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REVIEW

Ductal adenocarcinoma of the pancreatic head: A focus on current diagnostic and surgical concepts

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Abstract

Complete surgical resection still remains the only possibility of curing pancreatic cancer, however, only 10% of patients undergo curative surgery. Pancreatic resection currently remains the only method of curing patients, and has a 5-year overall survival rate between 7%-34% compared to a median survival of 3-11 mo for unresected cancer. Pancreatic surgery is a technically demanding procedure requiring highly standardized surgical techniques. Nevertheless, even in experienced hands, perioperative morbidity rates (delayed gastric emptying, pancreatic fistula *etc.*) are as high as 50%. Different strategies to reduce postoperative morbidity, such as different techniques of gastroenteric reconstruction (pancreatico-jejunostomy *vs* pancreatico-gastrostomy), intraoperative placement of a pancreatic main duct stent or temporary sealing of the main pancreatic duct with fibrin glue have not led to a significant improvement in clinical outcome. The perioperative application of somatostatin or its analogues may decrease the incidence of pancreatic fistulas in cases with soft pancreatic tissue and a small main pancreatic duct (< 3 mm). The positive effects of external pancreatic main duct drainage and antecolic gastrointestinal reconstruction have been observed to decrease the rate of pancreatic fistulas and delayed gastric emptying, respectively. Currently, the concept of extended radical lymphadenectomy has been found to be associated with higher perioperative morbidity, but without any positive impact on overall survival. However, there is growing evidence that portal vein resections can be performed with acceptable low perioperative morbidity and mortality but does not achieve a cure.

Key words: Pancreatic adenocarcinoma; Pancreatic fistula; Pancreatic surgery; Venous resection

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INTRODUCTION

Since many aspects of the pathogenesis and optimal man-

agement of ductal pancreatic adenocarcinoma (DPAC) remain unclear, this tumor entity continues to be the fourth leading cause of cancer related death in the Western world[1]. Even with the widespread use and refinements of diagnostic tools (e.g., contrast-enhanced transabdominal ultrasound (US), thin-sliced contrast-enhanced helical computer tomography (CT), contrast-enhanced magnetic resonance imaging (MRI), positron emission tomography (PET-CT), transduodenal ultrasound and fine-needle biopsy (FNB), early diagnosis of pancreatic cancer remains rare, since most patients (about 80% to 90%) at the time of diagnosis are found to have locally or even systemically advanced disease. Therefore, only 10% of patients with DPAC can undergo curative resection, which remains the only possibility of achieving long-term survival. Unfortunately, only 20% of resected patients remain free of any tumor recurrence five years postoperatively[2]. A national survey in France showed a relevant decrease in postoperative mortality after pancreaticoduodenectomy (PD) for DPAC from 11% to 3.3% between 1991 and 2010[3,4]. During the same period of observation, the overall survival of resected patients increased from 11% five years postoperatively to 25% after resection[3-5]. To date, there is insufficient solid data available regarding the exact role of neoadjuvant therapies, however, in the case of locally advanced disease, neoadjuvant chemo/radio-therapy has been reported to increase the number of patients who undergo curative surgery[6]. This review focuses on the clinical value of preoperative diagnostic and interventional techniques, results of different types of pancreatic head resection, the role of extended radical lymphadenectomy, vascular resections and perioperative medical and surgical approaches to decrease perioperative morbidity.

DIAGNOSIS AND PREOPERATIVE STAGING

Transabdominal US and contrast-enhanced US

The clinical finding of painless jaundice in an appropriately aged patient (fifth to sixth decade of life), must be considered pancreatic cancer until proven otherwise. Transabdominal US is rapid, non-invasive and inexpensive and is usually the first step in radiological evaluation. The sensitivity of US in diagnosing pancreatic cancer has a wide reported range. As a direct radiological sign, a hypoechogenic lesion can be visualized in about 55%-90% of patients[7-9]. Major limitations of US are the detection of small tumors (< 2 cm of diameter), lesions that are mainly located in the left side of the pancreatic gland, multifocal pancreatic lesions and obesity as the latter is a risk factor for pancreatic cancer[10]. Indirect radiological signs of pancreatic cancer such as dilatation of the main pancreatic duct (> 2 mm in combination with upstream areas of atrophied pancreatic gland), biliary tree, pseudocystic lesions, peripancreatic lymphadenopathy, ascites, pleural effusion and metastatic tumor deposits to the liver should strongly suggest pancreatic cancer. The great operator dependability of US with its above-mentioned diagnostic limitations has recently led to the introduction of contrast-enhanced ultrasonography (CEUS). In a very recently published multicenter study, CEUS was reported to diagnose DPAC with an accuracy of 87% in patients with an already visualized pancreatic mass by conventional US[11]. Such findings were also confirmed by other groups[12,13]. Although some experts in the field of CEUS propose its use as an additional work-up examination for pancreatic pathologies, CEUS is currently not considered a diagnostic standard.

Thin-sliced, intravenous contrast-enhanced CT

Thin-sliced, intravenous contrast-enhanced computer tomography (CECT) has become the imaging modality of choice to evaluate patients with pancreatic cancer. The overall sensitivity and specificity of CECT has been reported to be around 90% in experienced centers[14-18]. CECT with timed sequences to capture arterial and venous phases is able to demonstrate a hypodense pancreatic tumoral lesion in 80% to 95% of cases[14-16,19] (Figure 1). Dilatation of the biliary tree or the main pancreatic duct can be found in 86% and 88% of cases, respectively (Figure 1). Tumoral obstruction of the main pancreatic duct with upstream atrophy of the pancreatic parenchyma or pseudocystic lesions are present in 82% and 10% of patients[14,20] (Figure 1). The finding of a tumor that surrounds the entire circumference of a vessel is generally recognized as unresectable tumor encasement[14,21]. CECT criteria have been developed to indicate the probability of vascular involvement based on the relationship of tumor to adjacent vessels. A prospective case series by Lu *et al*[22] introduced a new classification based on tumor involvement of the portal and superior mesenteric veins and the celiac, hepatic and superior mesenteric arteries which was graded on a scale 0-4 scale based on circumferential contiguity of tumor to vessel by CECT (Grade 0, no contiguity of tumor to vessel; Grade 1, tumor contiguous to less than one quarter circumference; Grade 2, between one-quarter and one-half circumference; Grade 3, between one-half and three-quarters circumference; and Grade 4, greater than three-quarters circumferential involvement or any vessel constriction). A cut-off between Grade 2 and Grade 3 showed the lowest number of false-negatives and an acceptable number of false-positives for unresectability. Furthermore, such a cut-off level was reported to have a sensitivity of 84%, a specificity of 98%, a positive predictive value of 95%, and a negative predictive value of 93% for unresectability of the vessels[22]. In general, typical reports in the literature regarding the accuracy of CECT using the classification by Lu for predicting vascular invasion range from 62% to 92% with a somewhat higher sensitivity for arterial infiltration[17,23] (Figure 2). Positive overall predictive values for local surgical unresectability have been reported to be excellent (89% and 100%)[14,15,19,21]. CECT has a reported sensitivity of 75%-87% in diagnosing liver metastases[24,25]. In many cases, hepatic metastatic lesions missed by CECT are small, but originate from an already

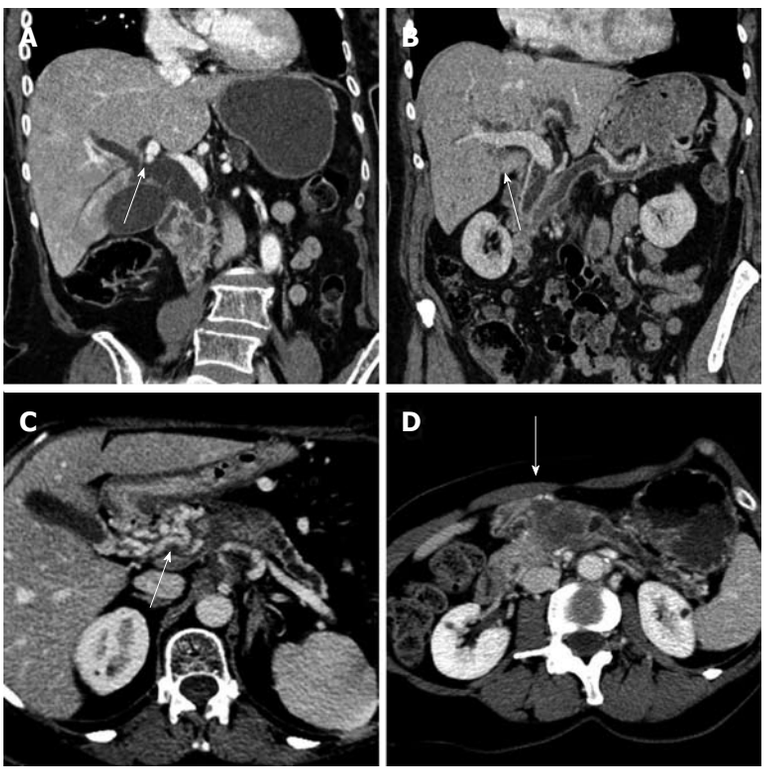

Figure 1 Ductal dilation, computer tomography 3-phase contrast-enhanced thin-slice helical scan. A: Heterogenous tumor of the pancreatic head with consecutive extra- and intrahepatic bile duct dilatation (arrow); B: "Double duct sign" due to a tumor of the papilla of vater (arrow); C: Tumor of the pancreatic neck with an upstream dilatation of the pancreatic duct and parenchymal atrophy of the pancreatic gland. Presence of a cavernoma due to tumor thrombosis of the portal vein (arrow); D: Classic radiological presentation of a pancreatic neck tumor with a less pronounced enhancement compared to the normal pancreatic parenchyma (arrow).

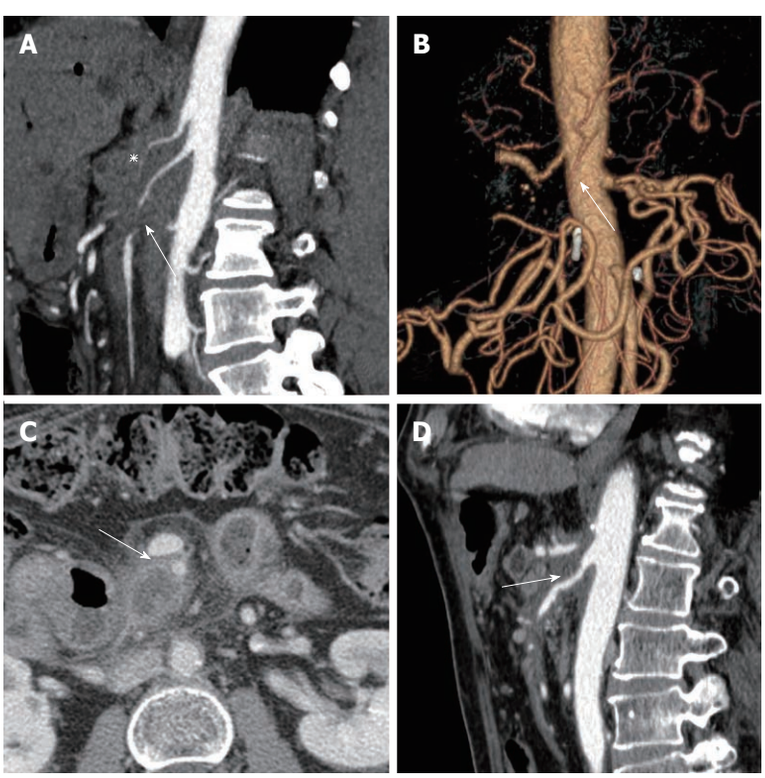

Figure 2 Vascular tumor extension, computer tomography 3-phase contrast-enhanced thin-slice helical scan, sagittal section and 3D reconstruction. A, B: Sheathing and thrombosis of the celiac trunk (asterisk) and superior mesenteric artery (arrow) with collateral blood flow *via* the inferior mesenteric vessels; C: Tumor of the pancreas (arrow) in contact with the superior mesenteric artery and infiltration of the portal vein; D: Tumor sheathing or the origin of the superior mesenteric artery (arrow) with irregularities as a sign of arterial invasion.

larger pancreatic tumor (> 3 cm)[26-28] and are therefore retrospectively not unexpected. The identification of lymphatic nodal involvement and peritoneal disease is difficult with all currently available imaging modalities. On cross-sectional imaging, size (> 1 cm) is the criterion for identifying nodal metastases, and therefore the accuracy of CECT remains limited at 54%[17].

MRI, MRI-cholangiopancreaticography

To diagnose and stage pancreatic cancer, the systematic use of MRI is still questioned by many clinicians. However, MRI has been found to offer several benefits in imaging the pancreatic gland. It inherently offers better soft-tissue contrast than CECT before the administration of an i.v. contrast agent, and images can be obtained

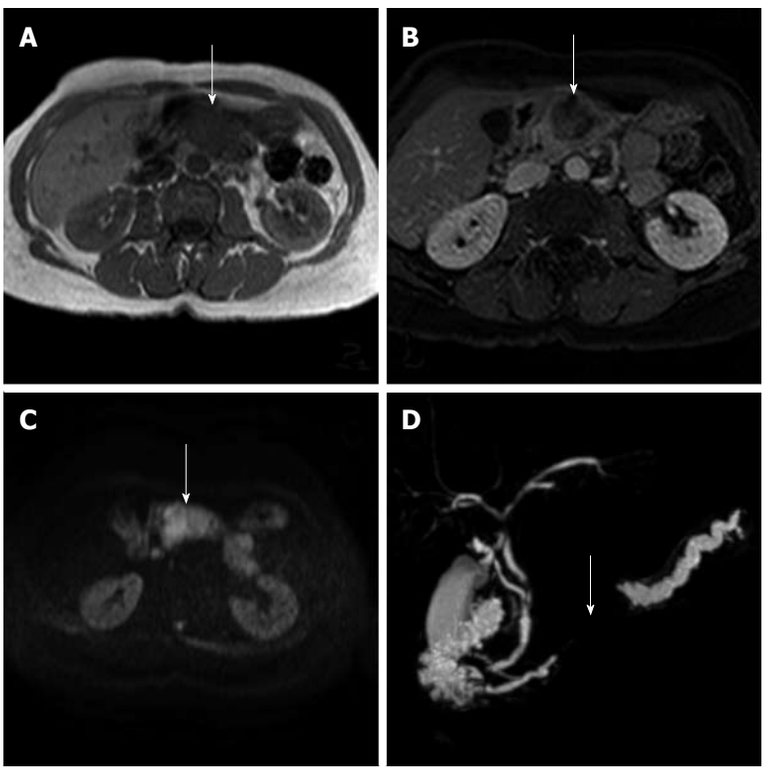

Figure 3 Magnetic resonance imaging appearance. A: T1 sequence showing an adenocarcinoma of the pancreas with a hypo-intense signal (arrow), whereas normal pancreatic tissue appears hyper-intense; B: T1 sequence with fat saturation injection: after injection of gadolinium, the pancreatic adenocarcinoma is hypo-enhanced (arrow) compared to the healthy parenchyma; C: A sequence of diffusion: hyper-intensity (arrow) signal due to the hyper-cellularity of the tumor; D: Sequence 3D-magnetic resonance cholangiopancreatography: stenosis of the main pancreatic duct (arrow) with upstream dilatation due to a tumor of the pancreatic isthmus.

in multiple planes. MRI can be performed in patients with a history of allergy to iodinated contrast agents and in those with renal insufficiency. Today, MRI has been shown to have high diagnostic value in cases where a clear diagnosis remains unclear even after CECT has been performed. Such a situation is mostly found in cases with a suspected tumor of the pancreatic head which is isodense on CECT and/or small lesions (< 2 cm). In such situations, MRI is superior to CECT at detecting or excluding a pancreatic tumor. The greatest advantage of MRI is found in patients in whom CECT demonstrates enlargement of the pancreatic head without clear definition of a pancreatic tumor. The overall sensitivity and specificity of MRI in diagnosing pancreatic cancer has currently been reported to be around 90% and 80%, respectively[29]. Magnetic resonance cholangiopancreatography (MRCP) is a special type of MRI exam that produces detailed images of the hepatobiliary and pancreatic systems, including the liver, gallbladder, bile ducts, pancreas and pancreatic duct. Additionally, MRCP has a clear advantage over ERCP in detecting pancreatic carcinoma since MRCP prevents inappropriate explorations of the pancreatic and common bile duct[30]. MRCP is a reliable and reproducible method of evaluating intraductal papillary mucinous neoplasms (IPMN), particularly in patients being followed non-operatively or in those who require surveillance of the pancreatic remnant after PD[31]. In a study comparing MRI with CECT, MRI had an accuracy of 93.5% for the detection of liver metastases compared with 87% for CECT[25]. However, a recently published meta-analysis showed equal overall capabilities of MRI and CECT to diagnose and stage pancreatic cancer[32-34]. Even the evaluation of vascular tumor infiltration can be evaluated by CECT or MRI with equal results[35]. MRI has lower diagnostic power to detect peritoneal carcinomatosis and/or local lymphadenopathy compared to CECT. MRI also has the potential to assess fat content which may be helpful in assessing the risk of pancreatic fistula (PF) following resection[36] (Figure 3).

Endoscopic US

When endoscopic ultrasound (EUS) was introduced, initial reports indicated a sensitivity higher than 90% for the identification of pancreatic tumors[9]. The superiority of EUS over classical CT was most evident for pancreatic lesions smaller than 3 cm in diameter. Therefore, EUS was considered the gold standard for diagnosing and staging pancreatic cancer. However, with the introduction of thin-sliced, intravenous CECT, the sensitivity and specificity of CECT for lesions smaller than 2 cm in diameter were reported to be as high as 77% and 100%, respectively[37]. Currently, EUS and CECT are considered to be equal in the diagnostic work-up of patients with suspected pancreatic cancer. However, EUS is still reported to be superior in assessing local tumor extension in the case of periampullary cancer compared to CECT and MRI (EUS: 78%, CECT: 24%, MRI: 46%)[38], however, due to the limited penetration depth of EUS, it is clearly inferior in detecting liver metastasis. In the case of suspected vascular infiltration (loss of interface between the tumor and the vessel wall; a tumor within the vessel lumen; collateral circulation; irregular vessel wall), sensitivity (85%-100%) and accuracy (55%-90%)[39] for EUS are reported to be equivocal compared to CECT/MRI. However, since these signs for vascular involvement are mainly indirect signs, these findings need careful interpretation, especially

Table 1 Summary of preoperative evaluation of pancreatic adenocarcinoma

Painless jaundice in an appropriately aged patient is highly suspicious for pancreatic cancer
Contrast-enhanced computer tomography is the diagnostic standard
High overall diagnostic sensitivity and specificity
Highly accurate in determining local respectability
Less adequate in identifying small hepatic metastases, extent of local lymphadenopathy and peritoneal tumor deposits
Magnetic resonance imaging gives additional information on small isodense or atypical pancreatic lesions
More accurate than contrast-enhanced computer tomography in detecting smaller hepatic metastases
Enhanced ultrasonography/fine-needle biopsy are reserved for the work-up of small lesions (< 2 cm), or in cases where a fine-needle biopsy is required before palliative or neoadjuvant therapy is initiated

in pancreatitis, IPMN or after biliary drainage (BD), not to exclude potentially resectable patients from curative surgery. Nowadays, EUS is used more selectively, mainly in cases of small pancreatic head tumors (< 2 cm), in which CECT and MRI findings remain equivocal. Furthermore, patients with locally unresectable or already distant metastatic disease, EUS guided transduodenal FNB is mandatory for diagnostic purposes before the initiation of neoadjuvant or palliative treatment.

18-F FDG PET-CT

18-F FDG PET-CT is mainly used in cases of preoperatively suspected distant metastatic disease or to investigate the response to neoadjuvant treatment. Currently, PET-CT is not considered a preoperative diagnostic standard and its routine use is only reported by some centers. Moreover, some studies found a comparable reliability rate of CECT and PET-CT in detecting distant metastasis[40-42]. Nevertheless, the preoperative routine use of PET-CT was found to change the management in 16% of patients who were deemed resectable based on standard staging examinations and was reported to be cost saving[43]. More recently, contrast-enhanced PET-CT has been shown to be a highly accurate staging tool as a 1-stop-shop procedure[43]. It is very likely that the use of this strategy will increase in the near future.

Preoperative FNB

Preoperative FNB is only required in cases of locally unresectable or already distant metastatic disease before non-surgical treatment (e.g., radio- and/or chemotherapy) is planned. Furthermore, FNB is required if there is any doubt about the underlying disease. If a FNB is planned, this should, whenever possible, be performed by the endoscopic route (transgastric/transduodenal) under endosonographic guidance with multiple biopsies taken to improve the diagnostic sensitivity (Table 1).

PERIOPERATIVE MANAGEMENT

Preoperative biliary drainage

In a recently published meta-analysis by the Cochrane Library, a statistically significant increased number of perioperative infectious complications, increased length of hospital stay, and higher overall hospital costs were reported in patients who had undergone preoperative BD[44]. These findings were confirmed in a prospective, randomized multicenter study. In addition, a significant increased risk of sustaining severe perioperative infectious complications (39% *vs* 74%) and a greater number of patients requiring hospital readmission (12% *vs* 33%) were also observed in drained patients[45]. As a relative indication for BD, in selected cases, patients suffering from severe malnutrition might benefit from BD and delayed surgery. Infection of the biliary tree is constantly (sub- or clinically) present after any drainage procedure of the biliary tree[46-48], and a peri-interventional antibiotic treatment is justified in all cases. Treatment with amoxicillin and clavulanic acid has been shown to be more efficient in decreasing septic complications than the use of second generation cephalosporins[4] (Table 2).

Perioperative supportive medical care «fast-track surgery» was not only applied for colorectal surgery

The concept of fast-track surgery is nowadays widely accepted by clinicians and has been shown to significantly enhance recovery leading to decreased hospital stay with a reduction in medical morbidity, but unaltered surgery-specific morbidity in a variety of procedures[49]. However, most data on fast-track surgery were generated by analyzing patients who underwent colorectal surgery - fewer data are available on pancreatic surgery. Nevertheless, fast-track surgery in patients undergoing major pancreatic surgery has been shown to be feasible and safe with a low readmission rate (3.5%-6.2%), in-hospital postoperative mortality (2%) and morbidity rates (35%), associated with improvements in delayed gastric emptying, earlier hospital discharge (10 d), but without compromising patient outcome[50,51]. Therefore, patients undergoing pancreatic surgery should not be excluded from the general principles of enhanced perioperative recovery programs.

INTRAOPERATIVE MANAGEMENT

Prevention of PF

The most frequent complication after pancreatic surgery is PF. The incidence of this complication varies widely between 5% and 30% depending on the different reported series[52]. However, this wide reported range is mainly based on the fact that there was, until recently, no uniform definition available for this complication. More recently, a uniform definition on the presence and

Table 2 Indications for preoperative biliary drainage

Total bilirubin > 250 mmol/L
Acute cholangitis
Severe malnutrition and delayed surgery scheduled (relative indication)
Patients who require neo-adjuvant chemotherapy
Perioperative antibiotic treatment with penicillin in cases with evident infection of the biliary tree and in all patients undergoing biliary drainage

Table 3 Prevention of pancreatic fistula

There is currently no favored pancreatico-digestive anastomotic technique with regard to decreased pancreatic fistula rates
The routine use of octreotide can only be recommended in the case of:
Friable pancreatic tissue
Small diameter of the main pancreatic duct (< 3 mm)
Trans-anastomotic, percutaneously placed drainage of the main pancreatic duct decreases the risk of pancreatic fistula formation

severity of postoperative PF has been proposed by the International Study Group on PF. A PF is a drain output of any measurable volume of fluid on or after postoperative day 3 with an amylase content greater than 3 times the serum amylase activity. The severity of PF is graded as follows: Grade A: PF managed medically; Grade B: PF requires endoscopic or radiological intervention; Grade C: reoperation[52]. In the case of a Grade C fistula, an increased mortality of 40% was found in a recently published French multicenter study of more than 680 consecutive patients[53]. Friable pancreatic tissue, a main pancreatic duct (Wirsung) smaller than 3 mm in diameter and low volume pancreatic surgeons are reported to be risk factors for the development of PF[54]. To decrease the incidence of PF, several different technical and medical strategies have been proposed: (1) internal or external perioperative drainage of the main pancreatic duct; (2) temporary fibrin glue sealing (TFGS) of the main pancreatic duct; (3) the perioperative systematic use of somatostatin or its analogues; and (4) the role of different types of pancreatic-enteric reconstruction [pancreatico-jejunostomy (PJ) *vs* pancreatico-gastrostomy (PG)] (Table 3).

Drainage of the main pancreatic duct (Wirsung)

A prospective randomized trial from the Johns Hopkins University failed to demonstrate any benefit of an intraoperatively placed internal main pancreatic duct stent regarding the incidence and/or severity of PFs[55]. In contrast, external drainage of the main pancreatic duct, especially in the case of soft or friable pancreatic parenchyma, significantly reduced the number of perioperative PFs. In a prospective, randomized trial, the effect of external pancreatic main duct drainage during duodenopancreatectomy was found to be associated with a significantly lower incidence of PFs (6.8% *vs* 29.3%; $P < 0.007$) compared to the group of patients without drainage[56]. This finding has been further supported by a prospective, randomized study which not only showed a significantly lower incidence of PFs (20% *vs* 6.7%; $P = 0.032$) but also a decreased length of hospital stay (23 d *vs* 17 d; $P = 0.039$) for the drained group[57]. Analogue findings were also reported in a recently published French multicenter study[58].

TFGS of the main pancreatic duct

Several studies have investigated the possible value of TFGS of the main pancreatic duct to decrease the number and/or severity of clinically evident PFs. One in particular is a multicenter study of patients who underwent pancreatic resection with the formation of a pancreatico-jejunal anastomosis. Patients in group 1 ($n = 80$) received TFGS, and the control group 2 ($n = 102$) underwent standard PJ without fibrin glue sealing. The incidence of PF was found to be equal in the two groups (17% *vs* 15%) with no significant difference in the incidence of intra-abdominal septic complications (15% *vs* 24%) and postoperative mortality (9% *vs* 6%)[59]. Based on the currently available data in the medical literature, TFGS does not decrease the incidence or the severity of PF, therefore, can not be recommended in daily routine practice.

Routine post-operative administration of somatostatin or its analogues

The systematic application of somatostatin or its analogues, which are known to decrease the secretory capacity of the endo- and exocrine pancreatic gland, has been assumed to have a protective effect against the formation and/or severity of PF.

If somatostatin or its analogues are used, they should be started before surgery[60]. In a meta-analysis of seven studies including a total of 1359 patients having undergone pancreatic surgery, the perioperative application of somatostatin or its analogues was found to be associated with a significant reduction in the incidence of PF after elective pancreatic surgery. However, this risk reduction was not associated with a significant difference in postoperative mortality. Another meta-analysis of 1918 patients found that somatostatin or its analogues did not reduce mortality after pancreatic surgery, but reduced overall morbidity as well as the incidence of biochemical fistula but not that of clinical anastomotic disruption[61]. However, there are also data showing that the routine use of somatostatin or its analogues is not beneficial in all patients and should be limited to certain situations with an increased risk for PF formation such as: low volume pancreas centers with a high PF rate > 10%, a small main pancreatic duct (< 3 mm) and a friable pancreatic gland[62,63].

PJ vs PG

There is an ongoing debate regarding the optimal pancreatico-enteric reconstruction technique after PD. When comparing PJ with PG, several clinical trials reported a decreased incidence of PFs after PG[64-66]. In contrast to these data, three prospective randomized trials comparing PJ and PG found equal outcomes for both tech-

niques[67-69]. In a meta-analysis published in 2007 by Wente *et al*[70], no difference was found between PJ and PG by analyzing prospective randomized trials, whereas observational clinical studies favored the use of PG with a reduced incidence of PF and postoperative mortality rates. The authors concluded, that there was a possible risk of publication bias in observational clinical trials and all randomized controlled trials failed to show an advantage of a specific type of reconstruction. Therefore, PG and PJ can be considered to be equally safe[70]. Theoretically, PG might lead to decreased activity of pancreatic enzymes due to inactivation by gastric acid which would result in an increased incidence of postoperative exocrine pancreatic insufficiency. However, this issue was refuted in a study by Lemaire *et al*[71] who found no difference in pancreatic exocrine insufficiency between PG and PJ.

Pylorus preserving PD or classic Kausch-Whipple

Proponents of pylorus preservation argue that the gastroduodenal physiology is better maintained and therefore, especially postoperative quality of life, is superior to the classic Kausch-Whipple (CKW) technique. In contrast, proponents of the CKW technique state that preservation of the pylorus does not follow the rules of radical tumor surgery with inadequate clearance of lymphatic nodes, inadequate tumor staging, and increased risk of tumor recurrence and impaired overall survival. In the most recently published meta-analysis by Fitzmaurice *et al*[72], 43 studies [6 randomized controlled trials, 12 prospective studies and 25 retrospectives studies; pylorus preserving pancreaticoduodenectomy (PPPD): n = 1870; CKW: n = 1923] were analyzed. To investigate the postoperative overall survival, a total of 26 studies with only surgery for pancreatic cancer patients were analyzed. The overall postoperative survival was found to be equal following PPPD and CKW. However, by only analyzing those studies of higher scientific quality, a significantly longer overall survival was found in patients who had undergone PPPD.

Thirty-three studies were eligible for analyzing postoperative mortality. The authors reported no significant difference between the two procedures. As far as the quality of life is concerned, the studies are difficult to compare since a large variety of different quality of life scores (if used at all) and parameters were used[72]. Another recently published meta-analysis has shown that PPPD reduced the operation time and reduced blood loss[73,74]. Therefore, the CKW operation should only be performed in situations where tumor spread towards the stomach cannot be ruled out or when lymph node metastases are suspected. Irrespective of whether PPPD or CKW is performed, antecolic reconstruction is preferred to decrease the incidence of postoperative delayed gastric emptying[75].

Is there a role for routine intra-peritoneal drainage?

The theoretical advantage of routine intraoperatively placed abdominal drainage is to drain the pancreatic juice in the case of PF formation which avoids the negative sequelae of free pancreatic juice in the abdominal cavity. The concept of the routine use of intra-peritoneal drainage (IPD) is still in the mind of many surgeons. In contrast to such paradigms, Conlon *et al*[76] found in their prospective, randomized study of patients having undergone pancreatic resections that the routine use of a closed IPD resulted in a higher number of patients suffering from local septic complications and an increased rate of PFs (22% *vs* 9%, $P < 0.02$). In another recently published trial, short-term abdominal drainage (< 3 d) in patients with a low risk of PF formation did not show any benefit in the routine use of an IPD. To date, there is a lack of evidence for the routine use of IPD in pancreatic surgery[77].

LYMPH NODE DISSECTION AND PATHOLOGICAL WORK-UP

Radicality of pancreatic resection

A strict surgical technique and a high quality pathological work-up of the surgical specimen are of utmost importance. To improve the number of R0 resections, transection of the main bile duct is performed just below the biliary confluence in a monobloc technique including the gallbladder - preparation is carried out in close contact with the right border of the superior mesenteric artery to achieve maximum retroperitoneal tumor clearance. Intraoperative frozen section analysis of the resection margins is mandatory - especially, as the pancreatic resection margin shows microscopic tumor infiltration in 10%-20% of cases[78].

Lymphadenectomy during pylorus PPPD/CKW

As for any other cancer type, the lymph node status is of major clinical and prognostic value. However, some controversies remain regarding how these should be reported (total number or lymph node ratio) and on the impact of an extended lymphatic clearance. Standard lymphadenectomy for PPPD/CKW includes the lymph nodes of the hepato-duodenal ligament, along the common hepatic artery, portal vein, cranial portion of the superior mesenteric vein as well as the right border along the superior mesenteric artery and celiac trunk. Extended lymphadenectomy includes in addition to the lymphatic reservoir of the interaortocaval space, the left-side of the celiac trunk as well as the left side along the superior mesenteric artery. In a study of 517 pancreatic cancer patients, no prognostic difference was found between peripancreatic lymph node metastases and second level lymphatic nodes N2 (along the common hepatic artery, portal vein, cranial portion of the superior mesenteric vein as well as the right border along the mesenteric superior artery and celiac trunk). Furthermore, in patients with one positive lymph node metastasis (N1), overall survival was similar to nodal negative (N0) patients. A poorer prognosis was reported with two or more positive lymphatic nodes (> N1), irrespective of the total number of affected lymph nodes[79]. The lymph node ratio has been introduced to

Table 4 Improvement of radicality of resection

Resection	Exclusion of resection
Standard lymph node clearance for PPPD/CKW include the regional peripancreatic lymph nodes, hepato-duodenal ligament, common hepatic artery, portal vein, cranial portion of the superior mesenteric vein, right border along the mesenteric superior artery and celiac trunk	Extended lymphadenectomy can not be recommended
Vascular resection of the portal vein or superior mesenteric vein is feasible and safe and should not be an exclusion criterion in curative surgery	Thrombosis of the mesenteric-portal vein or tumoral infiltration > 180° of these vascular structures are contraindications in attempting curative resection

PPPD: Pylorus preserving pancreaticoduodenectomy; CKW: Classic Kausch-Whipple.

characterize lymphatic tumor load and to create a prognostic parameter independent of the rough estimation N0 *vs* N1 or the overall number of affected lymph nodes[80,81]. There is still some debate about the exact cut-off level of the lymph node ratio which indicates poorer survival. In a study of 4000 patients, a cut-off of 0.2 was reported as a strong predictor of poor survival[82]. Currently, a minimum of 10-12 lymph nodes need to be cleared during PPPD/CKW[83]. The para-aortic lymph nodes are generally considered as metastatic disease (M1). However, some confusion exists whether clearance of these nodes improves survival. In a review by Glanemann *et al*[84], patients with para-aortal positive lymph nodes showed a poor survival. The authors concluded that such patients should not undergo resection. The role of extended lymph node dissection has been extensively investigated. No benefit was found for this approach[85,86]. Since extended lymphadenectomy increases perioperative morbidity and impairs quality of life, this procedure should not be performed routinely.

Resection margins

Surgical resection margin is a major prognostic factor. Any incomplete resection (R1) must be considered as palliative[87,88]. However, there are also data on long-term survival after R1 resections[88,89]. A possible explanation for such conflicting data is most likely due to the heterogeneity between the study populations and different pathological work-up standards of the surgical specimens. Indeed, the number of patients with a positive resection margin was found to be between 14% and 85%[90,91]. In fact, a standardized examination of the resected specimens showed intraoperative coloration of the retroperitoneal resection margin using India ink and in a higher number of paraffin-embedded thin-sliced sections. With this technique, more than two-thirds of patients were found to be R1 resected in the retroperitoneal margin[91]. The incidence of R1 resections was correlated with the number of thin-sliced sections performed[90]. A retroperitoneal margin of 1.5 mm was classified as a R0 resection. This, however, is unfortunately rarely achievable[92].

Management of vascular infiltration

Major arterial resection such as the superior mesenteric artery is technically feasible, major arterial resection during duodenopancreatectomy is currently not established and there are insufficient data to perform such a procedure[4]. In contrast, venous involvement is not a contraindication for excluding patients from undergoing curative surgery. Venous resection, partial or even circumferential with an adequate technique of reconstruction is associated with a survival similar to those groups of patients having undergone PD for adenocarcinoma[89]. However, if the tumoral infiltration of the portal vein is 50% or more of the vascular circumference, survival rates of such patients undergoing duodenopancreatectomy and venous resection are inferior compared to patients having undergone duodenopancreatectomy alone[93]. Unfortunately, the exact extent of venous tumoral infiltration is difficult to estimate preoperatively, and the definitive extent of vascular infiltration is only made by pathological examination of the resected specimen[89,94-97]. However, the impact of portal vein resection during PD remains unclear. The number of patients who undergo a R1 resection varies between 38% and 59%[97-101]. In a recently published review of 1600 patients having undergone pancreatic resection in combination with venous resection, the number of patients who finally had a R1 resection was 40%[102]. Several series have reported a similar survival after PD with or without venous resection[97,98,99-101]. In a review of 1646 patients having undergone portal/superior mesenteric vein resection, the long-term survival at 1-, 3- and 5-years was 50%, 16% and 7%, respectively[102]. Since PD and mesenteric or portal vein resection have the same reported morbidity and mortality as patients who have undergone PD without vascular resection, and the tumor involvement of such venous structures is a consequence of the tumor location rather than a reflection of highly aggressive tumoral behavior, venous resection during duodenopancreatectomy has become a standard procedure. However, vascular infiltration has been reported as a risk factor for local tumor recurrence[97]. In addition, the results remain disappointing since the reported median survival after duodenopancreatectomy and venous resection was only 13 mo[4,102] with a high number of patients (40%) not free of tumor (R1)[89] (Table 4).

CONCLUSION

The survival of patients with pancreatic cancer has only slightly improved over the last few years. An increase in median survival from 16 mo in the eighties to 20 mo nowadays was reported by the French Surgical Association in 2010. This achievement is poor compared to the

progress made in other cancer types (e.g., rectal cancer). Radical surgery so far remains the only chance of long-term cure. However, new molecular markers for early diagnosis[103-105], a deeper understanding of the molecular alterations during the genesis and progression of pancreatic cancer, specifically designed new neoadjuvant and/or adjuvant therapies which directly interact with the molecular cancer cascade need to be developed in the future. Without such progress, the prognosis of pancreatic cancer remains catastrophic.

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