

## Malignant Tumors of the Small Intestine – New Insights into a Rare Disease

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Tumors of the small bowel are very rare. They constitute only 2.4% of all gut tumors [1], which is a very small percentage compared to the 90% mucosal surface area of the small bowel. Data on small intestinal neoplasms were scarce until recently, with the publication of two large series: Severson et al. [2] reported on 1,609 cases, and Howe et al. [3] reviewed the national cancer database. Altogether they identified 4,995 patients with small bowel adenocarcinoma. About two-thirds of small bowel tumors are malignant, with most being adenocarcinoma; other types of tumors are carcinoids, lymphomas and sarcomas. Most tumors originate in the duodenum (55.2%), followed by the jejunum (17.6%) and ileum (13%) [3]. The significant rise in the incidence of these tumors is an important epidemiologic finding [2,3]. In contrast, the prevalence of the rare small intestinal lymphoma, occurring in developing countries and in the Mediterranean, is decreasing.

This review focuses on small bowel adenocarcinomas, the most common malignant tumor of the small bowel, and discusses its epidemiology, tumor biology, clinical presentation, and management.

### Epidemiology

Interestingly, the epidemiology of small bowel cancer correlates with that of colorectal cancer. Both are associated with a rising incidence in the western hemisphere, and increased fat and protein intake [4]. The highest incidence is found among the Maoris in New Zealand, and the lowest incidence in Africa and Asia [4]. In the United States the incidence of adenocarcinoma and carcinoids is somewhat higher in African-Americans than in Caucasians [5]. The incidence in males is considered higher than in females, according to three U.S. population-based registries [6], although in the National Cancer Database registry the distribution was almost equal (males 52.9%, females 47.1%) [3]. The mean age of diagnosis is in the sixth decade, for all histologic subtypes [3,6]. Throughout the last three decades a steady increase in incidence was observed in both genders [Figure 1].

### Risk factors

#### Familial cancer syndromes

- *Familial adenomatous polyposis*

Small bowel adenocarcinoma is the most common extracolonic carcinoma in patients who carry the APC

gene mutation, particularly peri-ampullary carcinoma that occurs in 1–4% of FAP patients [7]. In fact, duodenal peri-ampullary carcinoma was the most common cancer-related cause of death among 1,262 FAP deaths in the population registry of St. Mark's Hospital [7]. An explanation may be the high concentration of bile salts in this area. Duodenal bile from 29 FAP patients was found to be more mutagenic than that of 24 non-FAP patients [8]. Alternating gastroscopy and duodenoscopy every 2 years is therefore recommended.

- *Hereditary non-polyposis colorectal cancer*

The risk in these patients is 100 times greater than in the rest of the population [9]. As for colorectal carcinoma, the small bowel tumors appear at a younger age and carry a better prognosis than in the general population

#### Crohn's disease

The prognosis for this type of adenocarcinoma is grave [3]. Increased risk of 3 to 100-fold was shown in several studies [10], yet other studies performed in the same period negate this association [11]. The rarity of the disease makes the difference between the studies possibly non-significant. The mechanism is most probably the effect of chronic inflammation, but it has not been elucidated.

#### Cystic fibrosis

Only four cases of an association between cystic fibrosis and adenocarcinoma of the ileum have been reported [12].

FAP = familial adenomatous polyposis

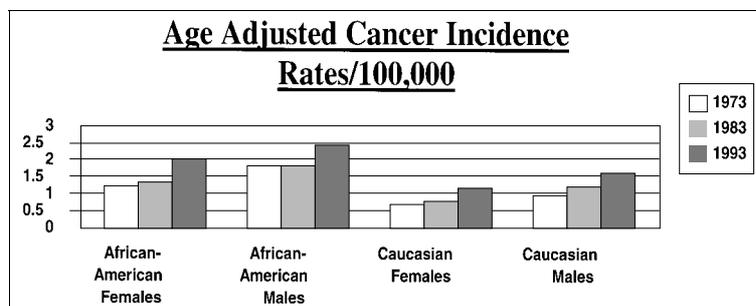


Figure 1. Changes with time in the incidence of small bowel malignancies in the U.S.

### Celiac disease

Celiac patients have been described to be at risk for several malignancies, particularly small bowel lymphomas [13]. Small bowel adenocarcinoma may be the only or the presenting symptom in an asymptomatic celiac patient. Chronic inflammation is the probable underlying mechanism [13].

### Dietary habits

Animal fat, protein consumption (particularly red meat), salt-cured and smoked food are associated with small bowel adenocarcinoma, and there might be a predisposition with increased consumption of bread, pasta, rice and sugar [12].

### Smoking and alcohol

The increased risk for small bowel carcinomas associated with smoking and alcohol consumption is 4.6 and 4 respectively. Recently, a European study showed no increased risk of small bowel adenocarcinoma among smokers, but a high intake of beer or spirits seemed to be a risk factor, although wine intake was not [12].

### Bile

Bile might be an important promoter, particularly for the peri-ampullary cancers [12].

### Occupation

In a recent study, certain occupations seemed to increase the risk for small bowel adenocarcinoma. These included caretakers of buildings, housekeeping women, general farm laborers, dockers, cleaners, launderers and textile workers [14].

### Secondary malignancy

Some data suggest that patients with small bowel adenocarcinomas are prone to second malignancy, and indeed an eightfold increase in secondary malignancies was found among these patients [15]. This association was prominent with colorectal cancer (1.6-fold for males and fivefold for women), while patients with colorectal cancers were also found to have an elevated risk for small bowel cancer (sevenfold for males and ninefold for women) [16]. Patients with small bowel tumors should therefore be followed closely due to the risk of secondary malignancies.

### Others

Radiation therapy, Wilm's tumor, Hodgkin's disease, anal cancer and squamous cell skin cancers have been implicated as possible risk factors [1].

### Resistance of small bowel mucosa to tumorigenesis

The small bowel is remarkably resistant to the evolution of benign and malignant tumors as compared to the rest of the gastrointestinal tract. The recurrence of colorectal tumors after ileocolonic anastomosis is significantly higher at the colonic site (14%) than in the small bowel (0.7%) [17]. A variety of protective antitumor mechanisms unique to the small bowel have been suggested [4,12], but none were investigated in humans:

- A very high cell turnover rate may cause shedding of partially transformed cells and inhibition of "critical cell mass" with carcinogenic mutations required for malignant transformation.
- Absence of bacteria; indeed certain carcinogens are known to induce colon cancer in normal animals, but not in bacteria-free animals [12].
- Rapid transit time minimizes exposure to carcinogenic products [12].
- Liquified chyme may reduce mechanical trauma and protect the small bowel mucosa from carcinogens [18].
- The alkaline pH of the small bowel can prevent the production of nitrosamines, which may be carcinogenic in the acidic environment of the stomach [18].
- Well-developed immunoglobulin A-mediated immune system; patients with IgA deficiency are at higher risk for small bowel cancer [19].
- Small bowel stem cells may lie deep within the crypts and are well protected from luminal potential carcinogens [18].
- Water-soluble tumor-inhibiting component in the small bowel [20].
- The microsomal enzyme benzopyrene hydrolase converts benzopyrene, a potential carcinogen, into a less active compound. This enzyme is abundant in the small bowel. Other, yet unknown, enzymes with similar functions may protect the small bowel mucosa against additional carcinogens [12].

### Biology and similarities to colorectal cancer

Small and large bowel cancers share many epidemiologic and biological features. In both, the adenoma-carcinoma sequence has been established and the size of the polyp predicts its malignant potential [21]. Some risk factors are common to both diseases [Table 1]. Extremely important are FAP patients with multiple colonic adenomas and carcinomas who tend to have multiple tumors in the small bowel [7,8]. Both malignancies tend to occur in the same individuals. In contrast to the recent understanding of

IgA = immunoglobulin A

**Table 1. Risk factors for small bowel tumors**

- |  |
|--|
| ● Inherited polyposis syndromes (FAP, HNPCC, Peutz-Jegher) |
| ● Prior surgery for benign or malignant tumor              |
| ● Crohn's disease  |
| ● Celiac disease   |
| ● Male gender  |
| ● Increasing age   |
| ● African-American ethnicity                               |
| ● Colorectal cancer  |
| ● High fat diet  |
| ● Cholecystectomy  |
| ● Peptic ulcer disease                                     |
| ● Cystic fibrosis  |
| ● Wilms' tumor   |
| ● Hodgkin's disease  |
| ● Anal cancer  |
| ● Squamous cell skin cancer                                |

some of the events leading to the evolution of colorectal cancer, very little is known about the molecular events in the process of small bowel carcinogenesis. The few studies done have revealed some similarities between small and large bowel tumors [4,17,22–24].

## Molecular genetics

### *ras* mutations

Reliable and reproducible molecular genetic data are sparse, but they are available for mutations in the *ras* oncogene [22,23]. Rashid and Hamilton [23] found mutations (at codon 12 and 13) in 6 of 15 cases of Crohn's associated adenocarcinoma and in 4 of 8 cases of sporadic adenocarcinoma. In a large study of 222 paraffin sections from the entire gastrointestinal tract, c-K-*ras* mutations at codon 12 were seen in 8 of 20 adenomas (40%) and in 10 of 28 adenocarcinomas (36%) [22].

### Cell cycle abnormalities

Cell cycle abnormalities were found to be early and important events in the multistep process of small bowel adenocarcinomas, like in colorectal carcinogenesis [24]. The levels of cyclin D1, cyclin E, p16, p21 and p27 proteins were determined by immunohistochemistry in 60 patients with small bowel tumors. Normal mucosa only expressed p27 protein. About 20% of the tumors displayed a decrease in the expression of this protein. The most frequent alteration was up-regulation of p16 protein. Advanced age and increased detection of cyclin D1 and p53 were associated with a decreased 3 year survival ( $P < 0.05$ ).

### Allelic loss of 5q

Allelic loss (40%) of the APC gene is significantly lower in small bowel as compared to large bowel tumors [23]. Recently a single report identified a small bowel adenocarcinoma with a somatic mutation in the  $\beta$ -catenin gene (deletion of 425 base pairs), which included the entire exon 3 [25].

### p53

Rashid and Hamilton [23] found elevated levels of p53 protein in 30% of adenomas and in about 50% of the cases of Crohn's disease-associated adenocarcinoma of the small bowel. Similar findings of increased expression of p53 was observed by us [24]. Increased expression of this protein was associated with tumor progression (45% of the adenomas and 65% of the adenocarcinomas,  $P < 0.05$ ). p53 levels were higher in women than in men and were associated with a poorer prognosis [24].

### Microsatellite instability

Microsatellite instability plays an important role in the pathogenesis of intestinal tumor formation. Replication errors were found in 14–45% of small bowel tumors examined [23,25].

### Tumor markers

Carcinoembryonic antigen was found in the serum of 73% of patients [26]. Increased expression of *ErbB-2-neu* was detected in about 60% of small bowel tumors and is associated with poor prognosis [26]. Transforming growth factor-alpha was found in 9 of 15 tumors in one study, but its levels were not associated with survival, tumor stage or grade [26].

## Pathology

Seventy-five percent of small bowel tumors are malignant. Adenocarcinoma is the most common tumor (35%), followed by carcinoid (28%), lymphoma (21%), mesenchymal tumors (10%), and other rare tumors (6%) [3]. The staging system is by TNM staging. Disease stage on presentation is usually more advanced in small bowel cancer than in colon cancer [Table 2].

## Diagnosis

The small bowel remains a difficult area for imaging and endoscopy. Physical examination, blood tests, or specific tumor markers are not useful in making a diagnosis. Plain abdominal film can be of help, but only in cases of bowel obstruction. Small bowel series and enteroclysis are the most valuable diagnostic tools, although the sensitivity of barium studies is only 30–50%. The sensitivity of gastroscopy is only 31% since it is limited to the region of the ligament of Teritz, yet 93% of all duodenal tumors can be identified [27]. The terminal ileum can be visualized and biopsied by colonoscopy. Enteroscopy – an important diagnostic tool – is sometimes difficult to perform and its extent is limited. Computed tomography can detect small bowel abnormalities in 50% of cases, but experience with CT preoperative staging is limited and has an overall accuracy rate of 50% [27]. Laparoscopy and intraoperative enteroscopy provide further diagnostic capabilities. Angiography and red blood cell scan are considered to be of limited value. Because of the limitations of the above mentioned modalities, the swallowable radio-telemetry capsules might be the optimal diagnostic tool [28]. It is currently approved in many countries, but its efficacy remains to be proven.

## Clinical manifestations [Table 3]

The clinical symptoms tend to be non-specific. Diagnosis is made late in the course of the disease with up to 2 years delay. Many

**Table 2.** Stage at presentation of small bowel adenocarcinoma

TNM Stage	Small bowel tumors (%)	Large bowel tumors (%)
0	2.7	3
I	12	23
II	27	30
III	26	25
IV	32.3	19

**Table 3.** Frequent clinical findings in patients with small bowel adenocarcinomas

Symptom	Frequency (%)
Abdominal pain	42–83%
Weight loss	23–87%
Anemia	18–75%
Bleeding	13–68%
Intestinal obstruction	16–65%
Nausea/Vomiting	27–54%
Abdominal mass	19–29%
Jaundice	18–30%
Anorexia	18–25%

times the diagnosis is made accidentally, with a very high rate of metastatic disease (70%) [29]. Approximately 75% of the symptomatic small bowel tumors are malignant, while about half of the benign lesions remain asymptomatic. The most common complaint by up to 83% of patients is abdominal pain, followed by weight loss and anemia. The symptoms are usually confined to the site of involvement and are affected by the size of the tumor. Patients with a benign tumor tend to suffer from gastrointestinal hemorrhage, while those with malignant tumors are more likely to develop an intestinal obstruction.

## Treatment

Benign lesions in the duodenum can be resected endoscopically or by local ampullary resection and intraoperative frozen section [30], although some authors recommend pancreaticoduodenectomy for low risk patients [31]. Before endoscopic resection, an endoscopic ultrasound should be performed to determine the size, growth pattern and blood supply of the lesion. Additionally, some form of sphincterotomy should follow adenoma resections in the ampulla of Vater to reduce risk of stricture formation. Patients should enter into a surveillance program following an adenoma resection. Colonoscopy should also be undertaken in these patients, and if the patient is young, genetic consultation is advised [1,29].

The ultimate treatment modality for neoplastic lesions is surgery, although in high risk or elderly patients endoscopic resection with negative margins may be sufficient [32]. The surgical resection rate of malignant tumors is almost 100%, and curative resection is achieved in approximately 50% of cases [33]. For duodenal tumors radical excisions are preferred: while pancreaticoduodenectomy is advocated for lesions in the first and second portions of the duodenum, segmental resection (sparing the pancreas) is done for tumors in the third and fourth parts of the organ. Aggressive resections are recommended even in large tumors with positive nodes if it can be performed with negative resection margins. In one study, the 5 year survival was 81% when resection was complete versus 40% in patients with incomplete resection [34]. Resection may cause relief of symptoms such as obstruction or bleeding. The operative mortality of surgery with a curative intent varies from 35 to 77%, and the 5 year survival is 10–62% [35,36]. Adjuvant therapy with 5-fluorouracil, adriamycin, mitomycin-C or other agents was tried in unresected tumors, and as adjuvant therapy in 26% of patients [3]. Many physicians offer their patients a standard adjuvant therapy protocol, as in colorectal cancer. Radiotherapy was not found to be effective [37]. Prolonged survival periods are reported with combinations of chemo-radiotherapy. Close follow-up is necessary as many patients harbor a second malignancy elsewhere in the gastrointestinal tract.

## Prognosis

Overall, the prognosis of small bowel tumors is poor. Most series report 5 year survival rates of 15–35% [35–38]. Only in one report was the 5 year survival rate 57% [34]. The poor survival rate can be attributed to the non-specific nature of symptoms, which contributes to significant delay in the diagnosis. Aggressive surgical management together with complete resection is the only means of

treatment that may offer patients with small bowel cancer a long-term survival. In a series of 100 patients, Veyrieres et al. [39] reported that the 5 year survival rate was 54% after curative resection and zero after palliative surgery. The same results were found by others, while a better survival rate was described in some well-defined subgroups such as Duke's B1 and well-differentiated tumors. Survival was not affected by gender, ethnicity, status, or the use of adjuvant chemotherapy [3,38]. Older age, advanced stage and poorly differentiated tumors are all associated with a poorer prognosis [3]. Lymph node status and surgical margins were also shown to have prognostic significance [36]. Symptomatic patients such as those with anemia have a better prognosis [39]. In the duodenum, the symptoms are more clear and specific and the diagnosis can be made earlier, yet the 5 year survival was found to be only 20–61% [3]. Factors contributing to this grave prognosis in duodenal tumors are the lack of cancer-directed surgery in 50% of patients [3] and advanced age (over 75 years), as compared to jejunal or ileal tumors. Yet, in other studies, 5 year survival was not dependent on the tumor location within the small bowel. Using the Cox regression, increased age, disease site (duodenum), cancer-related surgery and stage were all independent risk factors. The strongest single factor was the presence of distant metastases [3].

## Future directions

In recent years there is a trend of increasing incidence of small bowel adenocarcinoma in the USA [5]. The same trend was observed in Israel (unpublished data). Since the molecular background of small and large bowel cancers share many common factors, the genetic changes in small bowel adenoma and adenocarcinoma should be investigated further. If the pattern of genetic similarities is maintained, the much lower incidence of small bowel cancer is probably due to a general mechanism of resistance, like increased apoptosis or immunologic protection. It is of interest that in mice with deletion in the APC gene there is a much higher incidence of tumors in the small bowel than in the large bowel, in contrast to the situation in FAP [40]. It may be worthwhile to compare the physiology of small bowel tumors in mice to those in humans for a clue to the lower incidence of tumors. While the rarity of small bowel cancer discourages intensive study, the similarities to colorectal cancer suggest that lessons learned during research may prove extremely useful toward understanding the behavior of colorectal cancer, and perhaps other cancers as well.

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## Capsule

### News on Epstein-Barr virus

In their review on Epstein-Barr virus (EBV) published in the March 1 internet version of *Lancet Infect Dis* (2002;3), Macsween and Crawford describe EBV as a tumorigenic herpes virus that is ubiquitous in the adult population. The virus is generally spread to and between young children through salivary contact, and only causes clinical illness where primary infection is delayed until adolescence or beyond, when an intense immunopathologic reaction leads to the symptoms of infectious mononucleosis in roughly 50% of cases. More than 90% of the world's population carries Epstein-Barr virus as a life-

long, latent infection of B lymphocytes. Recent data show that by mimicking B cell antigen-activation pathways, the virus enters the long-lived memory B lymphocyte pool where it evades immune elimination by severely restricting its own gene expression. By influencing B cell survival mechanisms, Epstein-Barr virus may induce tumors such as B lymphoproliferative disease and Hodgkin's disease. Vaccines are being developed to prevent and/or treat these conditions, but an animal model is required to study pathogenesis before a rational vaccine strategy can be formulated.

