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SURGICAL TREATMENT OF CARCINOIDS AND ENDOCRINE PANCREATIC TUMOURS

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Abstract

The common association of neuroendocrine abdominal neoplasms, carcinoids and endocrine pancreatic tumours, with often severe endocrine symptoms has justified considerable efforts to improve treatment in these conditions. Surgery still constitutes the principle therapy for the majority of these tumours. However, the introduction of new means of medical treatment with cytostatic agents, or more recently interferon and a somatostatin analogue, seem to have impact on indications and the extent of surgery in malignant forms of these tumours. It is thus probable that a surgical tumour reduction will increase the possibilities to achieve positive effects of the medical treatment even in advanced malignancies. However, the existence of an alternative medical therapy has increased obligations that surgery should be performed without morbidity or mortality.

Key words: Carcinoids, endocrine pancreatic tumours, surgery.

Carcinoids

Carcinoid tumours may originate from neuroendocrine cells all along the gastrointestinal tract; about 85% of the tumours are located in the intestine, but they may also occur in the lungs or occasionally in the pancreas, biliary tract or thymus (1). About half of intestinal carcinoids are located in the appendix, the second most common location is ileum or jejunum while other locations: ventricle, duodenum, colon and rectum are more rare (1, 2).

The incidence of metastases from carcinoid tumours is dependent on the size of the primary tumour and also on its location (3–8). *Appendiceal carcinoids* are rarely malignant and lesions smaller than 1.5 cm may be safely treated by appendectomy, unless the tumour is at the base of the appendix when a caecectomy may be necessary. For the rare appendiceal tumour larger than 1.5 com ileocolectomy is recommended and this procedure is also justified if there is local invasion or lymph gland metastases. Appendiceal carcinoids are, in contrast to carcinoids in other parts of the intestine, more common in younger patients. In the rare elderly individual with an appendiceal carcinoid larger than 1.5 cm it may be appropriate to perform a simple appendectomy because of the relatively benign nature of the tumour (3, 6, 7).

Gastroduodenal carcinoids smaller than 1 cm may be locally excised by endoscopy. For larger, invasive tumours resection or subtotal gastrectomy and omentectomy is recommended (5, 8, 9).

In *rectal carcinoids* less than 1 cm in size the risk of metastases is minimal and the lesions may be treated by endoscopic excision. Tumours measuring 1–2 cm should preferably be operatively excised with margins. Irrespective of tumour size the depth of invasion should be investigated histologically. If there is invasion of the muscularis propria, or the tumour is larger than 2 cm, wider excision, generally in the form of anterior resection is recommended (8, 10, 11).

The treatment of *midgut carcinoid tumours,* originating from ileum, jejunum or more seldomly from the ascending colon often present a more difficult clinical problem mainly due to the frequent association with the carcinoid syndrome. Up to 90% of patients exhibiting this syndrome have a primary midgut carcinoid which is then often the most common gut endocrine tumour at referral centres (8, 12, 13). Midgut carcinoids may in relatively high frequency present with distant metastases also when the primary lesion is smaller than 1 cm (8). Metastases generally appear in mesenteric or retroperitoneal lymph glands but may also show up at distant sites as in the neck. Liver metastases are common and are generally spread in both lobes of the liver. The carcinoid syndrome is mainly encountered in patients with numerous or large liver metastases but occasionally also in a patient with only wide spread retroperitoneal growth (14).

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Midgut carcinoids grow slowly, rarely bleed and often spread silently and the patients may be without symptoms for several years until liver metastases and a carcinoid syndrome develop. Symptoms may also be caused by tumour obstruction of the intestine. The presence of an advanced intestinal carcinoid may, however, occasionally only be evident by the appearance of lymph gland metastases in the neck in which case a fine needle biopsy may establish the diagnosis. An increase in the urinary excretion of 5-hydroxyindolacetic-acid (5-HIIA) is diagnostic of the carcinoid syndrome but the metabolite is elevated only in patients' spread disease. Other diagnostic means like the pentagastrin stimulation test is also of value mainly in advanced cases (15, 16).

Malignant carcinoids generally induce advanced fibrosis which by knicking of the intestine and fibrous adhesions may cause mechanical obstruction also when the primary tumour is small. This is probably a more common ileus producing mechanism than obstruction by the tumour itself (4). The tumour may cause acute ileus but more often there has been a long period of chronic intestinal obstruction.

Intestinal carcinoids are generally too small to show up as filling defects on barium examinations and instead only the more advanced tumours will be visualized at this investigation by the mesenteric fibrosis and a typical arcading of the intestine (4, 17). Computed tomography (CT) is of value for demonstration of the mesenteric fibrosis and can be used to evaluate tumour extension in the mesenterium, the retroperitoneal space and the liver (18, 19). Angiographic findings are characteristic in advanced tumours showing segmental caliber changes or even occlusions of branches of the superior mesenteric artery which together with mesenteric veins may be entrapped by tumour or fibrosis (20). Collateral arteries may develop, especially along the intestinal arcades but also from other main arterial truncs as the coeliac or inferior mesenteric arteries. Angiography is the superior method for demonstration of hepatic metastates from carcinoid tumours.

Secretory products causing the carcinoid syndrome are considered to originate from the liver metastases as the liver is thought to metabolize outputs from other abdominal tumour masses (14). One may therefore in patients with proven liver metastases from a midgut carcinoid and the carcinoid syndrome be reluctant to remove the primary intestinal tumour or lymph gland metastases unless the patients have abdominal symptoms. As, however, a considerable number of patients will develop such symptoms and some of them also suffer serious complications of intestinal obstruction or intestinal ischemia (4) it may appear reasonable to perform an abdominal exploration and try to remove the primary tumour and possibly prevent this complication.

Local experience—treatment of advanced midgut carcinoids. We have at the Department of Surgery, University Hospital, Uppsala generally tried to remove the primary tumour and also single, accessible liver metastases in approximately 50 patients with midgut carcinoids and the carcinoid syndrome. As interferon has appeared effective in these patients (21, 22) we have extended our indications for surgery in order to achieve a reduction of the tumour mass and possibly better opportunities for the medical treatment. We have thus, during the recent 3 years, experienced 19 patients with more advanced midgut carcinoids, 9 of which were previously operated upon with intestinal resections or bypass procedures. To determine the tumour extension the patients were preoperatively investigated by CT and mesenteric angiography which showed, typically, a mesenteric tumour mass with retroperitoneal extension around main mesenteric vessels and desmoplastic mesenteric shrinkage. At laparotomy the majority of patients had large mesenteric, retroperitoneal tumours with extensive fibrosis entrapping the distal small intestine and generally also covering and sometimes partly obstructing the horizontal duodenum and occasionally the transverse colon. After transection of the retroperitoneal and mesenteric fibrosis, the primary tumour and a bulk of mesenteric tumour metastases could be dissected out and removed, taking great care to minimize the length of the resected intestine by free dissecting main mesenteric vessels and preserving collateral circulation. Two of the patients were at operation found to have threatening intestinal ischemia, one of them in a bypassed segment. It was possible to remove remaining primary intestinal tumours in all except one previously bypassed patient. In 10 patients a considerable bulk of metastatic tumour could be removed from the mesenterium and in 3 patients tumour metastases were also resected or enucleated from the liver. One patient with a carcinoid induced heart disease who had a large part of his right liver lobe occupied by tumour was subjected to a right-sided liver lobe resection.

Comments. Our adopted policy for appendiceal, foregut and hindgut carcinoids is similar to that previously outlined by several authors (5–11). We also agree that midgut carcinoids should, whenever possible, be radically removed together with mesenteric lymph glands, and that right-sided hemicolectomy may be needed to secure radical excision. However, in patients with more advanced midgut carcinoids our policy of a more aggressive surgical debulking of tumour tissue may be controversial and positive effects may be difficult to prove. However, the majority of these patients are at risk to develop abdominal complications of which intestinal ischemia is the most serious one. It is our belief that this may be prevented or delayed if the primary tumour and a bulk of mesenteric metastases are removed. The mesenteric dissection may reduce the length of the intestine that has to be resected with the primary tumour and by straightening the intestine the procedure will possibly to some extent prevent obstruction and should be preferable to bypassing of the intestine. Reduction of the tumour burden may, as we consider, be important in order to achieve optimal effects

of different forms of medical therapy that have evolved for the treatment of patients with the carcinoid syndrome (21–25).

Endocrine pancreatic tumours

Endocrine pancreatic tumours are even more rare than carcinoids and, as is the case for carcinoid tumours, an increased frequency of malignant variants may be seen at referral centres.

Insulinomas are most common among endocrine pancreatic tumours. They are benign and solitary in the majority of cases (90%) and therefore also generally effectively treated by surgery (26, 27). The superior radiographic method of insulinoma localization is selective angiography which gives a correct location in 60–90% (28, 29). CT and ultrasound are less efficient mainly due to the small size of the tumours (30). If an insulinoma has not been localized by other means, percutaneous transhepatic portal vein catheterization (PTP) and selective venous sampling for insulin determination is indicated (31, 32). This allows localization of the relatively rare insulinomas which are not palpable at operation and may also detect multiple tumours or islet beta-cell hyperplasia (32, 33). In patients with severe hypoglucemic symptoms, and in those where a suspected insulinoma has not been preoperatively localized, a diazoxide treatment test may be given preoperatively (34, 35). A positive response to diazoxide could, if an insulinoma is not found at operation, make it possible to close the abdomen without performing a blind distal pancreatectomy and by keeping hypoglucemic symptoms controlled by diazoxid new localization efforts could then later be made. The recent discovery that an intraoperative ultrasound examination may efficiently localize islet tumours with the size of only a few mm appears as an important finding, as its routine use may reveal multiple tumours, especially in multiple endocrine neoplasia (MEN-1) patients and also minimize the number of blind distal pancreatectomies (36, 37). Insulinomas in caput pancreatis may usually be enucleated even if they are large and a Whipple procedure should only be necessary in rare malignant cases (26, 27). Tumours in the corpus or tail of the pancreas may also be enucleated but when situated deeper in the pancreatic tissue distal pancreatic resections appear to entail less risk of pancreatic fistulation (26).

Gastrinomas. The management of patients with the Zollinger-Ellison syndrome has been controversial in several respects (38). Until recently the treatment of choice for most patients has been total gastrectomy (39). Medical treatment with H_2-receptor blockers or Omeprazole may now with few exceptions control the gastric hypersecretion. This has been claimed to have almost eliminated the need for total gastrectomy in the Zollinger-Ellison syndrome unless a patient is noncompliant (40, 41). It has furthermore been suggested that Zollinger-Ellison patients are nowadays detected earlier and that this, together with the available medical treatment, has increased the possibilities to make curative resections of gastrinomas (42). Although the symptoms may be controlled by medical treatment it is claimed that survival may be prolonged by tumour resection as many patients otherwise succumb to metastatic disease, which seem to develop in 60–90% of patients (41). Collected series of patients successfully operated on with curative resection of gastrinomas are still limited, but the strategy is now generally recommended and reported to enable cure of up to 30% of patients with gastrinomas (42–50). Thus, gastrinomas may be found at surgery in approximately 65% of cases, located in the pancreas in 40%, in the duodenum in 50% and in the remaining 10% in extrapancreatic, extraintestinal sites, i.e. mainly lymph nodes near the pancreas, within the intestinal mesenterium, within the liver, the ovary or hilum of the spleen (51). The tumours in Zollinger-Ellison patients are, however, often multiple and difficult to find. Gastrinomas with a size of only a few mm located in the duodenal wall or more rarely the ventricular antrum may apparently cause the full blown Zollinger-Ellison syndrome and these tumours may be especially amenable to curative resections. Patients have also been cured after surgical removal of lymph nodes near the pancreas containing gastrinoma cells or after removal of isolated gastrinomas in the liver (44, 52–54). It is thus apparently the extrapancreatic, duodenal or extraintestinal tumours which entails the best chance for cure by surgical resection (40, 44–46, 52).

Before submitting patients with the Zollinger-Ellison syndrome to surgery it is important to evaluate the extent of tumour spread and also to try to localize a tumour by available radiographic techniques. These methods will with fairly high accuracy tell if a patient has liver metastases, in which case medical treatment is generally recommended, although palliative resections of large tumour deposits has been reported to be beneficial in selected patients (49). CT may reveal gastrinomas in approximately 20% of patients, ultrasound in 40% and selective arteriography in 60% (50). Although the combination of these methods, or the utilization of infusion CT and arteriography may be even more successful, also large gastrinomas may be missed with these techniques. PTP and selective venous sampling for gastrin should therefore be of additional value by providing possibilities for regional localization (38, 55).

It is generally recommended that gastrinomas in the head of the pancreas are removed by enucleation and those in the tail or corpus by left-sided resections. Pancreatico-duodenectomy is generally not advised in Zollinger-Ellison patients unless there are multiple or large gastrinomas localized to the duodenum or the head of the pancreas which cannot be removed by other procedures (41). Blind pancreatico-duodenectomy should probably not be performed, even if microscopic gastrinomas may be found by this procedure, as the associated high morbid-

ity must be balanced against the favourable prognosis in Zollinger-Ellison patients where no tumour has been found at surgery (40, 50).

Other more rare endocrine pancreatic tumours: *vipomas, glucagonomas, somatostatinomas, pp-omas* should be treated with removal of the pancreatic tumour whenever that is feasible. Vipomas and glucagonomas are malignant in high frequency (50–70%) and have often spread with metastatic deposits in regional lymph nodes or the liver at the time of diagnosis (56–59). It is thus important to remove regional lymph nodes together with the primary tumour. The severe endocrine symptoms of these tumours will also often justify, sometimes repeated, efforts to debulk tumour tissue in the pancreas or the liver. The preoperative managment of these patients is important, which for patients with vipomas should imply correction of electrolyte- and fluid disturbances and treatment with the somatostatin analogue in order to control the diarrhoea. Patients with glucagonomas, who suffer general waisting and cachexia, should be given preoperative hyperalimentation and measures to prevent thrombosis.

Among *endocrine pancreatic tumours associated with (MEN-1)*, gastrinomas are found in approximately 60% of the patients, insulinomas in 30% while other tumours, vipomas, glucagonomas, are rare (60–62). Thus, one fourth of gastrinoma patients compared to 4–10% of those with insulinomas have MEN-1 (59, 61, 62). The MEN-1 patients always have hyperplasia or microadenomatosis of the pancreatic islet tissue and frequently several tumours with multiple hormone production. Insulinomas in these patients may generally be successfully treated by surgery which, however, should imply 75–85% distal pancreatic resection together with enucleation of visible tumours in the head of the pancreas (61). The treatment of gastrinomas in MEN-1 patients is controversial as few of these patients (2–5%) will be amenable to cure by resection (62). However, surgical exploration with principles outlined as for insulinomas could perhaps be undertaken if preoperative localization studies should indicate a single tumour focus (42). Intraoperative ultrasound examination may be of value in order to reveal multiple tumours. Total pancreatectomy is probably seldom indicated as the pancreatic tumours of MEN-1 patients often have comparatively benign courses.

Local experience. We have, during the recent 10-year period, at the Department of Surgery in Uppsala treated 36 patients with endocrine pancreatic tumours. Twenty patients had the hypoglucemic syndrome; due to benign insulinomas in 14 cases, islet cell hyperplasia in one and malignant insulinomas in 5 patients. The high proportion of malignant cases is due to referral of many of these patients to our centre. Several of the patients with benign insulinomas were comparatively young. Hypoglucemic symptoms had been present for generally relatively short periods except in one patient who had symptoms for 30 years and presented an unusually large (4 cm in diameter) tumour. With this exception the benign insulinomas were comparatively small (mean diameter 1.3 cm). Selective angiography was the superior method for localization but if this method failed, PTP and selective venous sampling for insulin determination was performed. During recent years, intraoperative ultrasound has been regularly utilized. Thus in one patient with an insulinoma, for which only PTP had provided region specific localization, the intraoperative ultrasound examination demonstrated a bilobated tumour deep in the pancreatic head with a close relationship to the common bile duct. This tumour could be enucleated after introduction of a catheter in the bile duct. Our general policy has been to enucleate insulinomas in the head of the pancreas and to perform distal pancreatic resections for tumours in the tail or corpus. Three patients had insulinomas together with the MEN-1 syndrome and in these cases an approximate 75–85% pancreatic resection was performed together with enucleation of tumours visible in the head of the pancreas. Intraoperative ultrasound was of value in these patients by establishing the line of pancreatic resection in relation to visualized tumours; tumours as small as 3 mm were seen by this method. One adult, non-MEN-1 patient had islet beta-cell hyperplasia and was treated first with an approximate 80% and later a 95% resection of the pancreas and now needs insulin substitution. Of the 5 patients with malignant insulinomas one had a recurrence 4 years after enucleation of a small, apparently benign insulinoma in the corpus of the pancreas. It was emphasized in retrospect that the enucleation of this tumour was more difficult than usual. The recurrent tumour was removed by pancreatic resection but the patient has later developed liver metastases and eventually succumbed to the disease. Two patients with malignant insulinomas have had primary tumours and apparently solitary liver metastases resected, one of these patients is apparently cured. Two patients had initially disseminated disease and were only subjected to diagnostic laparotomy.

Eight patients have been treated for gastrinomas implying tumour removal by resection of the corpus or tail of the pancreas, in 4 patients combined with total gastrectomy. One of these patients has been subjected to reresection of pancreatic tumour. The fifth patient had a primary pancreatic tumour enucleated from the head of the pancreas together with removal of 3 large lymph gland metastases. A further 3 patients had Zollinger-Ellison syndrome associated with MEN-1 and were subjected to distal pancreatic resection together with enucleation of tumours in the caput. A few of the more recent patients are not yet evaluated but we have this far achieved sustained normalization of gastrin levels in only 2 non-MEN-1 patients. The patients have, however, been easier to treat medically after the pancreatic operation.

Four patients had vipomas and were treated by resection of the corpus or tail of the pancreas, including removal of local lymph gland metastases. Two of these patients

have been subjected to repeated tumour removal at several occasions with improvement of the condition for some time. In one of the patients resection of a 5×8 cm tumour located in the right liver lobe, however, gave no sustained improvement as the patient had disseminated microscopic metastases throughout the liver.

The remaining 4 patients in our material have had non-functioning endocrine pancreatic tumours with apparently mixed secretion demonstrated immunohistochemically. None of these patients have been cured by operation but they have all had relatively long survival on various forms of medical therapy.

Comments. Our policy to try to resect also recurrent endocrine pancreatic tumours or dominating liver metastases in patients with malignant endocrine pancreatic tumours, especially when they are associated with severe symptoms, is probably not controversial. These patients may evidently be controlled for years with a combination of repeated surgery, embolization of liver metastases and different forms of medical treatment. In patients with MEN-1 we try to remove radiologically visualized pancreatic tumours by a combination of enucleation and 75–85% resection also when there is predominant gastrin production. Although it may be difficult to cure the Zollinger-Ellison syndrome we have felt that the removal of gross tumours may prevent metastatic spread and possibly prolong survival in these patients.

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