Cancer Treatment Reviews 77 (2019) 1–10

Contents lists available at ScienceDirect

Cancer Treatment Reviews

journal homepage: www.elsevier.com/locate/ctrv

Anti-Tumour Treatment

Optimizing the management of locally advanced pancreatic cancer with a focus on induction chemotherapy: Expert opinion based on a review of current evidence

Thomas Seufferlein[a,*], Pascal Hammel[b], Jean Robert Delpero[c], Teresa Macarulla[d], Per Pfeiffer[e], Gerald W. Prager[f], Michele Reni[g], Massimo Falconi[h], Philip A. Philip[i], Eric Van Cutsem[j]

[a] University Medical Center Ulm, Ulm, Germany
[b] Hôpital Beaujon (AP-HP), Clichy, and Université Paris VII-Denis Diderot, France
[c] Aix Marseille Université, Marseille, France
[d] Vall d'Hebron University Hospital, Barcelona, Spain
[e] Odense University Hospital, Odense, Denmark
[f] Department of Medicine I, Comprehensive Cancer Center Vienna, Medical University Vienna, Austria
[g] Department of Medical Oncology, IRCCS Ospedale San Raffaele, Milan, Italy
[h] Pancreas Translational and Clinical Research Centre, San Raffaele Scientific Institute, "Vita-Salute" University, Milan, Italy
[i] Department of Oncology, Barbara Ann Karmanos Cancer Institute, Detroit, MI, USA
[j] Digestive Oncology, University Hospitals Gasthuisberg Leuven and KU Leuven, Leuven, Belgium

ARTICLE INFO

Keywords:
Pancreatic cancer
Locally advanced disease
Systemic treatment
Induction therapy

ABSTRACT

Surgical resection of pancreatic cancer offers a chance of cure, but currently only 15–20% of patients are diagnosed with resectable disease, while 30–40% are diagnosed with non-metastatic, unresectable locally advanced pancreatic cancer (LAPC). Treatment for LAPC usually involves systemic chemotherapy, with the aim of controlling disease progression, reducing symptoms and maintaining quality of life. In a small proportion of patients with LAPC, primary chemotherapy may successfully convert unresectable tumours to resectable tumours. In this setting, primary chemotherapy is termed 'induction therapy' rather than 'neoadjuvant'. There is currently a lack of data from randomized studies to thoroughly evaluate the benefits of induction chemotherapy in LAPC, but Phase II and retrospective data have shown improved survival and high R0 resection rates. New chemotherapy regimens such as *nab*–paclitaxel + gemcitabine and FOLFIRINOX have demonstrated improvement in overall survival for metastatic disease and shown promise as neoadjuvant treatment in patients with resectable and borderline resectable disease. Prospective trials are underway to evaluate these regimens further as induction therapy in LAPC and preliminary data indicate a beneficial effect of FOLFIRINOX in this setting. Further research into optimal induction schedules is needed, as well as guidance on the patients who are most suitable for induction therapy. In this expert opinion article, a panel of surgeons, medical oncologists and gastrointestinal oncologists review the available evidence on management strategies for LAPC and provide their recommendations for patient care, with a particular focus on the use of induction chemotherapy.

Introduction

Pancreatic cancer is one of the leading causes of cancer-related deaths in developed countries [1]. Incidence rates vary between regions, with the highest in North America (7.4 per 100,000 people in 2012) and Western Europe (7.3 per 100,000) [1]. Mortality rates are almost as high as incidence rates (6.9 per 100,000 in North America and 6.8 per 100,000 in Western Europe), reflecting how lethal pancreatic cancer is [1]. Despite being the 11th most common cancer worldwide [1], it is the 4th most fatal cancer in both men (after lung, colorectal and prostate cancers) and women (after breast, colorectal and lung cancers) [2,3], with a 5-year survival rate of less than 5% [1].

* Corresponding author at: University Medical Center Ulm, Center for Internal Medicine, Department of Internal Medicine I, Albert Einstein Allee 23, D-89081 Ulm, Germany.
E-mail addresses: thomas.seufferlein@uniklinik-ulm.de (T. Seufferlein), pascal.hammel@aphp.fr (P. Hammel), delperojr@ipc.unicancer.fr (J.R. Delpero), tmacarulla@vhio.net (T. Macarulla), per.pfeiffer@rsyd.dk (P. Pfeiffer), gerald.prager@meduniwien.ac.at (G.W. Prager), reni.michele@hsr.it (M. Reni), falconi.massimo@hsr.it (M. Falconi), philipp@karmanos.org (P.A. Philip), eric.vancutsem@uzleuven.be (E. Van Cutsem).

https://doi.org/10.1016/j.ctrv.2019.05.007
Received 24 May 2019; Accepted 26 May 2019

Pancreatic cancer mortality has been increasing in both genders in recent decades [1]; predictions of cancer mortality rates in 2017 estimated that deaths due to pancreatic cancer in the European Union (EU) would remain stable in men, but would continue to rise in women [3]. A study in 2016 predicted that by 2017, more deaths would occur in the EU as a result of pancreatic cancer than breast cancer [4], suggesting that pancreatic cancer may soon become the third leading cause of female cancer-related death in the EU after lung and colorectal cancers.

The initial staging of pancreatic cancer is focussed on surgical resectability. Tumours are classified as resectable, borderline resectable, locally advanced or metastatic, according to the degree of contact between the tumour and adjacent vessels/organs, and the presence of metastases [2]. However, while the definition of resectability largely depends on tumour size, location and involvement of major blood vessels, the experience and attitude of the multidisciplinary team also plays a role – for example, some studies have described pessimistic attitudes of physicians in recommending surgery for early-stage pancreatic cancer [5,6]. Currently, only 15–20% of patients are diagnosed with resectable disease, whereas a larger proportion (30–40%) are diagnosed with non-metastatic, unresectable tumours that are confined to the pancreatic region, also known as locally advanced pancreatic cancer (LAPC) [2,7].

Surgical resection offers a chance of cure for patients with localized, resectable disease, and may be considered as an option in patients with borderline resectable pancreatic cancer (BRPC) following induction therapy to shrink the tumour and control potential micrometastatic disease [2]. However, true LAPC is considered unresectable and treatment usually involves systemic therapy with chemotherapy, with or without subsequent radiotherapy [2,8,9]. Despite these available treatments, the median overall survival (OS) following a diagnosis of LAPC generally remains poor, although variable, ranging from 9 to 32 months across various studies [10].

The management of LAPC is controversial and challenging, in part due to a number of factors relating to a lack of consensus on diagnosis and disease management. For example, varying criteria are promoted by different guidelines to distinguish BRPC and LAPC, there are differences in surgeon opinion between the definitions of borderline resectable and unresectable tumours, and there is a lack of consensus between international guidelines regarding the management of LAPC. There is also a notable lack of clinical trials in patients with LAPC.

To address these challenges, a group of expert surgeons, medical oncologists and gastrointestinal oncologists convened to review the available evidence on the current definitions and management strategies for LAPC. No systematic literature review was undertaken, but by pooling their clinical experience and adding it to their review of published evidence, the group aimed to provide further guidance for the optimal management of LAPC. The outcomes of the meeting are presented in this article.

Definition of LAPC

The wide variation in reported median OS rates (9–32 months) in patients with LAPC suggests a high degree of heterogeneity in this patient population [10,11]. Pancreatic tumour biology is poorly understood and further insights into the pathophysiology may reveal the reasons for this heterogeneity, but it is likely that LAPC comprises a spectrum of disease states resulting from differences in tumour biology and tumour sensitivity to therapy. The variation in survival rates may also reflect the lack of uniformity in the definition of LAPC and the challenges in differentiating LAPC from BRPC. In this respect, guidelines differ in their definition of BRPC (Table 1). While the criteria for differentiating unresectable LAPC from BRPC are not clear and limitations exist in the precision of imaging, the NCCN definitions of resectability are widely used (Table 2). However, classification of LAPC based on surgical assessment alone has been challenged as it may be heterogeneous and subjective. In a recent study of patients initially classified

Table 1
Common definitions of BRPC [58–62].

Affected vessel	AHPBA/SSAT/SSO/NCCN/ISGPS	MDACC	ACTO	IAP
SMV/PV	Abutment, impingement, encasement of the SMV/PV or short segment occlusion	Short-segment occlusion	Tumour-vessel interface ≥ 180° of vessel wall circumference and/or reconstructable occlusion	Tumour contact ≥ 180° or invasion of the SMV/PV with bilateral narrowing or occlusion, and not exceeding the inferior border of the duodenum
SMA	Abutment	Abutment	Tumour-vessel interface < 180° of vessel wall circumference	Tumour contact < 180° without stenosis or deformity
Common hepatic artery	Abutment or short-segment encasement	Abutment or short-segment encasement	Reconstructable short-segment tumour-vessel interface	Abutment without tumour contact with the proper hepatic artery and/or celiac artery
Celiac artery	No abutment or encasement	Abutment	Tumour-vessel interface < 180° of vessel wall circumference	Tumour contact < 180° without stenosis or deformity

ACTO, Alliance for Clinical Trials in Oncology; AHPBA, Americas Hepato-Pancreato-Biliary Association; BRPC, borderline resectable pancreatic cancer; IAP, International Association of Pancreatology; ISGPS, International Study Group of Pancreatic Surgery; MDACC, MD Anderson Cancer Center; NCCN, National Comprehensive Cancer Network; PV, portal vein; SMA, superior mesenteric artery; SMV, superior mesenteric vein; SSAT, Society for Surgery of the Alimentary Tract; SSO, Society of Surgical Oncology.

Table 2
NCCN guideline definitions for resectability [9].

Resectability status	Arterial involvement	Venous involvement
Resectable	No arterial tumour contact (CA, SMA, or CHA)	No tumour contact with SMV or PV or ≤180° contact without vein contour irregularity
Borderline resectable[b]	**Pancreatic head/uncinate process** ● Solid tumour contact with CHA without extension to CA or HA bifurcation allowing for safe and complete resection and reconstruction ● Solid tumour contact with SMA ≤180° ● Solid tumour contact with variant arterial anatomy (ex: accessory right HA, replaced right HA, replaced CHA and the origin of replaced or accessory artery) and the presence/degree of tumour contact may affect surgical planning **Pancreatic body/tail** ● Solid tumour contact with CA ≤ 180° ● Solid tumour contact with CA > 180° without involvement of aorta and with intact/uninvolved GA[a]	● Solid tumour contact with SMV or PV > 180°, contact ≤180° with contour irregularity of the vein or thrombosis of the vein but with suitable vessel proximal and distal to the site of involvement allowing for safe and complete resection and vein reconstruction ● Solid tumour contact with the IVC
Unresectable[b]	**Pancreatic head/uncinate process** ● Solid tumour contact with SMA > 180° ● Solid tumour contact with CA > 180° **Body and tail** ● Solid tumour contact of > 180° with SMA or CA ● Solid tumour contact with CA and aortic involvement	**Pancreatic head/uncinate process** ● Unreconstructible SMV/PV due to tumour involvement or occlusion (can be due to tumour or bland thrombus) ● Contact with most proximal draining jejunal branch into SMV **Body and tail** ● Unreconstructible SMV/PV due to tumour involvement or occlusion (can be due to tumour or bland thrombus)

CA, coeliac axis; CHA, common hepatic artery; GA, gastroduodenal artery; HA, hepatic artery; IVC, inferior vena cava; LAPC, locally advanced pancreatic cancer; PV, portal vein; SMA, superior mesenteric artery; SMV, superior mesenteric vein.
Note: Copyright permission to reproduce this table will be provided by the authors upon acceptance of the manuscript prior to publication.
[a] This criterion is sometimes preferred in the 'unresectable' (LAPC) category.
[b] Solid tumour contact may be replaced with increased hazy density/stranding of the fat surrounding the peri-pancreatic vessels (typically seen following neoadjuvant therapy); this finding should be reported on the staging and follow-up scans.

as BRPC or LAPC, 56% of BRPC patients and 14% of LAPC patients underwent resection after primary chemotherapy [12]. Remarkably, this large difference in resection rates did not translate to a difference in survival between the two groups, suggesting that classification of BRPC and LAPC on surgical assessment alone may be unreliable. Other methods, such as biomarker assessment, may provide a better way to classify patients and subsequently select those who may benefit from resection after primary systemic therapy [12].

Expert opinion summary statement: There is an unmet need for consensus between international guidelines on differentiation criteria for LAPC and BRPC.

Current guidelines for the management of LAPC

The current recommended approaches for the management of LAPC vary between guidelines (Table 3). ESMO guidelines recommend first-line therapy with 6 months of gemcitabine, with capecitabine-based chemoradiotherapy as an alternative option [2]. The ESMO guidelines state that the benefits of chemoradiotherapy are not clear, highlighting two trials that showed opposite results: one reported that OS was improved with gemcitabine alone (13 months) vs. chemoradiotherapy with 5-FU and cisplatin (8.6 months; p = 0.03) [13]; the other showed that OS was worse with gemcitabine alone (9.2 months) vs. chemoradiotherapy with gemcitabine (11.1 months; p = 0.017), although chemoradiotherapy was associated with increased toxicity [14]. More recently, the open-label, randomized LAP07 trial reported that in patients with LAPC controlled after 4 months of gemcitabine-based induction therapy, there was no significant difference in OS between patients receiving subsequent chemoradiotherapy (15.2 months) and those receiving chemotherapy alone (16.5 months; p = 0.83), although chemoradiotherapy was associated with decreased local progression (32% with chemoradiotherapy vs. 46% with chemotherapy; p = 0.03) [15].

It is worth noting that treatment practices have evolved since the publication of the ESMO guidelines in 2015, towards the use of FOLFIRINOX or *nab*-paclitaxel + gemcitabine for first-line therapy, which is reflected in more recent treatment guidelines from ASCO and NCCN. The initial treatment recommendation from ASCO is combination chemotherapy, but there is no recommendation for a specific regimen. For patients with good performance status (PS), newer regimens such as FOLFIRINOX or *nab*–paclitaxel + gemcitabine are highlighted as options, based on extrapolation from randomized trials in metastatic disease [8]. Chemoradiotherapy, most often with fluoropyrimidines or gemcitabine, may also be offered to certain patients, including those with local disease progression after primary chemotherapy. Stereotactic body radiotherapy (SBRT) may also be offered as an alternative to chemoradiotherapy, although clinical evidence in the LAPC patient population is currently limited [8].

The NCCN guidelines recommend that patients with LAPC and good PS should be encouraged to participate in clinical trials where available [9]. In the absence of a clinical trial, NCCN recommends that these patients should receive combination chemotherapy (options include FOLFIRINOX and *nab*–paclitaxel + gemcitabine) or 4–6 months of primary chemotherapy followed by chemoradiotherapy (with capecitabine, fluoropyrimidines or gemcitabine) or SBRT [9]. While both ASCO and NCCN guidelines include SBRT as an additional/alternative treatment option, there is wide heterogeneity in the types, doses and schedules of SBRT evaluated in clinical trials, making definitive recommendations for its use challenging. Currently, the optimal sequencing of chemotherapy and SBRT remains unknown [8,16].

The current recommendations for newer chemotherapy regimens are largely based on retrospective data in mixed populations of patients with BRPC and LAPC, or extrapolated from the results of prospective trials in metastatic pancreatic cancer, such as MPACT, which showed an OS benefit with *nab*–paclitaxel + gemcitabine (8.7 months) vs. gemcitabine alone (6.6 months; HR 0.72, p < 0.001) in metastatic disease [17] and PRODIGE4/ACCORD11, which demonstrated an OS benefit with FOLFIRINOX (11.1 months) vs. gemcitabine (6.8 months; HR 0.57, p < 0.001) in metastatic disease [18].

In addition to significant variations in treatment recommendations, the guidelines also differ in assessment and follow-up approaches. A biopsy prior to treatment is recommended by ESMO and NCCN [2,9],

Table 3
Summary of the current recommended management approaches for patients with LAPC in the ESMO, ASCO and NCCN guidelines [2,8,9].

	ESMO	ASCO	NCCN
Assessment	• Biopsy (if chemotherapy or chemoradiotherapy are planned) • CT scan • CA 19–9 measurement • Laparoscopy to exclude peritoneal metastasis not generally accepted	• CT scan • Other staging directed by symptoms • Assessment of symptom burden, psychological status and social supports	• Biopsy • CT or MRI scan • CA 19–9 measurement • Laparoscopy not recommended for unresectable disease
Recommended initial therapy	• 6 months of gemcitabine monotherapy	• Combination chemotherapy	• Good PS: Clinical trial • Poor PS: Single agent chemotherapy
Additional/alternative options	• Chemoradiotherapy with capecitabine	• Chemoradiotherapy • SBRT • Palliative RT	• Good PS: o Combination chemotherapy o 4–6 months induction chemotherapy followed by CRT/SBRT • Poor PS: o Palliative RT o Best supportive care
Follow-up	• Timing not specified • Should focus on symptoms, nutrition and psycho-social support	• Every 3–4 months • Physical examination, liver/renal function, CA 19–9 measurement and CT scan	• Resected patients: o Every 3–6 months for 2 years o Physical examination, CA 19–9 measurement and CT scan

ASCO, American Society of Clinical Oncology; CT, computed tomography; ESMO, European Society for Medical Oncology; MRI, magnetic resonance imaging; NCCN, National Comprehensive Cancer Network; PS, performance status; RT, radiotherapy; SBRT, stereotactic body radiotherapy.

but not by ASCO [8]. Laparoscopy is not generally recommended in LAPC by the ESMO and NCCN guidelines and is not considered in the ASCO guidelines [2,8,9]. Both ESMO and NCCN guidelines recommend CA 19–9 measurement before treatment, and NCCN also recommends CA 19-9 measurement as part of the follow-up schedule, whereas ASCO guidelines only recommend CA 19–9 assessments during follow-up [2,8,9]. The ESMO guidance on the follow-up of patients with LAPC does not provide any recommendations on the timing of follow-up appointments or specific assessments [2].

Overall, the group agreed that the current clinical practice guidelines do not provide sufficient support for the treatment and follow-up of patients with LAPC. In particular, it was noted that the guidelines do not provide an optimal protocol for neoadjuvant treatment in this patient population.

Expert opinion summary statement: There is a lack of prospective data from LAPC patient populations to guide treatment decisions, and consequently no clear consensus on the optimal management approach.

Optimizing the management of LAPC

Given the differences between current treatment guidelines and the poor prognosis of patients with LAPC, there is a clear need to optimize the management of these patients. One treatment approach is the use of chemotherapy or chemoradiotherapy as induction therapy – here we discuss the evidence, coupled with clinical experience, to support the use of induction therapy followed by resection, where appropriate, as a proposed approach to improve the management of patients with LAPC.

The role of induction therapy in LAPC

Due to the poor prognosis and high risk of micrometastases [19], patients with LAPC should be treated as early and as aggressively as possible, including the use of systemic therapy to target both the primary tumour and potential micrometastases. Primary chemotherapy or chemoradiotherapy should be considered in patients with a good PS, with the aim of controlling disease progression, reducing symptoms and maintaining quality of life [8]. In a small number of patients, primary chemotherapy may be successful in shrinking the tumour and converting unresectable LAPC to resectable disease, in which case it is termed 'induction therapy' [8,20].

To date there have been few prospective, randomized controlled trials to assess the benefit of induction chemotherapy in LAPC. The Phase II SCALOP and Phase III LAP07 studies reported that following induction chemotherapy and subsequent chemoradiotherapy or further chemotherapy alone, 58% (SCALOP) and 87% (LAP07) of patients with LAPC had tumour progression, making them unsuitable for subsequent curative treatment [15,21]. Retrospective data have demonstrated an improvement in OS in resected vs. unresected patients with LAPC who had received prior induction chemotherapy [22,23], and subgroup analyses of Phase II studies have reported good progression-free survival (PFS) (17.8–35.2 months) and OS rates (14.0–26.6 months), as well as good resection rates (40.7–41.9%) and R0 status following induction combination chemotherapy (modified FOLFIRINOX or gemcitabine + oxaliplatin) with or without gemcitabine-based chemoradiotherapy in patients with previously unresectable LAPC [24,25].

Expert opinion summary statement: There are retrospective and non-randomized prospective data to support the use of induction combination chemotherapy in patients with LAPC; however, limited data from prospective, randomized trials are available.

Patient selection for induction therapy

LAPC comprises a spectrum of disease states, ranging from patients with aggressive disease that progresses rapidly regardless of the treatment given, to patients who, after initial therapy, remain progression-free for years without further treatment. With this in mind, treatment selection in patients with LAPC should not rely solely on Tumor, Node, Metastasis (TNM) staging and anatomical definitions of resectability.

Conversion to resectable disease following induction therapy is not always prognostic; some patients who do not achieve resectability remain progression-free for years following initial treatment, which may be due to differences in tumour biology. In addition, as noted earlier, a recent study showed that, despite an almost 4-fold higher resection rate between patients with BRPC and LAPC following primary chemotherapy, median survival outcomes were similar between the two groups [12]. This further suggests that resectability status alone is not a reliable prognostic factor in this setting, and that BRPC and LAPC should not necessarily be considered as distinct prognostic subgroups.

In addition to anatomical considerations, patient selection for induction therapy should consider factors such as CA 19–9 levels, PS, weight loss and biochemical parameters. Multiple studies have described a correlation between baseline CA 19–9 levels and resectability or prognosis [26]. Changes in CA 19–9 levels during therapy have also been associated with prognosis; a reduction in serum CA 19–9 in

Table 4
Summary of studies of induction *nab*-paclitaxel + gemcitabine and induction FOLFIRINOX in patients with LAPC.

Ref.	Study type	Patients (n)	Treatment	Outcome
***Nab*–paclitaxel + gemcitabine**				
[63]	Single-centre, pilot study (preliminary analysis)	8	*Nab*–paclitaxel 125 mg/m^2 + gemcitabine 1000 mg/m^2 QW3/4 followed by FOLFIRINOX	5 PR; 3 SD 3 resections (1 pCR)
[64]	Phase I dose finding study (ongoing)	14	Weekly *nab*–paclitaxel (50, 75, 100 mg/m^2) + gemcitabine 600 mg/m^2 + RT	2 PR; 6 SD; 4 PD to date
[65]	Phase Ib dose-finding study	18 UR; 6 BR	*Nab*–paclitaxel (100, 125, 150 mg/m^2) + cisplatin, capecitabine, gemcitabine (PAXG)	16 PR; 8 SD 6 resections (including 3 initially UR) 3 R0; 3 R1
[12]	Retrospective study	223 BR and UR	*Nab*–paclitaxel + gemcitabine (n = 28) Other gemcitabine combinations (n = 195)	106 PR; 103 SD; 11 PD 61 resections 38 R0; 23 R1
[48]	Phase II LAPACT study	107	*Nab*–paclitaxel 125 mg/m^2 + gemcitabine 1000 mg/m^2 QW3/4	35 PR; 48 SD ≥ 16 weeks; 35 SD ≥ 24 weeks; 5 PD 16 resections 7 R0; 9 R1
[49]	Phase II PACT-19 study	54 BR and UR	*Nab*–paclitaxel + gemcitabine (n = 28) *Nab*–paclitaxel + cisplatin, capecitabine, gemcitabine (PAXG) (n = 26)	9 resections in *nab*–paclitaxel + gemcitabine arm (32%) 8 resections in PAXG arm (31%)
FOLFIRINOX				
[66]	Retrospective study	51	FOLFIRINOX ± chemoradiotherapy	10 R0 resections (4 BR; 6 UR)
[67]	Retrospective study	14	FOLFIRINOX	6 PR; 6 SD; 1 PD 4 resections 3 R0; 1 R1
[50]	Retrospective study	575	FOLFIRINOX (n = 125) Gemcitabine-based chemoradiotherapy (n = 322) Other/combinations (n = 128)	76 resections with FOLFIRINOX 31 R0; 45 R1 60.8% resection rate with FOLFIRINOX vs. 48.0% with other treatments
[68]	Phase II study	59 BR and UR	FOLFIRINOX ± chemoradiotherapy	16 resections
[47]	Meta-analysis	315	FOLFIRINOX	25.9% pooled resection rate 78.4% pooled R0 rate in resected patients

BR, borderline resectable; LAPC, locally advanced pancreatic cancer; pCR, complete pathological response; PD, progressive disease; PR, partial response; SD; stable disease; UR, unresectable.

response to neoadjuvant therapy for pancreatic cancer has been shown to correlate with OS (28.0 months in patients with > 50% reduction in CA 19–9 vs. 11.1 months in patients with an increase in CA 19–9; HR 0.26, p < 0.0001) and in patients with BRPC, R0 resection rate (80% in patients with any decrease in CA 19–9 vs. 0% with any increase; p < 0.001) [27]. These data are supported by a more recent retrospective study, which reported improved OS in patients with BRPC or LAPC showing a ≥50% reduction in CA 19–9 following primary chemotherapy (31.5 vs. 15.0 months in patients without a ≥ 50% reduction; p = 0.04) [12].

Performance status is a prognostic factor for patients with pancreatic cancer [11,28], and patients with a good PS may be considered suitable for aggressive treatment. However, cancer cachexia and sarcopenia are prevalent in patients with pancreatic cancer [29,30]. Patients with LAPC are particularly at risk of weight loss due to abdominal pain, fatigue, nausea or malnutrition, and it is important that weight and nutritional status is taken into consideration when selecting patients for treatment. There is evidence that, following induction chemoradiotherapy, patients with LAPC who are obese or who experience less weight loss tend to survive longer than those experiencing more substantial weight loss [31]. Specifically, a loss of visceral adipose tissues has been associated with poorer survival in patients with pancreatic cancer [30,32,33]. It is therefore important that patients showing signs of weight loss are identified early, as cachexia may be treated through nutritional support, exercise and pharmacological treatment; however, there are currently no guidelines on the clinical management of cachexia in pancreatic cancer and no proven pharmacological treatments [33].

In addition to these known prognostic factors, biochemical parameters may also be taken into account – for example, high pre-treatment albumin levels and a neutrophil/lymphocyte ratio ≤5 have been shown to correlate with better survival following SBRT in patients with LAPC [34], although this has not yet been studied in the setting of induction therapy.

Expert opinion summary statement: Selection of patients for induction therapy followed by surgical resection should be on a case-by-case basis and, in addition to TNM and anatomical features (e.g. tumour location, presence of arterial involvement, etc.), should also take into account factors such as CA 19-9 levels, PS, weight loss and biochemical parameters.

Choice of induction chemotherapy

Recommended chemotherapies in LAPC currently include gemcitabine monotherapy, gemcitabine-based combination therapy and the newer regimens of *nab*–paclitaxel + gemcitabine and FOLFIRINOX [2,8,9]. It has recently been proposed that the optimal initial chemotherapy regimen for LAPC should include either *nab*–paclitaxel + gemcitabine or FOLFIRINOX [7]. Supporting this, a recent study in patients with LAPC suggested that induction therapy with newer regimens (*nab*–paclitaxel + gemcitabine or FOLFIRINOX) may be associated with better survival outcomes than induction therapy with older regimens (gemcitabine or 5-FU) [22]. Median OS was 18.3 months with newer regimens vs. 12.7 months with older regimens (p = 0.096) and the use of a newer regimen was an independent predictor of OS on multivariate analysis (HR 0.593 vs. older regimens, p = 0.065).

However, the newer, more active regimens can lead to increased toxicity [7]; therefore the tolerability profiles of different regimens is also a factor in the choice of induction chemotherapy. Although tolerability data for these treatments in LAPC are limited, data from trials in metastatic disease may be extrapolated to the LAPC setting. In MPACT, which evaluated *nab*–paclitaxel + gemcitabine vs. gemcitabine monotherapy in patients with metastatic pancreatic cancer, 38% of patients receiving *nab*–paclitaxel + gemcitabine experienced Grade III/IV neutropenia vs. 27% receiving gemcitabine alone. Febrile neutropenia was

reported in 3% of patients receiving *nab*–paclitaxel + gemcitabine vs. 1% in the gemcitabine group [35]. FOLFIRINOX is particularly associated with high levels of haematological toxicities [7], with significantly more FOLFIRINOX-treated patients experiencing Grade III/IV neutropenia (45.7% vs. 21.0% with gemcitabine; $p < 0.001$) and febrile neutropenia (5.4% vs. 1.2%; $p = 0.03$) in PRODIGE4/ACCORD11 [18]. Clinicians must therefore balance the risk of these side effects against the potential benefits of the therapy – for example, in patients who are potential candidates for subsequent resection, a higher risk of toxicities may be more acceptable when balanced with the increased chance for curative resection. It has been suggested that the tolerability of newer regimens might be improved by dose modifications – for example, one study showed that the toxicities of FOLFIRINOX can be effectively managed by using an 80% dose in combination with growth factor support in carefully selected patients [7]. However, the potential impact of such dose modifications on the efficacy of the regimen remains unclear.

While several retrospective and/or non-randomized studies have investigated the use of *nab*–paclitaxel + gemcitabine or FOLFIRINOX as induction therapy in LAPC (Table 4), there have been no definitive randomized controlled trials or head-to-head trials comparing these regimens in this setting. While prospective trials to compare these regimens are underway, it is not currently possible to recommend one over the other for induction therapy in patients with LAPC.

Expert opinion summary statement: Induction chemotherapy with a newer combination regimen (i.e. *nab*–paclitaxel + gemcitabine or FOLFIRINOX) should be considered as an option, despite the lack of prospective data in LAPC. Currently, there are no prospective data to recommend one of these newer combinations over the other.

Duration of induction therapy and assessment protocol

Factors to consider when deciding the optimal duration of induction therapy include patient PS, tolerability of the induction chemotherapy regimen and tumour response during induction chemotherapy, as well as the impact of induction therapy duration on patient selection for surgery and the risk of surgical complications. There is a paucity of clinical trial data to guide the optimal duration of induction therapy in patients with LAPC, therefore the suggestions discussed here are based on the authors' clinical experience and expert opinion.

Most of the physicians in the group agreed that, depending on the specific induction chemotherapy regimen selected, a maximum of 6 cycles of induction therapy should initially be administered in patients with LAPC, providing the patient has a good PS and can tolerate the regimen. The group recommended that the duration of induction chemotherapy should not exceed 6 cycles in order to minimize the risk of surgical complications in patients who demonstrate evidence of conversion to resectable disease. The aims of this induction schedule are to control disease (including treating potential micrometastases) and reduce the size of the tumour, leading to subsequent evaluation of the patient's suitability for resection.

The group recommended that during induction chemotherapy, patients should be assessed and restaged every 2–3 months/cycles, and the findings discussed by a multidisciplinary team. Retrospective data have indicated that traditional computed tomography (CT) imaging is not always reliable for post-induction therapy evaluation in patients with LAPC; in a study of 40 patients with unresectable disease who received neoadjuvant FOLFIRINOX therapy, CT-based assessment of resectability identified 12/40 patients (30%) as having resectable disease after FOLFIRINOX treatment, however R0 was achieved in 35/40 patients (92%) [36]. In light of these findings, the physicians suggested that additional imaging approaches (e.g. magnetic resonance imaging or positron emission tomography) and assessments of surrogate tumour markers (e.g. CA 19–9 levels) should be considered in this setting. The group proposed that patients with a clear tumour response to induction therapy should be re-evaluated by the multidisciplinary team for resectability.

Expert opinion summary statement: Patients with LAPC should ideally receive a maximum of 6 cycles of induction chemotherapy in the absence of disease progression or undue toxicity, with regular assessment and restaging to determine clinical response and potential resectability.

Patient selection for surgery after induction therapy

There are currently no guidelines governing how to select patients with previously unresectable LAPC for surgery after primary therapy. Patient selection for surgical resection generally relies on radiographical imaging, however, this has limitations as the presence of dense stroma and treatment-related fibrosis may mask tumour shrinkage [37]. Tumours that appear unresectable on radiographical imaging may be surgically resectable; in a retrospective analysis of 122 patients restaged after receiving neoadjuvant therapy for BRPC, only 1 (0.8%) had their disease downstaged to resectable based on CT imaging, whereas 85 (66%) underwent surgical resection, of which 81 (95%) achieved R0 status [38].

Additional criteria are therefore needed to guide the decision to refer patients with previously unresectable LAPC to surgery after induction therapy. A recent retrospective analysis has suggested that CA 19–9 response to induction chemotherapy may be a clinical marker for referral to surgery in patients with LAPC [12]. In an analysis of data from a prospective study of patients with LAPC, a ≥30% decrease in CA 19–9 was associated with improved survival (22.4 vs. 12.7 months in patients without a ≥30% reduction; $p = 0.02$) and correctly classified 9/10 patients as resectable after induction chemotherapy [39]. Although these data are promising, further research into more effective markers, such as biological and molecular factors, is needed.

The physicians suggested that patients who do not show disease progression on radiological imaging may be considered for exploratory laparotomy, in line with the St Gallen EORTC Gastrointestinal Cancer Conference consensus recommendations for restaging after induction therapy in patients with BRPC [40]. Patients with no clear tumour response according to radiological imaging or surrogate tumour markers after 6 cycles of induction therapy should not be referred for surgical resection, and other treatment options, such as chemoradiotherapy or continuation with chemotherapy, may be discussed. Prospective clinical trials are needed to evaluate whether these patients may benefit from surgical exploration to confirm unresectability.

Expert opinion summary statement: There is an unmet need for guidelines on the optimal selection of patients who are suitable for resection following induction therapy. Radiographical imaging has been shown to be unreliable in these patients and more accurate markers are needed. Patients who do not have radiological evidence of disease progression may be considered for exploratory laparotomy.

Surgical outcomes following induction chemotherapy

Induction chemotherapy may impact on surgical outcomes, including effects on resection status (R0/R1/R2) and post-operative morbidity and mortality. R2 resections are known to be associated with a poor prognosis, with one retrospective study of almost 45,000 patients reporting a median survival of 9.8 months in patients undergoing R2 resection vs. 19.7 months for R0, 14.3 months for R1 and 10.3 months for no surgery [41]. Factors that influence R0 resection rates may include the specific definition of R0 used [42], variations in patient selection for resection, and the duration and type of induction therapy used. Currently, the impact of induction therapy on tumour downsizing and subsequent resection status can only be speculated based on studies in mixed populations of patients with LAPC and BRPC. Induction therapy with *nab*–paclitaxel + gemcitabine has been associated with high R0 resection rates (92–95%) in patients with resectable disease or BRPC [43,44]. In a retrospective study of patients with BRPC

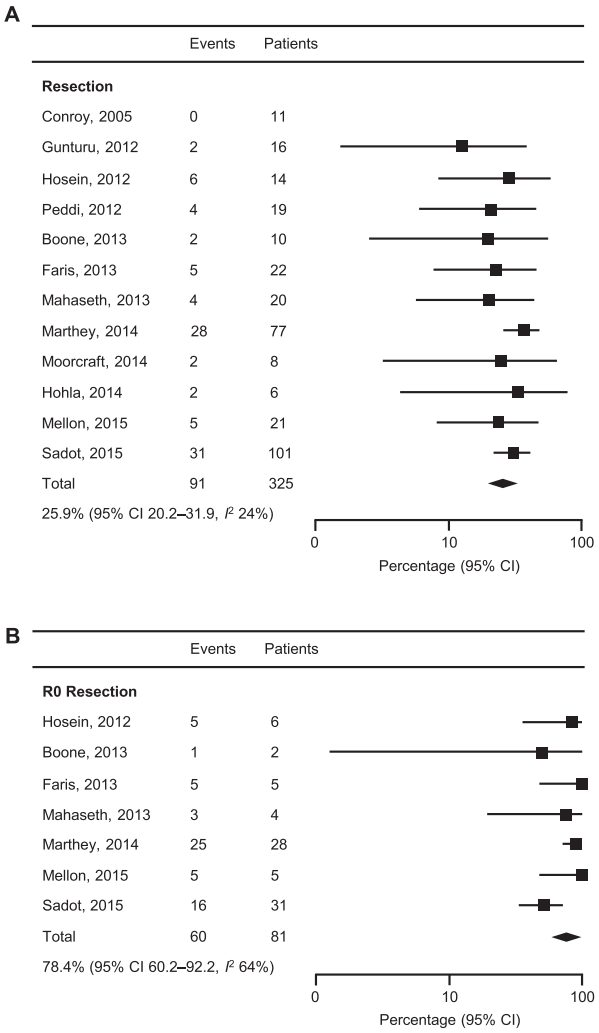

Fig. 1. Forest plots from meta-analysis showing the percentage of patients who underwent resection (A) and R0 resection (B) following induction therapy with FOLFIRINOX [47]. CI, confidence interval. Note: Copyright permission to reproduce these figures will be provided by the authors upon acceptance of the manuscript prior to publication.

or LAPC receiving induction FOLFIRINOX with or without chemoradiotherapy, R0 resection was achieved in 83.3% of patients and a pathologic major response was achieved in 23.2%, with improved outcomes achieved with the addition of chemoradiotherapy [45]. Other retrospective studies in patients with LAPC or BRPC have shown that induction therapy with FOLFIRINOX was associated with a lower positive lymph node rate (35%) than surgery alone (79%; $p < 0.001$) and a higher R0 resection rate (92% vs. 86% with surgery alone) [36]. Another study showed that induction FOLFIRINOX with or without chemoradiotherapy was associated with significant tumour size decreases and an R0 resection rate of 86% [46]. Furthermore, a recent meta-analysis reported that induction therapy with FOLFIRINOX was associated with a pooled R0 resection rate of 78.4% in patients with LAPC (Fig. 1) [47].

A prospective Phase II trial of induction *nab*–paclitaxel + gemcitabine in previously untreated patients with unresectable LAPC (LAPACT) was recently completed. In this trial, patients received treatment with 6 cycles of *nab*–paclitaxel + gemcitabine, after which patients without disease progression or unacceptable adverse events underwent continued treatment with *nab*–paclitaxel + gemcitabine, chemoradiotherapy or surgical resection. In total, 106 patients received induction therapy with *nab*–paclitaxel + gemcitabine. Of 45 patients who completed induction therapy and continued with protocol-specified treatment, 12 continued with *nab*–paclitaxel + gemcitabine, 17 received chemoradiotherapy and 16 underwent surgery [48]. Of the 16 patients who underwent surgery, 7 achieved R0 status. PACT–19 (NCT01730222) was a randomized, open-label Phase II trial of *nab*–paclitaxel + gemcitabine vs. PAXG regimen (*nab*–paclitaxel, gemcitabine, cisplatin and capecitabine) in 54 patients with LAPC or BRPC. Resection rates were 32% (9/28 patients) in the *nab*–paclitaxel + gemcitabine arm and 31% (8/26 patients) in the PAXG arm [49]. Other ongoing trials of note include NEOLAP (NCT02125136), a randomized, open-label Phase II trial comparing resection conversion rates in patients with BRPC or LAPC following primary therapy with *nab*–paclitaxel + gemcitabine followed by further *nab*–paclitaxel + gemcitabine or FOLFIRINOX, and CONKO-007 (NCT01827553), a randomized, open-label Phase III trial evaluating induction therapy with FOLFIRINOX or gemcitabine in LAPC, followed by chemoradiotherapy or chemotherapy alone, in which R0 rate is a secondary endpoint.

To date, studies have generally shown that induction combination chemotherapy regimens do not increase post-operative morbidity or mortality, compared with upfront surgery [50], although induction therapy with FOLFIRINOX in patients with LAPC and BRPC has been associated with longer operative times (394 vs. 300 min with no induction therapy; $p < 0.001$) and blood loss (600 mL vs. 400 mL; $p = 0.007$) [36]. The increase in operative time was considered to be due to the additional dissection of critical vessels, and these more technically challenging operations resulted in increased blood loss. However, despite the longer operation times and increased blood loss, overall post-operative morbidity was lower in the FOLFIRINOX group [36]. A further consideration is the association of pancreaticoduodenectomy with hepatic steatosis [51,52]. As FOLFIRINOX can affect liver function [53], it is important to be aware of an increased risk of post-operative liver complications in patients receiving FOLFIRINOX induction therapy.

Expert opinion summary statement: While induction therapy with *nab*–paclitaxel + gemcitabine or FOLFIRINOX may result in high R0 resection rates in patients deemed suitable for surgery, surgeons must be aware of the potential for induction chemotherapy to increase the risk of complications during or after surgery.

Management of resected patients (after induction therapy) with LAPC

Although results from mixed population studies and interim data from the LAPACT trial indicate that a reasonable R0 resection rate (36–95%) can be achieved in patients with LAPC who undergo induction chemotherapy followed by surgery, the risk of relapse remains high due to the likely presence of micrometastases in these patients [54]. In the absence of prospective data in patients with LAPC, the suggested approach to post-resection management of these patients is based on studies in BRPC and/or resectable disease.

Several randomized studies have shown that adjuvant chemotherapy after R0 or R1 resection consistently increases 5-year survival by at least 11% compared with surgery alone in patients with resectable pancreatic cancer [40,55–57]. On this basis, the physicians in the group suggested that patients with LAPC who undergo resection after induction therapy should receive adjuvant chemotherapy up to a maximum of 6 cycles. In patients achieving an R0 resection with negative lymph nodes after induction therapy, the group proposed that the same chemotherapy regimen should be continued after surgery up to a maximum of 6 cycles, provided there were no tolerability issues with the induction regimen and depending on cumulative toxicities, particularly neuropathy. In patients with an R1 resection and positive lymph nodes, some of the physicians proposed that chemoradiotherapy could be considered if not used pre-operatively. As this outcome suggests a suboptimal response to the induction chemotherapy used, a change in chemotherapy regimen could also be considered. The

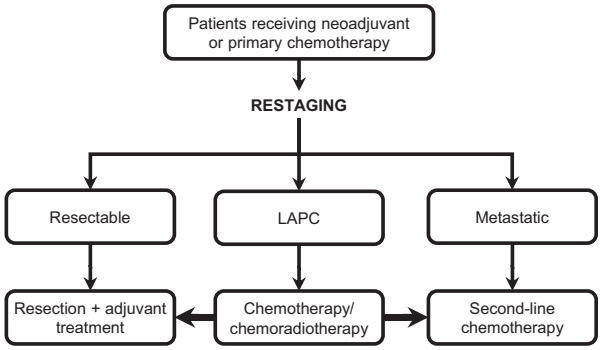

Fig. 2. Proposed algorithm for patients with LAPC receiving primary chemotherapy. LAPC, locally advanced pancreatic cancer.

physicians also highlighted that many patients are exhausted following induction therapy and surgery, and that not all patients are able to tolerate chemotherapy within a short timeframe after major surgery, so it is important to consider adjuvant treatment options on an individual patient basis.

Expert opinion summary statement: Patients with LAPC who undergo R0 or R1 resection after induction chemotherapy may be offered adjuvant chemotherapy to reduce the risk of recurrence. Chemoradiotherapy may be considered in patients with an R1 resection and positive lymph nodes, if not used pre-operatively. The choice of adjuvant therapy is influenced by response to induction therapy and patient tolerability.

Conclusions

LAPC is associated with poor prognosis and is generally considered incurable. Nevertheless, available evidence suggests that patients with LAPC benefit from primary chemotherapy to prolong PFS and OS, with a proportion of these patients subsequently achieving resectable status and an R0 resection. Fig. 2 outlines a proposed algorithm for the management of patients in this setting. Extrapolation from retrospective analyses as well as prospective data from the metastatic setting strongly suggest that newer combination chemotherapy regimens, such as *nab*–paclitaxel + gemcitabine and FOLFIRINOX, are more effective than older regimens in this treatment setting.

Randomized, controlled studies of induction chemotherapy in patients with LAPC are needed to confirm the optimal approach in this patient population. In the meantime, our expert opinion is that use of induction chemotherapy with either *nab*–paclitaxel + gemcitabine or FOLFIRINOX should be a treatment option included in international treatment guidelines for patients with LAPC who are able to tolerate chemotherapy.

Acknowledgements

The authors received medical writing support in the preparation of this manuscript from Sian-Marie Lucas and Angela Corstorphine of Kstorfin Medical Communications Ltd. This support was funded by Celgene International Sárl. The authors take full responsibility for all content and editorial decisions for this manuscript.

Declaration of Competing Interest

Thomas Seufferlein has received research grants from Celgene, Sanofi-Genzyme and Boehringer Ingelheim; personal fees from Celgene, Servier, Roche, Merck, Falk Foundation, Shire and Sanofi-Genzyme; and non-financial support from Merck, outside the submitted work; **Pascal Hammel** has received research grants from Celgene, AstraZeneca, Erythec and Halozyme; personal fees from Halozyme; and non-financial support from Erythec, during the conduct of the study; **Teresa Macarulla** has received research grants from Shire Pharmaceuticals, Roche, Tesaro, Baxter, Sanofi, Celgene, QED Therapeutics, Genzyme Europe, Baxalta, Bayer, Incyte and Genzyme; and travel support from Merck, H3 Biomedicine, Bayer and Sanofi, outside the submitted work; **Gerald W. Prager** has received advisory board honoraria fees from Celgene, Shire, Roche, Servier, BMS, Halozyme, Merck, Amgen, outside the submitted work, outside the submitted work; **Michele Reni** has received research grants from Celgene; personal fees from Celgene, Baxalta, Shire, Eli-Lilly, Pfizer, Novocure and Novartis; non-financial support from Celgene; and is a steering committee member for Celgene, AstraZeneca and Boston Pharmaceuticals, outside the submitted work; **Philip A. Philip** has received research grants and personal fees from Celgene and Ipsen during the conduct of the study; research grants and personal fees from Merck, Rafael, Halozyme and Bayer; and research grants from QED, Novartis, AstraZeneca and Eli-Lilly, outside the submitted work; **Eric Van Cutsem** has received research grants from Amgen, Bayer, Boehringer Ingelheim, Celgene, Ipsen, Lilly, Roche, Merck Sharp & Dohme, Merck KGaA, Novartis, Roche and Servier; and personal fees for consultancy from Amgen, Bayer, Boehringer Ingelheim, Celgene, Ipsen, Lilly, Roche, Merck Sharp & Dohme, Merck KGaA, Novartis, Roche and Servier, outside the submitted work; **Jean Robert Delpero, Per Pfeiffer** and **Massimo Falconi** have no conflicts of interest to disclose.

Author contribution statement

All authors contributed to the conception and design of the review, revised it critically for important intellectual content and approved the final version to be submitted.

References

[1] Ilic M, Ilic I. Epidemiology of pancreatic cancer. World J Gastroenterol 2016;22:9694–705. https://doi.org/10.3748/wjg.v22.i44.9694.
[2] Ducreux M, Cuhna AS, Caramella C, Hollebecque A, Burtin P, Goere D, et al. Cancer of the pancreas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2015;26(Suppl 5):v56–68. https://doi.org/10.1093/annonc/mdv295.
[3] Malvezzi M, Carioli G, Bertuccio P, Boffetta P, Levi F, La Vecchia C, et al. European cancer mortality predictions for the year 2017, with focus on lung cancer. Ann Oncol 2017;28:1117–23. https://doi.org/10.1093/annonc/mdx033.
[4] Ferlay J, Partensky C, Bray F. More deaths from pancreatic cancer than breast cancer in the EU by 2017. Acta Oncol 2016;55:1158–60. https://doi.org/10.1080/0284186x.2016.1197419.
[5] Salami A, Alvarez NH, Joshi ART. Geographic disparities in surgical treatment recommendation patterns and survival for pancreatic adenocarcinoma. HPB (Oxford) 2017;19:1008–15. https://doi.org/10.1016/j.hpb.2017.07.009.
[6] Woodmass J, Lipschitz J, McKay A. Physician attitudes and treatment patterns for pancreatic cancer. World J Surg Oncol 2011;9:21. https://doi.org/10.1186/1477-7819-9-21.
[7] Martin 2nd RC. Management of locally advanced pancreatic cancer. Surg Clin North Am 2016;96:1371–89. https://doi.org/10.1016/j.suc.2016.07.010.
[8] Balaban EP, Mangu PB, Khorana AA, Shah MA, Mukherjee S, Crane CH, et al. Locally advanced, unresectable pancreatic cancer: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol 2016;34:2654–68. https://doi.org/10.1200/jco.2016.67.5561.
[9] NCCN. Clinical practice guidelines in oncology. Pancreatic adenocarcinoma Version 1.2019; 2019. https://www.nccn.org/professionals/physician_gls/pdf/pancreatic.pdf [accessed 20 March 2019].
[10] Taieb J, Pointet AL, Van Laethem JL, Laquente B, Pernot S, Lordick F, et al. What treatment in 2017 for inoperable pancreatic cancers? Ann Oncol 2017;28:1473–83. https://doi.org/10.1093/annonc/mdx174.
[11] Vernerey D, Huguet F, Vienot A, Goldstein D, Paget-Bailly S, Van Laethem JL, et al. Prognostic nomogram and score to predict overall survival in locally advanced untreated pancreatic cancer (PROLAP). Br J Cancer 2016;115:281–9. https://doi.org/10.1038/bjc.2016.212.
[12] Reni M, Zanon S, Balzano G, Nobile S, Pircher CC, Chiaravalli M, et al. Selecting patients for resection after primary chemotherapy for non-metastatic pancreatic adenocarcinoma. Ann Oncol 2017;28:2786–92. https://doi.org/10.1093/annonc/mdx495.
[13] Chauffert B, Mornex F, Bonnetain F, Rougier P, Mariette C, Bouche O, et al. Phase III trial comparing intensive induction chemoradiotherapy (60 Gy, infusional 5-FU and intermittent cisplatin) followed by maintenance gemcitabine with gemcitabine alone for locally advanced unresectable pancreatic cancer. Definitive results of the 2000–01 FFCD/SFRO study. Ann Oncol 2008;19:1592–9. https://doi.org/10.1093/annonc/mdn281.

[14] Loehrer Sr. PJ, Feng Y, Cardenes H, Wagner L, Brell JM, Cella D, et al. Gemcitabine alone versus gemcitabine plus radiotherapy in patients with locally advanced pancreatic cancer: an Eastern Cooperative Oncology Group trial. J Clin Oncol 2011;29:4105–12. https://doi.org/10.1200/jco.2011.34.8904.
[15] Hammel P, Huguet F, van Laethem JL, Goldstein D, Glimelius B, Artru P, et al. Effect of chemoradiotherapy vs chemotherapy on survival in patients with locally advanced pancreatic cancer controlled after 4 months of gemcitabine with or without erlotinib: the LAP07 randomized clinical trial. JAMA 2016;315:1844–53. https://doi.org/10.1001/jama.2016.4324.
[16] Petrelli F, Comito T, Ghidini A, Torri V, Scorsetti M, Barni S. Stereotactic body radiation therapy for locally advanced pancreatic cancer: a systematic review and pooled analysis of 19 trials. Int J Radiat Oncol Biol Phys 2017;97:313–22. https://doi.org/10.1016/j.ijrobp.2016.10.030.
[17] Goldstein D, El-Maraghi RH, Hammel P, Heinemann V, Kunzmann V, Sastre J, et al. nab-Paclitaxel plus gemcitabine for metastatic pancreatic cancer: long-term survival from a phase III trial. J Natl Cancer Inst 2015;107. https://doi.org/10.1093/jnci/dju413.
[18] Conroy T, Desseigne F, Ychou M, Bouche O, Guimbaud R, Becouarn Y, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med 2011;364:1817–25. https://doi.org/10.1056/NEJMoa1011923.
[19] Kayahara M, Funaki K, Tajima H, Takamura H, Ninomiya I, Kitagawa H, et al. Surgical implication of micrometastasis for pancreatic cancer. Pancreas 2010;39:884–8. https://doi.org/10.1097/MPA.0b013e3181ce6daa.
[20] Puleo F, Marechal R, Demetter P, Bali MA, Calomme A, Closset J, et al. New challenges in perioperative management of pancreatic cancer. World J Gastroenterol 2015;21:2281–93. https://doi.org/10.3748/wjg.v21.i8.2281.
[21] Mukherjee S, Hurt CN, Bridgewater J, Falk S, Cummins S, Wasan H, et al. Gemcitabine-based or capecitabine-based chemoradiotherapy for locally advanced pancreatic cancer (SCALOP): a multicentre, randomised, phase 2 trial. Lancet Oncol 2013;14:317–26. https://doi.org/10.1016/s1470-2045(13)70021-4.
[22] Bednar F, Zenati MS, Steve J, Winters S, Ocuin LM, Bahary N, et al. Analysis of predictors of resection and survival in locally advanced stage III pancreatic cancer: does the nature of chemotherapy regimen influence outcomes? Ann Surg Oncol 2017;24:1406–13. https://doi.org/10.1245/s10434-016-5707-0.
[23] Gemenetzis G, Groot VP, Blair AB, Laheru DA, Zheng L, Narang AK, et al. Survival in locally advanced pancreatic cancer after neoadjuvant therapy and surgical resection. Ann Surg 2018. https://doi.org/10.1097/sla.0000000000002753.
[24] Stein SM, James ES, Deng Y, Cong X, Kortmansky JS, Li J, et al. Final analysis of a phase II study of modified FOLFIRINOX in locally advanced and metastatic pancreatic cancer. Br J Cancer 2016;114:737–43. https://doi.org/10.1038/bjc.2016.45.
[25] Fiore M, Ramella S, Valeri S, Caputo D, Floreno B, Trecca P, et al. Phase II study of induction chemotherapy followed by chemoradiotherapy in patients with borderline resectable and unresectable locally advanced pancreatic cancer. Sci Rep 2017;7:45845. https://doi.org/10.1038/srep45845.
[26] Chang JC, Kundranda M. Novel diagnostic and predictive biomarkers in pancreatic adenocarcinoma. Int J Mol Sci 2017;18. https://doi.org/10.3390/ijms18030667.
[27] Boone BA, Steve J, Zenati MS, Hogg ME, Singhi AD, Bartlett DL, et al. Serum CA 19–9 response to neoadjuvant therapy is associated with outcome in pancreatic adenocarcinoma. Ann Surg Oncol 2014;21:4351–8. https://doi.org/10.1245/s10434-014-3842-z.
[28] Khorana AA, Mangu PB, Berlin J, Engebretson A, Hong TS, Maitra A, et al. Potentially curable pancreatic cancer: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol 2016;34:2541–56. https://doi.org/10.1200/jco.2016.67.5553.
[29] Hendifar AE, Chang JI, Huang BZ, Tuli R, Wu BU. Cachexia, and not obesity, prior to pancreatic cancer diagnosis worsens survival and is negated by chemotherapy. J Gastrointest Oncol 2018;9:17–23. https://doi.org/10.21037/jgo.2017.11.10.
[30] Dalal S, Hui D, Bidaut L, Lem K, Del Fabbro E, Crane C, et al. Relationships among body mass index, longitudinal body composition alterations, and survival in patients with locally advanced pancreatic cancer receiving chemoradiation: a pilot study. J Pain Symptom Manage 2012;44:181–91. https://doi.org/10.1016/j.jpainsymman.2011.09.010.
[31] Naumann P, Habermehl D, Welzel T, Debus J, Combs SE. Outcome after neoadjuvant chemoradiation and correlation with nutritional status in patients with locally advanced pancreatic cancer. Strahlenther Onkol 2013;189:745–52. https://doi.org/10.1007/s00066-013-0393-3.
[32] Tan BH, Birdsell LA, Martin L, Baracos VE, Fearon KC. Sarcopenia in an overweight or obese patient is an adverse prognostic factor in pancreatic cancer. Clin Cancer Res 2009;15:6973–9. https://doi.org/10.1158/1078-0432.ccr-09-1525.
[33] Mueller TC, Burmeister MA, Bachmann J, Martignoni ME. Cachexia and pancreatic cancer: are there treatment options? World J Gastroenterol 2014;20:9361–73. https://doi.org/10.3748/wjg.v20.i28.9361.
[34] Alagappan M, Pollom EL, von Eyben R, Kozak MM, Aggarwal S, Poultsides GA, et al. Albumin and neutrophil-lymphocyte ratio (NLR) predict survival in patients with pancreatic adenocarcinoma treated with SBRT. Am J Clin Oncol 2018;41:242–7. https://doi.org/10.1097/coc.0000000000000263.
[35] Von Hoff DD, Ervin T, Arena FP, Chiorean EG, Infante J, Moore M, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. N Engl J Med 2013;369:1691–703. https://doi.org/10.1056/NEJMoa1304369.
[36] Ferrone CR, Marchegiani G, Hong TS, Ryan DP, Deshpande V, McDonnell EI, et al. Radiological and surgical implications of neoadjuvant treatment with FOLFIRINOX for locally advanced and borderline resectable pancreatic cancer. Ann Surg 2015;261:12–7. https://doi.org/10.1097/sla.0000000000000867.
[37] Verbeke C, Lohr M, Karlsson JS, Del Chiaro M. Pathology reporting of pancreatic cancer following neoadjuvant therapy: challenges and uncertainties. Cancer Treat Rev 2015;41:17–26. https://doi.org/10.1016/j.ctrv.2014.11.002.
[38] Katz MH, Fleming JB, Bhosale P, Varadhachary G, Lee JE, Wolff R, et al. Response of borderline resectable pancreatic cancer to neoadjuvant therapy is not reflected by radiographic indicators. Cancer 2012;118:5749–56. https://doi.org/10.1002/cncr.27636.
[39] van Veldhuisen E, Vogel JA, Klompmaker S, Busch OR, van Laarhoven HWM, van Lienden KP, et al. Added value of CA19-9 response in predicting resectability of locally advanced pancreatic cancer following induction chemotherapy. HPB (Oxford) 2018. https://doi.org/10.1016/j.hpb.2018.01.001.
[40] Lutz MP, Zalcberg JR, Ducreux M, Aust D, Bruno MJ, Buchler 3rd MW, et al. EORTC Gastrointestinal Cancer Conference: consensus recommendations on controversial issues in the primary treatment of pancreatic cancer. Eur J Cancer 2017;79:41–9. https://doi.org/10.1016/j.ejca.2017.03.022.
[41] Torgeson A, Garrido-Laguna I, Tao R, Cannon GM, Scaife CL, Lloyd S. Value of surgical resection and timing of therapy in patients with pancreatic cancer at high risk for positive margins. ESMO Open 2018;3:e000282. https://doi.org/10.1136/esmoopen-2017-000282.
[42] John BJ, Naik P, Ironside A, Davidson BR, Fusai G, Gillmore R, et al. Redefining the R1 resection for pancreatic ductal adenocarcinoma: tumour lymph nodal burden and lymph node ratio are the only prognostic factors associated with survival. HPB (Oxford) 2013;15:674–80. https://doi.org/10.1111/hpb.12019.
[43] Alvarez-Gallego R, Cubillo A, Rodriguez-Pascual J, Quijano Y, De Vicente E, Garcia L, et al. Antitumor activity of nab-paclitaxel and gemcitabine in resectable pancreatic cancer. J Clin Oncol 2012;30. Suppl. Abstr 4040.
[44] MacKenzie S, Zeh H, McCahill LE, Sielaff TD, Bahary N, Gribbin TE, et al. A pilot phase II multicenter study of nab-paclitaxel (Nab-P) and gemcitabine (G) as preoperative therapy for potentially resectable pancreatic cancer (PC). J Clin Oncol 2013;31. Suppl. Abstr 4038.
[45] Pietrasz D, Turrini O, Vendrely V, Simon JM, Hentic O, Coriat R, et al. How does chemoradiotherapy following induction FOLFIRINOX improve the results in resected borderline or locally advanced pancreatic adenocarcinoma? An AGEO-FRENCH multicentric cohort. Ann Surg Oncol 2019;26:109–17. https://doi.org/10.1245/s10434-018-6931-6.
[46] Wagner M, Antunes C, Pietrasz D, Cassinotto C, Zappa M, Sa Cunha A, et al. CT evaluation after neoadjuvant FOLFIRINOX chemotherapy for borderline and locally advanced pancreatic adenocarcinoma. Eur Radiol 2017;27:3104–16. https://doi.org/10.1007/s00330-016-4632-8.
[47] Suker M, Beumer BR, Sadot E, Marthey L, Faris JE, Mellon EA, et al. FOLFIRINOX for locally advanced pancreatic cancer: a systematic review and patient-level meta-analysis. Lancet Oncol 2016;17:801–10. https://doi.org/10.1016/s1470-2045(16)00172-8.
[48] Hammel P, Lacy J, Portales F, Sobrero A, Pazo-Cid R, Manzano Mozo JL, et al. Phase II LAPACT trial of nab-paclitaxel (nab-P) plus gemcitabine (G) for patients with locally advanced pancreatic cancer (LAPC). J Clin Oncol 2018;36. Suppl. Abstr 204.
[49] Reni M, Zanon S, Balzano G, Passoni P, Pircher C, Chiaravalli M, et al. A randomised phase 2 trial of nab-paclitaxel plus gemcitabine with or without capecitabine and cisplatin in locally advanced or borderline resectable pancreatic adenocarcinoma. Eur J Cancer 2018;102:95–102. https://doi.org/10.1016/j.ejca.2018.07.007.
[50] Hackert T, Sachsenmaier M, Hinz U, Schneider L, Michalski CW, Springfeld C, et al. Locally advanced pancreatic cancer: neoadjuvant therapy with FOLFIRINOX results in resectability in 60% of the patients. Ann Surg 2016;264:457–63. https://doi.org/10.1097/sla.0000000000001850.
[51] Kato H, Isaji S, Azumi Y, Kishiwada M, Hamada T, Mizuno S, et al. Development of nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH) after pancreaticoduodenectomy: proposal of a postoperative NAFLD scoring system. J Hepatobil Pancreat Sci 2010;17:296–304. https://doi.org/10.1007/s00534-009-0187-2.
[52] Mignot A, Ayav A, Quillot D, Zuily S, Petit I, Nguyen-Thi PL, et al. Extensive lymph node dissection during pancreaticoduodenectomy: a risk factor for hepatic steatosis? Abdom Radiol (NY) 2017;42:1880–7. https://doi.org/10.1007/s00261-017-1087-6.
[53] Marsh Rde W, Talamonti MS, Katz MH, Herman JM. Pancreatic cancer and FOLFIRINOX: a new era and new questions. Cancer Med 2015;4:853–63. https://doi.org/10.1002/cam4.433.
[54] Bittoni A, Santoni M, Lanese A, Pellei C, Andrikou K, Stefano C. Neoadjuvant therapy in pancreatic cancer: an emerging strategy. Gastroenterol Res Pract 2014;2014:183852. https://doi.org/10.1155/2014/183852.
[55] Neoptolemos JP, Stocken DD, Friess H, Bassi C, Dunn JA, Hickey H, et al. A randomized trial of chemoradiotherapy and chemotherapy after resection of pancreatic cancer. N Engl J Med 2004;350:1200–10. https://doi.org/10.1056/NEJMoa032295.
[56] Uesaka K, Boku N, Fukutomi A, Okamura Y, Konishi M, Matsumoto I, et al. Adjuvant chemotherapy of S-1 versus gemcitabine for resected pancreatic cancer: a phase 3, open-label, randomised, non-inferiority trial (JASPAC 01). Lancet 2016;388:248–57. https://doi.org/10.1016/s0140-6736(16)30583-9.
[57] Oettle H, Post S, Neuhaus P, Gellert K, Langrehr J, Ridwelski K, et al. Adjuvant chemotherapy with gemcitabine vs observation in patients undergoing curative-intent resection of pancreatic cancer: a randomized controlled trial. JAMA 2007;297:267–77. https://doi.org/10.1001/jama.297.3.267.
[58] Katz MH, Marsh R, Herman JM, Shi Q, Collison E, Venook AP, et al. Borderline resectable pancreatic cancer: need for standardization and methods for optimal clinical trial design. Ann Surg Oncol 2013;20:2787–95. https://doi.org/10.1245/s10434-013-2886-9.
[59] Varadhachary GR, Tamm EP, Abbruzzese JL, Xiong HQ, Crane CH, Wang H, et al. Borderline resectable pancreatic cancer: definitions, management, and role of preoperative therapy. Ann Surg Oncol 2006;13:1035–46. https://doi.org/10.1245/

aso.2006.08.011.
[60] Lopez NE, Prendergast C, Lowy AM. Borderline resectable pancreatic cancer: definitions and management. World J Gastroenterol 2014;20:10740–51. https://doi.org/10.3748/wjg.v20.i31.10740.
[61] Bockhorn M, Uzunoglu FG, Adham M, Imrie C, Milicevic M, Sandberg AA, et al. Borderline resectable pancreatic cancer: a consensus statement by the International Study Group of Pancreatic Surgery (ISGPS). Surgery 2014;155:977–88. https://doi.org/10.1016/j.surg.2014.02.001.
[62] Isaji S, Mizuno S, Windsor JA, Bassi C, Fernandez-Del Castillo C, Hackert T, et al. International consensus on definition and criteria of borderline resectable pancreatic ductal adenocarcinoma 2017. Pancreatology 2018;18:2–11. https://doi.org/10.1016/j.pan.2017.11.011.
[63] Kunzmann V, Hartlapp I, Scheurlen M, Einsele H, Mueller J, Kenn W, et al. Sequential neoadjuvant chemotherapy with nab-paclitaxel plus gemcitabine and FOLFIRINOX in locally advanced pancreatic cancer (LAPC): A PILOT study. J Clin Oncol 2013;31:e15193-e. https://doi.org/10.1200/jco.2013.31.15_suppl.e15193.
[64] Sueyoshi H, Ioka T, Tamura T, Takada R, Fukutake N, Ashida R, et al. Phase I study of chemoradiation therapy (nab-paclitaxel/Gemcitabine) in 15 patients with unresectable locally advanced pancreatic cancer (UR-LAPC). J Clin Oncol 2015;33:475. https://doi.org/10.1200/jco.2015.33.3_suppl.475.
[65] Reni M, Balzano G, Zanon S, Passoni P, Nicoletti R, Arcidiacono PG, et al. Phase 1B trial of Nab-paclitaxel plus gemcitabine, capecitabine, and cisplatin (PAXG regimen) in patients with unresectable or borderline resectable pancreatic adenocarcinoma. Br J Cancer 2016;115:290–6. https://doi.org/10.1038/bjc.2016.209.
[66] Khushman M, Dempsey N, Maldonado JC, Loaiza-Bonilla A, Velez M, Carcas L, et al. Full dose neoadjuvant FOLFIRINOX is associated with prolonged survival in patients with locally advanced pancreatic adenocarcinoma. Pancreatology 2015;15:667–73. https://doi.org/10.1016/j.pan.2015.08.010.
[67] Nitsche U, Wenzel P, Siveke JT, Braren R, Holzapfel K, Schlitter AM, et al. Resectability after first-line FOLFIRINOX in initially unresectable locally advanced pancreatic cancer: a single-center experience. Ann Surg Oncol 2015;22(Suppl 3):S1212–20. https://doi.org/10.1245/s10434-015-4851-2.
[68] Pfeiffer P, Ladekarl M, Mortensen MB, Fromm AL, Bjerregaard JK. Chemotherapy for patients with non-resectable pancreatic cancer with additional chemo-radiotherapy for patients with potentially resectable tumours: final results. Ann Oncol 2016;27:680P-P. https://doi.org/10.1093/annonc/mdw371.72.