

# Surgical treatment of small bowel neoplasms

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**Abstract.** – Small intestinal neoplasms are uncommon cancers. Benign small intestinal tumors (e.g., leiomyoma, lipoma, hamartoma, or desmoid tumor) usually are asymptomatic but may present with complications. Primary malignancies of the small intestine, including adenocarcinoma, leiomyosarcoma, carcinoid, and lymphoma, are often symptomatic and may present with intestinal obstruction, jaundice, bleeding, or pain. Metastatic neoplasms may involve the small intestine via contiguous spread, peritoneal metastases or hematogenous metastases. Because the small intestine is relatively inaccessible to routine endoscopy, diagnosis of small intestinal neoplasms is often delayed for months after onset of symptoms. During last years the increase of small bowel endoscopy and other diagnostic tools allow earlier non-operative diagnosis. Even though radical resection of small bowel cancer plays an important role, the 5yr overall survival remains low.

*Key Words:*

Small bowel, Adenocarcinoma, GIST, Carcinoid, Lymphoma, Laparoscopy.

## Introduction

Small bowel neoplasms represent 0.3% of all tumors, fewer than 2% of all gastrointestinal malignancies<sup>1,2</sup>, with an age-adjusted incidence of 1 per 100,000 and a prevalence of 0.6%<sup>3</sup>. Approximately, almost forty different histological types of both benign and malignant tumors have been identified<sup>4</sup>. Although 75% of the tumors found at biopsy are benign, most of the symptomatic lesions detected during surgery are malignant<sup>5</sup>. Benign tumors include leiomyomas, adenomas, lipomas and hamartomas. Malignant tumors include adenocarcinomas, carcinoids and lymphomas. Other types of small bowel malignant neoplasms are stromal tumors, which are considered as tumors with variable malignant power,

and metastatic diseases by malignant melanoma, bronchogenic tumors, breast cancer and intrabdominal cancers. Surgery is considered the first line therapy for most small bowel neoplasms, especially malignant and complicated benign tumors<sup>6</sup>.

### *Aim of the Review*

This review reports the goals of treatment for small bowel neoplasms particularly remarking the surgical treatment of small bowel malignant neoplasms.

### *Benign Neoplasms*

Benign neoplasms are usually asymptomatic and are only incidentally discovered, when cause a complication as obstruction or hemorrhage (more frequently occult). Despite the term “benign”, exists a risk of malignant change for adenomas (malignant changes at presentation over 40%, especially in large adenomas with villous component or atypia), and leiomyomas (risk for malignancy related to the tumor size and number of mitosis). Lipoma, hemangioma, Brunner’s gland hamartoma and intestinal nodular lymphoid hyperplasia have no risk of malignant evolution<sup>6-9</sup>. Because of their potential to undergo malignant transformation, adenomas and leiomyomas should be removed. For the others small bowel benign neoplasm indication for surgery is limited to symptomatic lesions (intussusceptions, obstruction, bleeding). These neoplasms are often multiple; a carefully inspection of the entire small bowel is recommended before the treatment. Surgical options are different: endoscopic treatment (endoscopic polypectomy or mucosectomy especially for benign neoplasms of duodenum or proximal jejunum), excision via enterotomy (especially for small lesions) and small bowel segmentary resection<sup>6,10,11</sup>.

### *Malignant Neoplasm*

A recent epidemiologic study concerning small bowel malignant neoplasms, conducted in

the United States on 67,843 patients from 1973 to 2005 by Bilimoria et al<sup>12</sup>, showed an overall increase, in the last thirty years, of small bowel cancers from 11.8 cases per million (in 1973) to 22.7 cases per million (in 2004). This rise was more evident for carcinoid tumors (from 2.1 to 9.3 per million), less pronounced for adenocarcinoma (from 5.7 to 7.3 per million) and lymphoma (from 2.2 to 4.4. per million) and relatively constant for stromal tumors (from 1.8 to 1.9 per million). In particular, the proportion of patients with carcinoid tumors increased significantly (from 27.5% to 44.3%) whereas the proportion of patients with adenocarcinoma decreased (from 42.1% to 32.6%); so, in 2000, carcinoid tumors prevailed over adenocarcinoma as the most common small bowel tumor. Incidence rates is low and similar for both men and women before the age of 40. There is a parallel increase between 40 and 55 yrs in both sexes and then a more rapidly growth in men than in women<sup>13</sup>. The highest risk sites for malignant neoplasm are duodenum, for adenocarcinoma, and ileum, for carcinoids and lymphomas<sup>1</sup>. Treatment modality and oncologic outcome differs as a result of histological type.

#### **Small Bowel Carcinoid** (Figure 1)

Small bowel, especially terminal ileum, represents the most frequent location of neuroendocrine tumors in the gastrointestinal tract (among 30%)<sup>14</sup>. Peak incidence is between the 6<sup>th</sup> and 7<sup>th</sup> decades of life<sup>15</sup>. Clinical manifestations



**Figure 1.** Small bowel carcinoid.

are vague or absent, and tumors are often incidentally detected at the time of surgery for other gastrointestinal diseases or during exploration for liver metastases. In approximately 20% of cases these neoplasms secrete bioactive mediators and give rise to the characteristic “carcinoid syndrome” (intermittent abdominal cramps, diarrhea, flushing, bronchospasm and cyanosis)<sup>16,17</sup>.

Carcinoids independent of diameter are frequently (over 40% of cases) associated with nodal metastases, whereas tumors >2 cm in diameter are usually associated (over 60% of cases) with liver metastases<sup>16,18,19</sup>. Whether liver metastases are present or not, resection of primary tumor with extensive resection of associated mesenteric lymph nodes is appropriate<sup>17</sup>. Patients who, only after surgery, are discovered to have small intestinal carcinoid may be candidates for further surgery, especially for extensive mesenteric lymphadenectomy. Metastatic lymph nodes by carcinoid cause fibrosis and shrinkage of the mesentery (bulky mesenteric adenopathy) that could cause intermittent intestinal obstruction and, sometimes, intestinal ischaemia with necrosis and perforation of the intestinal wall<sup>17</sup>. The indications for potentially curative liver resection are similar to those applicable to metastatic colorectal cancer, including an adequately fit patient, no unresectable extrahepatic disease, and sufficient residual liver for adequate liver function prior to full recovery. Bilobar disease is not a contraindication to surgery, although if >50% of the volume of the liver is replaced by tumour, resectability is likely to be affected<sup>17</sup>. Palliative resection, where 90% or more of the volume of intra-hepatic disease is removed by formal liver resection and/or enucleation, has also been used to control carcinoid symptoms and prolong survival<sup>20-22</sup>. Disease unsuitable for partial hepatectomy unresponsive to alternative therapies, producing life-threatening complications and carcinoids with low proliferation index could be considered for liver transplantation. After radical resection of carcinoid tumors the 5yr-OS is absolutely acceptable with an overall survival (OS) rate of 70-80% in case of localized disease, 60-75% in case of nodal involvement and 30-50% in case of liver metastases. In patients with liver metastases underwent to hepatectomy or liver transplantation 5y-OS is respectively 70-80% and 60-70%<sup>17</sup> (Table I).

#### **Small Bowel Adenocarcinoma** (Figure 2)

Adenocarcinoma represented the commonest histological type of small bowel tumors in the

**Table I.** Five year survival of midgut carcinoid by stage of presentation. (Approximate percentage survivals from collected publications that are higher for patients undergoing complete surgical resection)<sup>17</sup>.

Stage of presentation	5-y Survival*
<b>Jejunum and ileum</b>	
Localised disease	70-80%
Nodal disease	60-75%
Liver metastases	30-50%
<b>All patients with liver metastases</b>	
Hepatectomy	70-80%
Transplantation	60-70%
All cases	20-50%

western world (30-50% of small bowel malignant tumors)<sup>23,24</sup>. Duodenum and jejunum are the most frequent location sites. Peak incidence is in the 7<sup>th</sup> decade of life and there is a male preponderance<sup>25</sup>. The most important risk factor for small bowel adenocarcinoma is a preexisting adenoma, either single or multiple in association with one of the multiple polyposis syndromes<sup>26,27</sup>. Small bowel adenocarcinomas, because of the large lymphatic tissue in small intestinal mucosa, early metastasize to regional lymph node and liver<sup>6</sup>. The most common presentation symptoms of adenocarcinomas of the small bowel are obstruction, overt or occult GI bleeding, weight loss, and jaundice<sup>6</sup>. Surgical radical resection with the help of adjuvant chemotherapy represent the therapy of choice. For jejunal and ileal tumors curative resection (R0) consists in a surgical complete gross resection with regional lymph nodes dissection in a manner similar to colorectal tumors (en bloc resection in case of infiltration of continuous organs), with macro- and macroscopically clear margin of clearance; in case of distal ileal lesion a right colectomy should be considered to obtain

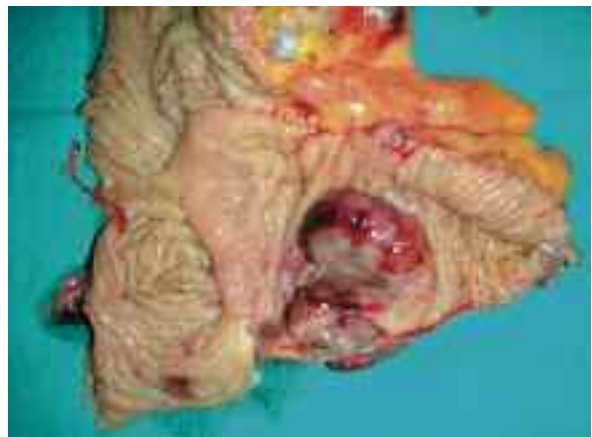


**Figure 2.** Small bowel adenocarcinoma.

a complete nodal station dissection. For duodenal tumors the surgical procedure is different if we considered proximal duodenal tumors (among II or III duodenal portions – duodenopancreatectomy) or distal duodenal tumors (IV portion – segmental resection with pancreas-preserving); clear resection margins are requested for both site of duodenal adenocarcinoma<sup>6,28</sup>. For locally advanced unresectable or metastatic adenocarcinoma a palliative treatment should be considered to avoid complication as obstruction (by-pass or stent) or bleeding (palliative resection of bleeding cancer). In case of single metastasis the role of liver resection is unknown<sup>28-31</sup>. Despite a radical resection the 5yr-OS rate is low. In a large landmark study conducted by the American College of Surgeons Commission on 5,000 small bowel adenocarcinomas, the overall 5-year disease-specific survival was 30.5%, with a median survival of 19.7 months<sup>32</sup>. Survival was lower in patients with duodenal tumors and in those who were more than 75 years of age, in part because of reluctance to pursue radical resection<sup>33</sup>.

#### **Small Bowel Lymphoma** (Figure 3)

Small bowel lymphoma can be primary or secondary. Primary lymphoma accounts for 15% to 20% of all malignant small bowel tumors and ileum represents the most common small bowel site involved by its<sup>34</sup>. Almost all primary intestinal lymphomas are non-Hodgkin's B-cell lymphomas of intermediate or high malignancy<sup>35</sup>. The usual clinical presentation of GI lymphoma includes intermittent abdominal pain, fatigue, diarrhea, weight loss, and, occasionally, fever. Less commonly, GI bleeding, obstruction, or even per-



**Figure 3.** Small bowel lymphoma.



**Figure 4.** Small bowel GIST.

foration (up to 25%) may be the initial manifestations of primary intestinal lymphoma<sup>6</sup>.

Chemotherapy at various level and variable dose of radiation therapy are the preferred therapy for GI lymphomas. Diagnosis of primary intestinal lymphomas requires histologic confirmation in a clinical setting in which palpable adenopathy and hepatosplenomegaly are absent and there is no evidence of disease on chest CT. Surgical exploration and resection of involved segments with regional lymph node dissection is requested to confirm diagnosis of lymphoma. Surgical treatment is required, too, in cases of complications as obstruction, bleeding and perforation. The overall prognosis of the more advanced stages of primary small intestinal lymphoma is only fair, with an expected 5-year survival of 25% to 30%<sup>36</sup>. A recent analysis of prognostic factors about lymphoma has shown no role for surgery in increasing oncologic outcome<sup>12</sup>.

#### **Small Bowel Stromal Tumor** (Figure 4)

Stromal tumors account <1% of all GI tumors. From 2000, the term GIST (gastro intestinal stromal tumor) was introduced in the most important international classifications of oncological disease as a well defined category of mesenchymal tumor which may present with either spindle-cell or epithelioid-cell histology and expresses the immunohistochemical diagnostic

marker CD117<sup>37,38,39</sup>. So, from 2000, 85% of tumors previously called leiomyosarcomas of GI tract are now known to be GISTs and GISTs represents the most common (over 90%) stromal tumors with malignant power of the GI tract. Many GISTs are discovered incidentally. When exist, symptoms of GISTs are obstruction and discomfort, consequence of the space-occupying nature of the tumor, hemorrhage or peritonitis<sup>39</sup>. Malignant power of GIST depend by mitotic index and tumor size<sup>40</sup>. Surgical complete gross resection with an intact pseudocapsule (non-disruptive techniques) and negative macroscopic margins (R0 or "R1" resection) is the definitive treatment for primary GISTs without evidence of peritoneal seeding or metastasis. En bloc resection is requested in case of infiltration of continuous organs<sup>41</sup>. GISTs rarely metastasize to lymph nodes. Routine lymph node dissection is not warranted except when there is evidence of gross nodal involvement<sup>42-45</sup>. It is recognized that in advanced cases, even if all abdominal metastases are surgically resected, surgery alone is not curative. Resection of intraperitoneal metastases should be considered if they are prone to intralesional bleeding, which may result in severe blood loss, peritonitis, and interference with Imatinib therapy<sup>42-45</sup>. Most GIST metastatic lesions, particularly those to the liver, are multifocal, diffuse, and technically difficult to resect<sup>46</sup>.

The 5-year survival rate after the surgical resection of GIST was 43–80% in the pre-Imatinib era (Table II) variable from 95% for low-risk GISTs to 0%-30% for high-risk GISTs. After the introduction of molecular targeted therapy with Imatinib and Sunitinib there is an improvement in the survival of the patients with GIST but most prospective randomized studies are needed.

#### **Metastatic Neoplasms** (Figure 5)

Secondary neoplastic involvement of the intestine is more frequent than primary small intestinal neoplasm. Extrinsic tumors may involve the gut by hematogenous metastasis, by direct inva-

**Table II.** Five year survival of small bowel stromal tumors.

Authors	N. pts	R0 Surgery	Recurrences	5y- OS	5y-OS in R0
De Matteo et al. 2000	93	80 (86%)	27 (33%)	60 months	66 months
Langer et al. 2003	39	35 (90%)	10 (28.6%)	63%	80%
Lyn et al. 2003	80	62 (78%)	31 (50%)	62.5%	73%
Tryggvason et al. 2007	53	46 (87%)	4 (8.7%)	54%	64.1%



**Figure 5.** Small bowel GIST.

sion, or by intraperitoneal seeding. Primary tumors of the colon, ovary, uterus, and stomach usually involve the small bowel, either by direct invasion or by intraperitoneal spread, whereas primaries from breast, lung, and melanoma metastasize to the small bowel hematogenously. Melanoma is the extraintestinal malignancy with the greatest predilection to metastasize to the bowel. Surgical resection does not improve prognosis but is sometimes requested in presence of complications<sup>6</sup>.

### **Role of Laparoscopic Surgery**

In the early and mid-1990s, concern was raised in regard to the appropriateness of laparoscopic methods for the treatment of malignancy. Less intra-operative bleeding, less post-operative morbidity, less analgesic drugs infusion, early first post-operative bowel movement, less immunological post-operative stress, shorter hospital stay, early renewal of work and aesthetic advantage represent the most important advantages of laparoscopy. About small bowel cancer, only for GISTs mini-invasive approach was proposed.

The 2004 NCCN Task Force Report generally discouraged laparoscopic or laparoscopy-assisted resection for GIST, limiting its use for tumors smaller than 2 cm at low risk of intraoperative rupture<sup>41</sup>. Two years later, however, Novitsky et al<sup>47</sup> found that both the efficacy and recurrence rates of 50 laparoscopically operated GISTs of mean size 4.4 cm (range, 1.0-8.5 cm) were similar or even superior to findings reported for historical open-surgery controls and suggested a revision of the 2004 NCCN guidelines. A number of other investigators also promoted the adoption

of expanded guidelines<sup>48-50</sup>. In response to the large increase in case reports and series reporting a favorable outcome of laparoscopic surgery for GIST, the 2007 update of the NCCN guidelines recommended that tumors measuring up to 5 cm in diameter were acceptable for laparoscopic resection, and that tumors larger than 5 cm might be resectable by hand-assisted laparoscopic techniques<sup>51</sup>.

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