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Evolution of oncosurgical management of pancreatic cancer

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Summary
Background Pancreatic cancer is the third leading cause of cancer-related death in the Western world and is projected to soon become the second commonest cause of cancer mortality. During the past two decades, there have been important clinical developments in the fight against this aggressive disease.
Objective The aim of this review article is to summarize the evolution of the multidisciplinary oncological and surgical management of pancreatic cancer.
Results The centralization of pancreatic surgery into specialized institutions has led to improvements in surgical techniques, with reduced surgical mortality rates of <5%. With the development of more effective neoadjuvant treatment options, we can now achieve resections in a considerably greater number of patients with borderline resectable and locally advanced tumors, including some with oligometastatic disease. New surgical technologies such as laparoscopic and robotic surgery may offer the opportunity for reduced postoperative morbidity and increased quality of life. Adjuvant chemotherapy has become the gold standard after upfront resection in patients with resectable pancreatic cancer yielding survival times of 30–50% at 5 years. The ESPAC-1, -3, and -4 trials have defined the efficacy of monotherapy with 5-fluorouracil/folinic acid and gemcitabine, and combination therapy with gemcitabine and capecitabine, respectively, whilst the PRODIGE 24/CCTG PA.6 trial showed that poly-agent FOLFIRINOX achieved a median survival of 54.4 months in selected patients.
Conclusion With the utilization of more effective neoadjuvant and adjuvant treatment regimens, improvements in surgical techniques, and the centralization of pancreatic surgery, the indications for pancreatic resection with improved survival have been greatly extended.

Keywords Pancreatic surgery · Adjuvant therapy · Neoadjuvant therapy · ESPAC · FOLFIRINOX · APACT

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Main novel aspects

1. Evaluation of the latest practice-changing studies in pancreatic cancer surgery.
2. Analysis of the impact of neoadjuvant therapies in extending resectability in locally advanced tumors.
3. Reporting of the latest adjuvant therapies from Europe and North America.

Introduction

Pancreatic cancer is presently the third leading cause of cancer-related death in the Western world and is projected to become the second leading cause of cancer-related mortality within the next few years [1, 2]. For all stages combined, the actual 5-year survival rate is only 9%, but actually represents a doubling of survival over the past 15 years [2]. Surgical resection in combination with adjuvant chemotherapy provides the only chance for long-term survival. However, only 10–20% of patients present with a surgically resectable tumor, while the majority of patients are diagnosed with advanced disease and are not candidates for (upfront) surgery [2]. During the past two decades, the clinical management of pancreatic cancer has undergone considerable change, which has not only caused some shift in the dismal prognosis of pancreatic cancer patients, but has also dramati-

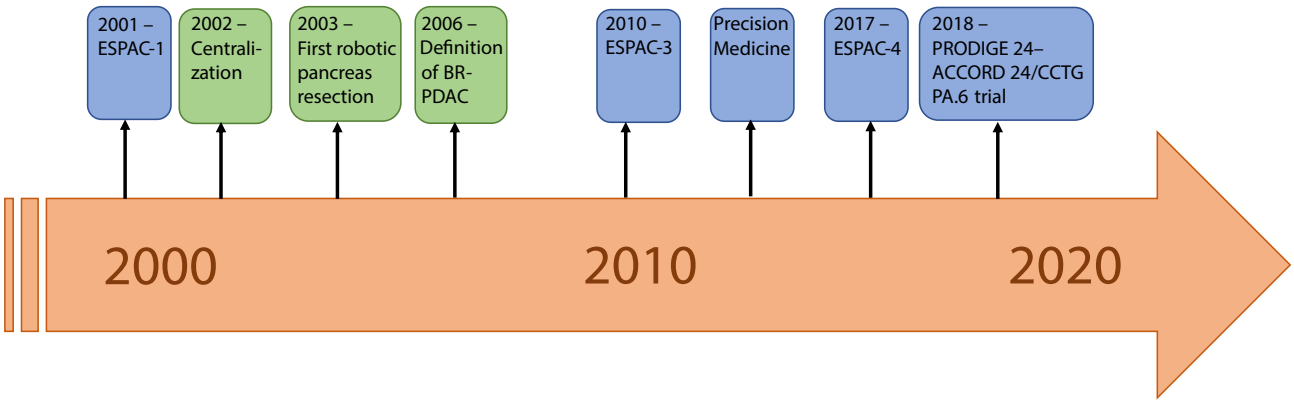

Fig. 1 Milestones in surgical (*green*) and oncological (*blue*) management of pancreatic cancer during the last 20 years. *ESPAC* European Study Group of Pancreatic Cancer, *BR-PDAC* borderline resectable pancreatic cancer

cally improved survival after resection, resulting from reduced postoperative mortality rates and effective adjuvant chemotherapy protocols [3]. High-quality randomized controlled trials are needed to change both oncological and surgical treatments [4]. The gold standard for upfront surgery followed by adjuvant chemotherapy has emerged from the basis of high-level evidence from multicenter randomized controlled trials [5, 6]. For new surgical approaches and technologies such as laparoscopic and robotic surgery, safety and efficacy data need to be generated in ongoing and future clinical trials [7]. Another important achievement is the conceptual development of *borderline resectable pancreatic cancer* [8]. In this review article, we summarize the evolution of both surgical and oncological management of pancreatic cancer, highlighting results from randomized trials and consecutive evidence-based changes in clinical management. Fig. 1 illustrates the most important milestones achieved during the last 20 years.

Evolution in pancreatic cancer surgery

The concept of borderline resectable pancreatic cancer

Over the past 15 years, a consensus has emerged that there is a subgroup of patients with primary tumors that are in between resectable and unresectable, specifically locally advanced tumors with contact to surrounding major vascular structures which are technically resectable but with a higher risk of positive margins and therewith potentially worse survival benefit from resection. Since its first description in 2006 by Varadhachary et al. from the MD Anderson Cancer Center [9], borderline resectable pancreatic cancer has been defined by several groups including the American Hepato-Pancreato-Biliary Association (AHPBA), the Society of Surgical Oncology (SSO), and the Society for Surgery of the Alimentary Tract (SSAT) [10]. The AHPBA/SSO/SSAT classification was further modified by the National Comprehensive Cancer Network (NCCN), and the NCCN resectability definitions were endorsed by the International Study Group of Pancreatic Surgery (ISGPS) in 2014 [11, 12]. All definitions are comparable and with tumor vascular involvement determining the criteria of either borderline resectable or locally advanced pancreatic cancer [13]. Contrast-enhanced computed tomography (CECT) using a pancreas-specific protocol represents the gold standard to determine local tumor extension including vascular infiltration and to exclude distant tumor spread [14]. A borderline resectable tumor is defined by distortion, narrowing or occlusion of the superior mesenteric vein (SMV)/hepatic portal vein (HPV), but with the technical possibility of reconstruction with or without using an interpositional graft. Semi-circumferential abutment of <180° of the superior mesenteric artery (SMA), and solid tumor contact with the hepatic artery without extension to the celiac axis (CA) is considered borderline resectable. Locally advanced pancreatic cancer is defined as >180° circumferential abutment/encasement of the SMA, CA, aorta or inferior vena cava, as well as any involvement of the SMV/HPV without the possibility of vascular reconstruction.

Centralization

In 1995, Bramhall et al. showed that the resection rate of 13,560 patients with pancreatic cancer treated in District General Hospitals of the West Midlands in the UK was only 2.6% (353 resections), whilst the 30-day mortality was 27.6% (40/145) even for the most recent 10-year period [15]. In contrast, a study of 1026 resections from 21 units (33 surgeons) from the UK showed a mortality rate of only 6% (58 deaths) and was shown to be significantly related to caseload [16]. This led to the UK becoming the first country to introduce centralized pancreatic cancer surgery based on a population catchment area of at least 2 million [17]. In the USA, Birkmeyer et al. showed that adjusted mortality rates for pancreatic resections were 16.3% at very low-volume compared to 3.8% at very

high-volume hospitals [18]. A study using the USA National Cancer Data Base of 7086 patients undergoing pancreatoduodenectomies for pancreatic cancer from 1998 to 2012 found a 30-day mortality of 2.0% in high-volume hospitals (≥16 resections per year) compared to 6.3% in low-volume hospitals (≤3.3 resections per year), with longer median survival times of 20.3 versus 15.7 months, respectively [19].

Minimally invasive approaches

There is increasing use of minimally invasive pancreatic surgery, in particular minimally invasive left resection, although the evidence for efficacy and safety is relatively weak. A meta-analysis of laparoscopic left pancreatectomy including 29 observational studies with more than 3000 patients showed significantly reduced intraoperative blood loss, less time to first oral intake, and shorter length of hospital stay compared to open distal pancreatectomy [20]. A Cochrane review comparing open and laparoscopic distal pancreatectomy for pancreatic cancer also identified the lack of randomized trial results, especially with regard to oncological outcomes [21]. Current results from the DIPLOMA trial, a pan-European propensity score matched study including 1212 patients who underwent laparoscopic or robot-assisted or open distal pancreatectomy for pancreatic cancer, found significantly reduced blood loss and hospital stay, but also reduced R0 resection rates and lymph node retrieval—emphasizing the need for randomized clinical trials [22]. Laparoscopic partial pancreatoduodenectomy is much more challenging than laparoscopic left pancreatectomy. A recent meta-analysis including 19 comparative cohort studies and two original registry studies with a total of >20,000 patients found that mortality rates were comparable between minimally invasive and open partial pancreato-duodenectomy surgery and identified a publication bias for the outcome postoperative pancreatic fistula [23]. Sharpe et al. showed that higher hospital volume (e.g., ≥10 laparoscopic partial pancreatoduodenectomies per year) was associated with a significantly lower 30-day mortality [24]. The multicenter randomized controlled LEOPARD-2 trial from the Amsterdam group reported an increased procedure-related mortality after laparoscopic compared to open pancreatoduodenectomy [25]. This difference might be partially related to limited experience, low volume, and a considerable learning curve in minimally invasive procedures. In contrast to laparoscopic surgery, robot-assisted approaches allow three-dimensional visualization and increased range of motion, which are likely beneficial characteristics for the performance of pancreatoduodenectomies including extended approaches with vascular resections. However, existing evidence for robot-assisted pancreatoduodenectomy is solely based on non-randomized studies so far. Robot assistance allows careful parenchyma-sparing resection of benign cystic lesions, which should also be investigated in future trials.

Prevention and management of postoperative complications

While mortality rates after pancreatic surgery for pancreatic cancer have decreased considerably over time [26], morbidity remains as high as approximately 50% [27]. Most complications can be managed by an interdisciplinary approach including interventional radiology, endoscopy, and intensive care medicine [8]. Modern radiological treatment strategies such as CT-guided percutaneous drainage, endovascular stenting, or coil embolization have helped to avoid reoperations including completion pancreatectomy for severe postoperative pancreatic fistula or post-pancreatectomy hemorrhage [28]. There may be other innovative approaches to prevent postoperative complications. Hackert et al. have shown that preoperative injection of botulinum toxin into the sphincter of Oddi may prevent clinically relevant postoperative pancreatic fistula after left pancreatectomy and is now the subject of a randomized trial [29].

The routine use of prophylactic abdominal drains may not be straightforward. In a study of 137 patients in the USA, patients without an abdominal drain had a higher incidence of intra-abdominal abscess within the first 30 postoperative days (25%) compared to those with a drain (10%), as well as a higher incidence of gastroparesis, intra-abdominal fluid collection, severe diarrhea, need for a postoperative percutaneous drain, and prolonged length of stay compared to those with a routine drain [30]. Following an increase in 90-day mortality from 3% to 12%, respectively, the Data Safety Monitoring Board stopped the trial early [30]. The PANDRA randomized controlled trial of 395 patients (202 with drain, 193 without drain) undergoing pancreatic head resection with pancreatojejunal anastomosis found that re-intervention rates were not inferior in the no-drain group as well as a comparable overall surgical morbidity (41.8%) and in-hospital mortality (3.0%) in the two groups, although clinically relevant pancreatic fistula (11.9% versus 5.7%) and fistula-associated complications (26.4% versus 13.0%) were significantly greater in the drain group [31]. In a population-based cohort study of 6730 patients using the American College of Surgeons National Surgical Quality Improvement Program, 3375 (50%) were classified as high risk for developing a postoperative pancreatic fistula and 3355 (50%) were low risk [32]. Drain placement in 3093 (92%) patients in the high-risk group was associated with a higher rate of postoperative pancreatic fistula (26%) than in those without a drain (16%), clinically relevant postoperative pancreatic fistula (20% versus 12% respectively), and longer hospital stay (9 versus 7 days respectively), but decreased serious morbidity (29% versus 35%

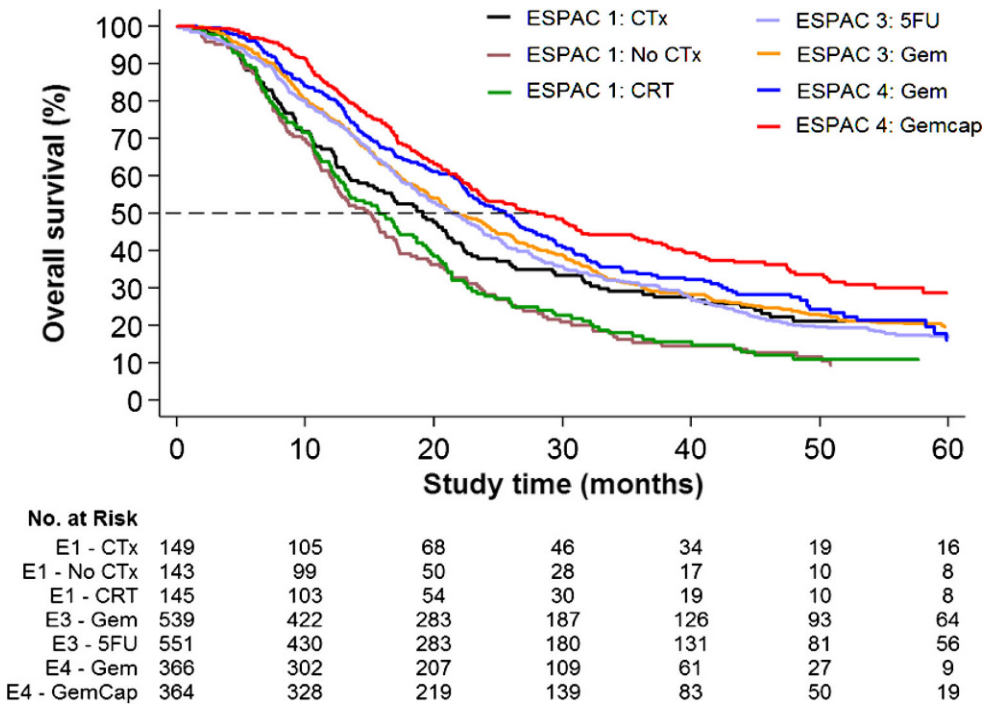

Fig. 2 Summary Kaplan–Meier survival curves for patients randomized in the European Study Group for Pancreatic Cancer phase III Trials ESPAC-1, ESPAC-3 and ESPAC-4. *CTx* Chemotherapy, *CRT* Chemoradiotherapy, *Gem* Gemcitabine, *5FU* 5-fluorouracil, *GemCap* Gemcitabine/capecitabine

respectively). The same was observed in low-risk patients [32].

Evidence-based pancreatic surgery

A recent systematic review on the quantity and quality of clinical trials in pancreatic surgery showed a particular lack of evidence from randomized controlled trials for pancreatic resections, except partial pancreatoduodenectomies, although the number has increased continuously from a mean of 2.8 during 1984 to 1996, to 13.1 per year since 2008 [4]. The quality of randomized trials has also improved significantly, with the only exception of blinding, which is exceptionally difficult and, with regard to the surgical team, often impossible in surgical trials. Exceptionally high-quality randomized controlled trials in pancreatic surgery have been conducted by the Study Center of the German Surgical Society such as the multicenter, randomized controlled DISPACT trial comparing stapler and scalpel resection during distal pancreatectomy in patients with any pancreatic tumor of the pancreatic body/tail [33]. The randomization of pancreatic cancer patients is in some regards delicate, which explains that for certain cancer-specific procedures, such as the extent of lymphadenectomy or vascular resections, the available evidence is primarily based on retrospective series.

Evolution in oncological management

Adjuvant chemotherapy

Until the 1990s there was no standard of adjuvant therapy for resectable pancreatic cancer. During the past 20 years, however, enormous progress has been made in the conduct of high-quality, multicenter randomized controlled trials resulting in a radical change in treatment guidelines [34]. The European Study Group of Pancreatic Cancer (ESPAC) developed the first major trial involving 541 randomized patients to assess the role of adjuvant chemotherapy or chemoradiotherapy in resected pancreatic cancer [35]. Following pancreatic resection, each patient was randomized to either chemotherapy (5-fluorouracil/folinic acid) or no chemotherapy, and chemoradiotherapy (20-Gy dose to the tumor given in 10 daily fractions plus 5-fluorouracil) or no chemoradiotherapy. Between 1994 and 2000, 289 patients were randomized into a 2×2 factorial design, where each patient was randomized twice to the two treatment options and the other 261 patients were randomized to either chemotherapy or no chemotherapy or to chemoradiotherapy or no chemoradiotherapy [36]. The results of the ESPAC-1 trial showed that adjuvant chemotherapy significantly increased survival compared to no chemotherapy, whereas survival was worse with chemoradiotherapy than with no chemoradiotherapy. Since then, adjuvant chemotherapy has become the standard of care in Europe and has been further investigated in succeeding trials, while chemoradiotherapy was no longer preferred.

The results of the ESPAC-3 trial showed that adjuvant gemcitabine monotherapy was not superior to 5-fluorouracil/folinic acid chemotherapy in terms of survival, but it was less toxic [37]. The ESPAC-4 trial then compared adjuvant gemcitabine monotherapy with gemcitabine plus capecitabine, demonstrating significantly longer median overall survival time in the gemcitabine plus capecitabine arm (28.0 versus 25.5 months respectively) and 5-year survival (28.8% versus 16.3% respectively; Fig. 2; [5]).

The most recent multicenter, randomized controlled PRODIGE24/CCTGPA.6 French Canadian trial showed even longer survival times in selected patients treated with adjuvant modified folinic acid, fluorouracil, irinotecan, and oxaliplatin (mFOLFIRINOX) compared to gemcitabine [6]. At a median follow-up of 33.6 months, the median overall survival was 54.4 months in the mFOLFIRINOX group compared to 35.0 months in the gemcitabine monotherapy group, with 3-year overall survival rates of 63.4% versus 48.6%. This survival benefit was, however, at the expense of a higher incidence of adverse events of grade 3/4 in the mFOLFIRINOX arm, illustrating that such aggressive treatment is only suitable for patients in an extremely good condition after pancreas resection. Despite improvements in the effectiveness of adjuvant chemotherapy protocols, however, recurrence occurs still in more than 75% of patients within the first 2 years after resection [38]. Consequently, accurate follow-up is mandatory even after "curative" resection and best management of recurrent disease needs to be defined in future studies.

A press release by Celgene on 12 March 2019 reported on the Celgene-sponsored, pivotal, randomized controlled phase 3 APACT® trial (NCT01964430) evaluating the investigational use of nab-paclitaxel in combination with gemcitabine as adjuvant treatment following surgical resection in patients with pancreatic cancer [39]. Compared to patients randomized to gemcitabine monotherapy, the patients randomized to gemcitabine-nab-paclitaxel did not achieve the primary endpoint of significant improvement in disease-free survival, as evaluated by independent radiological review. Celgene reported that overall survival, a secondary endpoint of the study, was improved, reaching "nominal statistical significance," with nab-paclitaxel in combination with gemcitabine compared to gemcitabine alone, but no further details were provided [39]. The USA Federal Drugs Administration does not approve nab-paclitaxel for the adjuvant treatment of pancreatic cancer.

Neoadjuvant chemotherapy in borderline resectable and locally advanced tumors

An emerging concept for borderline resectable and locally advanced pancreatic cancer is neoadjuvant chemotherapy with or without chemoradiotherapy [34]. There is considerable interest in this approach given remarkable findings in large, retrospective single-center series showing resection rates after neoadjuvant therapy of 47–61% in this group of patients. The median overall and 3-year survival rates in 292 patients with locally advanced pancreatic cancer who had neoadjuvant therapy and resection were 15.3 months and 23.0% compared to 8.5 months and 2.4% after exploration alone [40]. Fig. 3 illustrates successful resection of borderline resectable/locally advanced pancreatic cancer following neoadjuvant treatment.

A phase II clinical trial of 48 patients with borderline resectable/locally advanced pancreatic cancer undergoing neoadjuvant FOLFIRINOX followed by short- or long-course chemoradiotherapy depending on restaging resulted in resection in 67% of patients and a 2-year overall survival rate of 72% [41].

Neoadjuvant approaches are also increasingly used for resectable pancreatic cancer. Due to poor accrual, however, earlier randomized trials comparing neoadjuvant therapy with upfront resection failed to reach an appropriate sample size, illustrating the difficulties in patient recruitment in this setting [42, 43]. The Dutch PREOPANC-1 trial included patients with resectable and borderline resectable tumors randomized to either upfront resection with adjuvant chemotherapy (69 resectable tumors, 58 borderline resectable tumors) or to neoadjuvant chemoradiotherapy and gemcitabine chemotherapy followed by surgery and further adjuvant gemcitabine chemotherapy (56 resectable tumors, 63 borderline resectable tumors) [44]. The overall median survival was 17.1 versus 13.5 months, respectively, but was not statistically significant. This is a very poor survival outcome in the patients with upfront resection with a high rate of metastases at the time of surgical exploration and a median survival rate of only 16.8 months in those resected indicating poor trial design and inferior quality of surgery [44]. The randomized phase II/III Prep-02/JSAP-05 trial from Japan included 364 patients with resectable pancreatic cancer, randomized to neoadjuvant chemotherapy using gemcitabine and S-1, or to upfront surgery for patients with resectable pancreatic cancer with both arms also given adjuvant S-1 [45]. The median overall survival was 36.7 months in the neoadjuvant treatment arm, and 26.6 months in patients undergoing upfront resection with S-1 adjuvant therapy [45]. Although referred to as a trial in patients with resectable pancreatic cancer, resection was only achieved in 140 (81.4%) of 172 in the neoadjuvant arm and in 129 (72.5%) of 178 patients in the adjuvant arm. Moreover, the authors do not explain why the median overall survival in the adjuvant S-1 arm was only 26.6 months, yet in the JASPAC-01 adjuvant trial, the median survival in the S-1 adjuvant group was 46.5 months [46].

Alternatives to FOLFIRINOX neoadjuvant therapy are gemcitabine-based combination chemotherapies including gemcitabine with capecitabine and gemcitabine with nab-paclitaxel, but head-to-head com-

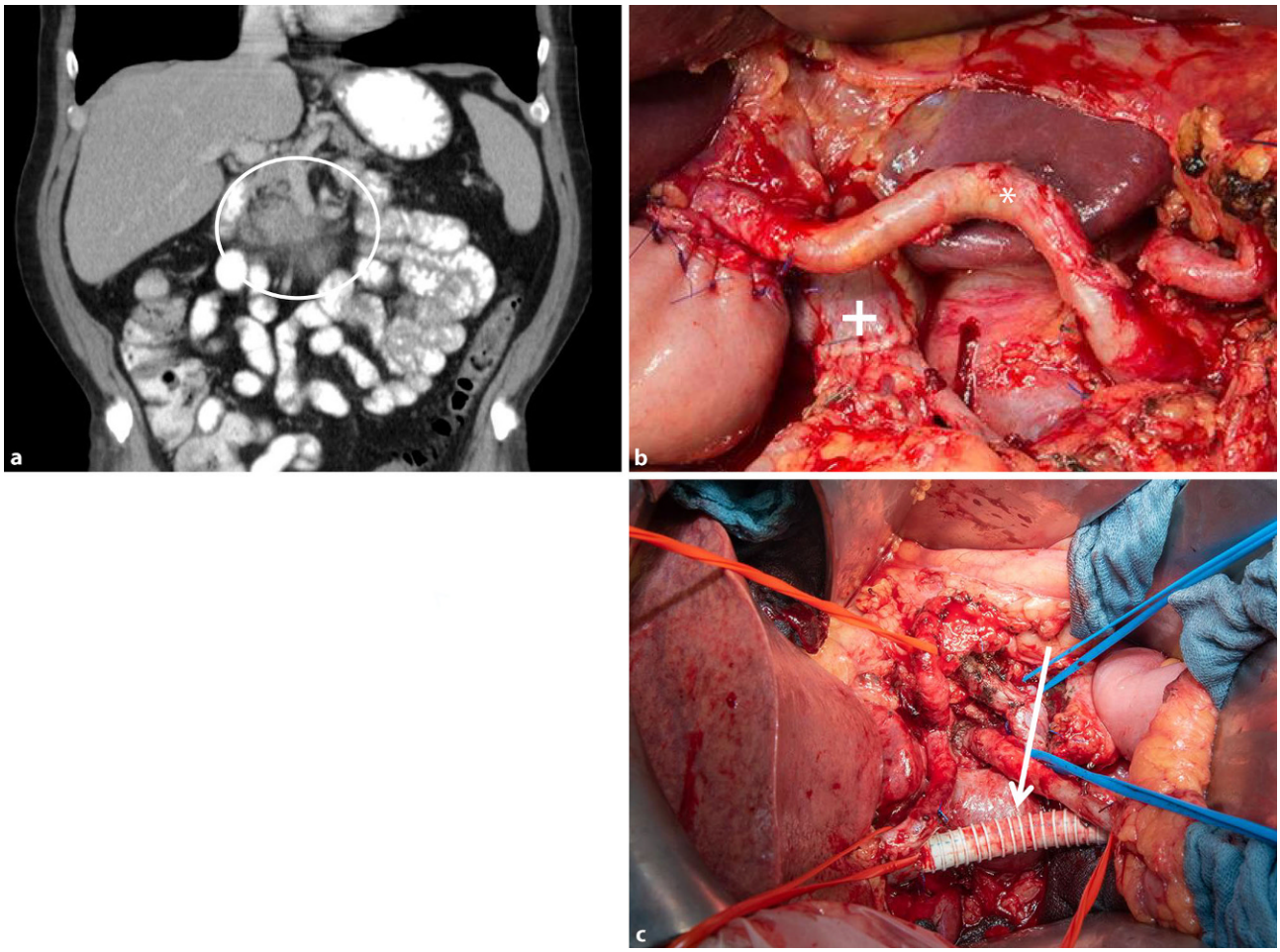

Fig. 3 Resection of borderline resectable/locally advanced pancreatic cancer after neoadjuvant therapy. **a** Borderline resectable pancreatic cancer with infiltration of the portal vein. **b** Total pancreatectomy with replacement of common hepatic artery by splenic artery transposition (*asterisk*), portal vein resection with end-to-end anastomosis (*plus sign*). Triangle procedure. **c** Spleen-preserving total pancreatectomy with replacement of the portal vein by prosthesis (*arrow*), venous splenorenal bypass, triangle procedure

parisons are lacking [47–49]. The ESPAC-5F study (ISRCTN89500674) is currently comparing upfront surgery, neoadjuvant chemotherapy with FOLFIRINOX or gemcitabine with capecitabine, or chemoradiation in borderline resectable patients and is awaiting analysis following event acquisition after closure of 91 patients from the target accrual of 100 randomized patients [50].

Personalized therapies

Selecting the best therapy in an individual tumor-specific fashion will offer the opportunity of better treatment responses and thereby prolonged survival times and reduced unnecessary side effects of cytotoxic regimens, but this remains a significant challenge [51]. In a USA study of 31 drugs with 38 FDA-approved indications, the estimated number of patients eligible for genome-targeted therapy in 2006 was only 28,729 (5.09%) of 564,830 patients with metastatic cancer, and 50,811 (8.33%) of 609,640 patients by 2018. For genome-informed therapy, the numbers were 59,301 (10.50%) patients in 2006, and 94,157 (15.44%) patients in 2018. The percentage of patients with benefit from genome-targeted therapy in 2006 was 0.70% and 4.90% in 2018, and for genome-informed treatment this was 1.31% and 6.62%, respectively. The median overall response rate for all genome-informed drugs was 54%, with a median duration of response of 29.5 months [51]. For pancreatic cancer, various transcriptional pancreatic cancer subtypes have also been described, which have potential clinical impact. There are two major subtypes that are now largely accepted as dominant: a classical subtype that is more responsive to chemotherapy and a very aggressive poorly differentiated squamous/basal-like subtype [52–56]. Up to 10% of patients will have tumors with actionable pancreatic cancer-driver mutations and a further 10–15% may also have sensitivity to licensed targeted agents [57–62]. A major improvement in survival might also be achievable by selecting patients especially sensitive to current chemotherapy regimens

based on treatment specific signatures [63]. Since intratumoral heterogeneity and the complex tumor microenvironment might hamper biomarker-guided strategies for therapy selection, direct functional response testings of personalized models of human pancreatic cancer might be an alternative approach to predict individual treatment responses. Several functional assays have been developed, such as stable tumor cell lines, 3 D organoids, or xenograft models from individual patients [64]. Those live tumor tissue models should recapitulate the complexity and genetic heterogeneity of the disease and enable therapy response prediction within a clinically relevant time frame. To bring such advances into clinical routine, prospective clinical trials are needed to investigate the potential oncological benefit of such personalized approaches compared to the standard therapies.

Summary

The management of pancreatic cancer surgery has changed substantially during the past 20 years. While open surgery has never been performed as safely and professionally as today, minimally-invasive procedures—especially robot-assisted pancreatic resections—need to be further investigated and developed, providing further refinements in the surgical treatment of pancreatic cancer. Even though the prognosis of pancreatic cancer patients is still poor, the past few years have seen considerable improvements in the available chemotherapy regimens with associated increased survival times, notably in the adjuvant setting. Neoadjuvant treatment concepts offer the prospect of further improvements and with the development of personalized approaches cure of pancreatic cancer patients might be achieved in the near future.

Conflict of interest U. Klaiber, S. Roth, T. Hackert, and J.P. Neoptolemos declare that they have no competing interests.

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