Pancreatic and periampullary cancers: treatment and outcome

Periampullary cancers arise within 2 cm of the major duodenal papilla and include cancers of the head of pancreas, distal common bile duct, ampulla of Vater and duodenum. Their anatomical locations and clinical features are similar, as are the therapeutic approaches; however, their long-term outcomes vary.

Despite its definition as the area within 2 cm of the ampulla of Vater, periampullary cancers account for 5% of all gastrointestinal tract malignancies (Albores-Saavedra et al, 2000). Pancreatic cancer occurs most often, accounting for 3%, while ampullary and duodenal cancer represent less than 1% and about 0.5% respectively of all gastrointestinal tract malignancies. It is important to recognize that reports on operative results for individual periampullary cancers do not represent their actual incidence. Among resected periampullary cancers, cancer of the head of the pancreas accounts for 50–70%, ampullary cancer for 15–25%, while distal common bile duct and duodenal cancers make up 10% each (Yeo et al, 1997). These data reflect the prevalence of resected cancers.

Although these tumours have different origins, the complex regional anatomy and their proximity generally dictate a common operative approach. Surgical resection using the Whipple pancreatoduodenectomy or its variant with preservation of the pylorus has been the main treatment for these cancers, especially with the currently low morbidity and mortality rates (Yeo et al, 1997). Although the perioperative outcomes for these different cancers are similar, they demonstrate a large disparity in long-term survival. The prognosis for curatively resected duodenal and ampullary cancers have reported 5-year survivals of 60% (Rose et al, 1996) and 50% (Allema et al, 1995) respectively, substantially better than those for distal common bile duct (27%) (Fong et al, 1996), or head of pancreas (10%) (Conlon et al, 1996). Studies have shown that there are inherent differences in the tumour biologies of the different types of periampullary cancers, which account for the observed survival differences (Sarmiento et al, 2001).

Clinical features

Presentation

The main difference in clinical presentation of periampullary cancers is the timing of the onset of jaundice in relation to constitutional cancer symptoms. In patients with cancers primarily located in the distal common bile duct (biliary and ampullary), jaundice is always the most common symptom, usually preceding weight loss and abdominal pain. With pancreatic cancers, jaundice as a result of either invasion or compression of the common bile duct occurs with a more advanced local progression, thus constitutional symptoms usually precede the onset of jaundice.

Other clinical features may help to distinguish between periampullary cancers. Fluctuating jaundice is characteristic of ampullary tumours and is thought to be caused by partial necrosis of the tumour. Some 5% of patients with pancreatic cancer will have developed diabetes mellitus within the previous 2 years while a further 5% will present with an atypical attack of acute or subacute pancreatitis. Duodenal cancer may present with occult gastrointestinal bleeding causing iron deficiency anaemia, or with epigastric fullness and vomiting as a result of gastric outlet obstruction. Although differences may exist between the clinical presentation of pancreatic and non-pancreatic periampullary cancers, they are not clinically or prognostically significant.

Investigations

The investigation of patients with suspected periampullary cancer should initially focus on establishment of the diagnosis and an assessment of the patient's fitness to undergo potentially curative treatment. The most useful initial investigation is ultrasonography, which can identify pancreatic tumours, dilated bile ducts and liver metastases. In selected patients, further investigation involves tumour staging and the assessment of local resectability. Dual-phase spiral computed tomography (CT) accurately predicts resectability in 80–90% of cases (McCarthy et al, 1998). CT features of irresectability include contiguous organ or vascular invasion, including the portal vein, coeliac axis and superior mesenteric artery, and distant metastases.

Magnetic resonance (MR) imaging detects and predicts resectability with accuracies similar to CT (Ichikawa et al, 1997). MR cholangiopancreatography (MRCP) provides detailed ductal images without the risk of endoscopic retrograde cholangiopancreatography (ERCP) induced pancreatitis, while MR angiography (MRA) can demonstrate vascular anatomy. ERCP is important in the diagnosis of ampullary tumours by direct vision and

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biopsy, provides the opportunity of aspiration or brushing of the duct system and is a therapeutic modality via biliary stenting to relieve jaundice. Although potentially resectable small tumours are not always visualized, each type of periampullary tumour has characteristic radiological features (*Figures 1, 2, 3* and *4*).

Recent advances include the use of endosonography (EUS) which is highly sensitive in the detection of small tumours and vascular invasion, and provides a further opportunity for biopsy or fine needle aspiration. Laparoscopy, including laparoscopic ultrasound, can detect occult metastatic lesions of the liver and peritoneal cavity not identified by other imaging modalities.

Although attempts should be made to obtain a tissue diagnosis during the course of investigative ERCP or EUS procedures, failure to obtain histological confirmation of malignancy does not exclude the presence of a tumour, and should not delay appropriate surgical treatment. Transperitoneal techniques to obtain a tissue diagnosis in patients with potentially resectable tumours (either percutaneously under ultrasound or CT guidance, or at the time of laparoscopy) have limited sensitivity and raise the concern of tumour seeding along the needle track, and thus should be avoided. Reasonable efforts, however, should be made to obtain a tissue diagnosis in patients selected to undergo palliative treatment, to exclude variant tumours which may have a better prognosis, and allow eligibility for participation in trials evaluating new therapies.

Treatment: resectional surgery

The fitness of the patient needs to be determined before being offered resection. Patients with periampullary cancers tend to be elderly and have significant incidence of co-morbidity. Chronological age is less important than physiological age, nevertheless all patients being offered surgery require a complete operative work-up. There is little evidence of benefit from routine stenting of jaundiced patients before resection. However, if surgery is delayed more than 10 days, it is reasonable to obtain internal biliary drainage and defer operation for 3–6 weeks to allow the jaundice to resolve. If a stent is placed before surgery, a plastic rather than a self-expanding metal stent should be inserted endoscopically.

The most widely used surgical procedure for periampullary cancers is the Whipple pancreatoduodenectomy or its variant with preservation of the pylorus (*Figure 5*). Operative mortality rates are less than 6% when undertaken in specialist centres, although morbidity is still

Figure 1. Pancreatic cancer with the double-duct sign. a. Schematic drawing. b. Computed tomography scan. c. Endoscopic retrograde cholangiopancreatography. There is dilatation of both the common bile duct (white arrow) and the pancreatic duct (black arrow).

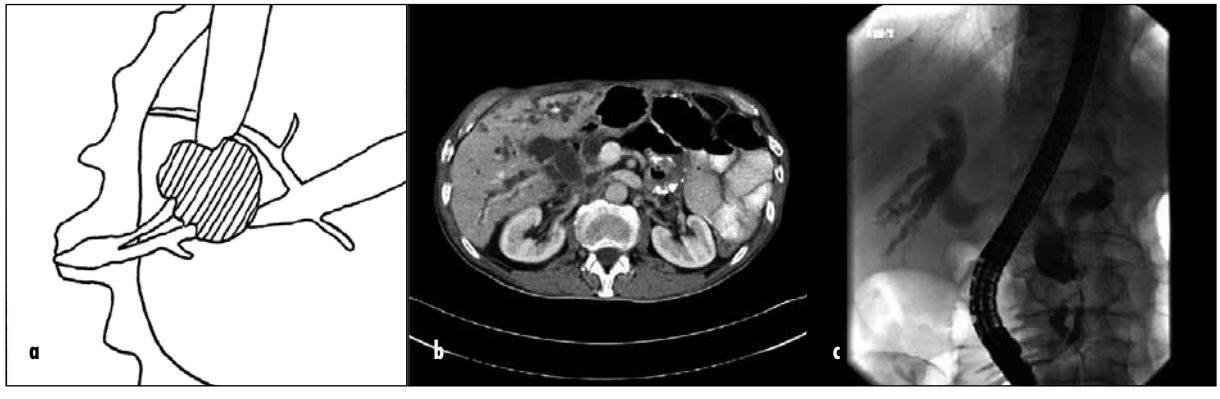
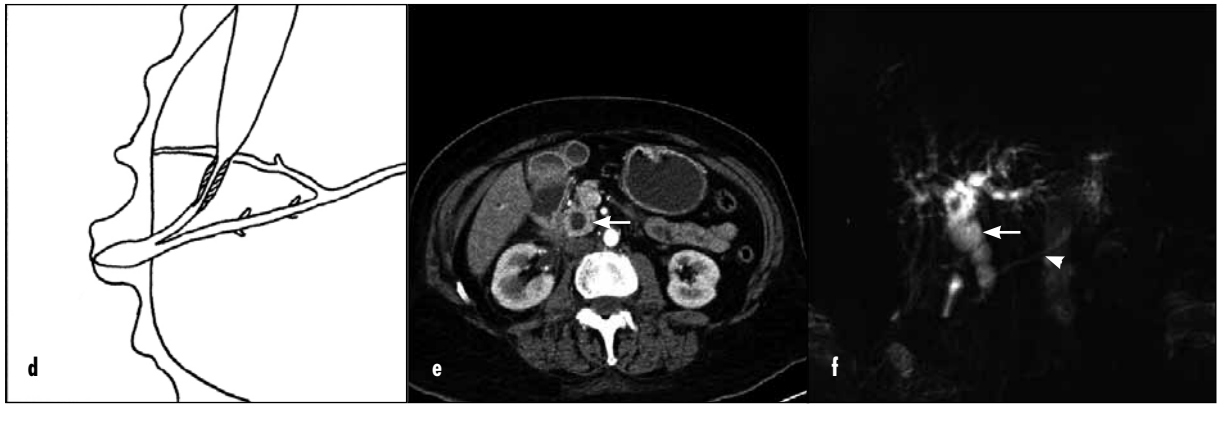


Figure 2. Distal common bile duct cancer causing biliary obstruction. a. Schematic drawing. b. Computed tomography scan. c. Magnetic resonance cholangiopancreatography. There is dilatation of the common bile duct (white arrow) while the pancreatic duct (arrowhead) is within normal limits.



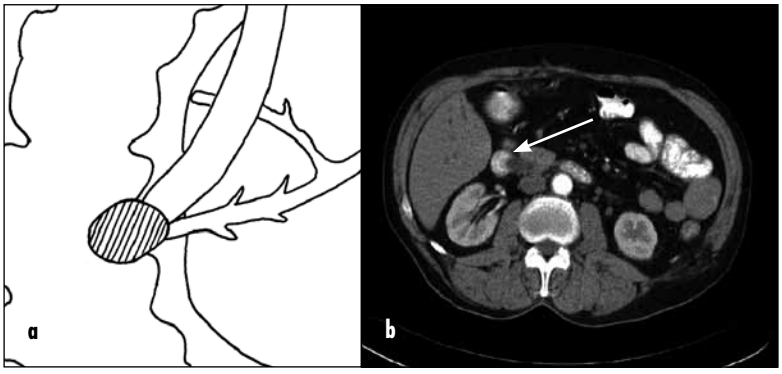


Figure 3. Ampullary cancer. a. Schematic drawing. b. Computed tomography scan shows duodenal bulging of the ampulla (arrow).

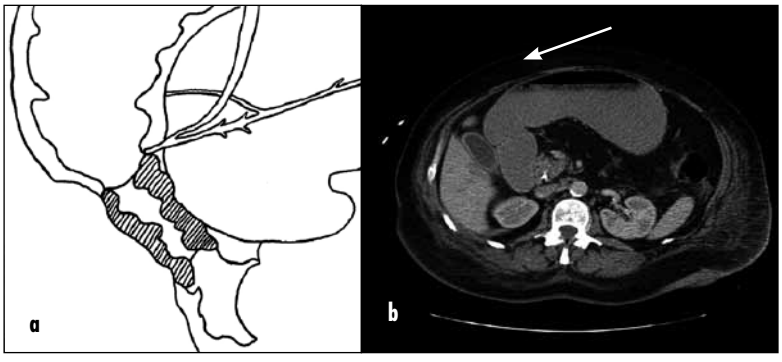


Figure 4. Periampullary duodenal cancer of the annular constricting type. a. Schematic drawing. b. Computed tomography scan shows distension of the stomach and proximal duodenum (arrow) while the distal duodenum remains collapsed.

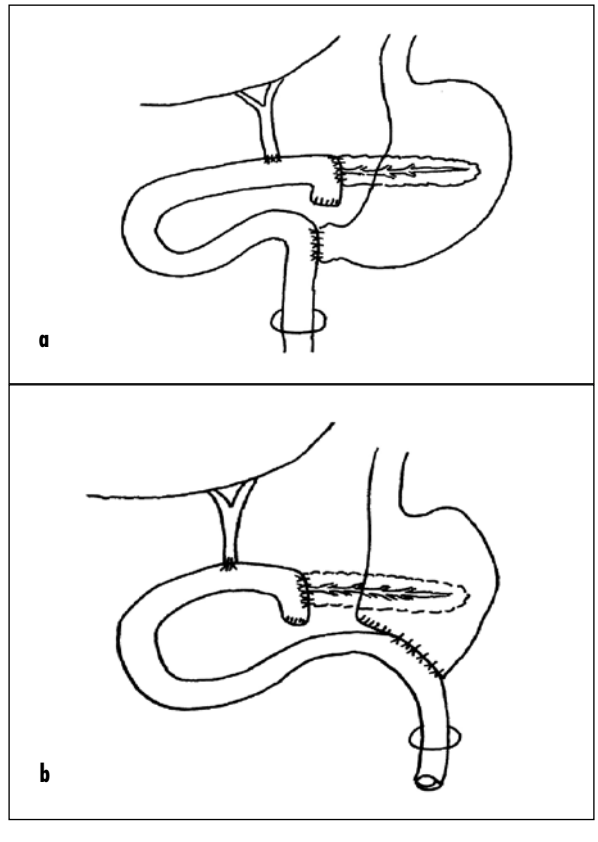
around 40% (Cameron et al, 1993). Unfortunately, only about 20% of patients with cancer of the pancreatic head have lesions that are suitable for resection (Trede et al, 1990). The resectability rates for other periampullary tumours are more favourable; in a German series over 90% of ampullary cancers were suitable for resection (Klempnauer et al, 1995).

Large series have indicated that the pylorus-preserving operation does not affect long-term survival compared with the standard Whipple operation for carcinoma of the head of the pancreas (Pitt, 1995). The main concern with the pylorus-preserving operation is its oncological adequacy for treating periampullary malignancy. The two potential drawbacks are tumour involvement of the duodenal transection line and incomplete removal of regional lymph nodes. These risks are avoided by routinely performing frozen section examination of the duodenal transection margin, and if positive converting the procedure into a Whipple pancreatoduodenectomy. The advantages of pylorus preservation include a reduction in entero-gastric reflux and improved postoperative nutritional status and weight gain in comparison to the standard Whipple operation.

More radical approaches have been adopted, such as total pancreatectomy. This has no advantage in long-term survival and has profound metabolic and nutritional side effects (Herter et al, 1982). The procedure may be justified when there is diffuse involvement of the whole pancreas without evidence of spread. Radical and extended resections to include the portal vein and a block of lymphatic tissue around the origins of the coeliac and superior mesenteric arteries have been proposed. Although centres have reported mortality rates between 3 and 7% (Satake et al, 1992), there are no data to indicate this more radical approach is associated with increased survival. Resection of the portal or superior mesenteric vein to ensure free margins is appropriate if vein involvement is discovered during operation. This extension of the procedure does not increase operative mortality or morbidity (Leach et al, 1998) nor is long-term outcome affected (Sasson et al, 2002).

Although pancreatoduodenectomy remains the treatment of choice for invasive periampullary cancer, more limited resections of non-pancreatic periampullary cancers have been used selectively in high-risk patients, carcinoma in situ, or both. The role of ampullectomy in selected ampullary cancers remains controversial. Despite the improvement in T-staging as a result of the use of EUS, the accurate preoperative histological diagnosis and staging of ampullary tumours is often difficult and inconclusive. If an adenoma has a component of carcinoma in situ or if the ampullary cancer is classified as T1N0M0 under the tumour, node, metastasis (TNM) system or is a well-differentiated tumour, then a transduodenal local excision is considered reasonable in

Figure 5. a. Reconstruction following pancreatoduodenectomy. b. Reconstruction after conventional Whipple procedure.



patients unfit for pancreatoduodenectomy. Well-differentiated TNM stage I duodenal cancers have also been successfully treated using limited pancreas preserving duodenectomy. Regardless of selection factors, overall survival is less for these procedures, and local recurrence rates are greater than those reported for pancreatoduodenectomy.

Long-term survival

The overall survival of patients with resected periampullary cancers is shown in *Table 1*. Overall 5-year survival is greatest for duodenal and ampullary cancers, intermediate for biliary cancers, and least for pancreatic cancers. These data support the clinical observation that pancreatic cancer has the most aggressive tumour biology of the periampullary cancers.

Factors influencing outcome

Large tumour size, lymph node metastases, undifferentiated tumours and positive resection margins adversely affect survival regardless of the origin of the periampullary cancer.

Histology

Ductal adenocarcinoma of the pancreas accounts for more than 90% of all exocrine pancreatic tumours. Its morphological variants (giant cell carcinoma, adenosquamous carcinoma and mucinous carcinoma) and acinar cell carcinoma all have similar or worse prognosis than ductal adenocarcinoma. A variety of other exocrine tumours arise from the pancreas. Some, such as serous and mucinous tumours, intraductal mucinous tumour, and solid pseudopapillary tumour, carry a better prognosis than pancreatic adenocarcinoma. Virtually all distal common bile duct, ampullary and duodenal tumours are adenocarcinomas. The full neoplastic spectrum, ranging from mild, via moderate, to severe dysplasia, to invasive disease resembling the multistep process of colorectal carcinogenesis, is seen in ampullary (Serafini and Carey, 1999) and duodenal (Ryan et al, 1986) cancers. The frequency of malignancy in periampullary villous adenomas approaches 25% (Baczako et al, 1985).

Duodenal cancers can be morphologically classified as polypoid, flat elevated, and ulcerative-invasive; ampullary and biliary cancers as papillary, nodular and sclerosing. Whatever the origin, polypoid and papillary cancers have been associated with a better prognosis. The degree of cancer cell differentiation varies widely among the periampullary cancers. Undifferentiated histology is typically greatest in pancreatic and least in ampullary cancers, and is frequently associated with a poorer prognosis than well-differentiated cancers, regardless of its origin.

Growth patterns

All periampullary cancers originate in intraluminal mucosa, their subsequent invasion of duct or gut wall has different implications. Extraductal invasion occurs in 60% of ampullary and 98% of pancreatic cancers (Yamaguchi and Enjoji, 1987). When pancreatic cancer invades adjacent tissue or a non-pancreatic periampullary cancer invades the pancreatic parenchyma, this represents advanced T stage of disease, and thus, a poorer prognosis with the frequency of lymphatic involvement increasing significantly. Invasion of ampullary cancers into the duodenal wall does not have the same adverse effect as pancreatic invasion.

Lymphatic spread

Ampullary cancers are associated with lymph node metastases in 30–50% of patients (Monson et al, 1991), they usually involve the posterior pancreatoduodenal

Table 1. Outcome of patients with periampullary cancers after pancreatoduodenectomy

Cancer (%)	Study	No. of patients	Operative mortality rate (%)	Operative morbidity rate (%)	Median survival (months)	5-year survival rate
Pancreatic	Sperti et al (1996)	113	15	–	–	12
	Conlon et al (1996)	102	3	–	14	10
	Yeo et al (1998)	148	–	–	12	15
Biliary tract	Fong et al (1996)	39	4	33	33	27
	Nakeeb et al (1996)	73	1	33	–	30
	Zerbi et al (1998)	27	4	44	22	13
Ampullary	Allema et al (1995)	62	6	65	–	50
	Klempnauer et al (1998)	94	10	26	–	38
	Beger et al (1999)	88	3	25	–	42
Duodenal	Rose et al (1996)	38	0	–	86	60
	Sohn et al (1998)	35	3	57	–	67

nodes and less commonly nodes to the left of the superior mesenteric artery and coeliac ganglion. Some authors have found no statistically significant difference in 5-year survival in patients with and without lymph node involvement (Allema et al, 1995), while other investigators have reported opposite results (Beger et al, 1999). In contrast, nodal involvement in pancreatic cancer is present in 56–79% of patients, tends to be more extensive involving both of the above nodal groups (Nagakawa et al, 1994), and is associated with a 5-year survival of only 5% (Yeo et al, 1998). Duodenal tumours exhibit very different behaviour: although there is a 36–47% incidence of positive lymph nodes, their 5-year survival rate approaches 60% (Rose et al, 1996). Lymph node involvement is present in 60% of distal bile duct cancers at presentation and is associated with poor surgical outcome (Yoshida et al, 1999).

Perineural invasion

Most patients with pancreatic cancer have perineural invasion, this is thought to lead to the high incidence of retroperitoneal recurrence. Perineural invasion in ampullary cancers, on the other hand, which has a lower local recurrence rate, occurs in only 5–17% of patients. Of note, when perineural invasion is present in non-pancreatic periampullary cancers, the prognosis is similar to pancreatic cancer.

Molecular factors

Several studies of periampullary cancers have examined the presence of genetic mutations and tumour markers in an attempt to explain similarities and differences in their pathogenesis and prognosis. Zhu et al (1996) demonstrated that epithelial membrane antigen, carcinoembryonic antigen, p53 and c-neu were all present in similar percentages in duodenal and ampullary cancers. These findings suggest a common pathway in their development and may explain their similar better prognoses. Other genetic alterations, such as the mutation of the K-ras oncogene or expression of epidermal growth factor receptor, are almost exclusive to pancreatic cancers which could in part explain their more aggressive behaviour (Ebert et al, 1998; Friess et al, 1999).

Adjuvant therapy following 'curative surgery'

There is no definitive answer to the question of which adjuvant treatment for periampullary cancers, if any, is the most effective. For pancreatic cancer, a prospective randomized controlled study of adjuvant chemoradiation using 5-fluorouracil (5-FU) and radiation followed by maintainance chemotherapy with 5-FU after pancreatoduodenectomy by the Gastrointestinal Tumour Study Group (Anonymous, 1987) demonstrated a survival advantage for multimodal therapy compared with resection alone. In contrast, a European Organisation for Research and Treatment of Cancer (EORTC) study of pancreatic and ampullary cancers found no benefit for patients treated with radiation and 5-FU but without maintenance chemotherapy (Klinkenbijl et al, 1999). Similarly the European Study Group for Pancreatic Cancer trial 1 (ESPAC-1), which compared 5-FU based chemotherapy, chemoradiotherapy, a combination of the two and no treatment, showed no benefit for chemoradiotherapy and a probable survival advantage for prolonged chemotherapy (Neoptolemos et al, 2001).

A further study is in progress comparing adjuvant 5-FU with folinic acid, gemcitabine, and no adjuvant therapy (ESPAC-3). A survival advantage was also demonstrated for adjuvant chemotherapy (5-FU, doxirubicin, mitomycin C) in another randomized controlled trial. Median survival was 23 months in patients receiving adjuvant therapy compared with 11 months in patients treated with surgery alone (Bakkevold et al, 1993). There are few data to support the use of adjuvant therapy for patients with non-pancreatic periampullary cancers. Many oncologists, however, extrapolate from pancreatic cancer studies to incorporate adjuvant therapy for patients who have undergone potentially curative resection and are at high-risk for recurrence. At present, adjuvant therapy in conjunction with surgery is not considered standard therapy for periampullary cancers and should only be given in the context of a clinical trial.

Neoadjuvant therapy

Neoadjuvant therapy makes use of external beam radiotherapy or chemoradiation before or during surgery. At present, reported studies are non-randomized and suggest that there may be an improvement in locoregional control but no significant improvement in survival.

Palliative treatment

Since fewer than 20% of patients with periampullary cancers are suitable for curative resection, good palliative therapy is extremely important. Palliative treatments are aimed at alleviating obstructive jaundice, relieving or preventing duodenal obstruction and controlling pain. In addition, radiotherapy and/or chemotherapy may prolong survival in patients with irresectable disease.

Relief of jaundice

A number of studies have shown that endoscopic stent insertion at the time of ERCP is associated with lower morbidity and procedure-related mortality rates than the percutaneous transhepatic approach, by minimizing the risk of bile leaks and bleeding (Speer et al, 1987). Percutaneous stenting with a self-expanding metal stent is associated with fewer complications than percutaneous plastic stent placement and is thus appropriate for patients with a better life expectancy but who are unsuitable for surgical palliation, after occlusion of a plastic stent, or when endoscopic placement has failed. The

average patency of metal stents in the distal common bile duct is about twice that of plastic stents, the latter lasting about 4 months (Davids et al, 1992).

The results of controlled trials of palliation of obstructive jaundice by stenting or surgical bypass do not favour one method for use in all cases. The advantages of surgery include unequivocal assessment of resectability, better long-term patency, lower risk of cholangitis, and the ability to perform a gastric bypass to provide prophylaxis against future duodenal obstruction. Stenting, on the other hand, has fewer immediate complications and shorter initial treatment time. Mortality rates and median survival times are similar with both techniques. Thus surgery is usually reserved for patients with good performance status and small tumours who are likely to survive longer than average, while stents are used in patients with advanced tumours who are unlikely to survive longer than the patency time of the stent.

Relief of duodenal obstruction

Following biliary bypass alone, approximately 17% of patients develop duodenal obstruction and require subsequent gastric bypass, and the addition of a gastrojejunostomy does not increase the operative risk (Watanapa and Williamson, 1992). For these reasons prophylactic duodenal bypass is recommended in patients with irresectable disease. Gastric outlet obstruction can also be relieved in some patients by an endoscopically placed self-expanding metal stent.

Relief of pancreatic pain

Although pain is often mild and settles after bypass surgery or stenting, in some cases it can be severe. In addition to oral and parenteral analgesics, other approaches to relieving pain include pancreatic ductal decompression by endoscopic or surgical means. Percutaneous, laparoscopic, or open ablation of coeliac ganglia using 5% phenol or 50% alcohol can provide effective palliation of pain as can thoracoscopic division of the splanchnic nerves. Finally, external beam radiotherapy can provide pain relief, particularly when pain recurs after coeliac plexus blockade.

Adjuvant therapy for advanced periampullary cancer

Patients with locally advanced pancreatic cancer have a median survival of 6–10 months. Although reports of treatment without a control group fail to provide evidence to judge efficacy, improved median survival has been demonstrated with a combination of external beam radiotherapy and 5-FU compared with radiotherapy alone (10 *vs* 6 months respectively; Moertel et al, 1969). Patients with metastatic pancreatic cancer usually only survive 3–6 months. Currently, if chemotherapy is to be used in their treatment, gemcitabine appears to be the agent of choice. In a randomized trial comparing gemcitabine with bolus 5-FU, patients treated with gemcitabine achieved modest but significant improvements in response rate and survival, and there was also evidence of improvement in disease-related symptoms (Burris et al, 1997). There are now a number of phase II and phase III studies of doublet and triplet regimens that include gemcitabine as one of the active agents.

Conclusions from predominantly phase II studies suggest that cholangiocarcinomas are relatively chemosensitive. Partial response rates to 5-FU and gemcitabine are 10–20% and 20–30% respectively. Gemcitabine in combination with cisplatin shows 30–50% response rates. There is no evidence for radiotherapy improving survival or the quality of life in advanced disease. There are few data to make firm recommendations about the efficacy of palliative chemotherapy for duodenal and ampullary cancers.

Conclusions

Surgery is the only curative treatment for patients with periampullary cancers. Although they share the same clinical presentations, anatomical locations, and therapeutic approaches, their long-term outcomes are varied. Overall survival after pancreatoduodenectomy is greatest for patients with ampullary and duodenal cancers, intermediate for bile duct cancers, and least for pancreatic cancers. The exact tumour origin is often difficult to clinically ascertain, thus an aggressive approach towards surgical resection is favoured to benefit patients with cancers that have a better prognosis. Recent data suggest that inherent differences in tumour biology account for differences in survival. Finally, although pancreatoduodenectomy remains the procedure of choice for resectable periampullary cancers, improvements in survival will probably only occur as the result of more effective neoadjuvant and adjuvant therapies. **BJHM**

KEY POINTS

- The long-term outcome of periampullary cancers is varied. Pancreatic cancer is the most frequently encountered and has the worst prognosis, ampullary and duodenal cancers are the least common but have the best prognosis.
- Jaundice is the commonest presenting symptom. Endoscopic stent placement is preferable to transhepatic stenting.
- Pancreatoduodenectomy (with or without pylorus preservation) is the most appropriate resectional procedure for all periampullary cancers. This should be confined to specialist centres, to reduce morbidity and mortality and increase resection rates.
- Adjuvant or neoadjuvant treatment in combination with surgery should be given in the context of a clinical trial.
- Efforts should be made to obtain a tissue diagnosis in patients selected for palliation.
- Duodenal bypass should be used in addition to palliative surgical biliary bypass.
- If chemotherapy is used for palliation, gemcitabine is the treatment of choice.

Conflict of interest: none.

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