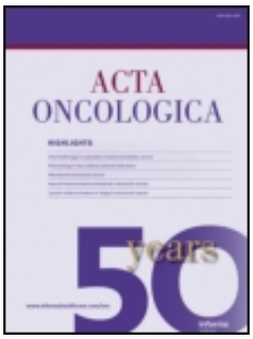

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FROM THE DEPARTMENT OF SURGERY, UNIVERSITY HOSPITAL, UPPSALA, SWEDEN.

ABDOMINAL SURGERY IN PATIENTS WITH MIDGUT CARCINOID TUMORS

G. ÅKERSTRÖM, C. MAKRIDIS and H. JOHANSSON

Abstract

In patients with midgut carcinoid tumors a curative, radical tumor removal should be attemped when possible. As these tumors are generally malignant, irrespective of size, the radical surgery implies that intestinal resection for excision of a primary tumor should be combined with an extended mesenteric resection. When the patients present with the carcinoid syndrome the disease is, with few exceptions, too advanced for curative surgery. However, surgery often has to be performed also in patients with the advanced carcinoids. Patients with more extensive disease may thus benefit from surgical debulking of large mesenteric or hepatic metastases. Moreover, when the patients present with abdominal symptoms it is important to exclude a threatening major abdominal complication, such as intestinal obstruction or ischemia. As these complications may cause malnutrition and deterioration, it is important to treat them properly, sometimes by repeated surgery.

Key words: Midgut carcinoids, surgery.

Based on their common origin from the embryologic midgut, carcinoid tumors of the jejunum, ileum and proximal colon are named midgut carcinoid tumors. Although lesions located in the small intestine are less prevalent than appendiceal carcinoids, especially when autopsy findings are included, they constitute the most common causes of the carcinoid syndrome. As this syndrome generally demands a complicated treatment, the midgut carcinoids tend to be the most frequently encountered carcinoid tumors at referral centres (1, 2).

The primary treatment of midgut carcinoid tumors is surgical. This implies that the intestinal tumor, often located in the terminal ileum, should be removed together with possibly present mesenteric lymph node metastases. Thus, if a midgut carcinoid is detected at an early stage and grossly radical tumor removal is accomplished, there is probably no need for further treatment. However, the patient has to be followed carefully as mestastases and symptoms related to a carcinoid syndrome frequently develop after several years and may then necessitate more aggressive treatment.

In the last few years new means of medical therapy have evolved for patients with malignant midgut carcinoids. As the beneficial effects of the most commonly used cytostatic agents streptozotocin/5-fluorouracil have been questioned this treatment is now consequently rarely recommended (3–6). Interferon appears to provide symptomatic relief in a considerable proportion of patients with midgut carcinoids and an associated carcinoid syndrome, and has also been considered to prolong survival, although this has not been evaluated by randomized trials (7, 8). More recently somatostatin and its analogue, Sandostatin (SMS 201–995), was shown to control symptoms related to the carcinoid syndrome and occasionally also induce partial regression of liver metastases (9, 10).

Few authors have described surgical treatment in patients with advanced midgut carcinoids. A better control of the carcinoid syndrome by medical treatment may imply that an increasing number of patients develop symptoms related to the intraabdominal spread of the tumor and therefore have to be considered for surgery. It is also possible that surgical debulking of metastatic tumors may be an important prerequisite for an optimal medical therapy.

Patients

In the last 10-year period, 140 patients with midgut carcinoids and generally also a carcinoid syndrome have been medically treated in Uppsala with streptozotocin/5-fluorouracil before 1982 and thereafter with interferon and

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sometimes also Sandostatin. Most of the patients were referred for therapy and more than half of them were operated upon before referral, with removal of the primary tumor by conventional intestinal resection or, in cases with apparently inoperable tumors, performance of an intestinal bypass (most frequently ileotransversostomy) or occasionally only explorative laparotomy. Some patients had undergone more than one previous operation. The patients were evaluated for surgery at our department with the intention of removing remaining primary tumors and, if possible, debulking mesenteric and hepatic metastases. This evaluation was continuously repeated during the ensuing medical treatment. Contributing indications for surgery were also a desire to relieve abdominal symptom, if present. Consistent with these indications, a total of 58 patients have so far been subjected to abdominal surgery. The findings among these patients operated upon have previously been reported in more detail (11).

Symptoms and indications for surgery

In a minority of the operated patients the carcinoid diagnosis was preoperatively not clinically evident but was diagnosed only in conjunction with laparotomy for acute symptoms, palpable tumor or various other reasons. In the remaining, approximately 80%, of patients operated upon, various symptoms related to the carcinoid syndrome were present, such as diarrhea, flush, bronchial asthma and even tricuspid valve insufficiency. Two-thirds of the patients had raised urinary 5-hydroxyindoleacetic acid (5-HIAA) values and one half of them radiologically visualized liver metastases, showing that they had an advanced carcinoid tumor. Abdominal symptoms, generally in the form of meal-related, intermittent abdominal pain, had been reported in two-thirds of the patients. In one-third, the symptoms were more severe, consisting of progressive abdominal pain, weight loss, clinical signs of ileus or increased diarrhea and frequently an inability to feed themselves perorally. A more or less acute surgical exploration had to be undertaken in some patients with symptoms indicating an abdominal complication.

Preoperative radiology

Preoperatively the patients were subjected to radiography to determine the intraabdominal tumor spread and to evaluate effects of the medical therapy. Plain abdominal and barium contrast examinations were of limited value for demonstration of primary tumors, but could establish the presence of partial or complete intestinal obstruction in patients with abdominal pain and malnutrition (Fig. 1). Computed tomography (CT) was utilized to monitor effects of medical therapy, due to its ability to demonstrate liver metastases. It was also superior for visualization of mesenteric and retroperitoneal lymph node metastases,

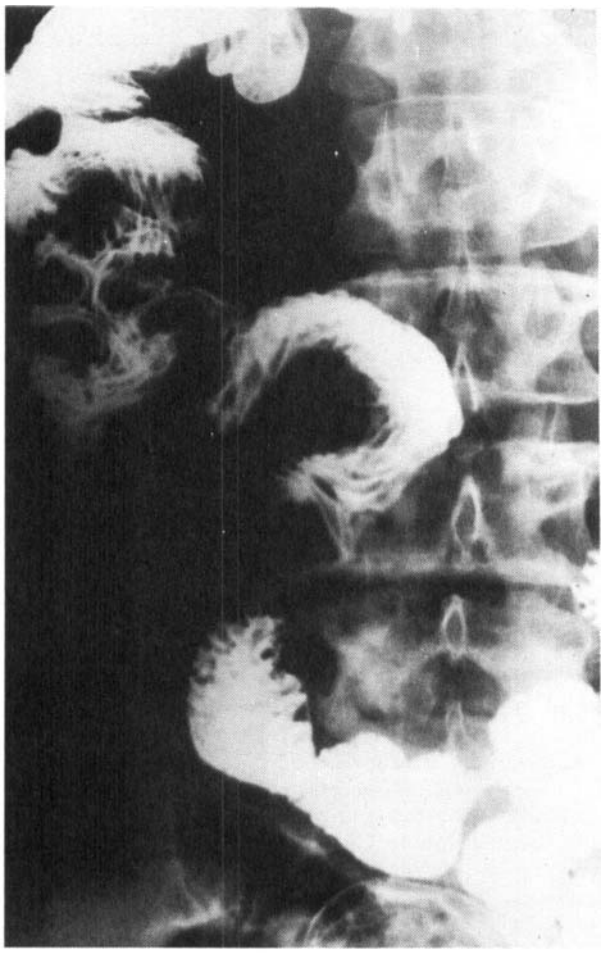
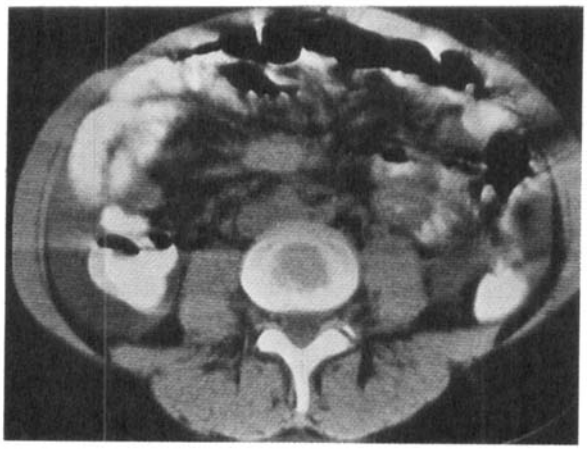


Fig. 1. Small bowel barium contrast examination demonstrating small intestine partially entrapped by carcinoid tumor and fibrosis.

showing frequent characteristic features, consisting of a mesenteric mass surrounded by radiating densities (Fig. 2 (12, 13)). Angiography was mainly utilized for mapping of the mesenteric tumor spread, by demonstrating typical caliber changes, segmental occlusions, tortuosity and curved dislocation of mesenteric arteries (Fig. 3 (14–16)). It was also valuable for preoperative visualization of collateral circulation to the intestine and anatomic aberrations, such as an arterial liver supply originating from the superior mesenteric artery. A few patients had occlusions of larger mesenteric veins.

Operative findings and surgical strategy

At operation remaining primary tumors were often evident only as a localized fibrosis on the exterior of the intestine. A majority of the tumors were located in the terminal ileum. Upon transection of the resected intestinal specimen, the primary tumors were found to be small, with a mean diameter around 1 cm. Multiple carcinoids, up to 11 in one patient and generally located close to the original



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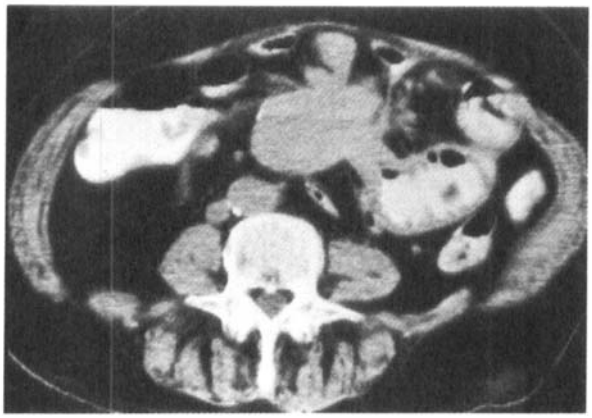


(b)

Fig. 2a–b. CT images of mesenteric carcinoid tumor metastases with typical radiating densities due to fibrosis.

primary tumor were found in almost 40% of the patients. Mesenteric lymph node metastases were present in more than 80%, also in patients with primary tumors no larger than 0.5–1 cm. These metastases, measuring up to 12 cm in diameter, were usually found in close proximity to the primary lesion and frequently extended along the origin of the mesenteric root to the retroperitoneum. Extensive fibrosis around the metastases caused considerable mesenteric shortening and fixation of parts of the ileum and sometimes also the jejunum as well as the right, transverse and even the sigmoid colon. Fibrous streaks attaching the mesenteric root to the retroperitoneum tended to stretch over and partly occlude the horizontal duodenum. A variable portion of the small intestine was often severely angulated and adherent, causing acute or chronic ileus in some patients. In others the bowel was entrapped by tumor and fibrosis and appeared partly occluded, without proximal dilatation, but frequently with a localized intestinal edema.

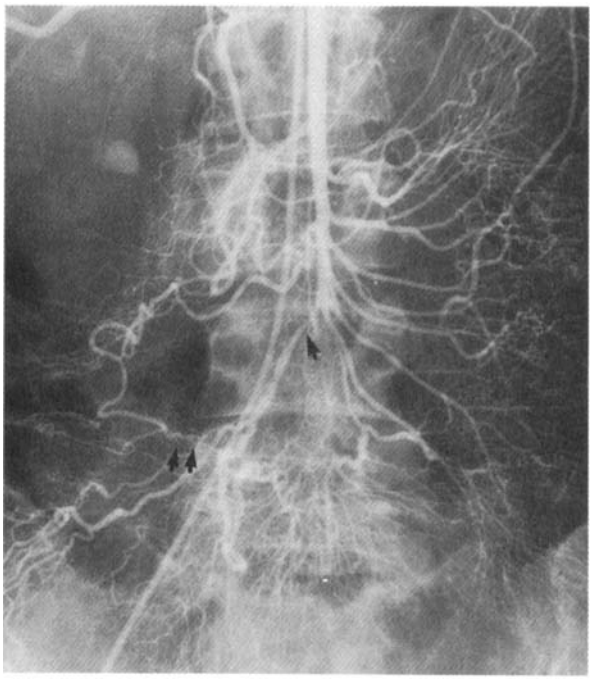


Fig. 3. Selective angiography of superior mesenteric artery showing partial segmental occlusion of main branch (arrow) and arterial tortuosity (two arrows).

In 10 of the patients a segment of the intestine appeared with pale ischemia or blue cyanosis, indicating incipient gangrene, due to insufficient arterial and/or venous circulation (Fig. 4). The intestinal ischemia of patients with midgut carcinoid tumors has previously been emphasized and attributed to compression of mesenteric vessels by tumor and fibrosis, but also to a specific mesenteric angiopathy,

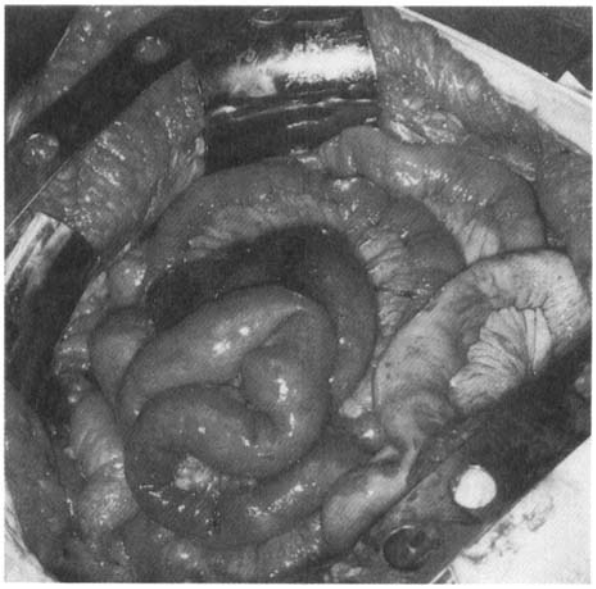


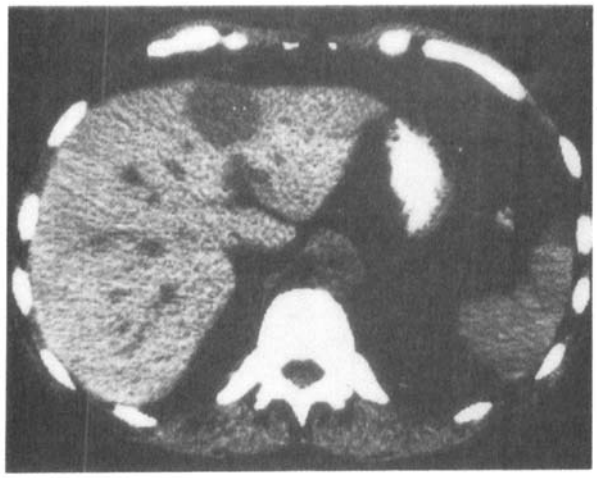
Fig. 4. Vascular impairment of small intestine resulting in blue dyanosis due to venous stasis.

consisting of elastic tissue proliferation within the adventitia of mesenteric arteries and veins (17–20). A compromised circulation was evident in the present series only in intestinal segments neighboring large mesenteric lymph node metastases, but has been described also in their absence and in intestinal segments remote from the tumors (17–20). Although venous obstruction and venous gangrene have been suggested as the most common severe vascular impairment in midgut carcinoids (21), several of our patients had insufficient arterial circulation or apparently both arterial and venous obstruction. One patient had diarrhea, rapidly progressing, during a disease history of three months, causing severe malnutrition. Angiography indicated occlusion of a main stem of the superior mesenteric vein, which was verified by transhepatic catheterizaton. At operation the distal 90 cm of the intestine was severely edematous and parts of it blue-cyanotic. Upon removal of this part of the intestine, followed by interferon treatment, the patient greatly improved. Malabsorption due to impaired venous drainage has been reported in association with midgut carcinoids (22) and may apparently be the cause of severe diarrhea. All patients with intestinal ischemia in the present study, were in a more or less pronounced malnourished state, a few had experienced increased diarrhea, others cessation of diarrhea, but most of them had prominent episodic abdominal pain, generally accentuated in connection with meals. This type of abdominal angina was often difficult to discriminate from the pain associated with acute or chronic ileus. The plain abdominal and barium contrast examination was of value by establishing in some of these patients the presence of ileus. Mesenteric angiography, however, rarely visualized the impaired circulation except in a few patients with occlusion of main mesenteric veins. All patients with intestinal vascular compromise evident at operation experienced considerable symptom relief postoperatively.

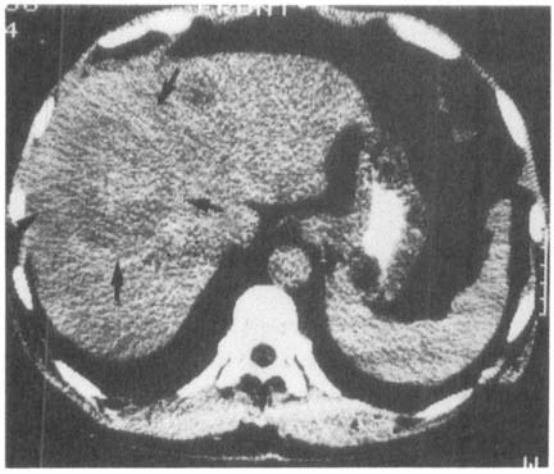
Acute or chronic ileus, seen in 12 patients, was somewhat less infrequent than reported in other series (23). More common was entrapment of the intestine with partial obstruction or localized edema of the intestinal wall. A few patients had concomitant obstruction of ileum and sigmoid colon, emphasizing the necessity to establish preoperatively the level of obstruction by radiographic methods. The sigmoid obstruction was invariably due to compression from the outside by carcinoid tumor and fibrosis.

Resections of the distal ileum, and occasionally the right colon, provided local, grossly radical and possibly curative tumor removal in a minority (less than 20%) of all patients. In the remaining ones the mesenteric tumor was impossible to remove radically, due to fibrosis and advanced tumor growth, extending to and around the origin of the mesenteric vessels and the retroperitoneum. However, although often apparently inoperable, it was generally possible to free-dissect and debulk major portions of the large mesenteric metastases and to remove intestinal segments containing a primary tumor or those being entrapped or with apparently impaired circulation. Dissection of mesenteric masses without sacrificing major mesenteric vessels was accomplished after transection of the harsh fibrosis around the metastases. An important part of this operation was the division of fibrotic streaks bridging to the retroperitoneum over the horizontal duodenum. By careful preservation of collateral circulation along the intestine it was possible to minimize the length of the intestinal resection, thereby avoiding to create a short bowel syndrome. This surgery was performed with increased difficulties in patients previously subjected to intestinal by-pass procedures. Sigmoid colon obstructions were easily relieved by cutting fibrotic streaks over the colon, except in one patient who needed an anterior resection.

Liver metastases were generally multiple and bilateral, often consisting of larger masses as well as minute, sometimes miliary lesions. Preoperative radiography, with either computed tomography, ultrasound or angiography, had frequently failed to visualize several of the smaller metastases. This inadequacy of radiological methods to reveal with certainty the extent of hepatic tumor involvement has been emphasized for tumors of other origin and has to be considered when effects of therapy on hepatic metastases are followed in carcinoid tumor patients, as the response among the different lesions may vary. The presence of small primary tumors together with considerably larger mesenteric lymph node or liver metastases, may suggest metastatic cloning of cells with special growth properties. Frequently also one or two mesenteric or hepatic metastases were conspicuously larger than surrounding lesions, indicating even more pronounced growth, or possibly occasionally an escape from medical therapy. A minority of patients harboring either solitary or major, dominating liver metastases were subjected to mainly atypical liver resections, and several other liver metastases were easily removed by simple enucleations or minor resections. When large liver metastases, measuring in one case 15 cm in diameter (Fig. 5), were removed, a resulting relief of the carcinoid syndrome was also associated with long survival, as emphasized by other authors (24–26). As, however, the patients also received medical treatment, the effects of surgery alone was sometimes difficult to evaluate. Hepatic artery ligation, which has been reported to provide efficient, although often short, palliation in patients with the carcinoid syndrome (25), was in the present series performed in only a few patients. After experiencing serious adverse effects in one patient, who barely survived, we have preferred to submit patients to, sometimes repeated, liver artery embolization. The method of temporary, operative liver dearterialization as reported by Nobin et al. (27) could, however, provide less side-effects and palliation of longer duration. It is furthermore possible that, concomitant with the development of medical therapy, it will be increasingly important to operatively reduce the tumor



(a)



(b)

Fig. 5. CT images of a) solitary and b) major dominating (arrows) hepatic metastases from midgut carcinoids removed by liver resection.

burden in the liver, by combinations of resection, enucleation, heat-coagulation or laser-evaporization of metastases.

Case histories

The following patients were chosen to represent some of the intricacies concerning abdominal surgery in midgut carcinoid tumor patients. In our opinion operative intervention is frequently necessary during the long-term follow-up and treatment of these patients.

Patient 1. The patient, a 45-year-old male had experienced diarrhea for 3 years, when he was subjected to laparotomy due to intestinal obstruction. Operation revealed a supposedly inoperable tumor, severely entrapping the distal small intestine. The entrapped and obstructed part of the small intestine, measuring 80 cm, was by-passed by an ileotransversostomy. Histological examination of biopsy specimen showed presence of a midgut carcinoid and the patient was referred to our department for further treatment. As the condition deteriorated with malnourishment, weight loss and increasingly severe abdominal pain a subacute operation was undertaken, with the suspicion of intestinal ischemia. At operation the by-passed intestinal segment appeared with impaired arterial circulation. A mesenteric mass was dissected and removed together with the previously by-passed intestine. Postoperatively the patient experienced considerable relief of the abdominal pain, was instituted on interferon and has thereafter regained weight and condition.

Patient 2. A 47-year-old male patient was, at acute laparotomy because of chronic subileus, found to have a midgut carcinoid in the terminal ileum, which was removed by resection, including the distal ileum and part of colon ascendence. Three years later he was at a new laparotomy for ileus found to have fixation by tumor and fibrosis of a major part of the small intestine and remaining right and transverse colon. The entrapped intestine was by-passed by ileotransversostomy which, however, gave no symptom relief. The patient continued to have abdominal pain, diarrhea and developed a condition of severe malnutrition, losing 20 kg in weight during a few months. He was then, as referred to our department, again evaluated for surgery. Due to abdominal distension radiography was performed, showing signs of ileus with obstruction of both the small intestine and the sigmoid colon. CT showed no large mesenteric mass and no liver metastases. A new operation was undertaken, revealing an extensive fibrosis, obliterating the peritoneal cavity. The peritoneal coverage of the right side of the abdomen, being attached to the intestine, had to be removed together with the previously by-passed, partly ischemic small intestine and right colon, leaving the patient with 1.3 m of the small intestine, most of the transverse and the left colon. Obstruction of the sigmoid colon was relieved by cutting the surrounding fibrosis. Postoperatively the patient improved considerably, has no diarrhea and has regained weight.

Patient 3. A 44-year-old female patient, suffering from a carcinoid syndrome with diarrhea, flush, asthma and a moderately severe tricuspid insufficiency, was shown at radiological investigation to have a solitary 15 cm large metastasis occupying central parts of mainly the right liver lobe. She was subjected to surgery consisting of a small intestinal resection removing the primary midgut carcinoid in the terminal ileum. At the same event the large hepatic metastasis was excised by an atypical liver resection, removing mainly central portions of the liver. Postoperatively she experienced considerable relief of the carcinoid syndrome and has been treated with interferon, showing at follow-up investigations up to three years later no signs of recurrent tumor in the liver.

Surgical strategy

Based on our experience the following surgical principles have been adopted concerning abdominal surgery in patients with midgut carcinoid tumors:

Radical surgery in patients with limited disease

A midgut carcinoid tumor should, as emphasized, be radically removed when possible. In contrast to carcinoids located elsewhere in the gastrointestinal tract, midgut carcinoids are associated with metastases in high frequency also when primary lesions measure less than 1 cm in diameter. Tumor removal by intestinal resection should therefore be combined with extended wedge resections of the mesentary in order to include also microscopic metastases in mesenteric lymph nodes. Frequently, however, the primary intestinal tumor has been removed by simple

resection at an acute operation for intestinal obstruction. If then the radicality of the previous procedure is questionable we recommend reoperation and a careful mesenteric dissection and removal of possibly metastatic lymph nodes. Removal of the intestinal tumor is generally also indicated in patients with liver metastases, as this may prevent abdominal complications. At referral centers, however, the radical, curative tumor removal generally constitutes only a minority of the surgical procedures undertaken in patients with midgut carcinoids. In patients previously subjected to intestinal resection it may be desirable to diagnose recurrent tumor early, in order to offer chances of a new operation. However, methods advocated for that purpose, like the pentagastrin-stimulation test, have, in our opinion, been of limited clinical value and we would rather submit patients liberally to reoperation.

Debulking operation of large or dominant mesenteric lymph node and hepatic metastases

Midgut carcinoid tumor patients presenting with a carcinoid syndrome generally have mesenteric lymph node metastases, whether the primary tumor has been removed or not. Even in previously operated patients it appears justified to try to reduce the tumor burden by operation. Although this surgery will rarely be radical, the shelling out of even large metastases from the mesenteric vessels is often possible once the surrounding harsh fibrosis has been divided. Such procedures may possibly prevent or delay development of the fibrosis, which has appeared especially abundant around large mesenteric tumors, and are suggested due to the local release of factors stimulating proliferation of connective tissue cells (28).

Only about 10% of our patients have appeared with excisable, solitary or major dominating liver metastases. Especially in cases with concomitant, multiple smaller metastases, atypical, parenchyma-saving liver resections seem advisable, possibly combined with wedge resections or simple enucleations of superficially located lesions.

The debulking liver surgery may be increasingly important in patients who no longer respond to medical therapy, as especially the larger metastases may have ceased to be affected by treatment.

Surgery for threatening abdominal complications on liberal indications

Various abdominal complications have appeared as major indications for surgery in our patients with midgut carcinoids. Concomitant with an apparently prolonged survival, in conjunction with different forms of medical treatment, approximately 20–30% of the patients have developed more or less predominating abdominal complaints. This may frequently constitute a major threat to the well-being and survival of the patients and it should be important to treat the patients in this respect, according to general surgical principles. Intestinal obstruction by tumor or fibrosis is a well-recognized complication, but in our experience, somewhat less prevalent than previously reported. Impaired intestinal circulation was equally frequent as a cause of the severe abdominal symptoms. When the intestine was severely entrapped by tumor or fibrosis a localized incipient ischemia had easily been missed even at a previous operation. As emphasized by our case reports, dealing only with the intestinal obstruction by performance of an intestinal by-pass, but not appreciating the incipient ischemia, would not suffice in such cases as this resulted in severe deterioration. As future surgery often becomes necessary in these patients we would suggest that by-pass procedures should be avoided, if possible. Moreover, the incipient vascular impairment, as well as the partial entrapment and obstruction of the intestine may probably contribute to the diarrhea in some patients. It may apparently also progress to a state of severe malnourishment, which may be misinterpreted as a malignant symptom in these patients. These causes of deterioration should also be important to exclude when patients with midgut carcinoid tumors are given medical therapy, as the condition has to be dealt with surgically.

Although advocating surgery in the patients with advanced midgut carcinoids we would like to emphasize the fact that these operations should not be taken lightly, as a mistake in the mesenteric dissection may devascularize a major part of the intestine. Moreover, we would routinely provide antibiotic coverage at operation, as otherwise postoperative infections may be a problem. We have not encountered carcinoid crisis (29) in any of the operated patients and would provide Sandostatin only to patients with a severe carcinoid syndrome or those who have flush or other symptoms at operation.

Corresponding author: Dr G. Åkerström, Department of Surgery, University Hospital, S-751 85 Uppsala, Sweden.

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