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Review article

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Preoperative chemotherapy, radiotherapy and surgical decision-making in patients with borderline resectable and locally advanced pancreatic cancer

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Abstract

Surgical resection combined with systemic chemotherapy is the cornerstone of treatment for patients with localized pancreatic cancer. Upfront surgery is considered suboptimal in cases with extensive vascular involvement, which can be classified as either borderline resectable pancreatic cancer or locally advanced pancreatic cancer. In these patients, FOLFIRINOX or gemcitabine plus nab-paclitaxel chemotherapy is currently used as preoperative chemotherapy and is eventually combined with radiotherapy. Thus, more patients might reach 5-year overall survival. Patient selection for chemotherapy, radiotherapy and subsequent surgery is based on anatomical, biological and conditional parameters. Current guidelines and clinical practices vary considerably regarding preoperative chemotherapy and radiotherapy, response evaluation, and indications for surgery. In this Review, we provide an overview of the clinical evidence regarding disease staging, preoperative therapy, response evaluation and surgery in patients with borderline resectable pancreatic cancer or locally advanced pancreatic cancer. In addition, a clinical work-up is proposed based on the available evidence and guidelines. We identify knowledge gaps and outline a proposed research agenda.

Sections

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Key points

- Preoperative multi-agent chemotherapy (for example, FOLFIRINOX or gemcitabine plus nab-paclitaxel) is now routinely used in patients with borderline resectable pancreatic cancer (BRPC) or locally advanced pancreatic cancer (LAPC), both to obtain local and systemic control and to select suitable candidates for surgery.
- Considerable variation exists among national and international guidelines and clinical practices regarding preoperative therapy in patients with BRPC or LAPC, including the type and duration of chemotherapy and the role, type, and timing of radiotherapy; a uniform, evidence-based international guideline with support from all relevant societies is needed.
- Three randomized controlled trials reported improved outcomes with neoadjuvant chemotherapy or chemoradiotherapy compared with upfront surgery in patients with BRPC; more randomized trials assessing the effect of modern multi-agent chemotherapy and radiotherapy are needed and several are ongoing.
- Response evaluation after preoperative chemotherapy and chemoradiotherapy is a major challenge as conventional cross-sectional imaging mostly underestimates the tumour response. Biological response evaluation is therefore advised (particularly a relative decrease of serum CA19-9). However, there is an urgent need for more accurate tumour markers.
- Surgery after preoperative therapy in patients with BRPC and LAPC requires high-volume expertise for patient selection, intraoperative decision-making, extended resections and postoperative care; preoperative counselling and shared decision-making are crucial.

Introduction

The global incidence of pancreatic ductal adenocarcinoma (hereafter referred to as pancreatic cancer) is increasing[1]. There has been limited improvement in survival during the past few decades and, as a result, pancreatic cancer will become the second-leading cause of cancer-related deaths within 10 years[2]. At the time of diagnosis, half of patients with pancreatic cancer have metastases and half have localized disease[3]. Localized pancreatic cancer can be divided into primary resectable pancreatic cancer (PRPC), borderline resectable pancreatic cancer (BRPC) and locally advanced pancreatic cancer (LAPC), mainly according to the presence and extent of tumour involvement with major visceral vasculature (that is, superior mesenteric artery, coeliac axis, hepatic artery and portomesenteric venous axis)[4].

Surgery combined with systemic chemotherapy is the cornerstone of treatment of localized pancreatic cancer, providing the best chance for 5-year overall survival[5]. In patients with BRPC or LAPC, an upfront surgical resection is considered suboptimal and is associated with poor survival[6–8], even in patients receiving adjuvant chemotherapy[9,10].

In the past decade, survival in patients with BRPC or LAPC has improved with the use of preoperative multi-agent chemotherapeutic regimens (that is, FOLFIRINOX and gemcitabine plus nab-paclitaxel)[11,12]. Use of these regimens is termed neoadjuvant therapy in patients with BRPC and induction therapy in patients with LAPC[13,14]. These preoperative regimens can both achieve local and systemic control and aid in selecting patients with more favourable tumour biology for surgery[15,16]. After all, patients with assumed localized pancreatic cancer often have occult micrometastases, which are not visible on conventional cross-sectional imaging[17], which underlines the importance of preoperative systemic treatment.

However, guidelines and international practices vary regarding the indications for and type and duration of preoperative chemotherapy and radiotherapy, subsequent response evaluation, and indications for surgery[18–21]. This Review provides an evidence-based overview of preoperative chemotherapy and radiotherapy in patients with BRPC or LAPC, divided into sections on disease staging, preoperative therapy, response evaluation, surgery and potential future research directions.

Disease staging

Disease staging is based on the presence and extent of apparent tumour contact with the portomesenteric venous axis (including the portal vein, confluence and superior mesenteric vein), superior mesenteric artery, coeliac axis and hepatic artery[20] (Fig. 1). Various anatomical staging systems exist, which differ particularly regarding portomesenteric venous and coeliac axis involvement[22–26] (Supplementary Table 2). However, the 2017 European Organisation for Research and Treatment of Cancer (EORTC) expert panel stated that resectability criteria should not solely be based on vascular involvement because there might be discrepancy between surgical–technical and oncological reasoning[27]. This statement is in line with the trend seen over the past decade, whereby biological and conditional parameters are incorporated into the resectability assessment[28–30]. Consequently, some classifications also focus on surgical risks and perceived survival benefits. This paradigm shift is illustrated by an alteration of terminology in the 2022 National Comprehensive Cancer Network (NCCN) guideline, which changed the term 'non-resectable' to 'locally advanced', with a prominent role for serum carbohydrate antigen 19-9 (CA19-9) in response evaluation[22]. In addition, the 2016 and 2019 American Society of Clinical Oncology (ASCO) guidelines emphasized that anatomical staging should not be the leading criteria in decision-making as biological and conditional factors are increasingly acknowledged to be primary parameters for patient selection. Nevertheless, these guidelines stated that tumour involvement of surrounding major vasculature remains an important means of estimating the probability of achieving a radical (R0) resection[31,32]. Whereas the ASCO guidelines used biological and conditional parameters in the staging of BRPC and LAPC[31–33], the 2015 and 2019 European Society for Medical Oncology guidelines focused on the anatomical NCCN classification[34,35]. However, the 2018 French intergroup guideline mentioned that CA19-9 might help to determine resectability (that is, <200 U/ml) versus non-resectability and/or metastatic disease (that is, >1,000 U/ml)[36]. The implementation of such more-nuanced definitions of BRPC and LAPC might improve clinical decision-making and help strive for a more personalized treatment.

Borderline resectable pancreatic cancer

In 2008, Katz et al.[37] proposed a multi-domain classification for BRPC by defining three categories: borderline resectability by vascular involvement (MD Anderson type A), by suspected extrapancreatic disease (MD Anderson type B), and by marginal performance status or severe comorbidities requiring additional evaluation (MD Anderson type C). In 2021, the MD Anderson categories have been changed into PRPC or

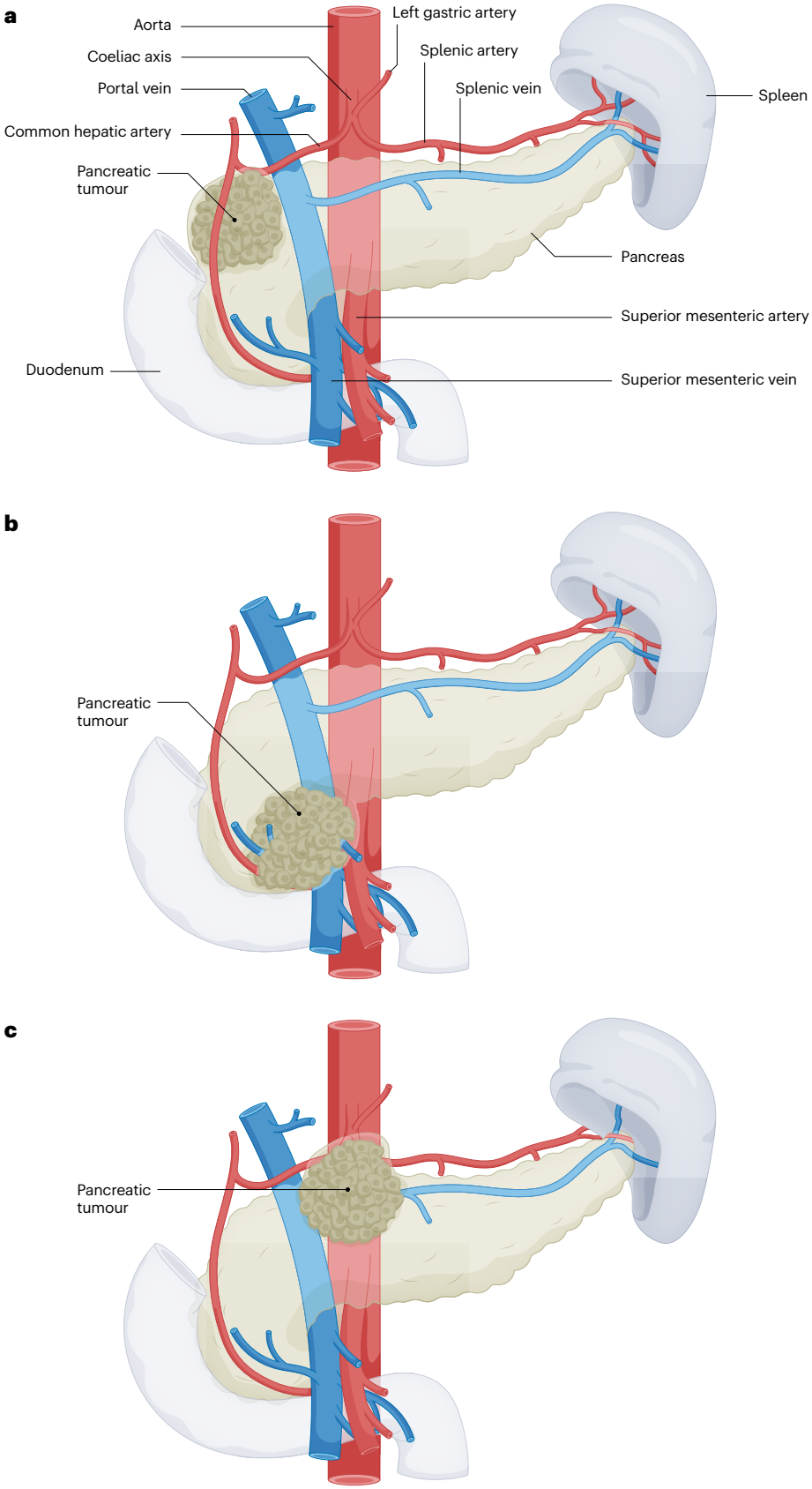


Fig. 1 | Borderline resectable and locally advanced pancreatic tumours. a, Borderline resectable pancreatic head tumour based on involvement with the common hepatic artery, which is reconstructable. **b**, Locally advanced pancreatic tumour located in the uncinate process, based on >180° involvement with the superior mesenteric artery and encasement of the superior mesenteric vein, including jejunal branches. **c**, Locally advanced pancreatic tumour located in the pancreatic neck and body, based on encasement of the coeliac axis with concomitant <180° involvement with the portal vein. Adapted with permission from S. van der Zon.

BRPC with or without high-risk features (that is, suspicion of metastatic disease, CA19-9 >500 U/ml and/or reversible and optimizable comorbidities)[24].

In 2018, an international expert group further developed the BRPC-ABC nomenclature[38]. Patients were defined as having BPRC either by anatomical (A), biological (B) or conditional (C) criteria (ABC). In addition to the anatomical criteria as stated by the Japan Pancreas Society (that is, BRPC-PV and BRPC-A)[26], this international expert group[38] considered a tumour to be biologically borderline resectable in the presence of preoperative CA19-9 of >500 U/ml and/or regional lymph node metastasis. Conditional borderline resectability was defined as an Eastern Cooperative Oncology Group (ECOG) performance status of ≥2. Tumours could be classified as BRPC based on the presence of at least one of these parameters.

The value of this approach was illustrated by a study conducted in 2021 comprising 345 patients who underwent resection, which demonstrated worse overall survival in patients with BRPC solely based on biological criteria as compared to resectable tumours[39]. The relevance of BRPC type C was illustrated by a retrospective multicentre study using the American College of Surgeons National Surgical Quality Improvement Program database. This study, including 8,266 patients who underwent a pancreatoduodenectomy, demonstrated that BRPC type C was associated with major morbidity and failure to rescue[40].

Locally advanced pancreatic cancer

LAPC involves a broad spectrum of type and degree of vascular involvement, covering a wide range of different opportunities for surgical or other local interventions. Therefore, anatomical subclassifications might be useful in addition to the ABC approach. Anatomical subclassifications could support patient counselling and shared decision-making, choosing the type of induction therapy, subsequently estimating the feasibility of obtaining a resection and its technical challenges and risks, and supporting referral of patients to expert centres. Various LAPC classifications have been proposed, mainly based on the probability to undergo (R0) resection.

In 2018, Isaji et al. incorporated the biological and conditional parameters into the LAPC definition[38]. Tsai et al. presented a two-tier system based on the extent of arterial involvement (that is, LAPC-A and LAPC-B)[41]. The likelihood to undergo a resection was 62% versus 24% for LAPC-A and LAPC-B, respectively[42]. In 2021, Fromer et al. published a seven-tier classification, based on literature and their clinical experience, using different patterns of vascular involvement[43]. However, this classification is mainly applicable to patients who require a vascular resection, while portomesenteric venous or arterial resection in patients with LAPC is not always needed[44]. The 2021 Johns Hopkins LAPC 1-2-3 Score seems to be a more clinically applicable tool; it is an anatomy-based stratification algorithm for LAPC based on imaging before induction therapy[45]. This score is based on the likelihood to undergo surgical resection: LAPC-1 (likely, 63%), LAPC-2 (unlikely, 40%) and LAPC-3 (highly unlikely, 17%). Naturally, the likelihood for a resection depends on local expertise and the surgical-oncological strategy but, nevertheless, this score might be useful to counsel patients in pancreatic surgery expert centres.

In addition to these anatomical subclassifications, the incorporation of biological and conditional parameters is crucial in patient selection to strive for more personalized medicine. Various nomograms for localized pancreatic cancer that could support the incorporation of such parameters into decision-making for preoperative therapy (and subsequent surgery) have been published in the past decade[46–58].

Preoperative therapy

Guidelines

Substantial variety exists among national and international guidelines for patients with BRPC and LAPC regarding neoadjuvant or induction therapy. For patients with BRPC, multi-agent chemotherapies are predominantly advised but the recommendations differ regarding the value of additional radiotherapy. See Supplementary Table 3 for an overview of recommendations by several national and international guidelines for neoadjuvant therapy in patients with BPRC.

For patients with LAPC, even more differences between guidelines for induction therapy are seen, particularly around the type and duration of chemotherapy as well as the possibility to switch to another regimen in case of insufficient disease response. In fact, the possibility to switch to another regimen is not always mentioned. Furthermore, the value of radiotherapy as part of induction therapy is unclear but seems to be of value for at least local disease control. See Supplementary Table 4 for an overview of recommendations for induction therapy in patients with LAPC from several national and international guidelines. Heterogeneity across guidelines is the consequence of limited level 1 evidence, although the evidence has expanded over the past 10–15 years.

Evidence from randomized trials and observational studies

Borderline resectable pancreatic cancer. A patient-level meta-analysis that included 283 patients with BRPC (from 20 studies) treated with neoadjuvant FOLFIRINOX (with or without radiotherapy) and eventually followed by a resection showed a median overall survival of 22 months (95% CI 19–26) in all patients combined (including those without resection)[59]. The intention-to-treat resection rate was 68% (95% CI 60–75%; R0 84%, 95% CI 77–89%)[59]. In intention-to-treat analyses identified by a systematic review, the median overall survival in patients with BRPC after neoadjuvant gemcitabine plus nab-paclitaxel (with or without radiotherapy) appeared to be similar, ranging from 15 to 28 months with a resection rate of 49% (95% CI 30–68%; R0 36%, 95% CI 17–58%)[60].

Improved outcomes with neoadjuvant therapy compared with upfront surgery in patients with BRPC has been reported by three multicentre randomized controlled trials: the 2018 trial by Jang et al. ($n = 50$)[61], the 2022 PREOPANC trial ($n = 113$)[62,63] and the 2023 ESPAC5 trial ($n = 86$)[64] (Table 1). Notably, the resection rates were (non-significantly) lower in the neoadjuvant arms in all three trials, but the intention-to-treat overall survival was nevertheless clearly improved in the neoadjuvant group[61–64]. The trial by Jang et al. and the PREOPANC trial combined gemcitabine monotherapy with external beam radiotherapy (EBRT)[61–63]. Both trial protocols were designed and began before the era of modern multi-agent chemotherapeutic regimens. The four-arm ESPAC5 trial compared upfront surgery followed by adjuvant chemotherapy versus neoadjuvant gemcitabine-capecitabine (two courses) versus neoadjuvant FOLFIRINOX (four courses) versus neoadjuvant capecitabine with EBRT[64]. In the neoadjuvant therapy arms, surgery followed by adjuvant chemotherapy was considered. Although 1-year overall survival was higher in the combined neoadjuvant groups compared with upfront surgery (HR 0.29, 95% CI 0.14–0.60), the trial was not powered to compare overall survival between the different neoadjuvant therapy arms[64]. By contrast, the single-centre NUPAT-01 phase II trial randomized 51 patients with BRPC to either FOLFIRINOX (two courses) or gemcitabine plus nab-paclitaxel (two courses), eventually followed by resection with S1 (that is, oral single-agent chemotherapy) adjuvant therapy for 6 months (both arms).

Table 1 | Published randomized controlled trials[a] on preoperative therapy in patients with BRPC and LAPC

Study	Population	Comparison	Resection rate	Survival
BRPC				
Jang et al. (2018)[61]	Republic of Korea; BRPC[b,c]	Neoadjuvant GEM (6 weeks)+EBRT (45 Gy in 25 fractions or 9 Gy in 5 fractions) followed by surgery and adjuvant GEM (4c)+EBRT (arm A) vs upfront surgery followed by adjuvant GEM (4c)+EBRT (arm B)	Arm A: *n*=17/27 (63%) R0: *n*=14/17 (82%) Arm B: *n*=18/23 (78%) R0: *n*=6/18 (33%) (*P*=0.010)	mOS: Arm A: 21 months Arm B: 12 months 2-year OS: HR 1.97 (95% CI 1.07–3.62)
Versteijne et al. (2020)[62] and Versteijne et al. (2022)[63] (PREOPANC)	The Netherlands; PRPC and BRPC[b,d,e]	Neoadjuvant GEM (3c)+EBRT (36 Gy in 15 fractions) followed by surgery and adjuvant GEM (4c) (arm A) vs upfront surgery followed by adjuvant GEM (6c) (arm B)	Arm A: *n*=28/54 (52%) R0: *n*=22/28 (79%) Arm B: *n*=38/59 (64%) (*P*=0.190) R0: *n*=5/38 (13%) (*P*< 0.001)	mOS: Arm A: 18 months Arm B: 13 months HR 0.67 (95% CI 0.45–0.99) 5-year OS: Arm A: *n*=6/54 (4%) Arm B: *n*=1/59 (2%)
Yamaguchi et al. (2022)[65] (NUPAT-01)	Japan; BRPC[b,c]	Neoadjuvant FFX (4c) (arm A) vs neoadjuvant GEM-NAB-PAC (2c) (arm B); both arms followed by surgery and adjuvant S1 (6 months)	Arm A: *n*=23/26 (88%) R0: *n*=19/26 (73%) Arm B: *n*=20/25 (80%) R0: *n*=14/25 (56%) (*P*=0.202)	3-year OS: Arm A: *n*=7/26 (55%) Arm B: *n*=7/25 (54%) (*P*=0.389) HR 0.946 (95% CI 0.391–2.289)
Katz et al. (2022)[110] (ALLIANCE A021501)	USA; BRPC[e,f]	Neoadjuvant mFFX (7c)+SBRT (6.6 Gy in 5 fractions) or HIGRT (5 Gy in 5 fractions) (arm A) vs mFFX (8c) (arm B); both arms followed by surgery and adjuvant mFFX (4c)	Arm A: *n*=19/55 (35%) R0: *n*=14/19 (74%) Arm B: *n*=32/65 (49%) R0: *n*=28/32 (88%)	mOS: Arm A: 17 months (95% CI 13–24) Arm B: 30 months (95% CI 21–37) 18-month OS: Arm A: 47% (95% CI 36–63) Arm B: 67% (95% CI 56–79)
Ghaneh et al. (2023)[64] (ESPAC5)	UK; BRPC[b,e]	Upfront surgery with adjuvant chemotherapy (arm A) vs neoadjuvant GEM-CAP (2c) (arm B) vs neoadjuvant FFX (4c) (arm C) vs neoadjuvant CAP+EBRT (50.4 Gy in 28 fractions for 5.5 weeks) (arm D); arms B, C and D followed by surgery and adjuvant chemotherapy	Arm A: *n*=21/31 (68%) R0: *n*=3/21 (14%) Arm B: *n*=11/19 (58%) R0: *n*=2/11 (18%) Arm C: *n*=11/20 (55%) R0: *n*=2/11 (18%) Arm D: *n*=8/16 (50%) R0: *n*=3/8 (37%)	1-year OS: Arm A: 39% (95% CI 24–61) Arm B: 78% (95% CI 60–100) Arm C: 84% (95% CI 70–100) Arm D: 60% (95% CI 37–97) (*P*=0.0028)
LAPC				
Loehrer et al. (2011)[309] (ECOG)	USA; LAPC[b,e]	Induction GEM (5c) (arm A) vs induction GEM (5c)+EBRT (50.4 Gy in 28 fractions over 5.5 weeks) (arm B)	Not described, probably no resection performed	mOS: Arm A: 9 months (95% CI 8–11) Arm B: 11 months (95% CI 8–16) (*P*=0.017)
Rich et al. (2012)[310]	USA; LAPC[e]	Induction GEM-PAC (6 weeks)+EBRT (50.4 Gy over 6 weeks) (arm A) vs induction GEM-PAC (6 weeks)+EBRT (50.4 Gy over 6 weeks)+farnesyl transferase inhibitor (arm B)	Not described, probably no resection performed	mOS: Arm A: 12 months (95% CI 8–13) Arm B: 9 months (95% CI 7–10) 2-year OS: Arm A: 11% (95% CI 6–18) Arm B: 4% (95% CI 1–10)
Mukherjee et al. (2013)[311] and Hurt et al. (2017)[312] (SCALOP)	UK; LAPC[b,e]	Induction GEM-CAP (3c) and — when a.o. RECIST non-progression — followed by randomization for GEM-CAP (1c) followed by CAP+EBRT (50.4 Gy over 5.5 weeks) (arm A) vs GEM-CAP (1c) followed by GEM+EBRT (50.4 Gy over 5.5 weeks) (arm B)	Arm A: *n*=2/36 (6%) R0: *n*=2/2 (100%) Arm B: *n*=3/38 (8%) R0: *n*=3/3 (100%)	mOS: Arm A: 18 months (95% CI 15–23) Arm B: 15 months (95% CI 11–16) HR 0.68 (95% CI 0.38–1.21)
Khan et al. (2016)[313] (PERU)	UK; LAPC[b,e]	Induction GEM-CAP (4 weeks) and when disease control followed by randomization for UFT/LV or CAP+RT (5 weeks) (arm A) vs UFT/LV or CAP+RT with cetuximab (5 weeks) (arm B)	Not described, probably no resection performed	mOS: Arm A: 16 months (95% CI 15–18) Arm B: 22 months (95% CI 0–50) (*P*> 0.05) 1-year OS: Arm A: 100% Arm B: 67% (*P*=0.801)

Table 1 (continued) | Published randomized controlled trials[a] on preoperative therapy in patients with BRPC and LAPC

Study	Population	Comparison	Resection rate	Survival
LAPC (continued)				
Evans et al. (2017)[314]	Europe, North America and Australia; LAPC[b,e]	Induction GEM+dasatinib (arm A) vs induction GEM (arm B) until disease progression; in both arms, optional EBRT±5-FU/CAP when no metastases after the first 6c GEM	Not described, probably no resection performed	mOS: Arm A: 375 days Arm B: 393 days HR 1.16 (95% CI 0.81–1.65)
Picozzi et al. (2020)[315]	USA; LAPC[b,c]	Induction GEM-NAB-PAC (6c)+pamrevlumab (arm A) vs induction GEM-NAB-PAC (6c) (arm B)	Arm A: *n*=8/24 (38%) R0: *n*=4/8 (50%) Arm B: *n*=1/13 (8%) (*P*=0.119) R0: *n*=1/1 (100%)	mOS: Arm A: 19 months (95% CI 13–28) Arm B: 19 months (95% CI 13–NR) 1-year OS: Arm A: 75% Arm B: 85%
Kunzmann et al. (2021)[94] (NEOLAP-AIO-PAK-0113)	Germany; LAPC[b,c]	Induction GEM-NAB-PAC (2c) and — when a.o. RECIST non-progression — followed by randomization for GEM-NAB-PAC (2c) (arm A) vs FFX (4c) (arm B); both arms followed by explorative laparotomy with intention for resection when a.o. RECIST non-progressive disease	Conversion rate[g]: Arm A: 36% (95% CI 24–49) R0: *n*=15/23 (65%) Arm B: 44% (95% CI 32–57) R0: *n*=20/29 (69%) (*P*=0.99) OR 0.72 (95% CI 0.35–1.45)	mOS: Arm A: 19 months (95% CI 14–22) Arm B: 21 months (95% CI 14–29) HR 0.86 (95% CI 0.55–1.36)
Cascinu et al. (2021)[76] (GISCAD)	Italy; LAPC[b,c]	Induction GEM (3c) (arm A) vs induction GEM-NAB-PAC (3c) (arm B); both arms followed by surgery[d] and palliative or adjuvant CAP+EBRT (40–44 Gy in 15 fractions)	Arm A: *n*=1/57 (2%) Arm B: *n*=4/63 (6%)	mOS: Arm A: 11 months Arm B: 13 months (*P*=0.075) 3-year OS: Arm A: 0/57 (0%) Arm B: 6/63 (10%)
Ioka et al. (2021)[316] (JCOG1106)	Japan; LAPC[b,e]	Induction S1+EBRT (50.4 Gy in 28 fractions over 5.5 weeks) followed by GEM (arm A) vs induction GEM (3c) followed by S1+EBRT (50.4 Gy in 28 fractions over 5.5 weeks) when a.o. no metastases (arm B); in both arms, subsequent GEM was continued in case of no progression and limited toxicity	Arm A: *n*=2/51 (4%) Arm B: *n*=3/49 (6%)	mOS: Arm A: 19 months (95% CI 15–21) Arm B: 17 months (95% CI 13–20) HR 1.25 (95% CI 0.82–1.93) 2-year OS: Arm A: 37% Arm B: 19%
Liermann et al. (2022)[317] (PARC)	Germany; LAPC[e]	Preoperative GEM-CET+IMRT followed by GEM maintenance (arm A) vs preoperative GEM-CET+IMRT followed by GEM-CET maintenance (arm B)	Arm A: *n*=3/35 (9%) R0: *n*=2/3 (67%) Arm B: *n*=11/33 (33%) R0: *n*=5/11 (45%)	mOS: Arm A: 12 months (95% CI 9–15) Arm B: 14 months (95% CI 10–19) (*P*=0.11) 2-year OS: Arm A: 15% (95% CI 9–15) Arm B: 27% (95% CI 10–19) (*P*=0.11)
Ozaka et al. (2022)[79] (JCOG1407)	Japan; LAPC[b,e]	Preoperative mFFX (arm A) vs preoperative GEM-NAB-PAC (arm B); in both arms, chemotherapy will be administered until disease progression	Arm A: *n*=5/62 (8%) Arm B: *n*=5/63 (8%)	1-year OS Arm A: 77% (95% CI 65–86) Arm B: 83% (95% CI 71–90) HR 1.096 (95% CI 0.726–1.654)
BRPC–LAPC				
Landry et al. (2010)[318]	USA; BRPC–LAPC[b,e]	Preoperative GEM+EBRT (50.4 Gy over 6 weeks) followed by surgery and adjuvant GEM (6c) (arm A) vs preoperative GEM-CIS with 5-FU+EBRT (50.4 Gy over 6 weeks) followed by surgery and adjuvant GEM (4c) (arm B)	Arm A: *n*=3/10 (30%) R0: *n*=1/3 (33%) Arm B: *n*=2/11 (18%) R0: *n*=1/2 (50%)	mOS: Arm A: 19 months Arm B: 13 months
Sahora et al. (2014)[319]	Austria; BRPC–LAPC[b,e]	Preoperative GEM (4c)+short treatment bevacizumab (arm A) vs preoperative GEM (4c)+long-treatment bevacizumab (arm B); both arms followed by surgery[d]	Arm A: *n*=4/11 (36%) Arm B: *n*=7/19 (37%) (*P*=0.97)	mOS: Arms A and B: 13 months (95% CI 12–14)

Table 1 (continued) | Published randomized controlled trials[a] on preoperative therapy in patients with BRPC and LAPC

Study	Population	Comparison	Resection rate	Survival
BRPC–LAPC (continued)				
Hammel et al. (2016)[109] (LAP07)	France, Australia, New Zealand, Belgium and Sweden; BRPC–LAPC[b,e]	Preoperative GEM (4c) (arm A) vs preoperative GEM-ERL (4c) (arm B), followed by second randomization — when a.o. RECIST non-progressive disease — for GEM (6 weeks) (arm A1/B1) vs CAP-EBRT (54 Gy in 30 fractions over 6 weeks) (arm A2/B2)	Overall: *n*=18/442 (4%) R0: *n*=11/18 (61%)[h] After completing the protocol: Arm A1/B1: *n*=8/136 (6%) Arm A2/B2: *n*=4/133 (3%)	mOS: Arm A: 14 months (95% CI 12–15) Arm B: 12 months (95% CI 10–14) HR 1.19 (95% CI 0.97–1.45) Arm A1/B1: 17 months (95% CI 15–19) Arm A2/B2: 15 months (95% CI 14–17) HR 1.03 (95% CI 0.79–1.34)
Su et al. (2022)[77] (TCOG T2212)	Taiwan; BRPC–LAPC[b,e]	Preoperative mFFX (3 months) followed by 5-FU–EBRT (28 fractions, 18–50.4 Gy over 6 weeks) when no metastases (arm A) vs preoperative GOLF (3 months) followed by GEM-EBRT (28 fractions, 18–50.4 Gy over 6 weeks) when no metastases (arm B)	Arm A: *n*=1/27 (4%) R0: *n*=0/1 (0%) Arm B: *n*=5/28 (18%) R0: *n*=3/5 (60%)[i]	mOS: Arm A: 20 months (95% CI 13–23) Arm B: 18 months (95% CI 13–24) (*P*=0.66)
Hewitt et al. (2022)[320]	USA; BRPC–LAPC[b,c]	Preoperative HAPa+FFX (5c)/GEM-NAB-PAC (3c) followed by 5-FU/CAP+EBRT (50.4 Gy in 28 fractions over 5.5 weeks) (arm A1/A2) vs preoperative FFX (5c)/GEM-NAB-PAC (3c) followed by 5-FU/CAP+EBRT (50.4 Gy in 28 fractions over 5.5 weeks) (arm B1/B2); both arms followed by surgery[d] and adjuvant GEM (6c); when no surgery, the initial chemotherapy was continued; chemotherapy switch was performed in case of progression	Arm A: *n*=33/145 (23%) Arm B: *n*=41/158 (26%) (*P*=0.52)	mOS: Arm A: 14 months (95% CI 13–16) Arm B: 15 months (95% CI 12–18) HR 1.02 (95% CI 0.66–1.58)

5-FU, 5-fluorouracil; a.o., among others; BRPC, borderline resectable pancreatic cancer; c, courses of chemotherapy; CAP, capecitabine; CET, cetuximab; CIS, cisplatin; EBRT, external beam radiation therapy, including intensity-modulated radiotherapy; ERL, erlotinib; FFX, 5-FU, leucovorin, irinotecan and oxaliplatin; GEM, gemcitabine; GOLF, GEM, oxaliplatin and 5-FU; HAPa, HyperAcute-Pancreas algenpantucel-L; HIGRT, hypofractionated image-guided radiotherapy; IMRT, intensity-modulated radiotherapy; LAPC, locally advanced pancreatic cancer; LV, leucovorin; mFFX, modified combination of 5-FU, leucovorin, irinotecan and oxaliplatin; mOS, median overall survival; NAB-PAC, nab-paclitaxel; NR, not reached; OS, overall survival; PAC, paclitaxel; PRPC, primary resectable pancreatic cancer; R0, microscopic radical resection; RECIST, Response Evaluation Criteria in Solid Tumors; RT, radiotherapy; SBRT, stereotactic body radiotherapy; UFT, uracil-tegafur. [a]Randomized controlled trials with only preliminary results are presented in Supplementary Table 5. [b]Intention-to-treat analysis. [c]Resectability is defined following the NCCN guideline. [d]Subgroup analysis from patients with BRPC are presented. [e]Other/unspecified criteria. [f]Incomplete intention-to-treat analysis. [g]Conversion rate is defined as a macroscopically radically resected tumour. [h]R status unknown in 5 patients. [i]An additional 4 patients underwent R0/R1 resection after maintenance and/or salvage treatment (that is, 2 patients in each treatment arm).

By intention-to-treat, the primary end point of R0 did not differ significantly (73% versus 56%; $P = 0.202$) and neither did the secondary end point of 3-year overall survival (HR 0.95, 95% CI 0.39–2.29)[65].

More randomized controlled trials are required to determine the efficacy of modern chemotherapeutic regimens and chemotherapy in relation to radiotherapy. Currently, various randomized controlled trials of neoadjuvant therapy for patients with BRPC are ongoing or have recently been completed. Several trials have randomized patients between multi-agent chemotherapy (for example, FOLFIRINOX or gemcitabine plus nab-paclitaxel) with or without radiotherapy (for example, stereotactic body radiotherapy (SBRT) or EBRT)[66–70]. Other trials randomize between type of multi-agent chemotherapy, particularly FOLFIRINOX and gemcitabine plus nab-paclitaxel[71–73]. The multicentre PREOPANC-2 trial, which was completed in 2021, randomized patients between 4 months of total neoadjuvant FOLFIRINOX and perioperative chemoradiotherapy with gemcitabine[74]. The multicentre PACT-21 trial has two randomizations. First, between FOLFIRINOX and gemcitabine plus nab-paclitaxel with capecitabine-cisplatin, and a second randomization performed in case of non-progressive disease after 4 months of chemotherapy, allocating patients to either surgery or 2 more months of chemotherapy followed by surgery[75]. See Supplementary Table 5 for the ongoing or unpublished randomized clinical trials on BRPC.

Locally advanced pancreatic cancer. Since the introduction of multi-agent chemotherapeutic regimens (with and without radiotherapy), survival in patients with LAPC has improved. FOLFIRINOX and gemcitabine plus nab-paclitaxel are predominantly used, along with other multi-agent regimens such as gemcitabine-S1 and gemcitabine-capecitabine (see Supplementary Table 4 for an overview of the guideline recommendations).

The 2021 multicentre GISCAD phase II trial randomized 124 patients with LAPC to receive either induction gemcitabine plus nab-paclitaxel or gemcitabine alone. The rate of disease progression was lower in the group receiving gemcitabine plus nab-paclitaxel (25% versus 46%; $P = 0.01$) but the median overall survival was similar (13 versus 11 months; $P = 0.075$)[76].

Although FOLFIRINOX is widely used as induction therapy, level 1 evidence for FOLFIRINOX compared with gemcitabine plus nab-paclitaxel or other multi-agent chemotherapeutic regimens in LAPC is scarce (see Table 1 for an overview of published randomized controlled trials in patients with LAPC). The 2022 multicentre TCOG T2212 phase II trial randomized 55 patients with BRPC or LAPC to either modified FOLFIRINOX followed by 5-fluorouracil (5-FU) plus EBRT versus gemcitabine-oxaliplatin with 5-FU, leading to a resection rate of 4% versus 18%, respectively, and similar median overall survival

(20 versus 18 months; $P = 0.66$)[77]. The 2022 multicentre JCOG1407 phase II trial randomized 125 patients with BRPC or LAPC (10% BRPC, 90% LAPC) between modified FOLFIRINOX versus gemcitabine plus nab-paclitaxel until disease progression (a 'pick-the-winner' design[78]) but demonstrated no difference in the primary end point of 1-year overall survival (HR 1.10, 95% CI 0.73–1.65) and similar resection rates (8% versus 8%)[79]. Currently, most evidence involving modern multi-agent induction chemotherapeutic regimens for LAPC derives from observational cohort studies. See Supplementary Table 6 for a list of multicentre studies including ≥100 patients with LAPC and Supplementary Table 7 for a list of single-centre studies including ≥200 patients with LAPC.

A patient-level meta-analysis including 315 patients with LAPC (from 11 studies) revealed a 24-month (95% CI 22–27) median overall survival after FOLFIRINOX with or without radiotherapy, including a resection rate of 28% (range 0–43%)[80]. In a 2021 systematic review that included 653 patients with LAPC (from 21 studies) treated with induction FOLFIRINOX with or without radiotherapy, the resection rate was 26% (95% CI 20–32%) with an 88% R0 resection rate (95% CI 78–95%)[81]. A systematic review on preoperative gemcitabine plus nab-paclitaxel for localized pancreatic cancer revealed that induction gemcitabine plus nab-paclitaxel chemotherapy with or without radiotherapy in patients with LAPC is associated with median overall survival rates ranging from 16 to 20 months and a 16% (95% CI 7–26%) resection rate, with a 77% R0 resection rate (95% CI 51–97%)[60]. These resection rates are substantially higher than in the previously mentioned JCOG1407 trial[79].

Various randomized controlled trials of chemotherapy and chemoradiotherapy in patients with LAPC are currently either ongoing or the results have not yet been published, particularly investigating the value of SBRT in addition to FOLFIRINOX chemotherapy[66,67,82–84]. Two other trials randomized patients between SBRT and EBRT after induction chemotherapy[85,86] but these two trials also include patients with BPRC. Furthermore, the single-centre CSPAC-28 phase III trial randomizes patients with BRPC or LAPC between perioperative modified FOLFIRINOX and gemcitabine plus nab-paclitaxel[73]. See Supplementary Table 5 for all ongoing or unpublished randomized controlled trials on LAPC.

Preoperative chemotherapy: duration. Consensus is lacking regarding the optimal duration of preoperative chemotherapy in patients with BRPC and LAPC[19] as illustrated by the variety of trial regimens (Supplementary Table 6). Some guidelines advocate 6 months of perioperative therapy in potentially curable localized tumours (2016 and 2019 ASCO guidelines) and at least 4 months of induction therapy for LAPC (2022 NCCN guideline)[22,31,32]. In an assessment of the National Cancer Database (USA), a duration of preoperative therapy with multi-agent chemotherapy (with or without radiotherapy) of ≥1–4 versus >4–6 versus >6 months in 1,114 patients with BRPC or LAPC (that is, defined as American Joint Committee on Cancer (AJCC) T4) was associated with a median overall survival of 8 (95% CI 7–8) versus 10 (95% CI 9–12) versus 13 months (95% CI 12–16), respectively, as measured from the start of preoperative therapy and landmarked at 6 months[87]. These findings are supported by a retrospective single-centre series of 279 patients with LAPC in which the administration of ≥12 courses of FOLFIRINOX was associated with longer overall survival in comparison to 4–11 courses of FOLFIRINOX[88]. These findings are at least partly explained by selection and immortal time bias. On the other hand, a retrospective single-centre study of 110 patients with BRPC or LAPC treated with preoperative FOLFIRINOX chemotherapy with or without radiotherapy suggested that >8 months between diagnosis and surgical resection was an independent predictor of worse disease-free survival[89].

Preoperative chemotherapy — tailored approach. It is considered important to monitor anatomical, biological and conditional parameters during preoperative chemotherapy and chemoradiotherapy. In the event of insufficient response or local disease progression, a chemotherapy switch could be considered. Two retrospective single-centre studies investigated the outcomes of patients with BRPC or LAPC who switched from FOLFIRINOX to gemcitabine plus nab-paclitaxel or vice versa. After the switch, 44% ($n = 11/25$) and 72% ($n = 100/139$), respectively, of patients who switched to another chemotherapeutic regimen proceeded to surgical resection[90,91]. Overall survival in patients who underwent a resection after chemotherapy switch was similar to those who underwent a resection after first-line chemotherapy (37 versus 41 months; $P = 0.939$)[90]. Moreover, a switch to another chemotherapeutic regimen was not a predictor of worse overall survival. The most common reasons for chemotherapy switch were radiological progression (42%), biochemical progression (39%) or the absence of an objective disease response (25%)[90]. The promising outcome of this 'tailored approach' is a step towards a more personalized treatment, but more data from prospective studies and randomized controlled trials are needed.

Chemotherapy — toxicity. Besides the favourable results of preoperative therapy in patients with BRPC or LAPC, a large prospective single-centre study of 680 patients with BRPC or LAPC revealed that almost one-third of patients did not complete preoperative therapy: 60% due to disease progression and 40% due to adverse events and toxicity. Only 18% of these patients received another treatment thereafter. Patients aged ≤75 years and those who received platinum-based regimens (that is, FOLFIRINOX or gemcitabine-oxaliplatin) were more likely to complete the intended 6 months of preoperative therapy[92]. A systematic review and meta-analysis that included patients with localized pancreatic cancer who started with neoadjuvant or induction therapy (125 studies; 11,713 patients) demonstrated that 7% (95% CI 6–10%) of patients with BRPC and 10% (95% CI 6–17%) of patients with LAPC did not undergo surgery because of toxicity[93].

Grade 3–4 adverse events, particularly haematological (for example, neutropenia) and non-haematological (for example, fatigue, diarrhoea) events, are common after FOLFIRINOX (60–76%)[10,11,59,80]. Similar rates and types of serious adverse events are reported after gemcitabine plus nab-paclitaxel[76,94]. In contrast, a retrospective comparative multicentre study of 147 patients with LAPC reported much lower rates of grade 3–4 adverse events after FOLFIRINOX and gemcitabine plus nab-paclitaxel (28% versus 27%; $P = 0.97$). However, the incidence of neutropenia and anaemia was non-significantly higher after gemcitabine plus nab-paclitaxel in comparison to FOLFIRINOX[95]. It is possible that the rates of grade 3–4 adverse events after both chemotherapy regimens were lower because this study was retrospective.

Dose reductions and composite changes of FOLFIRINOX can be made (that is, modified FOLFIRINOX) to reduce the burden of adverse events such as reducing the irinotecan dose or omitting bolus 5-FU. However, Conroy et al. found that 76% of patients treated with modified FOLFIRINOX (dose reduction of irinotecan and bolus 5-FU omission) developed adverse events[10]. A retrospective single-centre study of 199 patients with BRPC or LAPC demonstrated that modified FOLFIRINOX did not result in worse overall survival compared with conventional FOLFIRINOX[96].

Radiotherapy. The intention behind adding radiotherapy to preoperative chemotherapy is to increase the chance of R0 resection and to obtain local control in patients with LAPC who are not eligible for surgical resection. The role, timing and type of radiotherapy as part of induction chemotherapy for BRPC and LAPC remain unclear[97,98] as underlined by the 2019 American Society for Radiation Oncology and 2022 NCCN guidelines[22,99]. See Supplementary Tables 3 and 4 for the recommendations from various national and international guidelines.

In the past two decades, radiotherapy has evolved as a consequence of the introduction of intensity-modulated radiotherapy (IMRT), volumetric modulated arc therapy and SBRT, enabling better local targeting of radiation doses and thereby reducing the toxicity[100–103]. The use of radiotherapy in patients with LAPC in the USA has decreased in the period 2003–2011 from 73% to 53% (National Cancer Database; 13,695 patients with LAPC). In the meantime, among patients treated with radiotherapy, the use of IMRT increased from 27% to 72%[104]. Dose escalation of the biologically effective doses seems to further improve both loco-regional control and overall survival according to a retrospective single-centre study including 200 patients with LAPC[105]. Compared with IMRT or volumetric modulated arc therapy, SBRT enables even more precise targeting, hence smaller margins, and a much higher dosage without enhancing toxicity[97,106]. However, no differences in oncological outcomes were seen in two retrospective single-centre studies that compared IMRT with SBRT during preoperative therapy in patients with BRPC or LAPC, with 91 and 104 patients included, respectively[107,108].

The 2016 international multicentre LAP07 trial randomized 442 patients with BRPC or LAPC to preoperative gemcitabine (4 courses) with or without erlotinib, followed by a second randomization of 269 patients to gemcitabine versus capecitabine with EBRT for 6 weeks. Overall survival did not differ between the study arms[109]. However, the clinical relevance of these findings might now be seen as limited due to the emergence of new multi-agent chemotherapies and advancements in radiotherapy.

The 2022 multicentre ALLIANCE A021501 trial (which utilized a pick-the-winner design) randomized 126 patients with BRPC to neoadjuvant modified FOLFIRINOX (8 courses) or modified FOLFIRINOX (7 courses) followed by SBRT or hypofractionated image-guided radiotherapy. The radiotherapy arm was prematurely closed owing to an insufficient R0 resection rate. The primary end point of 18-month overall survival was worse in the radiotherapy arm (68% (95% CI 55–78%) compared with 47% (95% CI 34–60%)) and the resection rates were 58% (R0 42%) and 51% (R0 35%), respectively[110]. Although the trial was neither designed nor powered to prove the value of these modern radiation modalities[111], these findings are remarkable considering the paradigm that preoperative chemoradiotherapy for localized pancreatic cancer is associated with better local response and/or disease-free survival due to improved local disease control and sterilization of resection margins[102,112–117].

Various compositions of preoperative chemotherapy and radiotherapy are described in the literature, including chemoradiotherapy, chemotherapy followed by radiotherapy, and chemotherapy followed by chemoradiotherapy[118–120]. A large retrospective nationwide study from the USA including 8,689 patients with LAPC showed that chemotherapy followed by chemoradiotherapy was associated with improved overall survival compared with immediate chemoradiotherapy[119]. In addition, a retrospective single-centre study including 100 patients with LAPC suggested that longer induction chemotherapy before chemoradiotherapy was associated with lower progression rates, without influencing the overall survival[121].

In summary, more level 1 evidence is needed to elucidate the role of and indications for radiotherapy and its modalities as part of modern chemotherapeutic regimens as well as the optimal order of chemotherapy and radiotherapy. Various ongoing randomized controlled trials will hopefully answer these questions (Supplementary Table 6).

Response evaluation

Accurate response evaluation during and after neoadjuvant or induction therapy is important to determine which patients might benefit from surgery. Futile surgery without resection is associated with poor outcomes[122] and early disease recurrence remains a problem[8,16,123]. The current perspectives on response evaluation are based on anatomical, biological and conditional parameters.

Anatomy

For many years, anatomical staging was considered to be the key parameter for the selection of patients for surgery. A retrospective single-centre study reported a 93% R0 resection rate in 29 patients with BRPC who underwent resection in the presence of radiological vascular tumour involvement after neoadjuvant chemoradiotherapy[124]. This was confirmed in another single-centre study, demonstrating a 92% R0 resection rate after FOLFIRINOX with or without radiotherapy among 40 patients diagnosed with BRPC or LAPC[125]. These high R0 rates illustrate the inability of conventional contrast-enhanced computed tomography (CT) imaging to differentiate between vital tumour and fibrosis[126–128]. Thus, the extent of vascular involvement is often overestimated after preoperative therapy.

Owing to this limitation of CT imaging, the 2021 Japanese Society of Hepato-Biliary-Pancreatic Surgery[129] and the 2017 EORTC expert panel[27] considered 'progressive' disease to be the only reliable CT-based anatomical parameter after chemotherapy with or without radiotherapy, using Response Evaluation Criteria for Solid Tumors (RECIST)[130]. This approach is in agreement with the 2022 NCCN guideline, which stated that surgery may be considered after preoperative therapy in the absence of metastatic disease. On the other hand, caution is required in case of clear local progression, inability to perform a vascular reconstruction, unfavourable CA19-9 dynamics or inadequate performance status[22]. RECIST regression following preoperative therapy occurs only in a minority (10–31%) of localized pancreatic cancers[51,92,131]. Gemenetzis et al. developed an anatomy-based classification system for LAPC (as described in the section 'Disease staging'). In their resection cohort, improvement of the 2021 Johns Hopkins LAPC 1-2-3 Score after induction therapy was associated with improved median overall survival compared with patients with a stable or deteriorating LAPC score (61 versus 30 months)[45].

Various modified criteria and composite scores that aim to optimize the diagnostic accuracy of CT imaging after preoperative therapy have been proposed[132–134]. A meta-analysis including 10 studies demonstrated that modified criteria to predict R0 resection had a higher diagnostic accuracy compared with the standard NCCN criteria (0.78, 95% CI 0.74–0.82 versus 0.67, 95% CI 0.63–0.71)[127]. The modifications to the standard NCCN resectability criteria included, among others, tumour regression, perivascular halo and lack of vessel narrowing[127]. The presence of a 'string' or 'halo' sign on CT or magnetic resonance imaging (MRI) might differentiate between the presence or absence of vessel wall invasion, respectively[135,136].

A prospective multicentre study reported a large interobserver variability in the determination of vascular involvement by CT when assessing 69 arbitrarily chosen CT scans from patients with localized

pancreatic cancer scored by 11 radiologists and 11 surgeons[137]. However, this is contradicted by a retrospective single-centre study that revealed a pooled agreement of 0.84 (95% CI 0.77–0.91) for differentiating between PRPC or BRPC and LAPC (k = 0.67, 95% CI 0.54–0.81) as well as a 0.89 (95% CI 0.85–0.92) pooled agreement for tumour response grading (k = 0.73, 95% CI 0.64–0.82) in 77 patients after preoperative chemotherapy with or without radiotherapy[138]. Nevertheless, the inter-observer agreement was substantially lower when radiologists had to differentiate between PRPC, BRPC and LAPC (0.64, 95% CI 0.56–0.71) with k = 0.55 (95% CI 0.44–0.66)[138]. Irrespective of these uncertainties, it does not seem desirable to use only anatomical parameters for response evaluation and selection for surgery considering the importance of biological parameters and the condition of patients[28–30,139].

Biology

Serum tumour markers. Serum CA19-9 is the most useful tumour marker to assess the effect of preoperative therapy in pancreatic cancer and the only biomarker that is recommended for clinical use by pancreatic cancer guidelines[22,31,36,140]. However, serum CA19-9 has two main limitations: serum CA19-9 reactively increases in case of hyperbilirubinaemia and 5–10% of patients do not produce serum CA19-9 (refs. 141,142). Nevertheless, this marker is widely used in daily practice to estimate systemic disease load and to evaluate tumour response after chemotherapy with or without radiotherapy[143]. Given the link with hyperbilirubinaemia, it is vital to repeat the CA19-9 baseline measurement after biliary drainage when bilirubin levels have normalized and to determine serum CA19-9 and bilirubin levels simultaneously.

There are various approaches to interpreting CA19-9 levels, including the use of absolute values before and after chemotherapy with or without radiotherapy as well as absolute and relative changes[144–151]. A large variety of cut-off values have been described as predictors for resectability and/or survival[8,149–156]. When interpreting these results, it is important to realize that outcomes are often influenced by clinical decision-making in selected study cohorts. Furthermore, cut-offs are poorly validated and difficult to translate directly into clinical practice[157].

The 2022 NCCN guideline recommended surgery with intention for resection after preoperative therapy in patients with BRPC if CA19-9 levels are stable or have decreased without signs of radiological disease progression[22]. The same approach is advocated by the 2021 Chinese and Korean guidelines[140,158]. In patients with LAPC, the 2022 NCCN guideline advised a significant CA19-9 decrease as a criterion to consider surgery[22]. However, according to the French intergroup guideline, although a decrease or normalization of serum CA19-9 can guide decision-making, only confirmation with an intraoperative biopsy can confirm the true effect of preoperative therapy[36].

A systematic review of CA19-9 response after preoperative therapy for localized pancreatic cancer, which included 2,242 patients from 17 studies, demonstrated that a >50% relative reduction or normalization of CA19-9 was associated with better overall survival compared with patients without such a reduction or normalization (HR 0.49, 95% CI 0.42–0.55)[152]. A prospective single-centre study demonstrated that a ≥30% reduction of serum CA19-9 in patients with LAPC after FOLFIRINOX was predictive of resectability and overall survival[154]. On the other hand, a retrospective single-centre study including 131 patients with PRPC or BRPC showed that a normalization of CA19-9 after neoadjuvant therapy was an even stronger predictor for overall survival than the magnitude of change[147]. A post hoc analysis from the randomized controlled trial NEOLAP-AIO-PAK-0113 (ref. 94) (in which patients with LAPC with non-progressive disease after 2 months of induction gemcitabine plus nab-paclitaxel were randomized to either continue or switch to FOLFIRINOX for 2 months) showed that a CA19-9 decrease to <50 U/ml at restaging after 4 months of chemotherapy was more predictive of longer overall survival compared with several relative cut-offs[150].

In 2023, a system was proposed for five patterns of serum CA19-9 during preoperative therapy: type A (that is, always decreasing to normalization), type B (that is, bidirectional with eventual normalization), type C (that is, consistently normal), type D (that is, decrease without normalization) and type E (that is, elevating). These response types were associated with both recurrence-free and overall survival; type A and B patterns were associated with the best outcomes[148].

In patients who do not produce CA19-9, other tumour markers, such as carcinoembryonic antigen (CEA), carbohydrate antigen 125 (CA125) and Duke pancreatic monoclonal antigen type 2 (DUPAN2), might be of clinical use[159,160]. CEA is of particular interest as it is elevated in 30–60% of patients with pancreatic cancer[161,162].

Imaging. In addition to morphological assessment, functional imaging modalities can determine the metabolic and biological response to chemotherapy with or without radiotherapy[163]. Despite the limitations of CT, changes in tumour attenuation on CT imaging might be useful to predict an R0 resection[164] as might tumour homogeneity, which seems to correlate with disease-free and overall survival[165].

Several guidelines have described the role of fluorodeoxyglucose-PET with CT (FDG-PET–CT) to detect extrapancreatic disease but none has mentioned use of FDG-PET–CT for either morphological or functional evaluation[33,34,36,140,166,167]. In 2021, the *American Journal of Roentgenology* Expert Panel stated that FDG-PET–CT might be beneficial for response evaluation when CT is insufficient and in those who do not produce CA19-9, among others[128]. Moreover, the 2021 Japanese Society of Hepato-Biliary-Pancreatic Surgery guideline proposed the incorporation of the maximum standard uptake value (SUV_{max}) on FDG-PET–CT as a biological parameter in the ABC resectability criteria of Isaji et al.[38]. The value of this modality is supported by the literature, including mostly heterogeneous series analysing divergent FDG-PET parameters[168,169].

A retrospective single-centre series from the Mayo Clinic found that a major metabolic response on FDG-PET was more predictive of (near) complete pathological response than any degree of CA19-9 response in 202 patients with BRPC or LAPC who underwent resection after FOLFIRINOX or gemcitabine plus nab-paclitaxel. Furthermore, major metabolic response on FDG-PET was the only independent predictor of overall survival (HR 0.26, 95% CI 0.10–0.61)[170]. However, this study did not include patients who did not undergo resection. In the literature, various FDG-PET–CT parameters have been identified to predict disease-free and/or overall survival, including the absolute SUV_{max} before and after preoperative therapy as well as the SUV_{max} reduction ratio, for which diverging cut-offs are proposed[171–175]. Another imaging modality of interest is diffusion-weighted MRI, which is hypothesized to quantify the tumour response by detecting microstructural tumour changes[176,177]. However, further research with standardized techniques is required[163].

Pathology. Histopathological tumour response in resection specimens can be used as a biological parameter and as a surrogate marker of tumour sensitivity to the administered chemotherapy. Tumour regression has been identified as a predictor for recurrence-free and overall

survival[178]. Several studies identified (near) complete pathological response as an independent predictor of overall survival[179,180]; for example, a retrospective single-centre series including 194 patients with BRPC or LAPC after resection following total neoadjuvant therapy demonstrated a longer overall survival in patients with (near) complete pathological response compared with patients without (72 versus 35 months)[181]. A large National Cancer Database study from the USA also identified complete pathological response as an independent predictor of survival unlike near complete pathological response[182]. A retrospective multicentre study of 525 patients with localized pancreatic cancer revealed that (near) complete pathological response occurred more frequently after chemoradiotherapy than after chemotherapy alone (40% versus 10%)[183].

Complete pathological response is a rare phenomenon with an estimated incidence of 4% (95% CI 3–5%) in patients who have undergone resection[184]. Various predictors are identified such as longer preoperative treatment, radiotherapy and chemotherapy followed by chemoradiotherapy[185,186]. A single-centre retrospective study that analysed 186 patients with BRPC or LAPC after resection following preoperative chemoradiotherapy found a median overall survival exceeding 60 months in patients with a complete pathological response versus 26 months in other patients[187]. Nevertheless, almost half of the patients with a complete pathological response developed local and/or distant disease recurrence[188], illustrating the systemic character of this disease.

There are several different tumour response grading systems. These grading systems are based on the number of vital tumour cells or amount of fibrosis but, as stated by the International Study Group of Pancreatic Pathologists (ISGPP), a ground truth is missing[178]. Among pancreatic pathologists, variety exists in sampling strategy and there is a large interobserver variability in the grading of tumour response[189]. There is a need for standardized assessment of tumour regression grading to optimize the pathological response evaluation. This will improve its value for clinical decision-making regarding the need for and type of adjuvant chemotherapy[190]. Janssen et al. developed a promising artificial intelligence-based segmentation model to objectively assess the tumour response after chemotherapy with or without radiotherapy[191], but further studies are needed to explore its prognostic implications for oncological outcomes. Notably, grading of tumour regression seems to be prognostic for survival after both chemotherapy or chemoradiotherapy, but the prognostic value of the regression grades differed between the treatments, demonstrated by a retrospective multicentre study including 525 patients[183].

Patient condition

As described in the section 'Disease staging', factors related to the condition of a patient are incorporated into several resectability classifications[24,37,38]. In addition to its role in selecting for the type of preoperative therapy, patient health during preoperative therapy can be considered as a surrogate marker for disease response alongside the interpretation of anatomical and biological parameters. The clinical value of determining new-onset sarcopenia and changes in adipose tissue during preoperative therapy, assessable on CT imaging, is demonstrated[192,193]. These factors could be used as objective criteria for conditional response evaluation and risks for subsequent treatments.

Surgery

Surgery combined with chemotherapy is considered the cornerstone of pancreatic cancer treatment. The rapidly evolving literature suggests that sufficient duration of preoperative chemotherapy with or without radiotherapy and careful response evaluation are vital to appropriately select patients with BRPC or LAPC for surgery[88,92,95,117,194,195].

The chance to achieve a resection after preoperative therapy is reported to be lower in patients with LAPC (22%, 95% CI 17–29%) than in patients with BRPC (61%, 95% CI 71–83%) according to a systematic review comprising 125 studies of 11,713 patients with localized pancreatic cancer treated with preoperative therapy[93]. Nevertheless, several observational studies demonstrated that overall survival is similar between patients with BRPC and LAPC after resection[181,196,197]. Therefore, the differences in resection rates seem to be more related to technical issues than to tumour biology. However, the Trans-Atlantic Pancreatic Surgery consortium presented the largest series of localized pancreatic cancer, consisting of 1,835 patients who had received at least one course of preoperative FOLFIRINOX. The resectability status was predictive of overall survival (LAPC: HR 1.81, 95% CI 1.20–2.16; BRPC: HR 1.43, 95% CI 1.18–1.72, with PRPC as reference); patients with BRPC and LAPC underwent a resection in 53% and 18% of cases, respectively[198].

Intraoperative decision-making

Careful intraoperative disease staging is of vital importance to prevent a futile resection as a consequence of overlooking occult metastatic disease and/or ending up with a macroscopic non-radical (R2) resection of the tumour, leaving detectable cancer behind.

As small metastases can be missed by cross-sectional imaging, the 2022 NCCN guideline stated that a diagnostic laparoscopy can be considered before surgical exploration or even before the start of preoperative therapy, potentially combined with ultrasonography and/or peritoneal lavage[22]. According to the 2022 NCCN guideline, performing a diagnostic laparoscopy can be considered particularly in patients at high risk (for example, those with substantially elevated CA19-9, large primary tumour, regional lymphadenopathy or who are highly symptomatic)[22], which is consistent with the 2018 French guideline[36].

Various predictive factors for occult metastases are reported in the literature, including high serum CA19-9 and CEA levels, tumours located in the pancreatic body or tail, larger tumour size, and LAPC resectability status[199–204]. The single-centre prospective exploratory SLING study of 31 patients with high-risk PRPC or BRPC demonstrated the potential value of diagnostic laparoscopy combined with contrast-enhanced intraoperative ultrasonography and indocyanine green fluorescence imaging to detect radiologically occult metastases[205]. The yield of diagnostic laparoscopy to detect metastases is 19–37% in patients with BRPC or LAPC, either before or after preoperative therapy[200,201,206]. Some clinicians routinely perform a diagnostic laparoscopy separately or in the same surgical session as the intended resection, although a decreasing trend for use of diagnostic laparoscopy has been observed in the USA[207]. Possible reasons for the decline in the use of diagnostic laparoscopy are the improvement of cross-sectional imaging and increasing use of preoperative chemotherapy.

As previously discussed, assessing vascular involvement with cross-section imaging after chemotherapy with or without radiotherapy is challenging. A prospective multicentre study investigated the value of intraoperative ultrasonography in 38 patients with LAPC who were treated with induction FOLFIRINOX and subsequently underwent surgical exploration[208]. In all 38 patients, vascular involvement was assessed using intraoperative ultrasonography. In 32% of patients ($n = 12$), the resectability based on intraoperative ultrasonography differed from the resectability on preoperative CT[208]. Of these 12 patients, 10 (83%) seemed to have less vascular involvement and 2 (17%) had more vascular involvement according to ultrasonography[208].

Glossary

5-Fluorouracil
(5-FU). A single-agent chemotherapy.

ABC
(Anatomical – Biological – Conditional). Multi-domain parameters that are used to (re)stage patients with pancreatic cancer before and after preoperative therapy. This includes, among others, vascular tumour involvement (anatomical), tumour markers (biological) and patient fitness (condition).

Adjuvant therapy
Adjuvant therapy for patients with pancreatic cancer often concerns systemic chemotherapy (with or without radiotherapy) that is given with a curative intention after surgery.

Adverse events
Adverse events can be classified following the Common Terminology Criteria for Adverse Events, ranging from grade 1 (mild) and grade 2 (moderate) to grade 3 (severe or medically significant), grade 4 (life-threatening) or grade 5 (death).

American Joint Committee on Cancer
(AJCC). The AJCC developed a staging system for pancreatic cancer, comprising the three-tier system T stage (tumour), N stage (lymph nodes) and M stage (distant metastases).

Arterial divestment
A surgical technique whereby the (tumour) tissue is peeled off from an artery, without the need for an arterial resection.

Borderline resectable pancreatic cancer
(BRPC). Resectability of a pancreatic tumour is often based on the presence and extent of vascular tumour involvement. Biological and conditional factors can also be part of resectability criteria. A borderline resectable pancreatic tumour means that the benefit of removing the tumour by surgery is uncertain or debatable.

BRPC-A
Borderline resectable pancreatic cancer (BRPC) due to the presence of arterial involvement (that is, superior mesenteric artery, coeliac axis and/or hepatic artery).

BRPC-PV
Borderline resectable pancreatic cancer (BRPC) due to the presence and extent of tumour involvement with the portomesenteric axis (that is, portal vein, confluence and superior mesenteric vein).

Capecitabine
A single-agent chemotherapy.

Carbohydrate antigen 19-9
(CA19-9). A serological tumour marker that is measurable in 80–85% of patients with pancreatic cancer. It is the most commonly used tumour marker in patients with pancreatic cancer.

Carbohydrate antigen 125
(CA125). A serological tumour marker that might be of clinical value in patients with pancreatic cancer.

Carcinoembryonic antigen
(CEA). A serological tumour marker that is elevated in 30–60% of patients with pancreatic cancer and could be of clinical value.

Coeliac axis
The arterial branch that originates from the aorta and trifurcates into the common hepatic artery, left gastric artery and splenic artery in case of normal arterial anatomy.

Complete pathological response
The absence of vital tumour cells in the resection specimen in response to therapy.

Computed tomography
(CT). A type of cross-sectional imaging.

Cross-sectional imaging
Advanced imaging modalities such as computed tomography and magnetic resonance imaging.

Diffusion-weighted MRI
A specific modality of magnetic resonance imaging (MRI).

Duke pancreatic monoclonal antigen type 2
(DUPAN2). A serological tumour marker that might be of clinical value in patients with pancreatic cancer.

Eastern Cooperative Oncology Group (ECOG) performance status
A classification to indicate the condition of a patient, ranging from grade 0 (fully active) to grade 5 (deceased).

External beam radiotherapy
(EBRT). A conventional radiation modality.

Extrapancreatic disease
(Suspected) pancreatic cancer located outside the pancreas (that is, lymphadenopathy and/or distant metastases).

FDG-PET
Fluorodeoxyglucose-positron emission tomography (PET) is combined with either computed tomography or magnetic resonance imaging.

FOLFIRINOX
Multi-agent chemotherapy, comprising a combination of 5-fluorouracil, leucovorin, irinotecan and oxaliplatin.

Gemcitabine
A single-agent chemotherapy.

Gemcitabine-capecitabine
A multi-agent chemotherapy, comprising gemcitabine and capecitabine.

Gemcitabine-oxaliplatin
A multi-agent chemotherapy, comprising gemcitabine and oxaliplatin.

Gemcitabine plus nab-paclitaxel
A multi-agent chemotherapy, comprising gemcitabine and albumin-bound paclitaxel.

Gemcitabine-S1
A multi-agent chemotherapy, comprising gemcitabine and S1.

Histopathological tumour response
The presence (and extent) of tumour response on preoperative therapy in the resected specimen can be assessed and graded.

Hypofractionated image-guided radiotherapy
A type of radiation therapy that enables higher and more precise dosage whereby surrounding health tissue is spared.

Induction therapy
Preoperative therapy for patients with locally advanced pancreatic cancer, using chemotherapy with or without radiation.

Intensity-modulated radiotherapy
(IMRT). A type of radiation therapy that enables higher and more precise dosage whereby surrounding health tissue is spared.

Irinotecan
A single-agent chemotherapeutic drug but often used as part of the multi-agent chemotherapy FOLFIRINOX.

Localized pancreatic cancer
Pancreatic cancer without signs of metastatic disease.

Locally advanced pancreatic cancer
(LAPC). Resectability of a pancreatic tumour is often based on the presence and extent of vascular tumour involvement. A locally advanced pancreatic tumour means that the tumour has sufficient contact with major peri-pancreatic vasculature that an upfront surgical resection is associated with significant risks.

Magnetic resonance imaging
(MRI). A type of cross-sectional imaging.

Glossary (continued)

Maximum standard uptake value
(SUV_{max}). A measure of the highest metabolic activity on a fluorodeoxyglucose-positron emission tomography scan.

Neoadjuvant therapy
Preoperative therapy for patients with (borderline) resectable pancreatic cancer, using chemotherapy with or without radiation.

Pancreatic fistula
Leakage of anastomosis from the pancreas with stomach or jejunum, whereby pancreatic enzymes leak into the abdominal cavity.

Pancreatoduodenectomy
Resection of the pancreatic head, duodenum, gallbladder and proximal jejunum, eventually combined with resection of the distal stomach.

'Pick-the-winner' design
A method that can be used for randomized controlled trials in which the best treatment of choice is chosen, also weighing alongside the efficacy factors such as toxicity, quality of life and health-care costs.

Portomesenteric venous axis
The venous system that drains blood from the small bowel and colon to the liver. The main branches that are most relevant for the resectability from pancreatic cancer are the portal vein, confluence and superior mesenteric vein.

Primary resectable pancreatic cancer
(PRPC). Resectability of a pancreatic tumour is often based on the presence and extent of vascular tumour involvement. A primary resectable pancreatic tumour means that it seems beneficial to remove the tumour by surgery.

R0
R status indicates whether the resection margins are free from vital tumour cells: R0, margins are microscopically tumour-free.

R1
R status indicates whether the resection margins are free from vital tumour cells: R1, margins are microscopically (closely) involved by vital tumour.

R2
R status indicates whether the resection margins are free from vital tumour cells: R2, macroscopically tumour tissue is left after resection, examined intraoperatively.

Response Evaluation Criteria for Solid Tumors
(RECIST). A classification system used to classify disease response and/or progression over time or in disease response to treatment.

S1
A single-agent chemotherapy.

Stereotactic body radiotherapy
(SBRT). A type of radiation therapy that enables higher and more precise dosage whereby surrounding health tissue is spared.

Total pancreatectomy
Resection of the complete pancreas (that is, pancreatic head, body and tail), at least combined with resection of gallbladder, duodenum, proximal jejunum and, eventually, the distal stomach.

Upfront surgery
Immediate surgery without preoperative therapy with chemotherapy or chemoradiotherapy.

Volumetric modulated arc therapy
A type of radiation therapy that enables higher and more precise dosage whereby surrounding health tissue is spared.

However, further data are required. Frozen section biopsy samples from the suspected arterial tumour involvement are also useful to accurately decide whether to proceed with resection or to determine the required extent of the resection[209].

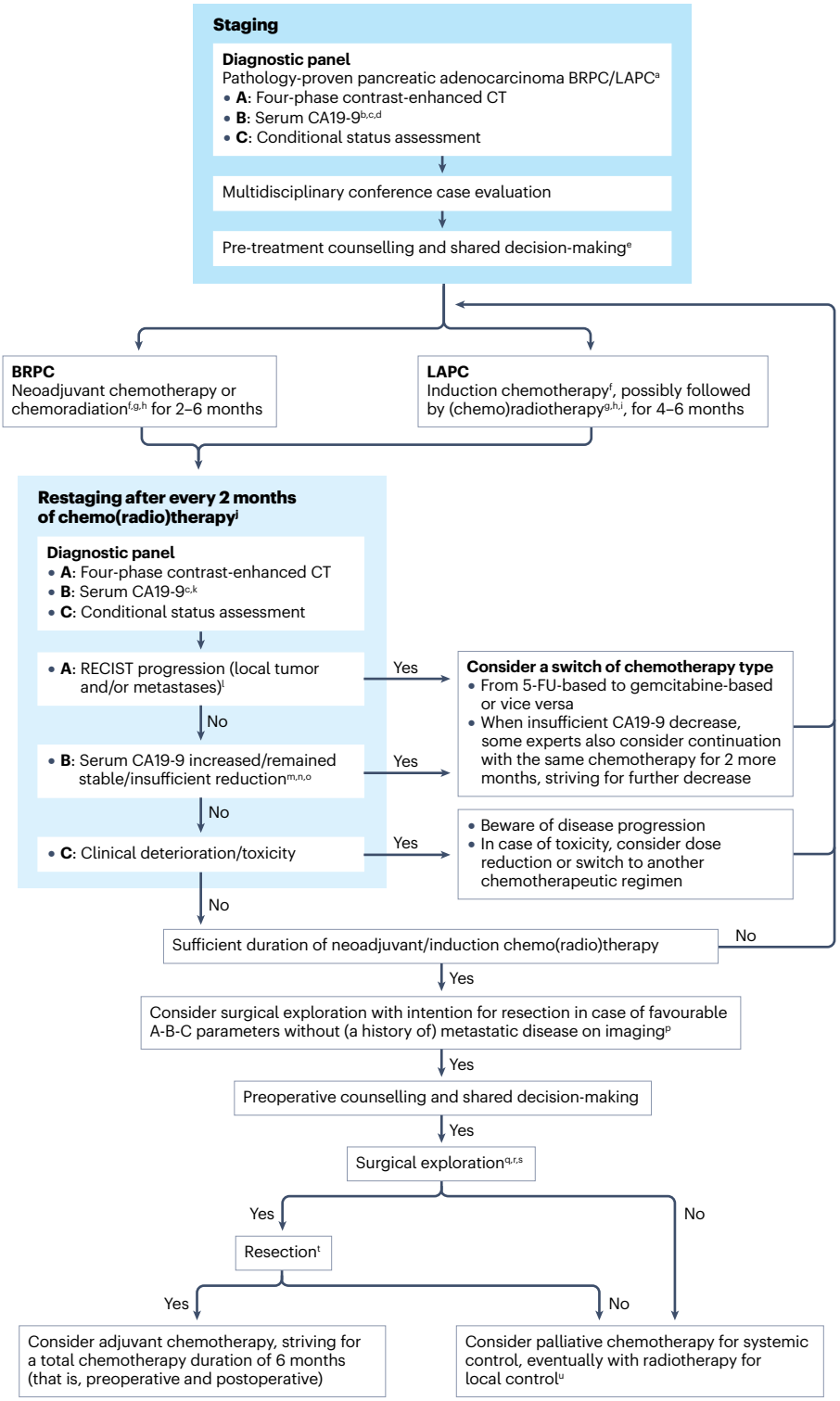
Extent of surgery

Resection rates following preoperative therapy in patients with BRPC or LAPC vary from 8% to 60%[210,211], which illustrates the differences in selection criteria and surgical expertise around the world[19]. Today, portomesenteric venous resections are regarded as a standard procedure in pancreatic cancer surgery[22,34] in high-volume centres, with in-hospital major morbidity ≤28% and mortality ≤4%[212]. Whereas the 2014 consensus statement from the International Study Group of Pancreatic Surgery recommended upfront surgery in patients with (limited) portomesenteric venous tumour involvement[213], a large retrospective international study of 1,192 patients reported an improved R0 rate and overall survival after preoperative therapy compared with upfront portomesenteric venous resection[214]. It is important to realize that portomesenteric venous resection comprises a diverse spectrum of resection and reconstruction types, which are associated with different surgical risks[215,216]. The subjective criteria of venous resectability (that is, whether the portomesenteric vein can be reconstructed or not) induce that the borders can be pushed regarding the feasibility to perform a portomesenteric venous resection[217,218], as described in the section 'Disease staging'.

The clinical practice for patients with major arterial involvement has also changed as a result of improvements in preoperative therapy as some tumours can now be divested (that is, peri-adventitial or sub-adventitial dissection) from the artery[44,219]. This is particularly the case when imaging does not show signs of vascular wall ingrowth (for example, presence of a perivascular halo sign and no vascular narrowing)[135,136]. Opinions differ regarding the value of frozen section biopsy samples from peri-arterial tissue due to reliability issues and limited consequences for surgical decision-making as divestment of the superior mesenteric artery is often a standardized part of the (total) pancreatoduodenectomy[44,220]. Furthermore, the possibility to remove (former) tumour tissue from the artery indicates the absence of vascular wall ingrowth. Some experts consider an outcome of either R0 or R1 in these situations irrelevant as both R0 and R1 resections are considered oncologically feasible[221]. Nevertheless, frozen biopsy samples might be of value to determine the required extent of divestment[209,219].

Even when divestment seems to be sufficient in the preoperative setting to achieve a resection, this clearly has to be performed in highly experienced centres, not only because of the complexity of intraoperative decision-making but also because of the potential need for an arterial resection in case of iatrogenic damage during divestment or when an arterial resection is indicated due to arterial tumour ingrowth[221–223]. Importantly, extensive arterial divestment of the coeliac axis and/or superior mesenteric artery could be associated with refractory diarrhoea due to damage to the nerve plexus[44]. Adequate management with anti-diarrhoeal opioids may control diarrhoea[220] and its negative effect on quality of life[224].

General reluctance persists among surgeons for arterial resection in patients with BRPC or LAPC because of the associated high morbidity and mortality rates with limited survival benefit[225,226]. However, some highly experienced centres have shown acceptable surgical and



oncological outcomes following preoperative therapy in highly selected patients with radiological non-progressive disease, optimal biological disease response (for example, normalization of serum CA19-9), and a good clinical condition with no or limited cardiovascular or other comorbidities[221,227–232]. Thus, the 2022 NCCN guideline concluded that, although evidence for arterial resections in pancreatic cancer surgery is limited, this surgery could be considered in highly selected patients[22]. Depending on the type of arterial resection (and reconstruction), various life-threatening complications can occur, including postpancreatectomy haemorrhage (each arterial resection), gastric ischaemia or

Fig. 2 | Proposed clinical work-up for patients with BRPC and LAPC. 5-FU, 5-fluorouracil; A, anatomical; B, biological; BRPC, borderline resectable pancreatic cancer; C, conditional; LAPC, locally advanced pancreatic cancer; RECIST, Response Evaluation Criteria for Solid Tumours. [a]See section 'Disease staging' for the different definitions of BRPC and LAPC. [b]Effective bile drainage is required first in case of serum hyperbilirubinaemia. [c]Consider the measurement of serum carcinoembryonic antigen (CEA) in addition to carbohydrate antigen 19-9 (CA19-9). [d]Some experts advice performance of fluorodeoxyglucose-PET–computed tomography (FDG-PET–CT) or FDG-PET–magnetic resonance imaging (MRI) as well, especially in cases of non-elevated CA19-9 at time of diagnosis. [e]Pre-treatment counselling about preoperative therapy and its adverse events. Important to emphasize, at this stage, that subsequent surgery depends on the anatomical, biological and conditional response on chemotherapy (with or without radiotherapy). For patients with LAPC, the Johns Hopkins Score might be useful (induction versus palliative therapy) to support pre-treatment counselling. [f]Multi-agent chemotherapeutic regimen, such as (modified) FOLFIRINOX (Eastern Cooperative Oncology Group (ECOG) performance status 0–1) or gemcitabine plus nab-paclitaxel or gemcitabine-capecitabine or gemcitabine-S1 (ECOG performance status 0–2). Consider monotherapy (for example, gemcitabine) when the conditional status does not allow multi-agent chemotherapeutic regimens. [g]Some experts perform a diagnostic laparoscopy at time of diagnosis or after chemotherapy before radiotherapy to exclude occult metastases. See section 'Intraoperative decision-making' for criteria for when and in which patients to perform a diagnostic laparoscopy. [h]Level 1 evidence on the benefit of radiotherapy in patients with BRPC or LAPC treated with preoperative chemotherapy who are candidates for surgical resection is lacking. Therefore, no international consensus exists on the indications for radiotherapy in a preoperative phase. Furthermore, when surgery is considered feasible after chemotherapy, some experts argue that radiotherapy should be avoided in case of major arterial tumour involvement because of the risk of postpancreatectomy haemorrhage or arterial pseudoaneurysm when arterial resection or divestment is needed. [i]There is no high-level evidence that supports the use of concomitant radiotherapy alongside induction chemotherapy in patients with LAPC to improve overall survival. [j]Results of restaging should be discussed in a multidisciplinary conference each 2–4 months of chemotherapy. Results of interim restaging should always be discussed in case of any signs of disease progression or insufficient disease response. [k]When an FDG-PET is performed at time of diagnosis, only repeat the FDG-PET at restaging in case of tumour avidity on the FDG-PET before preoperative therapy. [l]See section 'Anatomy'. [m]Different cut-offs of relative and absolute CA19-9 values are considered as sufficient response. See section 'Serum tumour markers'. [n]Increase of serum CEA is considered a sign of disease progression. Therefore, serum CEA can be used to the assess the biological tumour response in patients with non-elevated CA19-9 levels at time of diagnosis. However, data on optimal reductions or cut-offs are limited. [o]Eventually involving the tumour avidity at FDG-PET to evaluate the biological response; increase of tumour avidity suggests tumour progression. Beware of the effect of post-endoscopic retrograde cholangiopancreatography pancreatitis. [p]Surgery for initially metastatic disease is out of the scope of this figure. [q]Always consider prehabilitation before surgery. [r]Start the surgical exploration with diagnostic laparoscopy to exclude intra-abdominal occult metastases. [s]Some experts advise the use of intraoperative ultrasonography in addition to fresh frozen biopsy samples to assess the vascular tumour involvement. [t]When resection is not feasible, consider trial inclusion for local ablative therapy. [u]Palliative chemotherapy is generally advised and radiotherapy can be added in case of progressive disease (or in clinical trials when there are no signs of progressive disease after neoadjuvant or induction therapy). Radiotherapy without chemotherapy could be considered in the event of chemotherapy-related adverse events (even after dose reduction or a switch to single-agent chemotherapy) because of limited conditional status or patient preference.

perforation (coeliac axis resection), liver ischaemia (hepatic artery or coeliac axis resection) and intestinal ischaemia (superior mesenteric artery resection)[221,227,230,232–238], which are responsible for significant in-hospital or 90-day mortality rates, even in experienced centres, where short-term mortality rates range from 0% to 10%[221,227,229,234,238–240]. Some experts prefer a total pancreatectomy when arterial resection (with reconstruction) is performed[229,241] to avoid life-threatening erosive bleeding due to postoperative pancreatic fistula[242,243]; however, this is debated by others[221].

In 2021, Napoli et al. developed a nomogram based on preoperative parameters (that is, metabolic deterioration of diabetes, several laboratory tests and preoperative FOLFIRINOX chemotherapy) to predict survival in patients with LAPC who required an arterial resection. After excluding the 10% rate of 90-day mortality, overall survival in the high-risk, intermediate-risk and low-risk groups was 14, 24 and 31 months, respectively[239]. Garnier et al. emphasized the importance of biological selection in an observational bi-centre study including 105 patients with BRPC or LAPC who underwent complex vascular resections after FOLFIRINOX chemotherapy[244]. This was illustrated by a 3-year survival of 51% versus 0% in patients with preoperative CA19-9 <450 U/ml versus >450 U/ml after chemotherapy or chemoradiotherapy[244].

The general paradigm of pancreatic cancer surgery is that an R0 resection should be the aim, as R0 resections are associated with longer overall survival as compared to R1 resections[245], supported by national and international guidelines[22,31,34]. Interestingly, two observational single-centre studies including, respectively, 280 and 468 patients suggested that an R1 resection is not associated with overall survival and therefore provides adequate survival in case of sufficient biological disease response after preoperative chemo(radio)therapy[246,247]. As the rates of R1 resections are relatively high after vascular resection or arterial divestment in comparison to pancreatic resections without vascular resection or arterial divestment, these extended procedures could still be beneficial in the presence of favourable disease response after preoperative therapy[212,221,248].

Surgical risks

Initially, there was some reluctance among pancreatic surgeons towards preoperative chemotherapy with or without radiotherapy as this could affect the anatomical planes and might therefore complicate surgery. However, this has since changed because, among other studies, several nationwide series from the USA suggested that preoperative therapy does not adversely affect short-term outcome and mortality[249,250]. However, another national retrospective study in 6,936 patients revealed that chemotherapy combined with radiotherapy was associated with a doubled 90-day mortality compared with chemotherapy alone (6.4% versus 3.6%; $P < 0.001$)[251]. A systematic review that included 25,389 patients from 41 studies demonstrated that the rate of postoperative pancreatic fistulas decreased in patients undergoing pancreatoduodenectomy after chemoradiotherapy compared with chemotherapy only[252]. A retrospective single-centre series of 305 patients reported lower rates of postoperative pancreatic fistula and postpancreatectomy haemorrhage in patients after pancreatoduodenectomy following preoperative chemotherapy with or without radiotherapy compared with upfront surgery. However, the burden of complications was higher compared with upfront surgery[253]. Some experts argue that radiotherapy can worsen vessel wall texture and thereby increase the risk of postpancreatectomy haemorrhage

Box 1

Future directions: research agenda for clinical research

Staging

- Development of new resectability criteria based on anatomical, biological and conditional parameters.
- Improvement or development of diagnostic modalities to exclude metastatic disease more adequately.
- Validation of existing and identification of new molecular and genetic pancreatic cancer subtypes and liquid tumour markers for prognostication.

Preoperative therapy

- Development of new, internationally supported guidelines.
- Level 1 evidence on the efficacy of different preoperative chemotherapy agents[a,b,c].
- Level 1 evidence on the optimal length of preoperative chemotherapy[a,b,c].
- Level 1 evidence on the indications and timing of chemotherapy switch for patients with anatomical and/or biological disease progression without signs of metastases[a,b,c].
- Level 1 evidence on the efficacy of radiotherapy, including the efficacy of different radiation modalities in the (potentially) preoperative setting[b,c,d].
- Validation of existing molecular and genetic pancreatic cancer subtypes and liquid tumour markers for prognostication and to predict the efficacy of different oncological and surgical treatments.
- Identification of new molecular and genetic pancreatic cancer subtypes and liquid tumour markers for prognostication and to predict the efficacy of different oncological and surgical treatments.
- Level 1 evidence for selection of patients for differential use of various chemotherapy and radiotherapy regimens based upon anatomical, biological and/or conditional predictive factors[c].
- Development of new targeted therapies.

Response evaluation

- Identification and validation of absolute (that is, at diagnosis, during and after preoperative therapy) and relative cut-offs for serum carbohydrate antigen 19-9 (CA19-9). Serum CA19-9 response on preoperative therapy should be investigated in patients treated with modern multi-agent chemotherapy and at time of (early) restaging. Furthermore, it is not desirable to include only patients who underwent surgery to investigate serum CA19-9 cut-offs.
- Validation of established serum tumour markers as alternative to or in addition to serum CA19-9 (for example, carcinoembryonic antigen (CEA), Duke pancreatic monoclonal antigen type 2 (DUPAN2), carbohydrate antigen 125 (CA125)). It is not desirable to include only patients who underwent surgery to investigate serum CA19-9 cut-offs.
- Prospective studies on the prognostic value of fluorodeoxyglucose-positron emission tomography (FDG-PET) as a tumour marker, including patients who started with preoperative therapy with or without subsequent resection. Furthermore, the optimal FDG-PET measure (for example, peak or maximum standardized uptake values, metabolically active tumour volume, or total lesion glycolysis) has to be identified. Including only cohorts with patients who underwent resection is undesirable. FDG-PET scans have to be performed following standardized protocols.
- Validation and development of imaging-based markers (for example, radiomics or based on artificial intelligence) for anatomical and biological (re)staging.
- Development and validation of new solid and liquid tumour markers.
- Validation of modified resectability criteria on four-phase comuted tomography (for example, string versus halo sign, tumour density changes).
- Prospective studies on the prognostic value of contrast-enhanced magnetic resonance imaging for assessment of vascular tumour involvement after preoperative therapy, including the prognostic value of the halo versus string sign.
- Observational studies on the role of FDG-PET for anatomical restaging, using breath-correcting techniques and high-quality image resolutions.

Local treatment

- Clinical value (and indications) of diagnostic laparoscopy before laparotomy to identify occult metastatic disease, including combined diagnostic modalities (for example, indocyanine green fluorescence, peritoneal lavage, ultrasonography).
- Prospective studies assessing the clinical value of intraoperative ultrasonography for assessment of vascular tumour involvement.
- Investigating the risk of preoperative radiotherapy, including different radiation modalities, for postpancreatectomy haemorrhage or pseudo-aneurysm after arterial divestment or reconstruction.
- Standardized protocols for histopathological assessment of resected specimens, regarding tumour inclusion, histopathological response grading and residual disease status assessment.
- Development of a new method to adequately assess histopathological tumour response in patients who underwent resection after preoperative therapy.
- Level 1 evidence on benefit of surgical resection after preoperative chemotherapy with or without radiotherapy[a,b,c].
- Investigating the surgical safety, clinical benefit and oncological non-inferiority of minimally invasive robotic resections for patients with borderline resectable pancreatic cancer.
- Level 1 evidence on the benefit of local ablative therapies other than surgical resection, considering biological parameters and (type and timing of) systemic chemotherapeutic regimens in the study design.

(continued from previous page)

The statements are applicable for both patients with borderline resectable pancreatic cancer and those with locally advanced pancreatic cancer, unless indicated differently. [a]Comparative study arms should be designed in a manner in which the comparison is not negatively influenced by discrepancies between the study arms regarding radiation (modalities) and/or number of chemotherapy cycles. [b]Randomized controlled trials should be sufficiently powered with overall survival by intention-to-treat as primary end point. Other endpoints such as (R0) resection rate or progression-free survival are not appropriate for primary endpoints. [c]Considering the fact that anatomical resectability criteria still have an important role in clinical decision-making, clinical level 1 studies should study patients with borderline resectable pancreatic cancer or with locally advanced pancreatic cancer separately. [d]Comparative study arms should be designed in a manner in which the comparison is not negatively influenced by discrepancies between the study arms regarding chemotherapy regimens.

after arterial resections[254]. A large single-centre retrospective study investigated the effect of preoperative chemotherapy with conventional radiotherapy versus SBRT in 168 patients with BRPC or LAPC who had undergone resection, revealing similar major morbidity and mortality rates. However, only very few arterial resections with or without reconstruction were performed[255].

Alternative local therapy

If surgical resection is not feasible, local ablative therapy could be used to aim for local tumour control and improved survival. Its importance is illustrated by the fact that approximately 30% of patients with pancreatic cancer who die do not have metastases[256]. Various local therapies have been proposed, such as intraoperative radiotherapy, brachytherapy, SBRT, irreversible electroporation, radiofrequency ablation, microwave ablation, cryoablation, high-intensity focused ultrasound, laser-induced thermotherapy and photodynamic therapy[257–260]. However, only a few randomized controlled trials have so far been published[261,262], and various randomized controlled trials are ongoing, particularly on SBRT[263–281]. Although the value of these alternative local therapies is beyond the scope of this Review, it is important to emphasize that further high-quality randomized trials that incorporate upfront systemic therapy are urgently needed to elucidate the role of these modalities in the treatment of patients with BRPC and LAPC.

Shared decision-making

As recommended in the 2016 ASCO guideline[31], preoperative counselling with shared decision-making is of vital importance. After all, the hope for cure of patients regularly hampers a balanced decision between the chance for prolonged survival versus treatment-related risks[282,283]. Especially in surgical patients, the different procedures are associated with diverging surgical risks[284,285], short-term and long-term adverse events[286–290], and oncological benefits that require extensive longitudinal shared decision-making from diagnosis and throughout the treatment trajectory[291]. The need for improvement in clinician communication and interpersonal skills is illustrated by a multicentre study that prospectively studied patients with pancreatic or periampullary cancer and revealed a decrease in health care satisfaction after treatment[292].

Future directions

Figure 2 summarizes a clinical work-up for patients with BPRC and LAPC based on the identified evidence and guidelines. Nevertheless, there are still many uncertainties regarding the efficacy of preoperative therapy regimens (for example, type and duration of chemotherapy, chemotherapy switch, and indications and type of radiation therapy), strategies for treatment response evaluation and selection criteria for surgery. Box 1 presents a research agenda describing the most relevant knowledge gaps on the clinical aspects of staging, preoperative therapy, response evaluation and local treatments for patients with BRPC or LAPC.

In addition to a need for more efficient systemic and localized therapies for pancreatic cancer, expanding the possibilities for more personalized treatment, including targeted therapies, is important to improve survival outcomes and efficacy of treatments and to reduce treatment burden on patients. Molecular and genetic subtyping of pancreatic cancer is crucial for the development of personalized and targeted therapies[293,294]. However, the heterogeneity in the molecular characteristics of pancreatic cancer hinders the search for clinically relevant pancreatic cancer subtypes and biomarkers[295]. Therefore, in 2022, the NCCN guideline recommended genetic testing for all patients and molecular profiling for so-called actionable somatic findings in patients with advanced disease (that is, locally advanced or metastatic)[22].

Several clinical studies have described the potential clinical relevance of different molecular and genetic subtypes in patients with localized pancreatic cancer, including patients with BRPC or LAPC, for prognostication and clinical decision-making. For example, in a study of 196 patients with localized pancreatic cancer, Ecker et al. found that a driver mutation in *SMAD4* was associated with disease progression during preoperative FOLFIRINOX[296]. Additionally, a retrospective multicentre study of 199 patients with pancreatic cancer after resection (99% upfront surgery) demonstrated the potential value of differentiating between the molecular subtypes 'basal-like' and 'classical' as patients with basal-like tumours had worse overall survival (HR 1.49, 95% CI 1.01–2.19)[297]. In addition, the prospective COMPASS trial, which included 63 patients with locally advanced or metastatic pancreatic cancer, showed that those with a classical tumour type had a better disease response to first-line chemotherapy than patients with basal-like tumours[298]. A retrospective multicentre study showed that 4 out of 9 patients (44%) with BRPC with either a *BRCA1* or *BRCA2* mutation developed a complete pathological response after FOLFIRINOX chemotherapy, compared with 3 out of 30 patients (10%) without this germline mutation[299]. Molecular profiling has already been used in clinical practice to guide decision-making. Tsai et al. selected 6 predictive molecular targets for chemosensitivity, which were evaluated on pre-treatment tumour biopsy samples from 130 patients with PRPC or BRPC, with the aim to select the most effective neoadjuvant chemotherapy (that is, based on 5-FU or on gemcitabine). This resulted in promising resection rates of 92% and 74% in patients with PRPC and BRPC, respectively[300]. Thus, it appears that genome-wide profiling might be important to increase the evidence about potential therapy targets and biomarkers[295,298].

In addition to molecular and genomic profiling of pancreatic cancer, further steps have to be taken to validate and develop new tumour markers. A wide spectrum of promising biomarkers has been described such as inflammatory response parameters, circulating tumour

DNA and microRNAs, circulating tumour cells, imaging-based tumour markers, and chemotherapy-sensitivity assessment using organoids[129,143,301–308]. Development and validation of these new tumour markers is of importance in order to better predict and assess disease response after systemic chemotherapy. Thus, prognosis can be optimized by switching to another treatment modality and avoiding or reducing disease progression and unnecessary therapy toxicity. More importantly, the risk of disease progression after inadequate first-line treatment needs to be reduced by predicting tumour sensitivity for specific treatments and developing targeted therapies.

Conclusions

Improved outcomes have been achieved in selected patients with BRPC and LAPC mostly due to improved preoperative multi-agent treatment and patient selection combined with complex surgical care in experienced, high-volume centres.

Nevertheless, many questions about preoperative chemotherapy and radiotherapy (for example, indications, type, duration, tailored approaches), response evaluation (for example, validation of tumour markers and functional imaging modalities), surgery (for example, indications and extent), and other local ablative therapies remain. Ongoing and recently completed randomized controlled trials will provide important new insights into the multidisciplinary treatment of pancreatic cancer.

The identification of liquid and tissue biomarkers and the development of new targeted therapies are crucial as we strive towards personalized care, aiming to provide a better opportunity for long-term survival and even cure, and knowing which patients should not undergo extensive therapies owing to the expectation of limited or lack of benefit.

The treatment of patients with BRPC and LAPC requires a dedicated and multidisciplinary approach. Biology should be the main driver for surgical treatment as anatomical issues (for example, vascular involvement) are no longer an absolute barrier to treatment.

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Author contributions
M.G.B. and T.F.S. researched data for the article, made a substantial contribution to the discussion of content, wrote the article, and reviewed/edited the manuscript before submission. R.T.T. and L.W.F.S. researched data for the article, made a substantial contribution to the discussion of content, and reviewed/edited the manuscript before submission. The other authors reviewed/edited the manuscript before submission.

Competing interests
M.D.C. received an industry grant (Haemonetics, Inc.) to conduct a multicentre study to evaluate the prognostic implications of TEG in pancreatic cancer. M.D.C. is co-principal investigator of a Boston Scientific-sponsored international multicentre study on the use of intraoperative pancreatoscopy of patients with intraductal papillary mucinous neoplasms. T.F.S. and M.G.B. received two grants from the Dutch Cancer Society (KWF) and Deltaplan Alvleesklierkanker for the Dutch PREOPANC-4 trial on the multidisciplinary management of locally advanced pancreatic cancer (NCT05524090).

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Review criteria A systematic literature search on PubMed was performed (30 November 2022); see Supplementary Table 1 for the search strategy. Literature (n=2,978 records) was screened by title and abstract (by T.F.S., L.W.F.S. and R.T.T.) and the preliminary articles included (n=801) were subsequently screened by full-text (by L.W.F.S. and R.T.T.). Additional literature was identified via the references of included literature to further nuance certain topics. In addition, the WHO International Clinical Trials Registry Platform was searched (6 December 2022) for ongoing and completed randomized controlled trials. Trials about advanced pancreatic cancer were not included. On 6 February 2023, the status of included ongoing or completed trials was checked. Inclusion criteria concerned any type of original studies about preoperative chemotherapy or chemoradiotherapy for borderline resectable pancreatic cancer and/or locally advanced pancreatic cancer (LAPC; any definition), published in the period 2010(1) to 2022(11). Studies were included when they reported about (1) indications for preoperative chemotherapy or chemoradiotherapy or subsequent patient selection; and/or (2) (radical) resection rate and/or overall survival. Randomized controlled trials were included whereas primarily only observational studies with a sample size of ≥50 patients with borderline resectable pancreatic cancer and/or LAPC were selected. Single-centre studies with at least 200 patients with LAPC and multicentre studies with at least 100 patients were specifically included. Finally, smaller series were used to illustrate certain topics when larger series were not available.

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