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Surgical Management of Malignant Islet Cell Tumors

Clive S. Grant, M.D.

Department of Surgery, Mayo Clinic and Foundation, Rochester, Minnesota, U.S.A.

The surgical management of pancreatic islet cell carcinomas poses a complicated set of questions resulting from their rare occurrence and the difficulty in establishing a diagnosis in early cases or, conversely, the problems inherent in dealing with metastatic disease. However, because their biologic behavior is rather indolent, a real opportunity exists not only for cure but also for meaningful palliation. These goals apply both to the tumor itself and the effects of the hormones they may secrete. The challenge facing the multidisciplinary management team in general, and the surgeon specifically, is to achieve the optimal combination of surgical resection and other treatment options. While the precept of aggressive excision applies to most islet cell carcinomas, it is not universally applicable. In contrast to other islet cell tumors, insulinomas are overwhelmingly benign, and are well treated by enucleation or limited pancreatic resection. Although based on relatively few cases, cytoreductive surgery seems beneficial for malignant insulinomas. Advances that have occurred over the past decade in Zollinger-Ellison syndrome have markedly altered surgical management. Medication which reliably prevents ulcer formation has permitted the surgical perspective to be redirected from end organ ablation to curative tumor excision. Multicentricity and metastases, however, limit the extent to which cure can actually be achieved. Patients with vasoactive intestinal peptide-producing tumors and glucagonomas are very rare, and when possible, should undergo tumor resection to correct the severe hormonally caused metabolic derangements. Increasingly recognized are islet cell carcinomas that do not produce clinical syndromes. They may be confused with ductal carcinomas, but when resected, lead to distinctly superior survival rates among patients.

In sharp contrast to the minimal progress achieved in altering the outcome of the almost uniformly and rapidly fatal ductal pancreatic carcinoma, major improvements in the management of malignant islet cell tumors have occurred. This rapid evolution continues. The critical advances over the last three decades allow management of many of these tumors today to be vastly different and clearly superior. To classify an islet cell tumor as malignant usually requires demonstration of distinct local invasion of surrounding soft tissues or the presence of metastases [1] (most commonly to lymph nodes and liver). Therefore, by definition, the limitations inherent in establishing a firm diagnosis necessarily translate into a more advanced stage of disease. Moreover, because islet cell carcinomas occur in only approximately one to five persons per million population [2], specific treatment recommendations have been drawn from single case reports and a few small series.

A number of factors should be considered when planning the overall care of a patient with an islet cell carcinoma, some of which are specific to each clinical syndrome. Certain principles, however, may apply to the disease in general.

1. *Is the tumor benign or malignant?* The likelihood of malignancy varies depending on the type of hormonal syndrome (Table 1), but metastases may not be apparent at first presentation.
2. *Is the tumor functioning or nonfunctioning?* It is important to distinguish patients who have a clinical endocrine syndrome from those who do not. Even though some islet cell tumors stain positively for hormones by immunoperoxidase or other techniques, unless clinical symptoms of hormonal overproduction are present they would be categorized as nonfunctioning. Additionally, although functioning tumors may stain positively for more than one hormone, the clinical picture is usually limited to the effects of only one [3].
3. *Is the disease sporadic or part of the multiple endocrine neoplasia type I (MEN-I) syndrome?* Because in MEN-I patients the pancreatic disease is virtually always multicentric [4] (whether histologically described as multiple adenomas, adenomatosis, or nesidioblastosis), patients who undergo pancreatic resections less than total pancreatectomy may be expected to have persistent disease and eventually may experience recurrent symptoms.
4. *How well can the tumor be identified by localization techniques pre- and intraoperatively?* This question relates primarily to insulinomas and gastrinomas, as most other functioning and nonfunctioning islet cell malignancies are large and can be easily visualized by computed tomography (CT).
5. *What is the natural history of the tumor?* It depends on type of tumor and the disease stage. The complications and lethality of the hormonal effects as well as the tumor itself must be taken into account.
6. *What is the likelihood of surgical cure balanced against the morbidity and mortality of the surgical procedure?* Given the high frequency of metastases in all islet cell carcinomas, the opportunities to achieve a surgical cure are uncommonly encountered.
7. *If surgical cure is not possible, to what extent should*

Offprint requests: C.S. Grant, M.D., Mayo Clinic, 200 First Street SW, Rochester, MN 55905, U.S.A.

Table 1. Characteristics of functioning islet cell carcinomas.

Syndrome	Clinical presentation	Biochemical diagnosis	Rate of malignancy (%)	Metastases at diagnosis (%)	Localization (radiographic)	Ectopic sites (nonpancreatic)
Insulinoma	Neuroglycopenia Adrenergic response	Blood glucose < 40 mg/dL Insulin > 6 μU/ml Absence of insulin antibodies Nl/elevated C-peptide	5–15	15–30	US, preoperative angio, PVS (reoperative cases)	Rare
Zollinger-Ellison syndrome	Dyspepsia/ulcer Diarrhea	Elevated basal gastrin Elevated basal acid output Positive secretin test	50–60	50–80	US, CT, angio, PVS	Duodenum Rarely other
WDHA (VIPoma)	Profuse, secretory diarrhea Hypokalemia Hypo/achlorhydria hypercalcemia hyperglycemia	Elevated VIP	50	50	CT, occas. angio, PVS	Retroperitoneum Lung
Glucagonoma	Dermatitis Diabetes Weight loss Anemia	Elevated glucagon	75	60–70	CT	Rare
Somatostatinoma	Diabetes Cholelithiasis Diarrhea Steatorrhea	Elevated somatostatin	90–100	50–75	CT	Duodenum

WDHA: watery diarrhea, hypokalemia, achlorhydria; VIP: vasoactive intestinal peptide; US: ultrasonography; angio: angiography; PVS: portal venous sampling; CT: computed tomography.

resection be pursued for palliation? Major pancreatic resections even combined with liver resections can now be accomplished with acceptable mortality and morbidity [5]. Whether these operations are worthwhile, however, depends on the degree and duration of successful palliation. Additionally, the pros and cons of surgical palliation must be weighed against the potential of other means of palliation, such as radiographic hepatic arterial embolization, inhibition of hormonal effects with somatostatin analog [6], or chemotherapy [7].

The above principles must be addressed in the overall context of managing a patient with islet cell carcinoma: diagnosis, tumor localization, preoperative preparation, conduct of the operation, and outcome. Although rare tumors secreting neurotensin, pancreatic polypeptide, or multiple hormones have been identified, only nonfunctioning and the five principal functioning tumors (insulinomas, gastrinoma, VIPoma, glucagonoma, and somatostatinoma) are reviewed.

Insulinoma

Diagnosis

Symptoms of neuroglycopenia, such as blurred or double vision, incoherence, and abnormal behavior, which stimulate an adrenergic response of sweating, weakness, and palpitations are classic for insulinoma. It includes benign tumors and the 5% to 15% that are malignant [8]. To confirm the diagnosis the patient is hospitalized, and a 72-hour fast is initiated. Reliably, usually within 24 hours, hypoglycemic symptoms become evident, and blood should be obtained for glucose, insulin, and C-peptide assays before the patient is resuscitated with 50% glucose intravenously. A glucose level of less than 40 mg/dL with a concomitant insulin level of more than 6 μU/ml, in the absence of insulin antibodies or oral hypoglycemic agents in the urine (or if C-peptide is elevated, which excludes exogenously administered insulin), establishes the diagnosis [9]. Increased levels of proinsulin or the α and β fractions of human chorionic gonadotropic hormone have been found in patients with malignant insulinomas but have not been of significant clinical value in our experience.

Localization

Radiologic imaging of islet cell tumors in general and insulinomas in particular has advanced significantly. Previously, the gold standard was selective arteriography with subtraction views, which was successful in identifying the tumor in up to 70% to 90% of tumors [10]. This level of success has not been enjoyed by all, however, and interest in noninvasive methods has continued. CT has proved somewhat disappointing, but preoperative high-resolution, real-time ultrasonography has successfully localized the tumor in nearly two-thirds of patients [10]. As is true of ultrasonography in general, the quality is highly operator-dependent. The combination of intraoperative ultrasonography (IOUS) plus careful manual palpation by the surgeon has localized more than 95% of these tumors in recent experience [11, 12]. Therefore arteriography and portal venous sampling should generally be reserved for use in reoperative cases if the tumor could not be localized at the initial exploration.

Preoperative Preparation

The patient may be admitted to hospital the day prior to operation for limited bowel preparation and intravenous glucose administration. A few hours prior to commencing the procedure, the intravenous solution is changed to one without glucose to allow the serum glucose to drift downward and thereby better define the rebound effect when the tumor is resected. A trial period of preoperative diazoxide has been advocated [13]. However, because most insulinomas are benign, nearly all being curatively excised, this measure seems unnecessarily cautious.

Conduct of Operation

An intravenous catheter is placed to be used for serial glucose monitoring. Although the time interval and degree of rebound hyperglycemia following excision of the tumor is variable enough not to warrant additional pancreatic resection on that basis alone [14], it usually provides reassurance that the tumor has been removed.

For most islet cell tumors, a bilateral subcostal incision offers optimal exposure, but a midline incision is a satisfactory alternative. Following exploration of the entire abdomen, carefully palpating for small metastatic lesions in the liver, the pancreas is widely exposed [15]. The omentum is dissected from the entire extent of the transverse colon, the stomach is elevated, and adhesions to the pancreas are lysed. The duodenum is widely kocherized, and the spleen may be mobilized by incising its lateral peritoneal attachments. If necessary, the right and left gastroepiploic vessels may be transected, thereby exposing the entire face of the pancreas. To complete the mobilization of the body and tail of the pancreas, the peritoneum along the inferior border of the pancreas is incised and the posterior surface is gently bluntly dissected.

The insulinoma is sometimes visible on the pancreatic surface, but if not the tumor is usually palpable at this stage. We routinely use IOUS to help identify tumors, exclude multicentric disease, and delineate the relevant anatomy (especially the relation of the tumor to the pancreatic duct) [11].

Most tumors can be enucleated because of their compact nature, which gives the impression of encapsulation. The plane *immediately* adjacent to the tumor must be dissected to avoid damage especially to the pancreatic duct. It is of paramount importance in the head of the pancreas. Lesions overlying or to the patient's left of the superior mesenteric vein may be resected with a distal pancreatectomy if necessary. Rarely, a malignant insulinoma has infiltrating instead of the typical "pushing" borders. Resection, including radical pancreatoduodenectomy, rather than enucleation is generally indicated in these cases.

Only a single patient with MEN-I had a malignant insulinoma in our recent experience [16], and none was identified in the 25-year experience of the NIH [17]. Our patient had a single nodal metastasis and is well on no medication following 90% distal pancreatectomy.

Outcome

Even though 89% of patients in one series had metastases at the time of diagnosis [17], 4 of the 17 patients underwent curative resection. Three remained free of disease, the other died of disease at 2 years; the median disease-free survival was 5 years. The median survival time for patients who underwent palliative resection was 4 years. In isolated cases, resection of liver metastases has extended patients' lives from 3 years to 8 years [3].

Zollinger-Ellison Syndrome

Diagnosis

Because of widespread exceptionally strong interest in Zollinger-Ellison syndrome (ZES), the clinical presentation has shifted significantly to a much earlier stage than was originally described. Patients suffering from virulent, complicated ulcer disease have been replaced in large part by those being investigated for routine dyspepsia or diarrhea [18]. Elevated basal serum gastrin levels, in conjunction with marked gastric hypersecretion or elevation of gastrin levels following a secretin stimulation test solidify the diagnosis.

Therapy for ZES has evolved more than any other islet cell tumor. Because of the devastating complications of the ulcer disease, the original treatment was limited to total gastrectomy. The introduction of H_2-blocking drugs that effectively block acid production dramatically altered therapeutic perspectives. Advances in this class of medication together with the introduction of omeprazole have virtually eliminated complications of the ulcer disease when the syndrome is recognized and the medication is taken faithfully. Attention has been refocused on the treatment of the tumor. In contrast to insulinomas, gastrinomas are malignant in 25% to 60% of cases, half of which have metastases at the time of diagnosis [19]. Moreover, benign tumors are often multiple; perhaps one-third of ZES patients have MEN-I syndrome [13], leaving only an estimated 20% of all ZES patients as candidates for curative surgical resection.

Localization

Preoperative CT and ultrasonography may be useful for localizing the primary pancreatic tumor and associated liver metastases. Arteriography (with the possible addition of secretin infusion) [20] has a definite role but is unfortunately associated with false-positive and false-negative results [21]. Gastrinomas may reside in the submucosa of the duodenum; and although attractive in concept, endoscopic identification has been only variably successful.

Because up to 25% of ZES tumors may not be identified with all of these localizing techniques *plus* careful intraoperative palpation by experienced surgeons, more extensive invasive preoperative methods may well be justified. Transhepatic portal venous sampling (PVS), despite being invasive, uncomfortable, and expensive, and yielding only regional rather than specific localization, has been reportedly helpful [22].

Preoperative Preparation

If bilobar liver metastases are evident by preoperative imaging, there is rarely anything to be gained by surgical exploration, and the patient is managed medically.

The appropriate management of MEN-I patients with ZES

has yet to be resolved. To achieve lasting cure, total pancreatectomy would be necessary. The possible cure of ZES, dangerously presuming no occult metastatic disease exists, in exchange for pancreatic exocrine insufficiency and diabetes mellitus—to say nothing of the potential operative complications—is unacceptable. Recurrence of disease seems inevitable with lesser pancreatic resections. As a general rule, MEN-I patients should be managed medically [23].

In sporadic patients, no longer is a prolonged trial of medical therapy necessary because acid secretion and dyspeptic symptoms can be controlled in all patients using either H_2-blocking agents or omeprazole in sufficient doses. However, all patients require this control be instituted prior to undergoing exploration.

Conduct of Operation

The incision, operative exposure, and possible use of IOUS are similar to that described for insulinomas. An additional maneuver that should be considered if no tumor can be identified is to proceed with a duodenotomy to facilitate careful palpation of the entire duodenal wall for a tumor that is often less than 1 cm in size [24]. These duodenal tumors may be the most curable.

The concepts for enucleation or pancreatic resection of gastrinomas are similar to insulinomas. Localized tumor should be resected, but pancreaticoduodenectomy should probably be avoided. The addition of liver resection to pancreatectomy with curative intent has been successful but only in exceptional circumstances [25]. In contrast to most other islet cell tumors, because medical management of ZES is relatively simple and highly effective at controlling symptoms, palliative surgical resection has appropriately been discouraged [25].

Outcome

Even though 5- and 10-year survival rates of 42% and 30%, respectively, have been reported [26], patients with extensive metastatic disease may have only a 20% 5-year survival [25]. Important subgroups of patients who have ZES and either duodenal tumors or tumors outside the pancreas or duodenum seem to have a higher likelihood of cure following excision [27].

VIPoma

Diagnosis

Another name for VIPoma syndrome is WDHA (watery diarrhea, hypokalemia, achlorhydria), which is descriptive of the symptoms. The dominant symptom is profuse diarrhea, which may reach disabling proportions, even resulting in renal failure [19]. Marked hypokalemia may manifest as muscle weakness and lethargy, and may be further exacerbated by nausea and vomiting. Additionally, hypercalcemia and hyperglycemia may complicate management.

Vasoactive intestinal polypeptide (VIP) is elevated in most patients; it originates from a pancreatic tumor in 70%, but in 10% to 20% it is secreted by ganglioneuroblastomas or adrenal medullary tumors [28]. Nearly 50% of the pancreatic tumors are malignant, three-fourths of which are metastatic at the time of clinical presentation.

Localization

Because these tumors are often large and located in the body or tail of the pancreas in 80% of affected patients, the CT scan is usually definitive. Occasionally, angiography or PVS may play a role [29].

Preoperative Preparation

Use of somatostatin analog has been of great benefit to quell the refractory diarrhea and aid in reestablishing normal fluid and electrolyte balance [30].

Conduct of Operation and Outcome

When feasible, distal pancreatectomy for tumors or islet cell hyperplasia is the preferred treatment and may be curative for localized tumors. In MEN-I patients with a dominant mass, excision of that tumor may offer significant benefit [23]. Palliative subtotal resection of tumor and even curative resection of liver metastases [31] have ameliorated or resolved the symptoms.

Glucagonoma

Diagnosis

The distinctive clinical syndrome is chiefly heralded by a characteristic dermatitis, "necrolytic migratory erythema," plus diabetes in association with markedly elevated serum glucagon levels from a pancreatic D-islet cell tumor. Between two-third and three-fourths of these tumors are malignant, although this may not become evident for years following resection of the primary tumor.

Localization

Most tumors exceed 3 cm in diameter, and 90% are located in the body or tail of the pancreas. The CT scan is usually the only radiographic study necessary.

Preoperative Preparation

Marked weight loss, hypoaminoacidemia, anemia of chronic disease, stomatitis, and glossitis plus the painful, pruritic, and often secondarily infected rash result from the catabolic effect of glucagon. Additionally, nearly 30% of patients experience thromboembolic complications affecting both arterial and venous systems [15]. As in patients with VIPomas, preoperative somatostatin analog can achieve dramatic beneficial results in correcting these problems prior to operative treatment [31].

Conduct of Operation and Outcome

Similar to all other islet cell tumors, curative resection is optimal. Unfortunately, metastases are found in at least 60% of patients; but if they are confined to the liver, they may be amenable to curative resection [5]. Despite the severe metabolic derangements, the prognosis may be surprising with a reported 5-year survival of 50% [32].

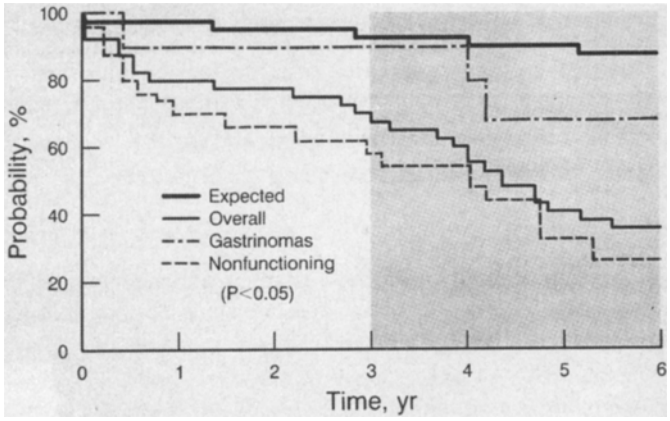

Fig. 1. Survival of patients with gastrinoma compared to that of patients with nonfunctioning islet cell carcinomas.

Somatostatinoma

Diagnosis

Only rarely recognized, the syndrome is subtle and reflects the "inhibitory" effects of somatostatin. Diabetes mellitus, cholelithiasis, steatorrhea, and indigestion in conjunction with a D-islet cell tumor that stains positive for somatostatin confirms the diagnosis.

Localization, Conduct of Operation, Outcome

Most tumors have been recognized late in their course and were large, single, and metastatic. They may originate in the pancreas, with a predilection for the head [33] or in the duodenum. Prognosis has been poor [34].

Nonfunctioning Islet Cell Cancers

The frequency of the nonfunctioning islet cell tumor may be increasing and is at least as common as the functioning tumors combined [16]. By definition, no hormonal effects serve to alert the physician to the diagnosis until the tumor itself causes symptoms—much like exocrine pancreatic carcinomas. In fact, only after resection with histologic review and possibly special chromogranin stains might the two be distinguished. Aggressive surgical resection including pancreaticoduodenectomy is warranted, with 3- and 5-year survivals of 58% and 35%, respectively [16] (Fig. 1).

Surgical Options for Metastases

A central theme of both functioning and nonfunctioning islet cell carcinomas is that they often follow a relatively indolent clinical course. Yet equally characteristic is their inexorably fatal outcome. If not due to complications of hormonal excess, patients succumb as a result of generalized malignancy—in which liver metastases predominate. Inferred from this fact is the usually protracted time extending from establishing the diagnosis—at which time liver metastases may already be present—to demise. As has been emphasized, both curative and palliative liver resections have been widely supported but generally are based on meager data.

McEntee et al. [5] reported 37 patients who had undergone such hepatic resections for both islet cell pancreatic and carcinoid tumors in 13 and 24 patients, respectively. Curative resections were performed in 17 patients with complete and incomplete relief of endocrine symptoms in 85% and 14%, respectively, extending a mean of 26 months. Disease-free survival was achieved in 59% of cases followed for a mean of 28 months. Palliative resection resulted in complete and incomplete symptomatic relief in 60% and 30%, respectively, but lasted only a mean of 6 months, with some degree of symptomatic relapse by 12 months in all patients. Hence curative resection seems well justified provided the operation can be accomplished safely. Less compelling but worth offering are palliative procedures.

Other options include applications of technology previously directed toward hepatomas or metastatic colon carcinomas. They include cryotherapy and alcohol ablation, which have been successful in destroying these primary and metastatic liver lesions [35]. Whether they may deserve a primary role or at least be adjunctive to hepatic resection should be considered in the near future.

Résumé

Les progrès importants des trois dernières décennies permettent de proposer un traitement de la plupart des tumeurs insulaires du pancréas, alors qu'autrefois leur traitement n'était pas du tout raisonnable. Pour chaque tumeur, il faut déterminer si elle est bénigne ou maligne, et si elle est fonctionnelle ou pas. Il est aussi important de savoir si la maladie est sporadique ou fait partie d'un syndrome de tumeurs endocrines multiples de type I. En ce qui concerne le traitement chirurgical, il faut savoir localiser la tumeur, soit en préopératoire, soit pendant l'intervention, et évaluer les chances d'exérèse par rapport aux risques de morbidité et de mortalité de l'intervention. Enfin, si la cure chirurgicale radicale n'est pas possible, il faut discuter du rôle et de l'étendue raisonnable de la résection à visée palliative.

Resumen

Se presenta una revisión actualizada de los tumores malignos de los islotes pancreáticos. Los importantes avances logrados en los últimos tres decenios permiten que en la actualidad sea posible el manejo de muchos de estos difíciles tumores, lo cual fué muy poco satisfactorio en el pasado. Como principios generales al enfrentar el manejo de cada uno de estos tumores, están la determinación de si la lesión es benigna o maligna, y de si es funcionante o no funcionante. Es igualmente valioso determinar si el tumor es esporádico o hace parte del síndrome de neoplasia endocrina múltiple tipo I. En términos del manejo quirúrgico, es importante saber qué tan bien puede el tumor ser identificado mediante técnicas de localización en la fase preoperatoria o en la intraoperatoria, y cual es la probabilidad de curación para confrontarla con la morbilidad y mortalidad del procedimiento quirúrgico. En este artículo se discute, finalmente, el papel de la resección paliativa y la magnitud de tal

resección en situaciones en las cuales no es posible la curación quirúrgica.

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