findings	7
Interval between primary cancer and small bowel metastasis (months) (median $\pm$ SD) 1	19.2 $\pm$ 47.8
1 Four patients who was presented with SB metastasis at initial time were excluded.	

The sites of SB metastasis were equally distributed in the duodenum (n = 10 [31.3%]), jejunum (n = 10 [31.3%]), and ileum (n = 11 [35.1%]). Afferent loop metastases were noted in 1 patient who underwent gastrectomy and Billroth II reconstruction.

Surgery was the main treatment for patients with acute abdomen, including peritonitis, bleeding, obstruction, and intractable pain (n = 18), and to relieve symptoms (n = 4). Surgical resection was the mainstay procedure for SB metastasis (n = 21). One patient underwent partial resection of the duodenum owing to duodenal metastasis. Colon resection (n = 2) and salpingectomy (n = 2) were performed concomitantly owing to metastatic involvement (Table 2). Seventeen patients received chemotherapy, targeted therapy, hormone therapy, and radiotherapy for metastatic cancer.

Table 2  
Clinical features and oncological results

Variable	N (%)
Site of small bowel metastasis	
Duodenum	10
Jejunum	10
Ileum	11
Afferent loop	1
Treatment of secondary small bowel metastasis <sup>1</sup>	
Surgery	22
Chemotherapy/ targeted therapy/ hormone therapy/ radiotherapy	17
Surgical indication	
Peritonitis	7
Gastrointestinal bleeding	7
Obstruction	3
Intractable pain	1
Abnormal imaging findings	4
Concomitant organ resection	
Colon	2
Salpingectomy	1
Concomitant organ metastasis <sup>2</sup>	
Liver	4
Lung	8
Brain	3
Bone	6
Abdominal wall	1
Atrium	1
Adrenal gland	2
Survival status <sup>3</sup>	

Variable	N (%)
Alive	5
Death	19
Loss of follow up <sup>4</sup>	7
Survival time following small bowel metastasis <sup>5</sup> (months) [median(range)]	6.6 (0.5–88.8)
<sup>1</sup> Patients may have more than one treatment. <sup>2</sup> Patients might have more than one distant metastasis. <sup>3</sup> Latest updated date: February 29, 2020 <sup>4</sup> Defined as loss of follow up $\geq$ 3 months <sup>5</sup> Latest recorded date minus small bowel metastasis date	

Twenty-one patients had concomitant distant organ metastases (Table 2), while the other 11 patients had only SB metastasis. On univariate analysis, only lung cancer was associated with sole SB metastasis ( $P = 0.02$ ; Table 3).

Table 3  
clinical features of sole SB metastasis v.s. SB metastasis plus multiple distant metastasis

	<b>Sole SB metastasis</b> <b>(n = 11)</b>	<b>Multiple metastasis</b> <b>(n = 20)</b>	<b>P value</b>
The age of small bowel metastasis (Median, IQR)	64 (10)	62.5 (13)	1.00
Sex (n, %)			1.00
Female	2 (18.18%)	5 (25%)	
Male	9 (81.82%)	15 (75%)	
The site of primary cancer (n, %)			
Lung cancer vs. other	7 (63.64%)	4 (20%)	<b>0.02</b>
Melanoma vs. other	0 (0%)	2 (10%)	0.53
GI tract cancer vs. other	1 (9.09%)	4 (20%)	0.63
Intra-abdominal ca vs. other	2 (18.18%)	6 (30%)	0.68
The interval between the diagnosis of primary cancer and small bowel metastasis (months) (Median, IQR)	11.64 (30.49)	17.33 (26.25)	0.27
We used the Mann-Whitney U test for continuous variables and Fisher's exact test for categorical variables.			

The overall median survival was 6.6 months (range, 0.5–88.8 months). For patients who underwent surgery, the median survival was 7.5 months (range, 0.5–88.8 months). For patients who did not undergo surgery, the median survival was 2.9 months (range, 0.5–29.0 months). There was no statistically significant difference in long-term survival between patients who did or did not undergo surgery ( $P=0.968$ ).

Only 5 patients were still alive on the day of telephone follow-up, while 19 had died and 7 were lost to follow-up. The longest follow-up duration after the diagnosis of SB metastasis was 88 months. This patient had lung cancer (pleomorphic carcinoma) and underwent wedge resection and chemotherapy for primary lung cancer and SB segmental resection for secondary SB metastasis.

## Discussion

The present study recruited patients with SB metastasis and excluded those with direct invasion or peritoneal carcinomatosis of the primary cancer. Our study showed that the SB is an extremely rare site for distant metastasis. Additionally, the presence of SB metastasis indicated an extremely poor outcome. Surgery in SB metastasis patients played an important role in rescuing those with critical status; however, surgery alone might not translate to long-term survival.

To the best of our knowledge, our series is the largest in recent decades to focus specifically on SB metastasis. Most studies to date discussed specific cancer types that metastasize to the gastrointestinal tract (GI), such as lung cancer and melanoma[3, 4]. In contrast, the case series discussing this topic was published decades ago<sup>1</sup>[1, 5, 6]. To the best of knowledge, state-of-the-art imaging studies may increase the rate of diagnosis, and new treatment modalities may improve the outcome of patients with SB metastasis, thus, presumably leading to the changing clinical course.

The mechanism of GI tract metastasis is largely hematogenous because of the abundant blood supply. Other mechanisms of GI metastasis include lymphatic spreading, intra-abdominal tumor spreading, and others[2]. In the literature, lung cancer and melanoma are more likely than other cancer types to metastasize to the SB.[4, 7]

In our study, lung cancer was the primary cancer that frequently metastasized to the SB (11 cases [35.5%]) although the GI tract per se is not a common site for lung cancer metastasis. The incidence of GI tract metastasis is noted in < 2% of the cases of primary lung cancer[7]. The actual incidence of GI tract metastasis was likely to be higher, as determined on autopsy, increasing to 8.9–14.0%[8, 9]. With respect to lung cancer-led SB metastasis specifically, Yoshimoto et al<sup>2</sup> and Antler et al<sup>3</sup> reported that the prevalence was 8.9% and 10.3%, respectively. The reported pathologic types of lung cancer that showed a tendency towards GI metastasis include squamous cell carcinoma, adenocarcinoma, and large cell carcinoma. In our case series, we noted that adenocarcinoma most frequently metastasized to the SB, followed by sarcomatoid carcinoma.

Notably, we found that only SB metastasis was a special pattern for lung cancer metastasis (Table 3). This finding was also observed in other large case series reported by Hu et al[3]. The mechanism underlying this observation is not clear.

Melanoma is another malignancy associated with SB metastasis in this study (2 cases [6.5%] in this study). The incidence of melanoma is relatively low among Asians compared to that among Caucasians[10]. Melanomas frequently metastasize to distant organs, such as the liver, lung, bone, and brain via the lymphatic route. Melanoma-led SB metastasis is rare, with a reported prevalence of 20% in patients who underwent surgery; however, the prevalence was 58% in an autopsy report<sup>4</sup>. For patients with melanoma SB metastasis, the 5-year overall survival rate is approximately 23%[4]. Surgical resection of SB metastasis may aid in the safe resolution of the symptoms; however, there is controversy regarding the efficacy of surgical resection for prolonging overall survival[4, 11].

Other cancer types that metastasized to the SB in this study were not common and were presented elsewhere only as case reports. These cancers included breast cancer[12], colon cancer, cervical cancer[13], tongue squamous cell carcinoma[14], endometrial cancer[15], bladder urothelial cell carcinoma[16], renal cell carcinoma[17], gastric cancer[18], peripheral nerve sheath sarcoma[19], primary heart sarcoma[19], and pancreatic cancer[19].

Hepatocellular carcinoma as the primary cancer occurred in 3 patients (9.7%) with SB metastasis. This result demonstrated a slightly higher frequency than those of previous studies[20–23]. This phenomenon might be explained by the fact that the incidence of hepatocellular carcinoma is higher in Eastern areas such as Taiwan.

The overall survival is poor, a median 6.6 months, even with advances in diagnostic imaging modalities and treatments. Only 7 patients (22.6%) were asymptomatic and diagnosed during regular primary cancer follow-up. Twenty-two patients (71.0%) underwent surgical intervention for acute abdomen or symptom relief. In this study, surgery seemed not to prolong survival; rather, it offered symptom palliation.

There are some limitations of this study that must be addressed. First, this was a retrospective study. We enrolled patients with SB metastasis by coding numbers from our hospital chart database. Potential candidates with SB metastasis but were misclassified or miscoded as those with non-SM metastasis might have been missed in this study. Second, most patients with SB metastasis were symptomatic. If the patients were asymptomatic and did not receive regular follow-up, SB metastasis would have been left undiagnosed. For example, 5 patients in the study were diagnosed with SB metastasis at 5 years after the primary cancer. Some clinicians might perform examinations annually or even less frequently, leading to a delayed diagnosis and the underestimation of SB metastasis. Third, our study was composed of a heterogeneous cancerous type. The surveillance protocol is diverse for different types of cancers, leading to time discrepancy in diagnostic timing of SB metastasis.

## **Conclusion**

The SB is a rare site for distant metastasis. SB metastasis is indicative of a worsening status and extremely poor prognosis. Surgery was performed for patients with SB metastasis with the aim of rescuing critical patients and resolution of symptoms; however, surgery may not translate to long-term survival.

## **Abbreviations**

SB: small bowel; GI: gastrointestinal

## **Declarations**

## **Ethics approval and consent to participate**

The study was approved by the Institutional Review Board, which waived the informed consent.

### **Consent for publication**

Not applicable

## Availability of data and material

All data generated or analyzed during this study are included in this published

## Competing interests

The authors declare that they have no competing interests.

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## Authors' contributions

MTL conceived the study. YTL collected the data, wrote the manuscript, and prepared the tables. MTL, BRL, YRL, CCC, and JTL critically revised the manuscript.

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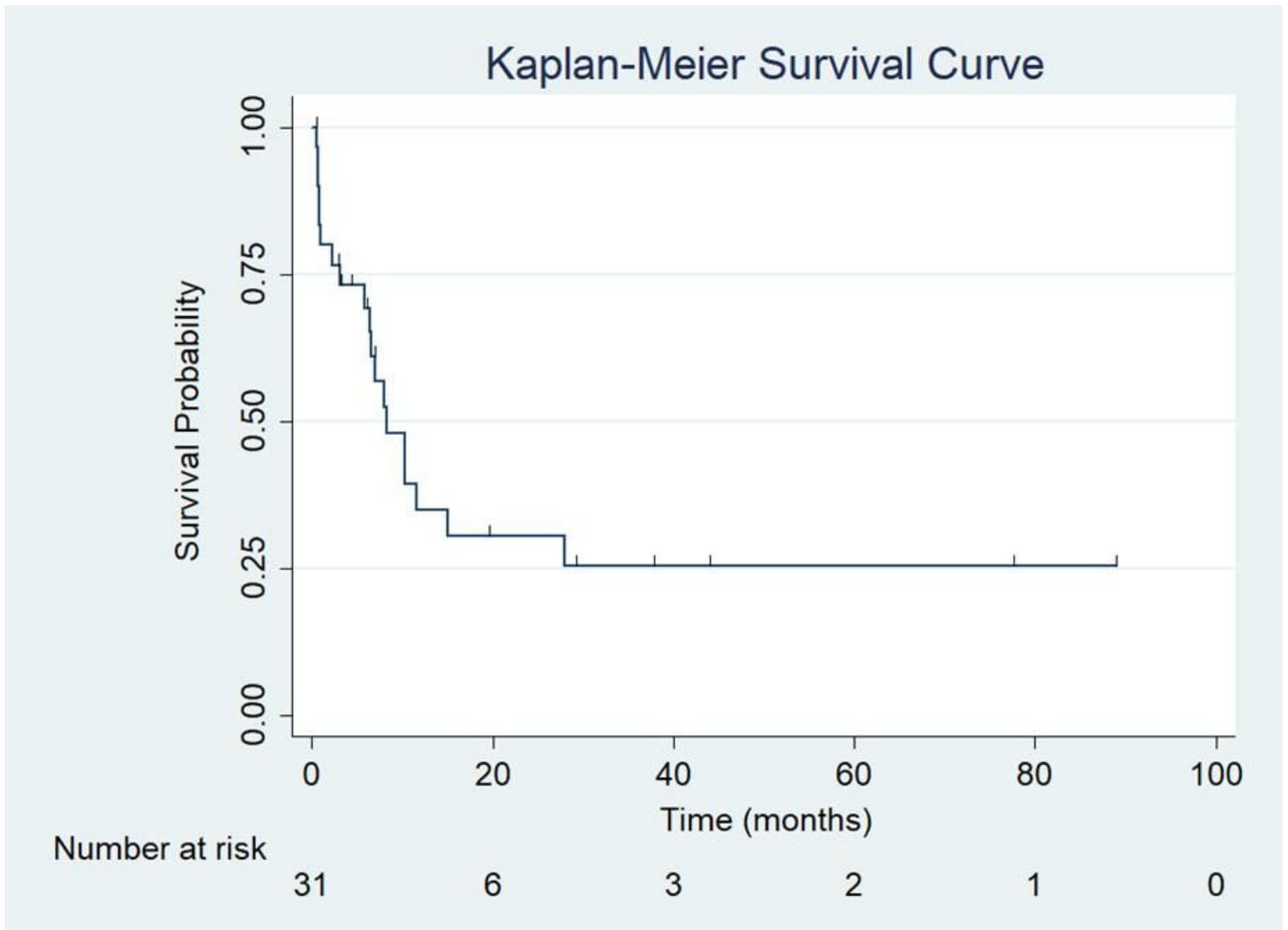
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## Figures



**Figure 1**

Survival curve of all patients

## Supplementary Files

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- [FigureS1Imagesofallcases.docx](#)