Improvement of surgical results for pancreatic cancer

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Surgery is the only potential hope of cure for patients with pancreatic cancer. Advantageous tumour characteristics and complete tumour resection are the factors most relevant for a positive prognosis, so detection of premalignant or early invasive lesions, combined with safe and oncologically adequate surgery, is an important goal. The experience and volume of both the individual surgeon and hospital are of paramount importance to achieve low morbidity and adequate management of complications. Most pancreatic cancers are locally advanced or metastatic when diagnosed and need multimodal therapy. With increasing evidence on surgical and perioperative aspects of pancreatic cancer therapy, short-term and long-term outcomes of resectable and borderline resectable pancreatic cancer are improving.

Introduction

Despite advances in cancer therapy, pancreatic adenocarcinoma is one of the most aggressive tumour entities and is one of the five most frequent causes of tumour-associated deaths in the European Union and the USA. Whereas the 5-year overall survival of patients with pancreatic cancer is roughly 5%, surgery is the only potential cure, and 5-year survival increases to more than 20% in patients who have had resection as part of multimodal therapy.1,2 Although pancreatic surgery has become a safer intervention, with low perioperative mortality in specialised centres, complete tumour resection combined with advantageous tumour characteristics are the most crucial factors to achievement of long-term survival, with 5-year survival of more than 50% in favourable subgroups of patients.1,2 This Review adds to a Seminar4 on pancreatic cancer that focused on tumorigenesis, diagnostics, and non-invasive therapy.

Guidelines differentiate between resectable, borderline resectable, locally advanced unresectable, and metastatic pancreatic cancer.7 Surgery embedded in a multimodal setting is the cornerstone of therapy for resectable and borderline resectable disease. Although few comparative data are available, results of small randomised controlled trials suggest that resection of locally invasive pancreatic cancer which included AJCC/UICC stage IIA and IIB tumours or those invading the portomesenteric vein results in longer survival than do chemoradiation7 or palliative gastrobiliary bypass.4 Measures to improve outcomes for patients with pancreatic cancer amenable to surgical resection can be clustered into three groups: tumour diagnosis at an early stage and timely patient referral to surgery; reduction of perioperative mortality by prevention of surgical complications combined with adequate management of complications; and improvement of oncological results by increasing the rate of complete tumour resections and implementing effective neoadjuvant and adjuvant therapies to reduce the risk of local or distal recurrence. Data presented in this Review are mainly on pancreatic ductal carcinoma but are also on other primary pancreatic malignant diseases (eg, periampullary or intraductal papillary mucinous carcinomas) where indicated.

Tumour diagnosis, precursor lesions, and referral to surgery

Small tumour size is one of the most relevant positive predictive factors in pancreatic cancer, and high-quality imaging techniques play a crucial part in the diagnosis of pancreatic tumours. In most cases, tumour diagnosis and resectability is adequately evaluable by use of only one cross-sectional imaging study, and current state-of-the-art imaging is contrast-enhanced multidetector CT with advanced volumetric processing techniques,7,10 MRI, including magnetic resonance cholangiography, might help to differentiate cystic pancreatic neoplasms, but does not add information about resectability. Endoscopic ultrasound can complement other imaging methods with valuable staging information, and is especially useful in detection of smaller lesions. Endoscopic ultrasound-guided fine-needle aspiration is the best method for obtaining a tissue diagnosis when needed—eg, before neoadjuvant or palliative therapy.7,10 Routine use of endoscopic retrograde cholangiopancreatography (ERCP) or ¹⁸F-fluorodeoxyglucose (¹⁸F-FDG) PET cannot be recommended.10 Routine preoperative biopsy of resectable pancreatic tumours is not advisable, because malignant disease cannot be ruled out reliably.11

With increasing use of screening imaging techniques, many cystic neoplasms are detected at an early stage.10 Intraductal papillary mucinous neoplasms (IPMNs) and mucinous cystic neoplasms are accepted precursor lesions of pancreatic ductal adenocarcinomas, similar to adenomas for colorectal cancer. Therefore, pancreatic surgery can curatively resect early stage pancreatic cancer or even precursor lesions before they become malignant tumours. Survival of patients with disease detected and resected early is excellent compared with survival in patients with further-progressed pancreatic cancer at diagnosis.11 Although main-duct IPMN is an accepted indication for resection because of its high malignant potential, the role of surgery for branch-duct IPMNs is highly controversial and has resulted in a revision of the Sendai guidelines.11 Whereas some groups advocate observation for smaller asymptomatic branch duct IPMNs without mural nodules,7,10 an analysis of 287 consecutively resected IPMNs from our hospital showed malignant features in many small...
Sendai-negative branch-duct IPMNs (according to the guidelines from 2006). Combined with an incorrect preoperative diagnosis in up to a third of incidentally discovered cystic neoplasms, even at experienced, high-volume centres, these data show that patients with cystic lesions need a thorough interdisciplinary evaluation and careful selection for observation or surgery to supply adequate therapy. Importantly, unnecessarily long follow-up might enable progression of branch-duct IPMNs into ductal adenocarcinomas.

Indicating deficits in the referral pattern of patients with pancreatic cancer, an analysis of the US National Cancer Database (1995–2004) showed that 38% of patients with clinical stage I tumours (T1/2 and N0) but without identifiable contraindications did not undergo resection. 5-year survival was 24–6% with surgery versus 2.9% without. The nihilistic attitude towards pancreatic cancer resection was less common in academic hospitals, National Cancer Institutes, and National Comprehensive Cancer Network hospitals, which substantiates the need for timely referral of patients to specialised centres to achieve good results.

**Perioperative morbidity and mortality**

**Risk factors and prevention of surgical morbidity**

The most relevant morbidity in pancreatic surgery derives from the pancreatoenteric anastomosis in pancreatic head resections, and from pancreatic stump leakage in distal pancreatectomies. Leakage increases the risk of subsequent intra-abdominal abscesses, postpancreatectomy haemorrhage, or delayed gastric emptying. Soft pancreatic texture with a small pancreatic duct diameter is one of the most relevant risk factors for leakage. Other risk factors include older age, overweight and obesity, and pulmonary or renal comorbidity. Factors that surgeons can influence include long operating time, high blood loss and the need for blood transfusion, vascular or multivisceral resections, type of anastomosis or pancreatic stump closure, and stent use.

**Pancreatic anastomosis in pancreateoduodenectomy**

Because of its clinical relevance, much effort has been made to reduce the risk of pancreatic leakage, and several randomised controlled trials and meta-analyses have focused on various aspects of leakage prevention. Several types of pancreatic anastomosis have been advocated as the superior method, but evidence is inconclusive. We believe one type of anastomotic technique should be used within a centre in a highly standardised way to minimise complication rates, irrespective of pancreas texture.

Pancreateicojugal anastomosis is the most commonly used method of pancreaticoenteric anastomosis after pancreateoduodenectomy. Randomised trials have compared end-to-side, end-to-end, duct-to-mucosa, and invagination techniques. Since a uniform fistula definition was not available before the implementation of the International Study Group of Pancreatic Fistula definition, comparison of the individual study results is difficult, and the range of fistula rates is wide. Also temporary or permanent main pancreatic duct occlusion does not reduce morbidity. Likewise, the benefit of intraoperative pancreatic duct stent placement was not supported in a meta-analysis of published randomised controlled trials when internal and external stents were analysed. However, similarly to a randomised, controlled trial not included, a subgroup analysis of external stents showed reduced clinically relevant pancreatic fistula and morbidity rates. The topical application of fibrin glue sealant to the surface of high-risk pancreaticojejunostomy did not reduce fistula or other complications.

Pancreateicojugalostomy seems to be a promising alternative to pancreateicojejunostomy and is favoured predominantly in smaller centres for patients with soft pancreatic texture and small duct size. Five randomised controlled trials have compared pancreateicojejunostomy with pancreaticoenterostomy. A randomised, controlled, multicentre trial supports the presumed lower risk of pancreatic fistula in pancreaticoenterostomy, although the incidence of overall postoperative complications and mortality did not differ significantly between groups.

**Closure of the pancreatic remnant in distal pancreatectomy**

Pancreatic fistulas are a persistent problem after distal pancreatectomy, and occur in up to a third of patients. Various techniques have been advocated to reduce fistula rates, including hand-sewn closure with or without selective duct ligation, stapler closure, and stump coverage with addition of fibrin glue or a falciform patch. Again, most evidence comes from non-randomised prospective or observational cohort studies. A randomised, controlled, multicentre trial that compared hand-sewn with stapler closure of the pancreatic remnant did not identify significant differences between the two groups.

Coverage of the pancreatic remnant with a falciform patch and fibrin glue or a seromuscular patch of jejunum showed inconsistent results regarding reduction of pancreatic fistula or intra-abdominal fluid collections. Likewise, prophylactic transpapillary pancreatic stent insertion, with the aim to facilitate pancreatic fluid drainage into the duodenum, did not reduce the rate or severity of pancreatic fistula. The best stump closure technique in distal pancreatectomy is therefore an unresolved clinical issue.

**Somatostatin**

Synthetic analogues of somatostatin, with their inhibitory effects on pancreatic enzyme secretion, have been well studied in patients undergoing pancreatic surgery. Theoretically, somatostatin analogues could reduce pancreatic fistula rate and thereby overall morbidity and mortality. With more than 2200 randomly assigned patients, a Cochrane review identified a significantly
lower pancreatic fistula rate and a lower overall number of patients with postoperative complications in the somatostatin analogue group. Clinically significant fistulas were not reduced when clearly distinguished, nor were reoperations or mortality. Whether somatostatin analogues should be recommended for routine use in all patients undergoing pancreatic resection or only in those with a high-risk anastomosis is unclear.

The beneficial role of somatostatin analogues in treatment of established pancreatic fistula is controversial, but no solid evidence showing a higher closure rate of pancreatic fistula with somatostatin analogues is available. More detailed conclusions about, for example, the time to fistula closure are not possible.

Pylorus preservation in pancreatoduodenectomy
Classic pancreatoduodenectomy, the so-called Kausch-Whipple procedure, has long been the standard surgical procedure for pancreatic head and periampullary carcinomas. The pylorus-preserving pancreatoduodenectomy was introduced with the aim of reduction of unnecessary stomach resection without constraining lymph node clearance or long-term survival. Several meta-analyses, including the Cochrane study, which compared pylorus-preserving surgery with classic pancreatoduodenectomy, showed no differences in mortality, morbidity, and survival. Importantly, delayed gastric emptying was not significantly increased with the pylorus-preserving technique, but operating time and intraoperative blood loss were significantly reduced. As a new technical variation, pylorus-resecting pancreatoduodenectomy was associated with significant reductions in delayed gastric emptying compared with pylorus-preserving pancreatoduodenectomy in a randomised controlled trial. Also focusing on intestinal transition, the antecolic reconstruction for gastrojejunostomy or duodeno-jejunostomy might be the preferred reconstruction technique during pancreatoduodenectomy because it seems to be associated with a lower rate of delayed gastric emptying. However, evidence for this is inconclusive.

Preoperative biliary drainage
Preoperative biliary drainage for pancreatic head cancer might alter perioperative morbidity. A Dutch multicentre, randomised trial that randomly assigned 202 patients to undergo early surgery or preoperative biliary drainage followed by surgery showed a significantly higher rate of serious complications in the drainage group, with no effects on perioperative mortality, length of hospital stay, or median survival. Likewise, a Cochrane review including five randomised studies (one trial with endoscopic drainage and four with percutaneous transhepatic biliary drainage) showed no evidence of benefit of biliary drainage before surgery in patients with obstructive jaundice, but it did increase hospital costs. On the basis of these results, preoperative biliary drainage should be reserved for patients with extraordinarily high bilirubin concentrations, which are associated with coagulation disorders, or for patients for whom neoadjuvant therapy is intended.

Laparoscopic pancreatectomy
Grade III to IV evidence shows that laparoscopic distal pancreatectomy is a feasible and safe technique associated with lower morbidity and shorter hospital stay than the open technique. However, no randomised studies are available and data come solely from retrospective studies, which mostly exclude converted patients from analysis (conversion rate of about 9%) and omitted intention-to-treat analysis. Furthermore, reported series mostly included patients with benign or borderline malignant disease, and little experience is available with malignant disease. Data do not allow for conclusions to be made regarding oncological long-term results for pancreatic adenocarcinoma. Despite this scarcity of data, laparoscopic distal pancreatectomy is increasingly done in malignant disease cases by many surgeons. Data for laparoscopic pancreatic head resections are scarce. Only the Mayo Clinic reported short-term results from a substantial number of patients, who were all operated on by one surgeon, had short hospital stays, and a moderate morbidity rate. Some authors assume that this highly demanding laparoscopic technique is unlikely to be widely accepted, and whether laparoscopic pancreatoduodenectomy can have a discrete role in a subset of patients is unclear.

Complication management
Since surgical morbidity after pancreatic resections is still about 40% in most large series, success of pancreatic surgery is closely associated with successful management of complications. Internationally accepted definitions of pancreatectomy-associated complications set the prerequisite for the comparability of studies and further developments in management of complications. Notable advances include the interventional drainage of pancreatic fistula and intra-abdominal abscesses, endovascular management of delayed postpancreatectomy haemorrhage, interventional stenting of bile-duct leakage, or endoscopic dilatation of narrowed gastroenteric anastomosis. The presence of interventional radiology at a hospital is statistically associated with lower perioperative mortality in pancreatic surgery, and adequate complication management makes the difference between low-mortality and high-mortality hospitals. Highly lethal delayed postpancreatectomy haemorrhage that predominantly emerges from pancreatic fistula formation is one of the most demanding complications of pancreatic surgery. Early angiography with embolisation or stenting, at best after a sentinel bleeding episode, should be the procedure of choice, and surgical intervention reserved for patients who cannot be resuscitated for an interventional approach or if no interventional radiology is available. Likewise, most pancreatic fistula and fluid collections after pancreatectomy can be managed safely with interventional
Hospital volume and outcome

Improvements of surgical and oncological results in pancreatic cancer therapy are strongly associated with hospital volume. Since the large analysis of hospital volume and outcome by Birkmeyer and colleagues in 2002, pancreatic surgery has been accepted as one of the most recognised high-risk, low-volume surgical procedures. Adjusted mortality rates for pancreatic resections are up to 16·3% in very low-volume hospitals and as low as 3·8% in very high-volume hospitals. Notably, long-term survival with pancreatic cancer was better in high-volume hospitals, even if corrected for mortality in the perioperative period. These findings were confirmed in a meta-analysis, in which a high hospital volume for pancreatic surgery was associated with significantly lower postoperative mortality and improved long-term survival. Reasons for outcome improvement attributable to high volume seem to be multifactorial. First, because pancreatic surgery is complex, technical performance and skills of surgeons can improve with experience and thereby decrease rates of complication and mortality. Second, greater exposure of medical and nursing staff to patients after pancreatic surgery increases their ability to detect and treat complications at an early stage, which might contribute to a decrease of postoperative mortality. This theory is supported by a report by Ghaferi and colleagues, in which although rates of complications and major complications did not vary significantly across hospital mortality quantiles, the rate of death in patients with major complications was almost twice as high in hospitals with high overall mortality as in those with low overall mortality. This difference shows the importance of avoiding surgical complications, but that improvement of the care patients receive after complications have occurred is even more important to the reduction of mortality. A third reason is expansion of experience with minimally invasive complication treatments using interventional radiology and endoscopy. Interventional complication treatment might decrease the need for complication-rich reoperations, and the presence of interventional radiology at a hospital was statistically associated with lower perioperative mortality. Fourth, with increasing numbers of patients, medical oncologists are more familiar with pancreatic cancer therapy, and adjuvant chemotherapy is offered more frequently. Use of multimodality treatments differs between high-volume and low-volume hospitals, which contributes to increased overall survival.

Since the initiation of a centralisation process in pancreatic surgery, a 19% decrease in pancreatic cancer surgery was associated with lower hospital mortality mortality in the USA in the past decade has been explained largely by higher hospital volumes. Likewise, a regional Dutch cancer registry showed increasing resection rates, notably decreasing in-hospital mortality rates (from 24·4% to 3·6%) and increasing 2-year survival after resection (from 38·1 to 49·4%) with implementation of centralisation agreements. These data clearly indicate that success in pancreatic cancer surgery demands experienced surgeons and highly efficient interdisciplinary complication management.

Oncologic surgery and outcome

Prognostic parameters

Second to favourable tumour characteristics, complete tumour resection is probably the most relevant prognostic factor for patients with resectable pancreatic cancer. Evidence from randomised controlled trials comparing surgical with non-surgical therapy is scarce because studies on this issue are hampered by ethical concerns. However, a multicentre trial comparing resection and chemoradiotherapy for locally invasive resectable pancreatic cancer (tumour stages IIA and IIB) showed significantly better outcomes in the surgery group, despite the premature termination of the trial. In patients with resected pancreatic cancer, data for the role of complete (R0) tumour resection is controversial, with no differences in survival between R0 and R1 resections in an analysis of 875 patients from four randomised controlled trials. However, results might be greatly affected by histopathological resection specimen evaluation and definition of R1. With application of histological reporting as suggested by the Royal College of Pathologists and R1 definition as microscopic evidence of tumour extension within 1 mm of resection margins, survival of patients with R0 resection was significantly better than that with R1 resection. Therefore, surgical and multimodal attempts to increase the rate of R0 resections are a main objective in pancreatic surgery.

Other well-established prognostic factors in resectable pancreatic cancer include tumour-specific characteristics such as perioperative CA19-9 concentrations, tumour size and differentiation, lymph node involvement, and perineural infiltration or lymphovascular invasion. On the basis of these variables, prognostic scores and nomograms have been suggested that might alter intraoperative and perioperative decision making. Because some patients do not benefit from tumour resection or radiochemotherapy, a search continues for valid markers that can be used to help to minimise non-beneficial therapies and interventions.

Definition of resectability and borderline resectability

Pancreatic surgeons generally agree that localised, non-metastatic pancreatic tumours without the involvement of the portal mesenteric vein and the main visceral arteries (tumour stage I and II; table) are resectable. The presence of distant metastases (tumour stage IV), however, is viewed as a non-resectable disease for which chemotherapy should be the first treatment (figure 1).
The circumferential encasement of the coeliac axis, the hepatic artery, or the superior mesenteric artery with suspected arterial tumour infiltration (T4 or tumour stage III) is also categorised as non-resectable in most cases. Extended resections, such as the Appleby procedure, which combines extended distal pancreatectomy with resection of the coeliac trunk for locally advanced body and tail tumours, or the use of neoadjuvant therapy, might make the disease resectable in some patients when treated at specialised centres. Several definitions of borderline resectable tumours are available and an expert consensus statement has undertaken to provide a generally acceptable definition (panel). However, with increasing experience in vascular surgery, fewer pancreatic surgeons view vascular involvement as a criterion for non-resectability. In particular, involvement of the superior mesenteric or portal vein, even in cases with circumferential encasement or occlusion, allows for primary resection and reconstruction by end-to-end anastomosis in most cases in experienced centres, as long as a suitable vessel proximal and distal to the area of vessel involvement is present (figure 2). Although clear and widely accepted definitions of resectability and borderline resectability are needed for clinical trials and to allow comparison of results from different centres, the surgeons’ capabilities, rather than the cross-sectional imaging findings, define resectability in many cases. Nevertheless, we have to keep in mind that the biology of the disease that might need effective multimodal therapy also raises the question of whether we should resect all we can resect.

Lymphadenectomy
Results of several studies, including a large, population-based analysis, have verified the negative predictive value of lymph-node involvement in pancreatic cancer. Both the number of lymph nodes assessed in N0 disease and the lymph node ratio in N1 disease were among the most powerful factors associated with survival. The aim to improve survival, extended lymphadenectomy including retroperitoneal soft-tissue clearance has been investigated in several comparative studies and in four randomised controlled trials. A meta-analysis did not support a positive effect of extended lymphadenectomy on overall survival but instead showed a tendency towards higher rates of delayed gastric emptying. Therefore, standard but not extended lymphadenectomy should be regarded as the procedure of choice in pancreatoduodenectomy. No data from randomised trials exist for the effects of extended lymph-node and soft-tissue clearance in distal pancreatectomy.

Artery-first approaches and retroperitoneal-pancreatic-tissue transection
Pancreatic cancers often invade the retroperitoneal-pancreatic tissue that surrounds the first 3–4 cm of the superior mesenteric artery origin behind the superior mesenteric vein, with characteristic perineural tumour growth and lymphovascular invasion. Tumour-positive histological findings at this transection margin after pancreatoduodenectomy have been associated with impaired prognosis in pancreatic cancer. More importantly, avoiding macroscopic incomplete tumour resections (R2 resections) is essential because of poor results. Determination of tumour non-resectability, which is crucially associated with tumour infiltration of the superior mesenteric artery, needs to be done before an irreversible step of the operation. Various surgical techniques have been described with the intention of complete clearance of the peripancreatic retroperitoneal tissue and of minimising the rate of R2 resections. So-called artery-first approaches enable exclusion of tumour infiltration into the superior mesenteric artery early in the operation. Transection of the mesopancreas with radical soft-tissue clearance directly right-lateral of the superior mesenteric artery and with optimum control of bleeding can be achieved by optimised surgical techniques—eg, the so-called uncinate process first
Panel: Resectable and borderline resectable pancreatic cancer

Tumours viewed as being localised and resectable should show the following:

- No distant metastasis
- No radiographic evidence of superior mesenteric vein and portal vein abutment, distortion, tumour thrombus, or venous encasement
- Clear fat planes around the coeliac axis, hepatic artery, and superior mesenteric vein

Tumours viewed as being borderline resectable include the following:

- No distant metastasis
- Venous involvement of the superior mesenteric vein or portal vein showing tumour abutment with or without impingement and narrowing of the lumen, encasement of the superior mesenteric vein or portal vein but without encasement of the nearby arteries, or short segment venous occlusion resulting from either tumour thrombus or encasement but with suitable vessel proximal and distal to the area of vessel involvement, allowing for safe resection and reconstruction
- Gastrroduodenal artery encasement up to the hepatic artery with either short segment encasement or direct abutment of the hepatic artery, without extension to the coeliac axis
- Tumour abutment of the superior mesenteric artery not to exceed more than 180° of the circumference of the vessel wall

According to the consensus statement of the AHPBA/S50/SSAT.7 Without a widely accepted consensus, the term borderline resectability is presently used for a wide variety of more or less extended tumours, mainly depending on the surgeons’ or the centres’ experience with vascular resections. AHPBA=American Hepato-Pancreato-Biliary Association. SSAT=Society of Surgical Oncology. SSAT=Society for Surgery of the Alimentary Tract.

Vascular resections and extended pancreatectomy

Pancreatic head and body tumours grow close to the main visceral vessels, and infiltration of the portomesenteric vein and the superior mesenteric artery or the coeliac axis is a common clinical finding in locally advanced tumours. Whereas venous infiltration is included in the T3 category according to the TNM grading system, mesenteric artery or coeliac axis infiltration is a prognostically unfavourable T4 or tumour stage III and is generally deemed to be unresectable, because of surgical complexity and poor long-term survival (table). Likewise, splenic artery infiltration has been associated with poor survival in pancreatic body and tail cancer. A meta-analysis of largely retrospective cohort studies confirmed that arterial resection in patients undergoing pancreatectomy is associated with substantial morbidity and mortality and poor long-term survival which, however, was favourable compared with that in patients who did not have resection for locally advanced pancreatic cancer.8 Unlike arterial resection, which cannot generally be recommended, portomesenteric-vein resection is a standard procedure at high-volume pancreatic centres. With no randomised controlled trial data, two meta-analyses with 1458 patients with pancreaticoduodenectomy and 2247 patients with pancreatectomy showed no differences in morbidity, mortality, or 5-year overall survival between patients with venous resection and those without.8,9 These data affirm that experience in vascular surgery is indispensable for a pancreatic surgeon. For locally advanced tumours, extended pancreatectomies are also very feasible at specialised centres.8,10 Long-term results seem comparable to matched standard pancreatectomies, but increased perioperative morbidity demands a close postoperative surveillance of patients. In the absence of larger randomised trials, whether patients with locally advanced pancreatic cancer and other prognostic risk factors benefit more from multimodal regimens that include tumour resection or from chemotherapy or chemoradiotherapy alone is unclear.

Multimodal therapy

Adjuvant therapy

Pancreatic cancer is characterised by a high metastatic potential with possibly systemic dissemination early in the course of the disease. Minimum residual disease after pancreatic resection is the rationale for adjuvant therapy. Since the promising results of the ESPAC-1 trial,11 adjuvant therapy has advanced to such an extent that it now plays an inherent part in pancreatic cancer treatment. The European Study Group of Pancreatic Cancer (ESPAC) was the first to report significantly increased median and 5-year survival with adjuvant fluorouracil plus folinic acid after R0 or R1 resection compared with surgery alone. This survival benefit was
Neoadjuvant therapy

The role of neoadjuvant therapy in pancreatic cancer is not well understood, and evidence supporting its benefit originates from phase 1 and 2 trials and retrospective analyses. The rationale for neoadjuvant therapy is two-fold. First, locally non-resectable or borderline resectable tumours that infiltrate the superior mesenteric artery or the coeliac trunk, or both, or the portal mesenteric vein, could be downstaged with the aim to make subsequent resection possible (figure 3). With this intent, irradiation of the local tumour site is the main element of neoadjuvant therapy to achieve tumour shrinkage. Second, occult metastatic disease at the time of primary diagnosis might be adequately treated by the chemotherapeutic component of neoadjuvant therapy. By separating progressive from non-progressive disease, use of neoadjuvant therapy could help to identify patients with favourable tumour biology who could benefit most from resection. Patients with poor tumour biology and disease progression are selected, thereby avoiding the morbidity of unnecessary surgical intervention.

Results of systematic reviews and meta-analysis have shown that about a third of tumours initially designated unresectable were resectable after neoadjuvant chemoradiotherapy, with a reduced risk of positive resection margins.\(^\text{57}\) The risk of perioperative mortality in patients receiving neoadjuvant chemoradiotherapy might be higher, without detrimental effects on overall survival, which is comparable with that of patients who were primarily staged as resectable. However, the quality of available data is poor and influenced by selection bias of patients, and which patients will benefit from neoadjuvant chemoradiotherapy is unclear. In the group of primarily resectable patients, resection and survival rates after neoadjuvant therapy are similar to those in primarily resected tumours that are treated with adjuvant therapy.\(^\text{57}\) Neoadjuvant chemoradiotherapy, which is associated with relevant grade 3–4 toxic effects, cannot be considered as standard treatment in primarily resectable patients.\(^\text{7}\) Phase 3 trials of neoadjuvant combination chemotherapies in resectable pancreatic cancer are in progress (eg, NEOPAC study).

The absence of widely accepted definitions of unresectability or borderline resectability is the most important problem for studies and meta-analyses for neoadjuvant therapy in locally advanced disease. Phase 3 trials involving patients with well defined locally unresectable or borderline resectable tumours and applying state-of-the-art chemoradiotherapy regimens, possibly consisting of induction chemotherapy and subsequent chemoradiotherapy, are much needed. The value of neoadjuvant FOLFIRINOX, which is increasingly used since having been proved highly effective in the palliative setting, remains to be investigated in controlled trials.

Figure 3: CT imaging of a large T4 adenocarcinoma

Before (A) and after (B) neoadjuvant chemoradiotherapy. Histopathological examination of the resection specimen after pancreaticoduodenectomy with segmental portal vein resection showed complete tumour remission (ypT0 pN0).
Perspective

In pancreatic cancer, favourable prognosis is closely correlated with preinvasive or small localised cancerous lesions. Prevention and early identification of pancreatic cancer are therefore the most desirable objectives. Efforts to achieve this have included the development of epigenetic biomarkers to assess cancer risk and early tumour detection, which are ideally measured in blood or, more invasively, in pancreatic fluid. Similarly, implementation of screening programmes for asymptomatic high-risk patients with a strong family history and an inherited pancreatic cancer predisposition seems highly advisable. Rapidly growing genetic and clinical understanding of IPMNs and mucinous cystic neoplasms might help to prevent or adequately treat premalignant lesions. New functional (diffusion-weighted MRI or dual-energy perfusion CT) or molecular imaging techniques could overcome the limitations of morphological imaging, with improvements in the detection and discrimination of pancreatic lesions. With new radiation methods such as proton or ion beams new opportunities arise to produce dose distributions that are more effective in the target volume and reduce the dose and toxic effects to uninvolved normal structures. Initial clinical data from retrospective analyses and prospective phase 1 and 2 trials support the hypothesis of the superior characteristics of proton versus photon beams. Improvements in systemic treatment strategies that modulate the immunosuppressive microenvironment in pancreatic cancer (eg, CD40 agonist, CTLA4 antagonists, or antibodies against PD1) could open new perspectives for neoadjuvant or adjuvant approaches. Routine postoperative follow-up with abdominal imaging and CA19-9 measurement has to be proven effective at improving the prognosis of patients with pancreatic cancer. Notably, in a distinct subgroup of patients, resection for isolated recurrence of pancreatic cancer is associated with encouraging survival rates.26

Contributors

WH, JW, and MWB contributed to the writing of the surgery sections; WH, DJ, and JD contributed to the writing of the multimodal therapy section. All authors contributed to the writing of the introduction, tumour diagnosis, precursor lesions, and referral to surgery, and perspective sections. All authors approved the final version of the Review. For further reading see appendix.

Conflicts of interest

We declare that we have no conflicts of interest.

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