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Review article

Preoperative staging and evaluation of resectability in pancreatic ductal adenocarcinoma

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Background

Cancer of the pancreas is a common disease, but the large majority of patients have tumours that are irresectable at the time of diagnosis. Moreover, patients whose tumours are clearly beyond surgical cure are best treated non-operatively, if possible, by relief of biliary obstruction and percutaneous biopsy to confirm the diagnosis and then consideration of oncological treatment, notably chemotherapy. These facts underline the importance of a standard protocol for the preoperative determination of operability (is it worth operating?) and resectability (is there a chance that the tumour can be removed?). Recent years have seen the advent of many new techniques, both radiological and endoscopic, for the diagnosis and staging of pancreatic cancer. It would be impracticable in time and cost to submit every patient to every test. This review will evaluate the available techniques and offer a possible algorithm for use in routine clinical practice.

Discussion

In deciding whether to operate with a view to resecting a pancreatic cancer, the surgeon must take into account factors related to the patient, the tumour and the institution and team entrusted with the patient's care. Patient-related factors include age, general health, pain and the presence or absence of malnutrition and an acute phase inflammatory response. Tumour-related factors include tumour size and evidence of spread, whether to adjacent organs (notably major blood vessels) or further afield. Hospital-related factors chiefly concern the volume of pancreatic cancer treated and thus the experience of the whole team. Determination of resectability is heavily dependent upon detailed imaging. Nowadays conventional ultrasonography can be supplemented by endoscopic, laparoscopic and intra-operative techniques. Computed tomography (CT) remains the single most useful staging modality, but MRI continues to improve. PET scanning may demonstrate unsuspected metastases and likewise laparoscopy. Diagnostic cholangiography can be performed more easily by MR techniques than by endoscopy, but ERCP is still valuable for preoperative biliary decompression in appropriate patients. The role of angiography has declined. Percutaneous biopsy and peritoneal cytology are not usually required in patients with an apparently resectable tumour. The prognostic value of tumour marker levels and bone marrow biopsy is yet to be established. Preoperative chemotherapy or chemoradiation may have a role in down-staging an irresectable tumour sufficiently to render it resectable. Selective use of diagnostic laparoscopy staging is potentially helpful in determination of resectability. Laparotomy remains the definitive method for determining the resectability of pancreatic cancer, with or without portal vein resection, and should be undertaken in suitable patients without clear-cut evidence of irresectability.

Keywords

adenocarcinoma, pancreas, operability, resectability, imaging, cytology, resection

Introduction

The present paper aims to review factors that govern operability and ways to determine preoperative resectability. Factors of potential relevance are discussed individually on the basis of recent reports, to suggest their present role in the preoperative staging of patients with suspicion of pancreatic ductal adenocarcinoma. It is important to select diagnostic measures that provide accurate preoperative information without substantially delaying further management.

Background

In most countries the annual incidence of ductal

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pancreatic adenocarcinoma exceeds 100 cases per million inhabitants. Overall, the disease has an appalling prognosis and generally represents between the fourth and sixth leading cause of cancer death. There is pronounced inconsistency in reporting outcome following resection for pancreatic cancer, and unrealistically high 5-year survival rates have been achieved by performing calculations on subsets of patients and using methods such as Kaplan-Meier for calculating survival. In most units a true 5-year survival of 'ordinary' pancreatic cancer is exceptional. Gudjonsson has emphasised the poor prognosis of the disease in a review of 340 papers on pancreatic carcinoma [1]. An overall survival rate of <0.4% was found, the best overall survival rate among surgical studies being only 3.6% at an average cost for each resection of at least 150 000 USD. Nevertheless, in the absence of credible alternative cures, surgical resection remains the only option with any potential for cure of pancreatic adenocarcinoma.

Resectability rates overall usually range from 15% to 20% of all patients, and data from specialised centres imply a somewhat better outcome than that reported by Gudjonsson. Thus, 5-year survival rates following 'radical' pancreatoduodenectomy for pancreatic adenocarcinoma of up to 15% have been reported in several specialised centres dealing with the disease, with hospital mortality rates in the range of 2–5%, and 30–40% rates for total complications, which include the dominant problems of delayed gastric emptying, pancreatic fistula and wound infections [2–3]. At present, therefore, surgical resection offers patients the best hope while awaiting future effective adjuvant or alternative therapies. This review will concentrate on optimal methods for determining the operability and resectability of pancreatic cancer.

Operability

Factors that govern operability and resectability can be classified simply as those that relate to the patient; those that relate strictly to the tumour; and those that are related to the hospital, surgeon, and team taking care of the whole perioperative course (Table 1). Patient-related factors include malnutrition, risk assessment, age, presence of pain, and the potential influence of the patient's inflammatory status. Tumour-related factors include size of the tumour (diameter <2 cm may be associated with a more favourable outcome) [4], the exclusion of vascular entrapment and other signs of local spread (e.g. lymph node metastases) or more distant spread (e.g. hepatic or pulmonary metastases), which should be ruled out during preoperative work-up and imaging. Hospital-related and surgeon-related factors are closely linked to the throughput of similar cases. The experience of the individual surgeon is of undoubted importance for the outcome, as is the existence of an established team to deal with perioperative management, plus clearly defined routines for patients undergoing pancreatic resection, including formal evaluation of outcome and follow-up.

Table 1. *Determination of operability in pancreatic adenocarcinoma*

Patient-related factors
- Malnutrition
- Risk assessment, ASA score
- Age
- Pain
- Inflammatory status

Tumour-related factors
- Tumour size
- Vascular invasion
- Local/distant spread

Hospital/surgeon-related factors
- Volume, experience, established team, routines and evaluation of outcome

ASA, American Society of Anesthesiologists

Patient-related factors

Malnutrition

Malnutrition, defined as weight loss of at least 10% of the body weight, and especially severe malnutrition (>15% weight loss), may be associated with an increase in postoperative morbidity and mortality rates Malnutrition is frequent in patients with pancreatic cancer, and the wasting increases during progression of the disease. The effects of malnutrition include, for example, an increased risk of infectious complications and prolonged rehabilitation. Furthermore, malnutrition can impair wound healing, immune response and skeletal muscle function, while the nutritional status affects the quality of life [5].

Risk assessment

The determination of operability should include an overall risk assessment, taking the patient's general condition into consideration. Of value is the American

Society of Anesthesiologists (ASA) classification from 1 to 5, in which 1 indicates a perfectly healthy individual and 5 a moribund patient.

Pain as predictor of outcome

The existence of preoperative moderate to severe pain has been reported as a negative predictor of resectability and also of overall survival as compared with patients without pain. Even in patients undergoing resection, the presence of preoperative pain was associated with a poor prognosis in one study [6]. Similar results have been reported by others, and the presence of back pain predicts both irresectability and a poor long-term prognosis after resection [7].

Age

Several studies have reported that radical pancreatic resection safely can be performed in elderly patients, although the threshold for 'advanced age' varies from 65 to 70 years of age [8, 9]. The upshot is that resection with radical intent can be performed in selected patients of 'advanced age', although such patients may not tolerate complications as well as their younger counterparts. The observation that long-term survival after resection of cancer of the pancreatic head was truncated in older patients (age >74 years), together with an increased complication rate in the older subgroup, emphasises the need for careful and critical patient selection [10].

Acute phase response

The presence of an acute phase response in patients with pancreatic cancer has been associated with accelerated weight loss, hypermetabolism, anorexia and shortened survival [11, 12]. In these studies, the acute phase response has been measured as an increase in C-reactive protein (CRP), and the association between poor prognosis and CRP level has basically been made in patients with unresectable pancreatic cancer. It remains to be shown if the magnitude of the acute inflammatory response also represents a determinant for resectability and a prognostic factor in patients subjected to radical resection.

Hospital volume

Complications following pancreatic resection are dangerous, threaten the patient's life and are extremely costly for society owing to the need for intensive care, prolonged hospital stay and prolonged rehabilitation. A number of studies have pointed to the inverse correlation between the case volume for pancreatic cancer resections and the rates of postoperative morbidity and mortality [13–17]. High volume hospitals offer fewer complications, reduced hospital stay and costs, and improved survival following resection for pancreatic cancer. The relationship appears to apply more to the institutional volume than to the individual surgeon's caseload. In determining operability and resectability, therefore, it is necessary to consider where and by whom the potential pancreatectomy is to be performed. Present data and future changes in policy seem likely to result in the regionalisation of pancreatic cancer operations.

Resectability

The different types of investigation for the determination of resectability require systematic consideration with particular reference to recent reports. Besides various diagnostic imaging techniques, laparoscopy (with or without laparoscopic ultrasound), fine-needle aspiration (FNA), cytology and the use of tumour markers may be of potential help, and preoperative chemoradiation can be used in an attempt to down-stage the tumour from irresectable to resectable. As many of these techniques are under active evaluation at present, it is important to identify how much of the potentially available diagnostic work-up is of clear-cut benefit for the patient and should therefore be performed routinely. Moreover, the intensity of preoperative investigation will reflect the surgeon's attitude towards palliative treatments. There is little role for a palliative operation in elderly or unfit patients with tumours of borderline resectability, for whom non-operative stenting offers a safe alternative to relieve jaundice. On the other hand, in better-risk patients with disseminated disease, laparotomy allows confirmation of diagnosis and resectability and a safe means of circumventing present or future obstructions of the bile duct and duodenum [18].

Diagnostic imaging

Ultrasonography. Ultrasonography is often used as the first imaging technique in patients with presumed extrahepatic biliary obstruction. This strategy is supported by its ready availability and low cost. Although state-of-the-art grey scale and colour Doppler ultrasonography can be as accurate as spiral computed tomography

(CT) and CT angiography for determining the resectability of peri-ampullary cancer [19], bowel gas can limit its accuracy and success is highly dependent on the skill and persistence of the operator. Thus, ultrasonography is generally followed by CT for more complete staging of potential pancreatic adenocarcinoma. However, ongoing developments of the ultrasonographic technique – including the use of microbubble contrast agents and endoscopic, laparoscopic and intraoperative ultrasound – are valuable adjuncts to staging, as well as helping to guide adequate FNA biopsy when indicated [20, 21].

CT. Spiral CT with intravenous contrast enhancement has been considered the optimal method for diagnosis and staging of pancreatic adenocarcinoma [22, 23], but a major limitation is its sensitivity for demonstrating small hepatic metastases [24]. Modern techniques using a pancreatic protocol with thin slices appear to improve detection of both distant metastases and vascular invasion and underline the role of CT in diagnosis and staging [25, 26].

Endoscopic ultrasonography (EUS). Endoscopic ultrasonography can improve diagnostic accuracy in staging pancreatic carcinoma by better demonstration of local vascular invasion supplemented by targeted FNA biopsy [27–29]. EUS-guided FNA biopsy is also useful for determining nodal status [30]. EUS may be even more accurate than CT and angiography in showing portal vein and/or arterial involvement [31, 32]. As a single investigation, however, EUS may not accurately stage all pancreatic cancers and does not predict resectability of stage T3 tumours, for example [33]. Nevertheless, in connection with magnetic resonance imaging (MRI), EUS can have a positive predictive value for resectability of 89% [34]. As with conventional ultrasound, EUS is highly operator-dependent and it is also a time-consuming investigation.

Magnetic resonance imaging (MRI). MRI is potentially as accurate as CT (or even more so) in staging pancreatic cancer, e.g. by detecting small liver metastases [35, 36]. It also avoids the radiation exposure. At present, MRI should at least be considered as an additional modality if diagnostic difficulties persist after CT. A substantial benefit with MRI is the additional possibility of performing magnetic resonance cholangiopancreaticography (MRCP), thereby providing further information on the pancreatic and biliary ducts, and adding to the preoperative evaluation of suspected pancreatic malignancy. Thus, relevant information can be obtained by MRCP, sparing many patients from undergoing invasive procedures such as ERCP. The latter can then be restricted to more therapeutic indications and cases with specific diagnostic problems [23, 37–40]. As with all these tests, the technology continues to improve.

Positron emission tomography (PET). This relatively new imaging technique will potentially improve the staging of pancreatic adenocarcinoma and is of potential value in identifying metastatic disease [29]. At present, PET cannot replace CT in defining local tumour extension and resectability [41, 42], but the technique needs further refinement to become more than a supplement to currently available imaging modalities.

Endoscopic retrograde cholangiopancreatography (ERCP). The presence of the 'double duct sign' in pancreatic cancer usually implies a sizeable tumour, although in practice most pancreatic cancers involve the main pancreatic duct as well as the bile duct. The length of the pancreatic duct stricture as measured on ERCP correlates with both size and stage of the cancer [43]. The routine use of ERCP in the diagnosis of pancreatic carcinoma [44] and routine preoperative endobiliary stenting has been questioned in jaundiced patients [45, 46], although stenting is still frequently performed if a delay in operation is anticipated. Diagnostic ERCP may not be indicated in patients with clinically evident pancreatic cancer, but it may valuable if tumour is suspected despite negative results on ultrasonography and CT, or may be used as an additional aid to differentiate between chronic pancreatitis and cancer.

Angiography. The use of angiography for diagnosis, staging and obtaining a 'road map' for operation can no longer be considered to have a place in the routine diagnostic work-up of patients with suspected pancreatic malignancy. Some authorities regard CT, angiography, MRI and EUS as superior techniques for demonstrating major vascular involvement [23], but angiography may still have a role if appearances are equivocal.

FNA cytology

Histological verification of a suspected pancreatic cancer has a high specificity, but a negative FNA certainly does not exclude an adenocarcinoma, because of the possibility of sampling error. Furthermore, there is a small but definite risk of tumour seeding in the needle track, although this risk may be lower with EUS-guided FNA biopsy. In most

centres FNA is not considered to be part of the preoperative routine assessment of a patient with a resectable pancreatic tumour. It is generally restricted to patients with irresectable disease who are not considered candidates for laparotomy, so as to achieve a histological diagnosis before initiating chemotherapy [47–49]. In addition, percutaneous biopsy has a role in determining treatment for unusual tumours in and around the pancreas such as neuroendocrine carcinoma, lymphoma or metastases.

Diagnostic laparoscopy

Diagnostic laparoscopy may reveal the presence of liver metastases that have been overlooked by CT in up to 40% of patients, thereby avoiding a substantial number of unnecessary laparotomies [50–52]. In combination with laparoscopic ultrasound it can further improve diagnostic accuracy but may still underestimate portal vein and regional lymph node involvement [53–57]. Some of the initial enthusiasm for this invasive and costly investigation has waned as state-of-the-art CT can reduce the incidence of 'overlooked' liver metastases to <10%. Thus, several authors have emphasised a more selective use of laparoscopic staging [58–60].

Peritoneal cytology

A positive peritoneal cytology has been associated with advanced disease, and can thus help to predict unresectability in patients with pancreatic adenocarcinoma, as positive rates increase with disease progression [61–63]. However, peritoneal cytology is rarely positive if the tumour is resectable on radiological growths, so its value may be limited [64]. Moreover, no statistically significant difference was found in cumulative survival rate after pancreatic cancer resection when comparing patients with positive and negative peritoneal cytology without macroscopic peritoneal metastases [65].

Tumour markers

The predictive values of individual tumour markers has usually been low, even though high levels of carbohydrate antigen 19-9 (CA 19-9) have been associated with very low resectability rates [66]. Thus, the routine use of tumour markers has been adopted, yet a combination of tumour markers including CEA, CA 19-9 and CA 72-4 has been reported to improve diagnostic accuracy [67]. At present, tumour marker measurements have a limited role in determining the resectability of pancreatic cancer.

Bone marrow metastases

The finding of micrometastases in the bone marrow in patients with pancreatic carcinoma, obtained by aspiration from the ileal crest, may predict a significantly shorter survival time [68]. However, cytokeratin staining can be falsely positive, so the value of bone marrow biopsy is not yet established.

Preoperative chemoradiation

For a number of gastrointestinal cancers today, the use of more liberal and aggressive chemotherapy regimens has raised the possibility of down-staging the tumour so that it comes to fulfil the criteria for surgical resection. By this means, patients with irresectable or inoperable tumours may become candidates for tumour resection, and this strategy may also be applicable to pancreatic cancer. Preoperative chemoradiation using 5-fluorouracil with or without mitomycin C or gemcitabine plus radiation therapy (50.4 Gy) was performed in 26 patients with pancreatic adenocarcinoma, four of whom had further chemoradiation postoperatively. In this subset of patients with a poor prognosis, preoperative chemoradiation was followed by surgical resection in 14 of the 26 patients, 10 of whom required vascular reconstruction. The median postoperative survival was 34 months for the group with resection, compared with 8 months for the group without resection [69]. In another study, preoperative chemoradiation with 50–56 Gy irradiation, sensitised with an intravenous infusion of 5-fluorouracil, in patients with marginally resectable pancreatic cancers, was well tolerated and seemed to improve resectability, with a median survival time of 13 months as compared with 8 months in those without resection [70, 71]. It therefore appears that preoperative chemoradiation is well tolerated in patients with advanced and potentially irresectable adenocarcinoma of the pancreas and may result in down-staging in some tumours, thereby improving resectability rates. The value of preoperative chemoradiation still needs to be confirmed by randomised clinical trials, but the preliminary results do suggest a potential benefit in a subgroup of patients with marginally resectable pancreatic cancer.

Vascular involvement

Resection of pancreatic cancer is rarely appropriate in patients with evidence of vascular encasement [72]

although portal vein resection may be technically possible. In some centres vascular reconstruction per se has not been considered a contraindication for an attempt at radical pancreatectomy and performed without associated co-morbidity [73, 74]. A lower survival rate has, however, been reported following pancreatoduodenectomy including portal vein resection [75].

Conclusion

Patients with suspected ductal pancreatic adenocarcinoma should undergo an overall risk assessment as for any other major abdominal intervention, taking into account the magnitude of the operative procedure and the generally less favourable prognosis. Extra-abdominal metastases have to be excluded by CT of the thorax or ordinary chest X-ray but not, at present, by routine bone marrow biopsy. Routine preoperative staging and determination of resectability should include thin-sliced spiral CT as the main imaging technique, reserving MRI for equivocal cases. ERCP may be superseded by MRCP for diagnostic purposes, but preoperative biliary decompression is still indicated for deeply jaundiced patients, particularly if delay is anticipated before operation. A more selective use of staging laparoscopy, including laparoscopic ultrasound, is advocated and may be of particular use in patients with tumours of the pancreatic body or tail. Patients thought to have resectable disease should then be subjected to exploration. Although preoperative imaging has become increasingly sophisticated and accurate, the laparotomy findings remain the final determinant of resectability. The presence of unsuspected liver or peritoneal metastases, inability to separate the portal vein from the pancreatic tumour and/or encasement of the superior mesenteric artery will generally indicate the need to abandon resection in favour of a bypass procedure. Novel imaging and staging techniques should be evaluated in randomised clinical studies before they are incorporated into routine clinical practice.

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