1995 Roussel Lecture. Management of adenocarcinoma of the head of the pancreas: 10 questions for the 1990s

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Carcinoma of the head of the pancreas is a lethal condition because it presents clinically late in the disease and because of its unfavourable biologic course. Surgical approaches have become progressively more aggressive in recent years, without a significant increase in long-term survival. Controversy persists as to the appropiate surgical procedure for this disease, nonoperative or operative palliation, and future prospects for management. This review considers questions often posed by clinicians and offers answers based on a literature review and the experience of the hepatobiliary service at the Toronto Hospital, Toronto General Division.

Le cancer de la tête du pancréas est mortel parce qu'il se manifeste sur le plan clinique vers la fin de la maladie et à cause de son évolution biologique défavorable. Les stratégies chirurgicales sont de plus en plus agressives depuis quelques années sans augmenter pour la peine la survie à long terme. La controverse persiste quant à l'intervention chirurgicale qui convient dans le cas de cette maladie, à la palliation opératoire ou non opératoire et aux perspectives futures de traitement. Cette revue porte sur les questions souvent posées par des cliniciens et présente des réponses fondées sur une recension des écrits et l'expérience du service hépatobiliaire au Toronto Hospital, Toronto General Division.

Adenocarcinoma of the head of the pancreas is one of the most devastating of the diseases whose management challenges the surgical oncologist today. This review is an attempt to answer questions that have plagued general surgeons and their referring physicians for decades and to give an account of the current approach to diagnosis, selection of patients and treatment. Although other periampullary adenocarcinomas and less common malignant lesions of the head of the gland complicate clinical decision making in affected patients, I shall focus on adenocarcinoma of the head of the pancreas. The following 10 questions have been approached through a review of the literature, coloured by my own experience in a teaching institution with a high-volume hepatobiliary practice.

1. What are the problems?

In 1990, there were almost 25 000 deaths from carcinoma of the pancreas in the United States,[1,2] and approximately 75% of the tumours arose in the head of the gland. The incidence of the disease is increasing around the world, having doubled in Western Europe, tripled in the United States and quadrupled in Japan over the last 4 decades.[3,4] Despite this increase in frequency, which may be related to improved recognition, fewer than 20% of cases are suitable for curative resection, and the overall survival rate remains at 1% to 3%.[5] The cause of the disease is unknown, although risk factors such as advancing age and smoking have been suggested.[6–9] Spread of the disease appears in most cases to be early and involves direct extension into peripancreatic retroperitoneal tissues and adjacent structures such as the portal venous system and, importantly as far as prognostic indicators are concerned, lymphatic spread to peripancreatic nodes, periportal nodes and periaortic

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lymphatics.[10,11] Peritoneal involvement and hematogenous spread to liver and elsewhere are also common. In addition, a perception still exists in the minds of many referring physicians that the resection required is too extensive and too dangerous and that even if patients survive the operation they become gastrointestinal cripples. Recurrence after surgery is frequent, symptoms from both the initial disease itself and the recurrence are troublesome and nonsurgical treatment has been ineffective.

The problems, therefore, are many, but as I hope to demonstrate they are being enthusiastically addressed in a variety of academic centres and from a number of perspectives.

2. Is the operation worse than the disease?

Since Whipple, Parsons and Mullins[12] introduced a two-stage radical pancreaticoduodenectomy in 1935, technical modifications have been suggested so as to widely resect what is often a small tumour in a complex anatomic location. Despite enthusiasm in a variety of centres over the last 60 years, death rates from the procedure have been sobering; even an extensive review[13] as late as 1987 indicated an operative death rate of 16%. This has led some to become "resectional nihilists." They strongly believe that the operative risks of radical resection outweigh the possible benefits;[14–16] however, a number of more recent reports[17–22] from centres specializing in hepatobiliary surgery have countered that the death rate associated with the operation can consistently be below 5%. In fact, the surgical literature has been sprinkled with reports[21,23] from groups professing to have performed ever greater numbers of Whipple procedures for a variety of indications without a single operative death. Even caution concerning elderly patients is not currently shared by Fernandez-del Castillo, Rattner and Warshaw,[24] who found that the operation was equally safe in patients over 70 years of age.

Generally, the recent excellent results have been ascribed to better selection of patients, improved surgical technique with minimal blood loss (necessitating fewer transfusions), better anesthesia and judicious, aggressive postoperative management, including the timely treatment of complications when they occur. In fact, the death rate associated with Whipple resection is now significantly less than that after palliative bypass,[25] not just because of patient selection, but because of more meticulous attention to detail in those patients who undergo resection.

Despite the encouraging postoperative death rates, complications of major pancreatectomy remain frequent and often life-threatening; bleeding, sepsis and pancreatic fistula head the list, but complication rates are decreasing.[24]

Of major concern to many referring physicians and patients is the ability to live with normal digestion after pancreaticoduodenectomy. This subject has not been studied frequently, but a recent report[26] from our centre, comparing patients who had undergone radical pancreaticoduodenectomy with a matched group of post-cholecystectomy patients, was revealing. In an intensive evaluation of a number of quality-of-life parameters, the patients who underwent the Whipple procedure or total pancreatectomy fared surprisingly well. In fact, in virtually every parameter examined, the result was quite clear: post-pancreatectomy patients can lead normal, active and productive lives, enjoy normal digestion and maintain their weight.

3. How radical should resective surgery be?

The frequency of metastatic lymph nodes in resected pancreatectomy specimens and the high incidence of local recurrence in and around the pancreatic bed have led surgeons to become more aggressive in their attempts to achieve total clearance of all macroscopic and microscopic disease. The most radical operations have been performed in Japan and Germany,[27–31] where meticulous dissection of retroperitoneal soft tissues and node-bearing areas is undertaken. Although this approach may bear fruit with other periampullary tumours (such as carcinoma of the ampulla, common duct or duodenum, where resection of node-positive disease may be followed by long-term survival), the survival rates after removal of node-positive carcinoma of the head of the pancreas remain discouraging. Most surgeons now feel that extended nodal dissection for adenocarcinoma of the head of the pancreas probably does not change the ultimate outcome.

Total pancreatectomy has been advocated, stemming from the recognition that adenocarcinoma of the head of the pancreas is frequently multicentric and may be a cause of local recurrence.[32–38] Up to 40% of resected specimens have contained evidence of tumour beyond the usual resection margin,[38] but whether this revelation has clinical relevance (analogous perhaps to some breast carcinomas) is unclear. An additional rationale for total pancreatectomy was to avoid the much-feared pancreatic fistula seen after the Whipple operation. Recent reports[17,35,39–41] have indicated no advantage for total pancreatectomy, and in fact, presumably because of steadily decreasing problems with the pancreaticojejunal anastomosis after the Whipple procedure, total pancreatec-

tomy may have a higher death rate.[17,40,42,43] Crist and Cameron[44] suggested that total pancreatectomy should be reserved for patients with histologic evidence of tumour at the margin of resection, those with gross multicentric disease and perhaps those with a soft friable gland (which is much more common with periampullary tumours *other* than carcinoma of the head of the pancreas), which would make anastomosis very tenuous.

Attempts to resect all structures in the area of the pancreatic head led to the concept of "regional resection" as proposed by Fortner[45] and others;[46,47] however, operative morbidity, mortality and long-term survival statistics do not seem to support this notion. Another group has gone even further, and reported[48] "radical foregut resection," which included partial gastrectomy, pancreaticoduodenectomy, total hepatectomy, splenectomy and ascending/transverse colectomy followed by reconstruction of the various organs and an orthotopic liver transplantation. One of the six patients on whom this prodigious procedure was performed actually had adenocarcinoma of the head of the pancreas and died of recurrence in the first 6 months after surgery. Starzl's group[49,50] also described an abdominal organ "cluster" transplantation, which can best be described as experimental, having little relevance to carcinoma of the head of the pancreas.

The fundamental problem with adenocarcinoma of the head of the pancreas as it relates to attempted radical surgery is that the resection margins consist not only of the cut ends of the common bile duct, stomach, jejunum, duodenum and neck of pancreas, but *radial* margins, which include all retroperitoneal tissues having contact with the pancreatic head and uncinate process: retroperitoneal areolar tissue, the inferior vena cava and superior mesenteric artery and vein. The presence or absence of microscopic nodal metastases at the time of resection certainly correlates well with survival, but it does not appear as though further attempts to "clear" this bed has an effect on that survival.

4. Which patients should be selected for surgery?

Since these patients have a devastating disease that is cured in only a relatively small percentage of cases by a major procedure with all its possible attendant problems, selection of those to undergo resection is critical. This selection is probably the critical factor in improved recent survival statistics from some centres. The patient presenting with jaundice and abdominal pain or discomfort initially undergoes ultrasonography or computed tomography (CT), or both, to identify a mass in the head of the pancreas. Improved techniques of CT have made magnetic resonance imaging in this disease virtually redundant.[51,52] The selection of further tests to confirm the diagnosis or assess resectability is controversial. Some feel that a clear definition of the biliary tract by endoscopic retrograde cholangiopancreatography (ERCP) or percutaneous transhepatic cholangiography (PTC) is essential in the treatment of this disease.[44] Although most patients have had some form of definitive biliary imaging by the time they are seen at our referral centre at The Toronto Hospital, Toronto General Division, there is concern about the lack of useful information produced by these investigations and the complications that frequently follow the tests themselves. Duodenoscopy in the presence of a mass in the pancreatic head in a jaundiced patient is essential to identify the more favourable duodenal or ampullary tumours, but a clear picture of an obstructed pancreatic or bile duct is frequently not necessary to confirm the diagnosis. All too often, forceful injection of contrast into obstructed ducts can convert a sterile biliary tract into a contaminated one, or a congested, obstructed pancreas into an inflamed one. *Gentle* ERCP is advocated, in which only the initial sections of the ducts are opacified, and overinjection is avoided. If the ERCP is not successful in providing a radiographic diagnosis, PTC is usually not justified; the possible untoward effects of needling obstructed intrahepatic ducts outweigh the potential gain. Specific situations such as sepsis may, however, mandate such intervention (see question 5).

The preoperative determination of resectability is crucial and has been approached in a variety of ways. Some centres now use endoscopic ultrasonography as a tool to define the relationship of a pancreatic head tumour to the portal and superior mesenteric veins.[53–55] Celiac and superior mesenteric angiography with venous studies remains an important tool in some hands not only to identify arterial or venous encasement but also to recognize a replaced right hepatic artery, which may have a bearing on future operative dissection.[56,57] Warshaw and colleagues[58] reported that angiography predicted unresectability in 95%, with 66% sensitivity, and in their opinion angiography with CT and laparoscopy provided maximal accuracy. Despite our early enthusiasm, however, we do not routinely use angiography because of its modest inaccuracy in determining resectability, its possible morbidity, its undesirability for patients about to undergo radical surgery, and the surgeon's ability to recognize a replaced right hepatic artery at laparotomy without angiography. Our most useful examination preoperatively to

determine the relationship of the superior mesenteric and portal veins to the tumour mass, is Doppler ultrasonography, which has been very helpful in determining who should at least receive further intervention.

Although in our hospital we have not made extensive use of laparoscopy as an initial operative step to identify intraperitoneal and hepatic metastases unrecognized by preoperative tests, this appears to be a very reasonable method to save a few patients the insult of a laparotomy incision.[58–61] Cuschieri[60] was able to demonstrate unresectability on laparoscopy alone in 42 of 73 patients with carcinoma of the pancreas. In fact, in Europe some patients with unresectable and "inoperable" disease have even been spared a hospital admission because the final selection was made on an outpatient basis — 51 of 78 patients were deemed unresectable by means of short-stay laparoscopy.[62]

Preoperative biopsy has proved accurate in some hands, but concerns about lack of specificity, inability to determine resectability and possible needle-tract seeding have decreased enthusiasm for this procedure.[63,64] We reserve fine-needle aspiration biopsy for patients deemed to have tumours unresectable by other means and who may require confirmation of their disease before palliative therapy.

Intraoperative cytology has been used to determine unresectability but is not widely employed. Warshaw[65] examined cytologic aspirates obtained by laparotomy or laparoscopy in 40 patients and found that in 12 positive cases only one tumour was technically resectable.

A natural extension of careful preoperative and endoscopic ultrasonography is the application of this method intraoperatively.[66] However, we have found with respect to pancreatic head tumours that once the abdomen is opened and intraperitoneal spread ruled out, the most valuable tool is the surgeon's operative judgement based on identification of all critical anatomic structures and their relation to hopefully a localized tumour in the head of the gland situated lateral to the superior mesenteric and portal vessels.

The issue of intraoperative biopsy is a controversial one. If the surgeon is prepared to perform a wide resection using standard techniques and is also prepared to accept positive nodes in the specimen as not precluding resection, then only those areas *outside* the proposed resection margins need be sampled to determine resectability. If a surgeon believes strongly that carcinoma of the head of the pancreas with any nodal involvement represents incurable disease, then biopsy of nodes *within* the potential resected specimen may be justified. However, because of other issues such as final identification of cell type only after resection (see section on curability), we prefer to adopt the more aggressive route. Although some still advocate taking a biopsy of tumours before resection,[67–69] we believe that intraoperative biopsy of the primary tumour itself is usually not required. In addition to the concern about transgressing tumour planes and maintaining classic cancer resection technique, we believe in the adage "negative means nothing"; in other words, an intraoperative needle or other biopsy read on quick section by the pathologist as indeterminate or negative (the answer is often equivocal) still leaves the surgeon with the ultimate clinical and operative decision concerning resection. This attitude inevitably leads to occasional removal of benign tissue, while giving optimal treatment for malignant lesions.

We feel, therefore, that clinical evaluation, CT, Doppler ultrasonography, careful ERCP imaging and a methodical anatomic assessment by an experienced hepatobiliary surgeon are the most important steps in assessing resectability. An immediate preoperative laparoscopy is a logical addition to that plan.

5. Should the biliary tract be decompressed preoperatively?

A number of groups recognized that major operations in jaundiced patients were followed by a disturbingly high death rate when compared with historical controls.[70–72] The deleterious effects of an obstructed biliary tree on myocardial and renal function, and on endotoxin activity,[73] have been documented. Although the literature in this area is difficult to evaluate, subsequent randomized trials comparing patients with preoperative percutaneous transhepatic drainage of the biliary tree with those without preoperative drainage showed no ultimate difference in operative death rates.[74–77] There is no current justification therefore for preoperatively draining the biliary tree on a routine basis, especially since complications of both insertion and maintenance of endoscopic and transhepatic stents can be serious.[78,79] One unfortunate, practical fact is that many referral centres first see patients who have already had an endoscopic or percutaneous stent inserted at the initial referring centre. This not only introduces potential complicating factors into the patient's care but also may make assessment of resectability more challenging; periductal and pancreatic inflammation caused by the stent itself can make precise ultrasound and Doppler evaluation problematic.

Therefore, we reserve preoperative biliary drainage for patients who have had cholangitis (notably the infection

is commonly introduced by the previous procedures themselves!), evidence of renal failure or malnutrition that requires correction before major surgery. Occasionally, when the surgeon at initial consultation is concerned about the general acceptability of a patient for major surgery, procrastination and biliary drainage for 4 to 6 weeks may be useful as a "test of life," to determine whether a patient becomes ultimately suitable for surgery or deteriorates quickly enough so that inoperability becomes obvious. In general, unless these clear indications are present, routine preoperative biliary drainage should be avoided, despite the temptation at ERCP, for example, to place a stent at the same sitting.

6. Are there any recent operative or perioperative innovations?

There have been no revolutionary changes in operative techniques over the last 20 years. We generally have become more meticulous in our retroperitoneal dissection around the uncinate process, especially with respect to the superior mesenteric artery and vein, and stapling manoeuvres in this area may save time. We use a two-layer end-to-side pancreaticojejunostomy with the end of the jejunal loop stapled or sutured; a pancreatic duct stent is almost always placed to maintain an anastomosis, the inner layer of which incorporates pancreatic ductal tissue whenever possible (depending on the size of the duct). On the outer layer we use nonabsorbable sutures placed and tied with care so as not to tear through delicate pancreatic tissue. A stent is not used in the single-layer end-to-side choledochojejunostomy, and the abdomen is liberally drained with closed suction, the drains being removed only after the patient is drinking well and has no signs of delayed gastric emptying, sepsis or fistula formation. Marcus, Cohen and Ranson[80] believe that in high-risk patients, end-to-end invagination of the pancreas into jejunum constitutes the safest anastomosis. A recent report[81] on the use of erythromycin, a motilin agonist, to prevent delayed gastric emptying is encouraging. We make a practice of treating the patient perioperatively with the somatostatin analogue octreotide, especially in patients who have relatively normal pancreatic stumps; Buchler and associates[82] found that the overall complication rate after pancreatic resection fell from 55% to 32% with the use of the pancreatic secretion inhibitor. However, the majority of those patients with carcinoma of the pancreatic head have rather rubbery pancreatic remnants that are much easier to sew and probably have a lower incidence of postoperative fistula formation. Pancreaticogastrostomy may be an innovation to consider and is practised by a number of groups.[83,84]

Postoperatively we cover our patients indefinitely with H_2 blockers, since the incidence of marginal ulcer, though not high, is real. Although an earlier report[85] suggested a high rate of stomal ulcer formation, prompting us to include truncal vagotomy in our standard Whipple procedure, a more recent publication[86] has suggested that the realistic figure is approximately 5%. This fact, along with the advent of even more powerful inhibitors of gastric secretion, has caused us to abandon vagotomy in our standard or pylorus-preserving Whipple (PPW) operations. Considerable time, effort and literature space has been devoted to the PPW procedure. This operation was designed to decrease the significant incidence (at least 20% to 25%) of postoperative delayed gastric emptying (DGE) after standard pancreaticoduodenectomy, and to a lesser extent, post-gastrectomy dumping. In addition, it was felt that the operation was easier and faster without antrectomy, despite concerns that leaving behind node-bearing tissue might compromise the cancer operation. Traverso and Longmire[87] popularized this procedure after 1978, and it now has proponents who claim, in consecutive series, that the incidence of DGE is low.[43] However, in other consecutive series,[86–88] DGE appears to be a significant problem, occurring in 20% to 50% (depending on the definitions) after both the PPW and the standard Whipple procedures. Fernandez-del Castillo, Rattner and Warshaw[24] recently reported that DGE, defined as the inability to maintain oral intake by 14 days after surgery and prompting institution of parenteral nutrition, was seen after 24% of their pylorus-preserving procedures. In either case, the dysfunction appears to be temporary and is adequately treated with gastric decompression accompanied occasionally by parenteral or enteral nutrition. In other words, the operation was designed to minimize a recognized post-standard Whipple motility problem, and to date the problem still exists with approximately the same frequency as previously. The cause of this entity, whether related to the disease itself (auto-vagotomy has been postulated) or to the treatment (radical dissection of the retroperitoneal tissues, which may include autonomic nerves) remains obscure, but it is hoped that with routine institution of motility agents or erythromycin, this recurring nuisance can be successfully alleviated. Although in most cases the DGE is transient and mysterious, one must always rule out abdominal sepsis or pancreatic fistula as an underlying cause.

The avoidance of pancreatic fistula and appropriate management when it

does develop are both critical to the success of treatment. Incidence has varied from 5% to 20%, and in the past this complication has directly resulted in death in as many as one-third of cases. Trede and Schwall[89] described a fistula rate of 11% (25 of 233 patients); surprisingly, 17 of these required reoperation and 5 of the 25 died of this complication. We reported a rate of 14%,[20] but recently an incidence of 6.3% was reported by Fernandez-del Castillo, Rattner and Warshaw.[24] We attribute the decrease in incidence of pancreatic fistula to the meticulous attention to detail during the pancreaticojejunal anastomosis as described above. Even though Trede and Schwall[89] have reported that pancreatic fistulas often require surgical correction, we have found, like Fernandez-del Castillo, Rattner and Warshaw,[24] that virtually all can be treated conservatively. Papers on this issue may, however, simply reflect the time of reporting, since the liberal use of percutaneous drainage for abdominal sepsis has frequently avoided surgical reintervention in recent years.

7. Who should be doing these operations?

Fundamentally, major pancreatic surgery should be performed by oncologic surgical teams that can select the patients appropriately, perform radical but safe operations and provide patients with acceptable survival rates. Much of the reduction in operative death has been attributed to increased experience in tertiary referral centres, where a formidable team of surgeons, housestaff, anesthetists, radiologists, intensivists and nurses all participate in the management of these clinical problems.

Improvement in the immediate outcome is reflected not only in the operative death rate, but also in morbidity and reoperation rates,[17,90] which are significantly lower in regional centres. Reoperation rates as low as 1.2% (three reoperations in 231 cases in a recent series[24]) attest to the virtues of this team approach.

The modern view of health care delivery also dictates consideration of financial issues when selecting the appropriate hospital to care for a patient with a particular diagnosis. There is no doubt that the financial cost of surgical treatment of carcinoma of the head of the pancreas is high, and, considering the survival rates, yield remains relatively low; this fact may raise questions as to the ultimate viability of major surgery for this disease.[91] Notwithstanding that issue, Cameron's group[92] studied the cost and outcome for pancreaticoduodenal resection in their regional provider centre, Johns Hopkins Hospital, in comparison with 38 other Maryland hospitals. The hospital death rate was significantly decreased, length of stay shorter and mean cost of care for survivors significantly lower ($24 478 v. $31 205) in the regional centre. Improvement in death rates and survival statistics are crucial to patient outcome, but more *cost-efficient* care will undoubtedly in future be an additional important arbiter in the decision as to who may provide this service both in Canada and the United States; the recognition of "centres of excellence" may of necessity affect referral patterns.[93,94]

8. If the patient is not curable, what is the best palliation?

Considering current results of treatment, the question of palliation for this disease is extremely important because unfortunately most patients can be offered no more. There have been several areas of dispute that require evaluation. A superb review was done by Watanapa and Williamson,[25] who addressed a number of these issues with respect to changing surgical attitudes over the decades of the 1970s and 1980s.

If the patient has a diagnosis of carcinoma of the head of the pancreas and the tumour is considered unresectable, it is important to palliate only those symptoms that are of concern to the patient. It must be pointed out that jaundice is often more disturbing to the patient's relatives and the doctor than it is to the patient; it is only when intense pruritus accompanies the jaundice that palliation is unequivocally required.

When the tumour is deemed inoperable and the patient's jaundice requires treatment, especially when the patient does not have gastrointestinal symptoms, some form of nonoperative stenting is the best choice. An endoscopically placed straight large stent is preferred, even though the incidence of ultimate blockage and infection is relatively high;[95–97] if this occurs, the stent may be removed and replaced quickly to re-establish palliation. Frequently, however, especially with very sclerotic pancreatic head carcinomas, the duct may be difficult to stent endoscopically, and the percutaneous transhepatic route must be adopted. Palliation may then be achieved by external drains, internal/external drains that can be clamped on the outside or percutaneously placed internal stents. The internal stents may be virtually the same as the endoscopic variety, or the recently reported Wallstent, which consists of a metal coil that expands inside the duct and tumour when placed appropriately by the interventional radiologist.[98] We have found this particular option problematic in these days of fiscal restraint because of the high cost of the stent itself. In addition, our interventional radiologists are hesitant

to place an internal stent, especially one that cannot be removed endoscopically if it becomes blocked — they prefer to have the "safety valve" of an internal–external stent, which may be changed easily over a guidewire when complications arise; unfortunately, these complications are virtually guaranteed by the mere presence of an external–internal drain, which frequently causes pain and often becomes obstructed and infected.

If a patient has been subjected to laparotomy and the tumour is found to be unresectable, the surgeon must select the appropriate surgical biliary bypass, because, clearly, the long-term success of surgical bypass with respect to obstruction and sepsis is better than that of an endoprosthesis. Cholecystojejunostomy, choledochojejunostomy and choledochoduodenstomy are still performed in some centres. Rosemurgy, Burnett and Wasselle[99] reported that in a randomized trial choledochoenterostomy was associated with a lower death rate (7% v. 23%) than cholecystoenterostomy with similar morbidity. A meta-analysis of eight series[25] comparing the two procedures demonstrated that choledochoenterostomy had a better initial success rate (97% v. 89%) and a lower rate of recurrent jaundice or cholangitis (8% v. 20%). We would agree that choledochojejunostomy is the procedure of choice and that cholecystojejunostomy should be reserved for those patients who are not expected to live long because of the presence of significant life-threatening metastases such as intraperitoneal or hepatic spread unrecognized before laparotomy. A suggestion has also been made that if cholecystoenterostomy is chosen, cholecystography and cystic duct cholangiography be carried out to verify the patency of this system.[25]

The use of a Roux-en-Y choledochojejunostomy has been questioned, as Sarr and Cameron[100] demonstrated no difference between this procedure and a loop choledochojejunostomy. However, we have found that a Roux-en-Y loop can more easily provide a tension-free choledochojejunostomy, especially in the presence of a sizeable pancreatic mass; we prefer the accompanying gastrojejunostomy to be inserted into the afferent loop proximal to the enteroenterostomy rather than into the Roux-en-Y itself, because of potential emptying problems associated with the efferent limb.

If the patient has symptoms of duodenal obstruction related to tumour growth and is well enough to consider palliation, gastrojejunostomy is an obvious temporary solution. However, most discussion has centred around the routine addition of a gastroenteric bypass in a patient who presents with jaundice but without gastrointestinal obstruction. In a review of 1600 cases drawn from 15 articles published from 1973 to 1990,[25] no difference in death rate was noted by the addition of an elective gastrojejunostomy. On the other hand, approximately 17% of patients who had biliary–enteric bypass alone required a gastric bypass at a later date, which was attended by an operative death rate of 22%. It seems reasonable, then, that a patient who undergoes operative biliary bypass should also undergo gastrojejunostomy unless widespread metastases imply a very short survival. What needs to be examined, however, is the incidence of delayed gastric emptying after routine gastroenterostomy in a patient without preoperative gastrointestinal symptoms. We have all had experiences that question our decision to carry out this added procedure in individual patients who have a prolonged hospital stay related to DGE after gastrojejunostomy.

Palliation of pain is perhaps the greatest challenge. Although carcinoma of the head of the pancreas is classically said to present as "painless jaundice," some degree of pain is experienced in approximately 70% of patients, and pain in those patients with persistent or recurrent disease frequently becomes debilitating. The extent to which pain is relieved by any surgery depends on the cause of the pain in the first instance; pain may be related to involvement of retroperitoneal somatic nerves, pancreatitis or obstruction of the bile duct, pancreatic duct or gastrointestinal tract, or perhaps a combination of these.

Back pain likely related to retroperitoneal nerve involvement is most refractory. Like others, we have tried celiac injections of phenol or alcohol with variable benefit; some have had encouraging results with this method. (Adequate relief was reported in 70% of patients in one study of phenol in almond oil.[101]) Radiotherapy used in the setting of either a previous pancreatic resection with recurrence or unresected disease may also provide some pain relief. Whittington and colleagues[102] reported on a group of 23 patients who presented with pain; 90% of them enjoyed at least partial relief of discomfort with external beam radiotherapy. The problem of back pain is more common in carcinoma of the body of the gland or with carcinoma of the pancreatic head that has been resected and has recurred.

Occasionally patients are offered radiotherapy or chemotherapy, or both, for incurable disease without any symptoms.[103–106] Although some patients and oncologists approach this kind of treatment with enthusiasm, expectations are modest. Many groups have boasted increased survival with aggressive treatment, the results being deemed statistically significant. Whether or not the clinical result of living a few weeks or months longer in the setting of possibly morbid ther-

apy is an improvement in outcome is debatable. Certainly many patients opt for active treatment because doing nothing is unacceptable to them.

Now that resection in selected cases is followed by minimal mortality, the question of resection for palliation will inevitably be addressed. We believe our group has confirmed that the quality of life after these major interventions is surprisingly acceptable;[26] however, we have not applied the same standards to those who undergo a Whipple operation or other procedures in a setting that ultimately is not curative. Certainly reports of any survival advantage with respect to resection of pancreatic head tumours and nodal metastases is marginal; consequently, any measurements of quality of life in this group of patients over such a short period may be clinically meaningless.

9. Is adenocarcinoma of the head of the pancreas curable at all?

Approximately 15% of patients presenting with carcinoma of the head of the pancreas are ultimately suitable for resection.[25] Of these, only 5% to 20% will survive 5 years, consistent with our earlier report of 7% 5-year survival.[20] In addition, it should be noted that some patients die of disease *after* 5 years, suggesting that we may be simply palliating some patients for longer periods, the result being altered by lead-time bias.[17,35,105] The overall cure rate for carcinoma of the head of the pancreas, therefore, is 1% to 3%, so we must realize that surgical and oncologic manoeuvres have attempted to manipulate only a tiny minority of patients. Some groups have recently reported encouraging survival results after resection,[18,21] but unfortunately, since the surgical treatment varies little, the improved survival is more likely attributable to the selection process. The Mannheim group[21] reported a 25% 5-year survival, and the Hopkins group[18] a 19% long-term survival after resection.

Nodal involvement definitely correlates with poor prognosis and, as we have seen, more radical surgical removal of these nodes does not seem to alter the outcome.[17–19,27] Size of the primary tumour appears to be important, since patients with tumours less than 3 cm in diameter had a lower incidence of metastatic nodal disease and enjoyed a prolonged survival.[31] Tumours 4 cm or greater in dimension are usually not resectable,[106,107] but as our group pointed out previously, the exact size of a tumour is sometimes difficult to evaluate pre- and intraoperatively because of a degree of surrounding pancreatitis in approximately 30% of cases.[20] In the Hopkins series,[18] 36% of patients had tumours less than 2 cm in diameter, and the patients surviving 5 years had a tumour size of 2.7 cm in contrast to 3.2 cm for those who did not survive 5 years. Again, this fact may suggest a more careful selection of patients or a referral pattern particular to the Johns Hopkins Hospital as being the major reasons for the improved 5-year survival rates after resection.

In terms of intraoperative decision making regarding resection for cure, our centre found that despite the surgeons' best efforts it was difficult in approximately 15% of cases to differentiate adenocarcinoma of the head of the pancreas from the more favourable invasive adenocarcinoma of the common bile duct (duodenal and ampullary carcinomas should be diagnosed preoperatively on endoscopy) or other periampullary neoplasms.[20] We have therefore been concerned that to leave a technically resectable lesion in-situ might conceivably deprive a patient with a curable lesion appropriate radical treatment. Similarly, the Mayo Clinic group[108] has recently emphasized the importance of pathologic re-review to ensure that reported cases are all in fact cases of adenocarcinoma and not more favourable periampullary adenocarcinoma or even other malignant disease, such as neuroendocrine tumours.

The occasional confusion about tissue of origin and size of tumour in carcinoma of the head of the pancreas, the improved survival rates and reasonable quality-of-life after major pancreatic resection and the remote but real possibility of survival even in the presence of local nodal spread have led us to an aggressive approach to this disease. Therefore we do not reject a patient because the tumour is 3 to 4 cm in diameter or because there is a local positive node in part of the specimen to be resected.

Some interesting work has been done in the area of adjuvant treatment for disease in the potentially curative setting. Merrick, Dobelbower and Konski[109] reviewed the recent results of a number of teams using *intraoperative* radiotherapy. Most centres focussed mainly on patients with unresected tumours, but a review from nine centres of 102 patients who underwent intraoperative radiotherapy was carried out. Doses of 10 to 40 Gy were administered and followed by a median survival time of 2.6 to 14 months, with three deaths. The main benefit of intraoperative radiotherapy, therefore, as stated in question 8, seems to be pain relief in patients with unresectable tumour.

Postoperative adjuvant radiotherapy and chemotherapy may play a positive role by enhancing curability. The Gastrointestinal Tumor Study Group[110] and Kalser and Ellenberg[111] administered adjuvant radiotherapy and chemotherapy after pancreatic resection for adenocarcinoma. In the latter report,[111] 43 patients received either external beam irradiation and 5-fluorouracil or no ad-

juvant therapy. Median survival time in the test group was 20 months compared with 11 months in the control group, and the 5-year survival was 14% and 4.5% respectively.

Pilepich and Miller[112] reported on the use of *preoperative* radiotherapy in 17 patients; 6 patients ultimately underwent resection, with 2 of them living for 5 years. Kopelson[113] reported anecdotal success, but patient numbers and diversity of treatments make conclusions impossible. An interesting report from Ishikawa and associates[114] suggested that preoperative radiotherapy diminished tumour size from 3.3 to 2.0 cm and allowed 16 of 18 patients to undergo resection. Survival statistics were not available. The fact that chemotherapy may potentiate radiotherapy was reported in a pilot study by Weese and colleagues[115] in which 16 patients (14 of whom had carcinoma of the head of the pancreas) received 5-fluorouracil, mitomycin C and external beam radiotherapy 1 month before surgical exploration. Although two patients died postoperatively of sepsis, six remained free of disease from 4 to 40 months later. It is hoped that other such neoadjuvant trials will demonstrate that a combined approach to carcinoma of the head of the pancreas will maximize outcome.

It seems clear that, to this date, gains with adjuvant pre-, intra-, and postoperative treatment have been modest at best.

10. What is our current approach to carcinoma of the head of the pancreas, and what are the future prospects?

Review of results at our centre and others confirms that carcinoma of the head of the pancreas is a lethal disease for which surgery remains the only reasonable chance of cure. In recent years the technical aspects of radical pancreatic resection and perioperative care have been continually modified to the point at which further refinements of the operation itself will not likely produce major improvements in survival. In addition, adjuvant treatment preoperatively, intraoperatively and postoperatively appears to offer marginal survival benefits, even though these benefits may be judged statistically significant.

We continue to select patients carefully with the use of clinical evaluation, CT, ultrasonography including Doppler, and in most cases biliary-tract imaging. Patients who are suitable undergo a radical resection even though local spread such as nodal involvement or perineural invasion may be suspected. Those not suitable for exploration will undergo either no treatment if jaundice is not bothersome, or endoscopic or percutaneous stenting if severe pruritus exists. Patients who undergo laparoscopy and subsequently laparotomy for cure but are found to have unresectable disease, undergo a double bypass consisting of Roux-en-Y choledochojejunostomy and gastrojejunostomy.

Clearly, the bulk of attention and the substance of this review have concentrated on a small percentage of potentially curable patients. Any hope for improving the results in management of carcinoma of the head of the pancreas appears to lie in prevention or earlier diagnosis of a smaller tumour that can be resected with a reasonable chance of cure. To discover such a lesion before the development of pain or jaundice suggests screening procedures that to date are either inadequate or prohibitively expensive, given that cause and risk factors are so poorly defined. If the incidence of this lethal disease continues to rise in various parts of the world, such screening may become justifiable.

Currently, the only patients who likely deserve careful assessment, at least by abdominal ultrasonography, are those who are suffering from chronic pancreatitis or unexplained diabetes mellitus.[116,117] (Even if adenocarcinoma develops in a patient with chronic pancreatitis, there is real doubt that any chance at surgical cure exists.) A variety of other factors have been reported to be associated with pancreatic cancer, including smoking, coffee drinking,[118,119] and meat consumption[120] (with a protective effect provided by fruits and vegetables[121]), but these are so common in our society that target groups for screening would be impossible to assemble. The use of the tumour marker CA 19-9 was popular in the last decade, but its lack of specificity and cost limit its usefulness in this disease.[122–124] It may still be useful, like carcinoembryonic antigen (CEA) in the colonic carcinoma situation, as a method of follow-up of patients who undergo curative resection; however, this practice is even more questionable than follow-up CEA determinations because of the lack of available options if the pancreatic carcinoma recurs.

Fundamental to the solution of this apparently insoluble problem will be a better understanding of the disease. DNA content in pancreatic carcinoma is frequently abnormal, and patients with resected diploid tumours measured by absorption photocytometry may live significantly longer than patients with aneuploid neoplasms.[125] Carcinoma of the head of the pancreas is one tumour that virtually always expresses the mutated K-*ras* proto-oncogene,[126–128] implying that the development of K-*ras* mutations may be a vital step in neoplastic progression in this disease. In addition, 50% to 70% of resected pancreatic carcinomas demonstrate mutations of the human tumour suppressor gene p53.[129] Fami-

lies with multiple affected members are currently being examined and, accordingly, a National Familial Pancreatic Tumor Registry has been organized at Johns Hopkins Hospital[126] to study specific genetic mutations that ultimately may lead to earlier diagnosis and more effective treatment; targeting of those mutations could conceivably be employed as a management strategy. When the biology of this disease is better understood, the 85% of patients now helped in only marginal ways may then see a glimmer of hope rather than receive the current, often inadequate "palliation." Meanwhile, we will continue to be aggressive with the minority who have a chance at surgical cure.

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