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## Small bowel adenocarcinoma (SBA) three years after colonic adenocarcinoma in an elderly patient: Case report in a National Institute of Health and Aging (INRCA) and review of the literature



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## ABSTRACT

**INTRODUCTION:** Adenocarcinoma of the small intestine is a rare malignancy (the annual incidence in the USA is approximately 3.9 cases per million persons with median age between 60 and 70 years) with limited data available to guide therapeutic decisions. Nonspecific signs and symptoms associated with difficulty in performing small bowel examination is the cause of delayed diagnosis made between 6 and 9 months after appearance of symptoms with the majority of patients presenting with late stage disease and either lymph node involvement or distant metastatic disease.

**PRESENTATION OF CASE:** An 87-year-old man treated 3 years previously for colonic adenocarcinoma with left colectomy, was brought to our attention with a 4.5 cm × 3.5 cm mass in the proximal jejunum associated with another abdominal wall enhancing mass of 5 cm in diameter in the rectus muscle. Diagnosis on gross examination after surgical resection was adenocarcinoma stage III (T4N1M0) with involvement of lymph nodes.

**DISCUSSION:** According to an analysis of the Surveillance, Epidemiology and End Results (SEER) database, patients who develop either a small or large intestine adenocarcinoma are at increased risk for a second cancer at both intestinal sites. The role of adjuvant therapy in patients who undergo curative resection is unclear. Recent retrospective and prospective studies have helped to clarify the optimal chemotherapy approach for advanced small bowel adenocarcinoma.

**CONCLUSION:** With our work, we present our personal case of metachronous primary carcinoma of small bowel following resected colorectal carcinoma and review the literature.

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### 1. Introduction

The annual incidence of SBA (Small Bowel Adenocarcinoma) in the USA is approximately 3.9 cases per million persons with median age between 60 and 70 years.<sup>1,2</sup> According to 1992–2006 data from the Surveillance, Epidemiology and End Results (SEER) the average annual age-adjusted incidence rates per 100,000 population of carcinomas of the small intestine is 1.45 and 1.00 for males and females respectively. Rates for blacks is more than twice those of whites (1.29 vs. 0.63).<sup>2,3</sup>

Despite the small intestine representing approximately 70–80% of the length and 90% of the surface area of the alimentary tract, the incidence of adenocarcinoma of the small intestine is approximately forty- to fifty fold less common than colorectal cancer and the reason is largely unknown but has been hypothesized to be

related to several mechanisms such as the much quicker transit time of food in the small intestine than in the large intestine with the shorter time of exposure of its mucosa to carcinogens or the lower bacterial load of small intestine, which decreases concentration of potential carcinogens from bile acid breakdown and other factors (Overman, 2009).<sup>2,4</sup>

Adenocarcinoma is the most common malignancy particularly in the proximal small intestine, as reported by Overman, according to a review of 25,053 patients from the National Cancer Data Base, involving the following sites: 56% duodenum, 16% jejunum, 13% ileum, and 15% not identified. The cause of this propensity for adenocarcinomas to occur in the duodenum rather than in the jejunum/ileum is unknown. Lowenfels and others, have ascribed this difference in risk to the higher concentration of bile and its metabolites in the duodenum, secondary to the presence of the ampulla of Vater.<sup>1–5</sup>

Most SBAs arise from preexisting adenomas with one third of solitary small bowel adenoma transforming into invasive carcinoma. Nonspecific signs and symptoms associated with difficulty in performing small bowel examination is the cause of a delayed

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diagnosis made between 6 and 9 months after appearance of symptoms.

Patients treated for a colorectal cancer have an increased risk of developing a second primary malignant disease (30–40%, Enblad et al., 1990).<sup>6</sup> With our work, we want to present our personal case of metachronous primary carcinoma of small bowel following resected colorectal carcinoma and review the literature.

## 2. Clinical case

An 87-year-old man was brought to our attention with a several month history of nausea, abdominal bloating, early satiety and weight loss. He had a prior history of hypertension, diabetes mellitus, peptic ulcer disease and left colectomy for primary sigmoid adenocarcinoma 3 years earlier (T4N0M0) without adjuvant therapy due to his advanced age.

His hemoglobin measured 12 g/dL, serum ferritin 16.2 µg/mL, iron 41 µg/dL, and total iron binding capacity 370 µg/dL. His iron saturation level was 11.1%, consistent with iron deficiency anemia. The remaining blood tests, including hepatic and renal function, were normal. The patient underwent a complete workup for iron deficiency anemia.

An initial upper endoscopy was normal. Duodenal and gastric antrum biopsies were negative for *Helicobacter pylori*. Colonoscopic evaluation showed only diverticular disease. Small bowel follow-through (SBFT) examination was normal. The patient was treated with proton pump inhibitors, antiemetics, and iron supplements, then was lost to follow-up for approximately 10 months.

Subsequently, he was readmitted with persisting nausea and abdominal bloating with new-onset diarrhea, chest pain, and shortness of breath. Physical examination demonstrated gastrointestinal distension associated with a 5 cm mass in rectus muscle, bilateral pulmonary rales and tachycardia. His hemoglobin measured 8 g/dL with iron deficiency. At this time an abdominal computed tomography (CT) scan was required and it showed a 4.5 cm × 3.5 cm mass in the proximal jejunum with a “target jejunum image” like an intestinal invagination associated with another abdominal wall enhancing mass 5 cm in diameter in the rectus muscle (Fig. 1). Cystic areas were found in the left iliac zone. The chest and the pancreas on CT imaging appeared normal. Serum Carcino Embryonal Antigen (CEA) level was also normal.

At this point, the patient underwent an exploratory laparotomy with resection of the mass, which was located approximately 60 cm distal to the ligament of Treitz, using an intestinal resection and side to side hand-sewn anastomosis, resection of rectus muscle mass and pelvic lymphadenectomy.

On gross examination, the resected specimen showed a well-circumscribed exophytic mass with central ulceration, measuring 4 cm in size with clear margins and involving the mesentery (Fig. 2).

Diagnosis was jejunal adenocarcinoma stage III (T4N1M0) with involvement of mesenteric and pelvic lymph nodes, the mass of rectus muscle was defined as metastasis of sigmoid adenocarcinoma.

Due to age and his Karnofsky stage, no adjuvant chemotherapy or radiation was administered by the oncologists. The patient’s GI symptoms resolved following surgery.

The total time from the onset of symptoms to the diagnosis of the small-bowel adenocarcinoma was 12 months. After resection the patient continued to do well with normal hematocrit levels at 6 months follow-up, then he suffered new abdominal pain in association with anemia, fatigue and weight loss with a recurrence of iliac mass in the lower right quadrant. He died after one year of follow-up for cardiovascular and pulmonary complications (24 months from the onset of symptoms).

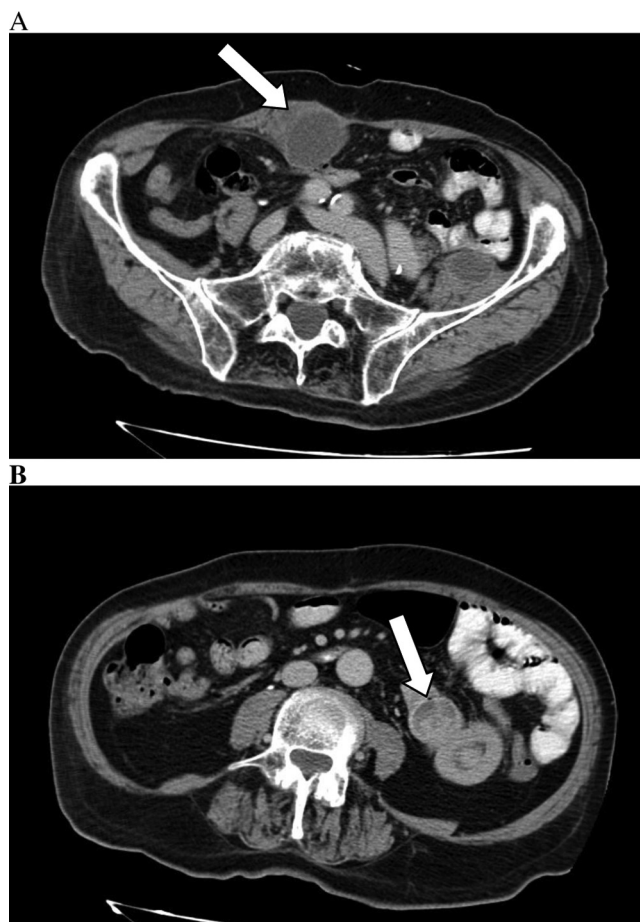


Fig. 1. Abdominal computed tomography. (A) rectus muscle mass and (B) proximal jejunum mass.

## 3. Discussion

SBA is a rare tumor and to our knowledge few published studies in the literature to date have addressed it adequately, for these reasons clinical characteristics, treatment modalities and prognosis of patients with this tumor are not well known.<sup>7,8</sup>

All those patients, in earlier clinical visits, showed predisposing conditions such as HNPCC (Hereditary Non Polyposis Colorectal

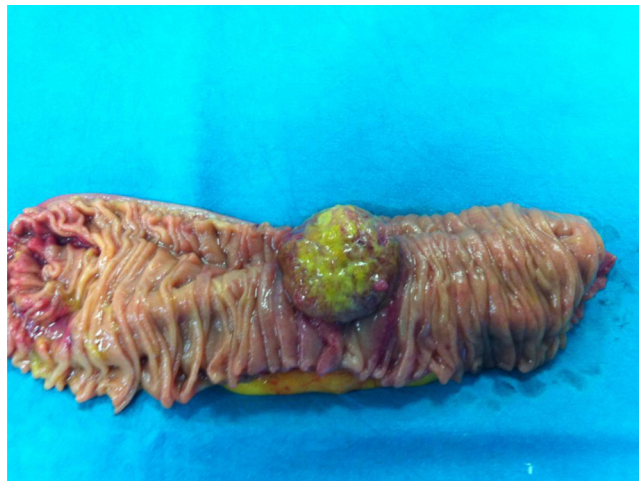


Fig. 2. Macroscopic aspect of the mass.

**Table 1**  
TNM staging for adenocarcinoma of the small intestine Overman.<sup>2</sup>

Primary tumor (T)			
TX	Primary tumor cannot be assessed		
T0	No evidence of primary tumor		
Tis	Carcinoma in situ		
T1	Tumor invades lamina propria or submucosa		
T2	Tumor invades muscularis propria		
T3	Tumor invades through muscularis propria into the subserosa or into the nonperitonealized perimuscular tissue (mesentery or retroperitoneum) with extension 2 cm or less <sup>a</sup>		
T4	Tumor perforates the visceral peritoneum or directly invades other organs or structures (includes other loops of small intestine, mesentery, or retroperitoneum more than 2 cm, and abdominal wall by way of serosa; for duodenum only, invasion of pancreas)		
Regional lymph nodes			
NX	Regional lymph nodes cannot be assessed		
N0	No regional lymph node metastasis		
N1	Regional lymph node metastasis		
Distant metastasis			
MX	Distant metastasis cannot be assessed		
M0	No distant metastasis		
M1	Distant metastasis		
Stage grouping			
Stage 0	Tis	NO	M0
Stage I	T1	NO	M0
	T2	NO	M0
Stage II	T3	NO	M0
	T4	NO	M0
Stage III	Any T	N1	M1
Stage IV	AnyT	AnyN	AnyM1

Adapted from AJCC Cancer Staging Manual, Sixth Edition.

<sup>a</sup> The peritonealized perimuscular tissue is for the jejunum and ileum, part of the mesentery; and for duodenum in areas where serosa is lacking, part of the retroperitoneum.

Cancer), FAP (Familial Adenomatous Polyposis), inflammatory bowel disease (IBD), or celiac disease.

In particular, Crohn's disease is a recognized risk factor for cancer of the small intestine, as reported in a meta-analysis that reported a relative risk of 33.2 (95% CI: 15.9–60.9) while it is unclear for patients with ulcerative colitis.<sup>3,9–11</sup>

Celiac disease' prevalence is nearly 1% of the general population and the relative risk of adenocarcinoma in these patients is reported between 60 and 80.<sup>3,10</sup>

It is suggested that adenocarcinoma of the small bowel follows the same sequence of colon cancer. In a retrospective analysis of 192 villous adenomas of the duodenum, the incidence of malignant changes at the time of presentation was 42%. Most of the adenomas in the small bowel occur in the duodenum. Villous histology, increasing size and a higher grade of dysplasia of the adenoma increase the risk of neoplastic transformation from adenoma to carcinoma.<sup>3,10</sup>

In fact, 3–5% of patients with FAP, where the prevalence of duodenal adenomatosis is 50–90%, develop duodenal cancer, while a meta-analysis of 210 patients with PJS (Peutz–Jeghers Syndrome) presented a statistically significant increase in relative risk for cancer of small bowel (RR = 520), stomach (RR = 213), colon (RR = 84), esophagus (RR = 57), pancreas (RR = 132), lung (RR = 17), breast (RR = 15.2), uterus (RR = 16.0) and ovary (RR = 27) respectively. The relative risk of small bowel cancer in patients with HNPCC has been estimated to be more than 100 compared with the general population, with a lifetime risk of 1–7%.<sup>3,10,11</sup>

Moreover, various studies have shown that the risk of SBA following primary colorectal cancer was elevated (30% and 40% respectively for colon and rectum cancer)<sup>6</sup>; also, in those diagnosed with primary SBA, there was a 4–5-fold risk of developing colorectal cancer. These studies suggest etiological similarities between cancers of the small intestine and colorectal cancers but, to date, potential common carcinogenic agents have not been elucidated in analytic epidemiological studies.<sup>3–11</sup>

The most commonly reported symptoms of SBA are abdominal pain, nausea/vomiting, weight loss, and gastrointestinal bleeding and they are identified with barium follow-through examination in only 33% of cases, whereas 90% of them could be identified with small bowel enema. Overall sensitivity, specificity, and accuracy of multidetector row helical computed tomography (CT) enteroclysis for small bowel disease are 100%, 95%, and 97%, respectively, and 86%, 98%, and 97%, respectively, for magnetic resonance (MR) enteroclysis, while video capsule enteroscopy (VCE) was introduced in 2001 and its diagnostic yield is approximately 50% to 60% for small bowel lesions.<sup>2–9,12–14</sup>

Staging for small bowel adenocarcinoma is performed according to the American Joint Committee on Cancer (AJCC) guidelines, which is based on the TNM staging system (Table 1).<sup>2</sup>

In a review from the National Cancer Data Base, from 1985 to 1995 5-year disease specific survival by stage was 65% for stage I, 48% for stage II, 35% for stage III, and 4% for stage IV.<sup>2,15–17</sup>

The mainstay treatment of SBA remains surgery, in particular laparotomy for resection of the involved segment (10 cm distant from proximal and distal margin of the tumor), the mesentery and the lymphatics up to the superior mesenteric vessels. Morbidity and mortality are respectively between 13% and 44% and between 3% and 12%. The 5 year overall survival varies between 9% and 50%.<sup>2–9,16–18</sup>

Only a limited number of single-institution retrospective studies have evaluated the role of adjuvant chemotherapy although the benefit has not been clearly demonstrated. Capecitabine or infusional 5-FU combined with oxaliplatin appears to be one of the most active combinations and should be considered for front-line treatment of patients with this cancer (median survival in the range of 14–20 months).<sup>2–18–20</sup>

Different studies have tried to determine patterns of treatment and factors that can influence survival of patients with SBA. Howe (1999) reported, according to the National Cancer Database (NCDB) information on 4995 patients with SBA, that patient age was the

**Table 2**  
Poor prognostic factors from multivariate analyses Overman.<sup>2</sup>

Study	Time period	No. Pts	Multivariate factors
Small intestine Bilimoria	1985–2005	25,053	Age > 55 years Male Black ethnicity Duodenal or ileal location T4 tumor stage Lymph node involvement Metastatic disease Poor differentiation Positive margins
Howe	1985–1995	4995	Regional or distant disease Age > 75 years Duodenal location Poor differentiation
Dabaja	1978–1998	217	Lymph node ratio > 75% Curative resection
Wu	1983–2003	80	TNM stage III/IV Curative resection Lymph node involvement
Agrawal	1971–2005	64	T4 tumor stage Non-curative resection Metastatic disease
Duodenum Rose	1983–1994	79	Metastatic disease Non-curative resection
Bakaeen	1976–1996	68	TNM stage III/IV Positive margins Weight loss Lymph node involvement

only factor related to Overall Survival (OS). The relative risk of death was 1.8 times higher for patients age > 75 years.<sup>21–23</sup>

In a French study of 100 patients with SBA, Veyrieres (1997) reported that curative resection resulted in a 5-year survival rate of 63% without lymph node involvement and 52% with lymph node involvement. He also reported that the survival rate was 57% in cases without serosal involvement, 53% in those with serosal involvement, 56% when the tumor was well or moderately differentiated compared with 40% when it was undifferentiated.<sup>1–3,23</sup>

In a review of 77 patients with SBA, undifferentiated histologic grade was associated with a trend toward shorter OS but this did not reach statistical significance ( $P=0.4$ ). Thirty-five percent of patients presented with advanced stage disease (Stage IV), possibly as a result of delayed diagnosis. In the same study, Maglante found an average delay in diagnosis of 8.2 months attributable to the physician’s failure to order the appropriate tests and a delay of 12 months

due to the radiologist’s failure to make the diagnosis. Duodenal adenocarcinoma was associated with a shorter median OS compared with patients with tumors located in the jejunum or ileum (18 months vs. 26 months), a finding that is in accordance with previously published studies. These patients were significantly older ( $P>0.001$ ) and tended to present with late stage disease (69% with Stage III disease) compared with patients with distally located adenocarcinoma (jejunum and ileum), which may explain the shorter survival.<sup>1,2,5–8,24</sup>

To date, there are no clear associations between tumor markers and small intestine adenocarcinoma. Some patients with small intestine adenocarcinoma have been found to have elevated serum CA19-9 or CEA concentrations. Recurrences were observed in 40–70% of patients who underwent curative resection, with most recurrences at distant sites.

The various factors that have been associated with poor prognosis in multivariate analyses from the literature are reported in Table 2, in particular they are late disease stage, lymph node involvement, poor histologic differentiation, elderly age, duodenal primary, and positive margins.<sup>2,17–24</sup>

To summarize, early diagnostic workup of patients with vague abdominal symptoms and complete surgical resection remain the most significant variables in improving outcome of patients with small bowel adenocarcinoma.

**Conflict of interest**

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**Ethical approval**

This article is not a research study, ethical approval is not necessary.

**Author contributions**

Dott Danilo Coco has done data collection, data analysis and interpretation and he has written the text.

Dott.ssa Silvana Leanza has written the text.

Dott. Gianfranco Boccoli is the Director of general surgery department and he is the supervisor.

**Key learning points**

- Curative resection is currently the only factor that can prolong patient survival. Consequently, early and accurate diagnosis is crucial to improve patient outcomes.
- Physician’s suspicion and awareness of SBA (Small bowel adenocarcinoma) is crucial to make appropriate diagnostic investigation for earlier detection and increasing resectability of SBA.
- Due to the rarity of these tumors, multi institutional cooperation is essential for the success of these studies.

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