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Personalized treatment in localized pancreatic cancer

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Summary The treatment elements used for pancreatic ductal adenocarcinoma (PDAC) include surgical resection, systemic cytotoxic agents, and targeted drugs. For second- and third-line therapies in PDAC, approximately 15% of patients have actionable mutations although only 2.5% receive matched targeted treatment but with a significant improvement in survival of around 16 months. For the majority of PDAC patients the current most effective strategy is surgical resection of the primary tumor and systemic combination chemotherapy. The chemotherapy regimens and the order of delivery relative to the resection reference point have been based to a large extent on randomized trials using a newly developed empirical staging (Em) system. Although the reductionist TNM based AJCC and UICC systems work well for pathology staging, they are less accurate and less manageable for treatment decision-making. This Em system defines locally resectable (EmR), borderline resectable (EmBR), and unresectable (EmUR) stages, plus the emerging entity of oligometastatic disease (EmOm). For EmR patients, 6 months of adjuvant chemotherapy achieves 5-year survival rates of 30–50%. In EmBR short-course (2 months) neoadjuvant plus 6-month adjuvant chemotherapy increases 12-month survival rates to around 77%, compared to 40% for upfront surgery, despite resection rates of 64–85% and 75%, respectively. Longer-course (4 months) neoadjuvant chemotherapy has also been shown to achieve an 18-month overall survival of 67%. In EmUR, induction therapy (3–6 months) may result in resections rates of 20–60% with significantly improved survival rates compared to no resection. For all stages including the polymetastatic (EmPm) setting, patients with good performance status receive combination chemotherapies based on either oxaliplatin (FOLFIRINOX or NALIRIFOX) or gemcitabine (GEM-CAP, or Gem-NabP). Molecular subtypes (Moffitt, Collisson, Bailey, and Cheng-Sen-Yue) are shown to be associated with treatment responses. Transcriptomic signatures have also been developed as classifiers for determin-

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ing either oxaliplatin- or gemcitabine-based therapies (PurIST, Tiriac, GemPred+, and ESPAC) and are being evaluated in various studies. Most notably the ESPAC transcriptomic signature is being used as the treatment classifier in the experimental arms of the randomized ESPAC6 adjuvant trial in EmR patients and the ESPAC7 induction therapy trial in EmUR patients. Genomic and transcriptomic profiling at baseline and over time is an integral part of ESPAC6/7 to deepen our understanding of tumor plasticity during the course of therapy, identifying the intrinsic (persister cell) and acquired (genetic) tumor plasticity evolving over time and in reaction to different therapies in order to enable a scientific approach to overcoming clonal-resistance clades.

Keywords Localized PDAC · Empirical chemotherapy · Reductionist chemotherapy · Molecular subtypes · Personalized treatment

Introduction

Pancreatic ductal adenocarcinoma (PDAC) remains one of the most lethal cancers with a 5-year relative survival of 11% [1]. The late stage of diagnosis, rapid progression, and resistance to systemic therapies are the most important factors that are attributed to the low survival rate. Nevertheless, the past two decades have witnessed momentous strides in combating this relentless disease. The advent of improved surgical techniques combined with multimodal systemic chemotherapy and the introduction of empirical staging systems, centered on the assessment of resectability, have emerged as pivotal tools in helping to improve survival [2–6]. By contrast, few patients benefit from targeted therapies and for only a limited survival period [7]. Primary surgical resection in localized PDAC is now achieved in 15–20% of patients as well as secondary resection after neoadjuvant or induction chemotherapy in many of the 30–35% of patients with locally advanced disease [3, 7]. The integration of adjuvant multiagent chemotherapy after primary resection has significantly improved prognosis from 10% or less with surgery ± chemoradiotherapy to 30–50% with combination regimens, depending on patient selection [8–13]. The pivotal proof-of-concept study was the first European Study Group for Pancreatic Cancer (ESPAC) trial using adjuvant 5-fluorouracil (5-FU) monotherapy and the 5-FU enhancer folinic acid (FA; [8, 9]). The ESPAC3 showed that while there was less toxicity with adjuvant gemcitabine, it did not improve the overall survival of 5-FU/FA [11]. Combination regimens have increased survival even longer. The evolution in adjuvant chemotherapy regimens has been developed to more potent combination therapies such as gemcitabine plus capecitabine (GEMCAP) with a 5-year survival rate of 30% in unselected patients including those aged over 80 years, and in younger patients with more stringent criteria a 5-year survival rate of 50% has been achieved using modified FA, 5-FU, irinotecan, and oxaliplatin (mFOLFIRINOX) albeit with greater toxicity [12, 13].

Despite significant strides in achieving higher resectability and improving survival outcomes through advanced surgical techniques and adjuvant chemotherapy, the prospect of long-term survival remains elusive for most patients with PDAC. While empirically driven systemic cytotoxic drugs and reductionist-driven targeted therapies show promise in patients with advanced-stage and metastatic PDAC, they have yet to yield major breakthroughs in extending survival [3–7]. More recently neoadjuvant therapies have gar-

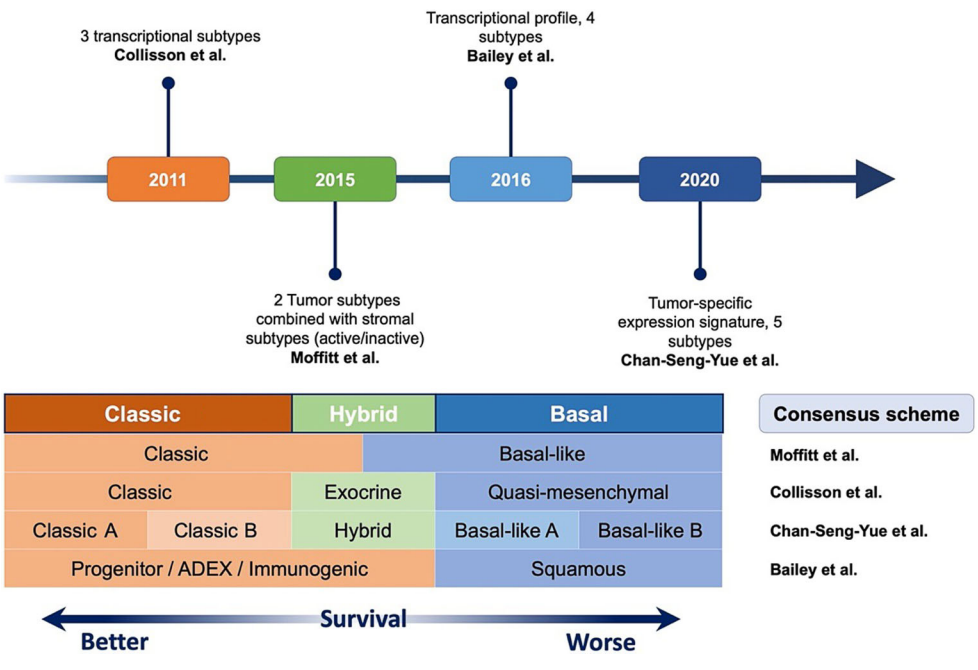

Fig. 1 Molecular classification based on transcriptomic profiling. The four main classifications have overlapping subtypes that can be resolved into classic-, basal-, and hybrid-like molecular phenotypes

nered immense interest in the PDAC landscape [3]. The goal is to extend the survival of patients with resectable tumors and to increase resection rates and survival rates in those with borderline-resectable tumors, even exploring possibilities in selected patients with locally advanced tumors and/or oligometastatic disease [3].

With the development of sequencing technology, several molecular classifications of PDAC tumors based on transcriptomic or whole-genome sequencing have been identified in the past 12 years aiming to better understand treatment responses and hence treatment selection, which has been shown to be associated with treatment responses (Fig. 1; [14–17]). While molecular subtypes enable a broad phenotypic classification, they are too broad at present to permit more direct treatment allocation, and several transcriptomic signatures have been developed, serving as classifiers to distinguish between oxaliplatin- or gemcitabine-based therapies, notably PurIST, Tiriac, GemPred+, and ESPAC ([18–20]; NCT05314998). These signatures are currently under evaluation in various research studies and differ significantly in their mode of development: The PurIST signature derived from various types of tumor samples from 321 patients and has 16 genes defining FOLFIRINOX; the Tiriac signature has 138 genes defining gemcitabine and 98 genes defining oxaliplatin derived from 60 organoids; and the GemPred+ has 420 genes derived from 38 primary cell cultures defining gemcitabine treatment [18–20]. The ESPAC signature is unique in using RNASeq data from standardized fresh frozen PDAC tumor samples that have undergone epithelial cell enrichment, defining gemcitabine-based and oxaliplatin-based therapies [NCT05314998].

The traditional view of basing the treatment of pancreatic cancer is to use a reductionist pathological staging systems such as the Union for International Cancer Control (UICC) American Joint Committee on Cancer (AJCC) TNM systems, avoiding surgery in patients in whom an R0 resection cannot be achieved, to consider the tumor as a fixed phenotype, and to give all patients what seems to be the most effective systemic chemotherapy—presently mFOLFIRINOX [21].

Table 1 Assessment of empirically based (Em) tumor resectability according to preoperative computed tomography

	AHPBA/SSAT/SSO [22]	MD Anderson [25]	Alliance [26]	NCCN [21]
Superior mesenteric vein-portal vein				
EmR: Resectable	No abutment, encasement or occlusion	Abutment or encasement without occlusion	Interface between tumor and vessel measuring < 180°f	No tumor contact or ≤ 180° contact without vein contour irregularity
EmBR: Borderline Resectable	Abutment, encasement, or occlusion	Occlusion	Interface between tumor and vessel measuring ≥ 180°, and/or reconstructable occlusion	Solid tumor contact measuring > 180°, or solid tumor contact ≤ 180° with contour irregularity or thrombosis
EmUR: Locally uresectable	Unreconstructable	Unreconstructable	Unreconstructable	Unreconstructable
Superior mesenteric artery				
EmR: Resectable	No abutment	No abutment	No interface between tumor and vessel	No solid tumor contact
EmBR: Borderline Resectable	Abutment	Abutment	Interface between tumor and vessel measuring < 180°f	Solid tumor contact ≤ 180°
EmUR: Locally uresectable	Encasement	Encasement	Interface between tumor and vessel measuring ≥ 180°f	Solid tumor contact > 180°
Common hepatic artery or its first-order branches				
EmR: Resectable	No abutment or encasement	No abutment or encasement	No interface between tumor and vessel	No solid tumor contact
EmBR: Borderline Resectable	Abutment or short-segment encasement	Abutment or short-segment encasement	Reconstructable a, short-segment interface between tumor and vessel of any degree	Solid tumor contact without extension to CA or hepatic artery bifurcation
EmUR: Locally uresectable	Unreconstructable	Unreconstructable	Unreconstructable	Unreconstructable
Celiac trunk				
EmR: Resectable	No abutment or encasement	No abutment or encasement	No interface between tumor and vessel	No solid tumor contact
EmBR: Borderline Resectable	No abutment or encasement	Abutment	Interface between tumor and vessel measuring < 180°	Solid tumor contact ≤ 180°
EmUR: Locally uresectable	Abutment or encasement	Encasement	Interface between tumor and vessel measuring ≥ 180°	Solid tumor contact > 180°

AHPBA Americas Hepatopancreatobiliary Association, *SSO* Society of Surgical Oncology, *SSAT* Society for Surgery of the Alimentary Tract, *Alliance* Alliance for Clinical Trials in Oncology, *NCCN* National Comprehensive Cancer Network

Empirical staging: assessment of resectability

The UICC and AJCC TNM staging systems are commonly used to classify the pathological disease stages of PDAC based on tumor, nodes, and metastasis criteria. While this system is effective for pathological and radiological assessments, it has limitations in accurately determining maximum tumor diameter, lymph node involvement, and small metastases [22, 23].

More importantly, PDACs are genetically and biologically heterogeneous, and even using the simplest dichotomized molecular classification subtypes (basal-like and classic-like) there are considerable differences across all of the TNM stages, as well as PDAC neighborhood subtypes and responses to therapy [14–17, 24]. The TNM pathology systems used in PDAC have been based on general (assumed a priori and reductionist) oncological principals. There is a shortfall, however, in this reductionist approach, as in clinical practice the TNM does not completely match decision-making (resection being the treatment nodal point), nor the biological nature of PDAC at the diagnostic start point and the subsequent biological behavior in response to time (tumor evolution and acquired mutational resistance) and interventions including surgery and chemotherapy (enrichment of intrinsic persister cell resistance). Thus, an empirically derived staging (Em), based on practical (a posterior) experience, is an alternative approach, with an unbiased discovery scope [3].

Surgical resectability is determined practically using empirical staging criteria established by various organizations (Table 1), including the Americas Hepato-Pancreato-Biliary Association, the Society of Surgical Oncology, the Society for Surgery of the Alimentary Tract (AHPBA/SSO/SSAT), The University of Texas MD Anderson Cancer Center, the Alliance for Clinical Trials in Oncology, and the National Comprehensive Cancer Network (NCCN; Fig. 2a–c; [21, 23, 25, 26]). Each of these criteria sets characterizes the anatomy of the primary tumor and its relationships with crucial blood vessels such as the superior mesenteric vein, portal vein, superior mesenteric artery (SMA), common hepatic artery, its first-order branches, and the celiac trunk (Table 1). They can be applied to stage tumors located in the head, body, or tail of the pancreas. However, there are differences in how radiologists, surgeons, and multidisciplinary teams interpret and utilize each system for staging tumors. To ensure consistency and accuracy, it is essential to clearly report the staging criteria used and rigorously apply them as a condition for patient enrollment in clinical trials. Most of trials such as ESPAC-5 and Alliance A021101, A021501, and A021806 have stricter enrollment criteria ([26–28]; NCT04340141). They mandate prospective centralized specialized review of the staging images of each patient, ensuring that all enrolled patients meet the stringent staging requirements.

To include other important prognostic factors, such as the inherent biological characteristics of the tumor, the physiological condition of the patient, or radiographically occult disease that might not be detectable with routine imaging protocols, the MD Anderson system takes a more comprehensive approach

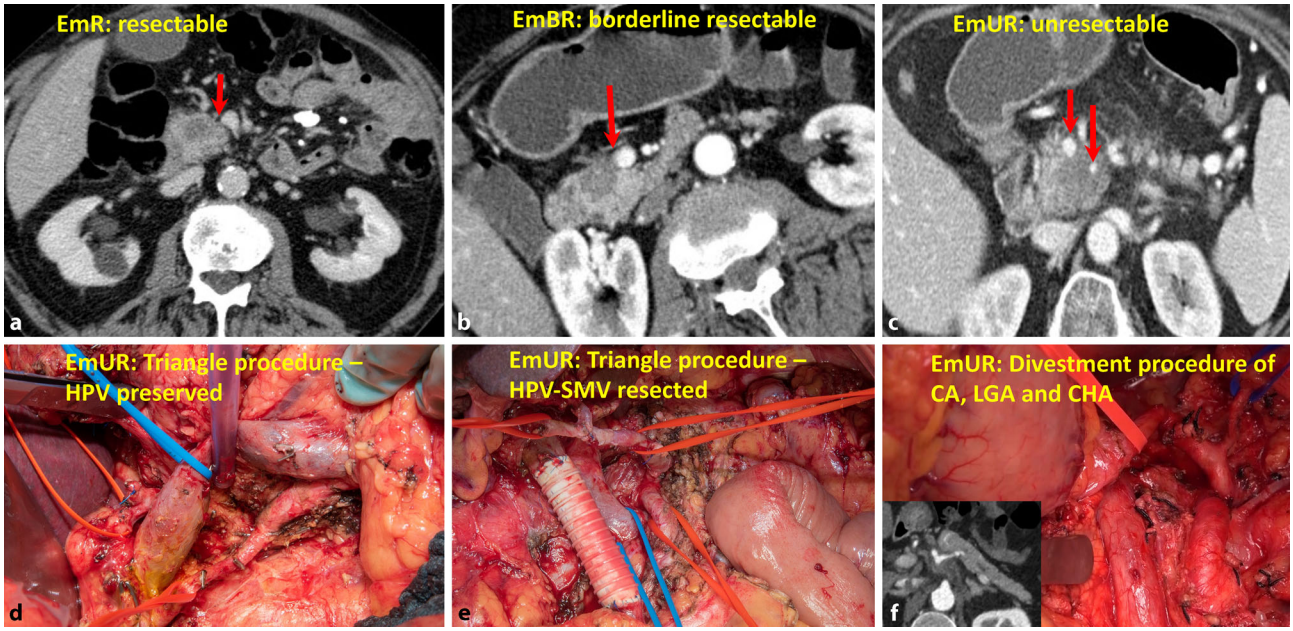

Fig. 2 Empirical staging shown on preoperative computed tomography (CT) scans (**a–c**); resection photographs demonstrating the triangle procedure for EmUR without hepatic portal vein (*HPV*) resection (**d**) or with HPV and superior mesenteric vein (*SMV*) resection and an interposition graft (**e**); and preservation of the celiac axis (*CA*), left gastric artery and common hepatic artery (*CHA*), using the divestment technique, all of which were encased as shown by the preoperative CT scan in the *inset* (**f**)

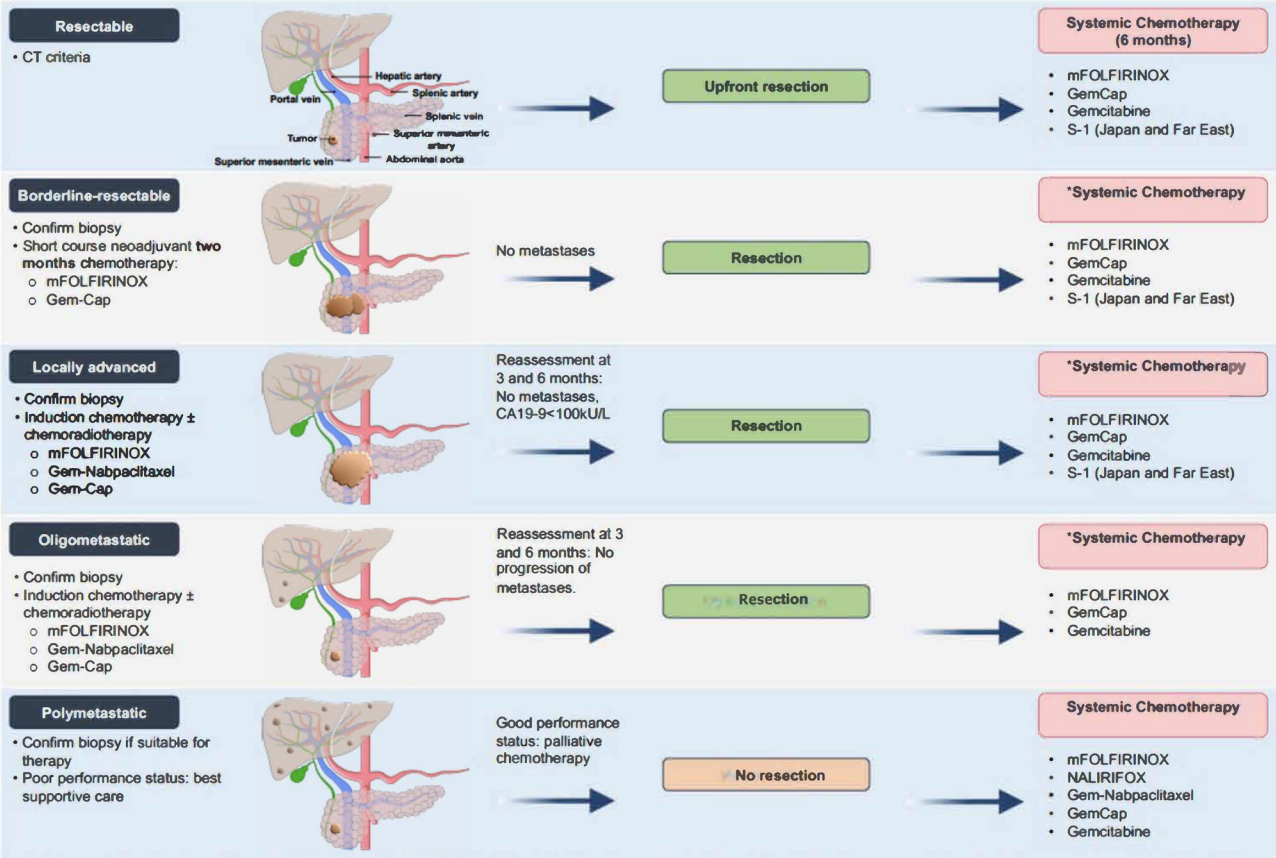

Fig. 3 Staging and management of pancreatic cancer based on the empirical staging system

by incorporating additional factors such as serum carbohydrate antigen 19-9 (CA19-9) levels and performance status, in addition to tumor anatomy [29, 30]. This system has been integrated into international consensus criteria to facilitate more nuanced prognosis assessments. Biological staging of potentially resectable PDACs focuses on a subset of tumors that are anatomically potentially resectable (EmBR, EmUR, EmOm) but may exhibit clinical features suggestive of occult distant polymetastatic disease (EmPm). These worrying features may include a serum CA19-9 level >500 kU/L or the presence of regional lymph node metastases diagnosed through biopsy sampling and/or positron emission tomography–computed tomography (PET-CT). Considerable further refinement of this concept is required as studies from France and Japan have shown that the biological aspect of these criteria has limited clinical impact [31, 32]. Therefore, the investigation into biological staging and its relationship to tumor plasticity and acquired and inherent resistance continues to be a critical focus of research [3].

Surgery and cytotoxic therapies in empirically staged tumors

Over the past 50 years numerous clinical trials have been conducted in pancreatic cancer. The majority of these studies have been phase I/II trials, evaluating the potential survival benefits of newer agents and various treatment approaches, including chemoradiation. Unfortunately, many of these trials have not yielded successful outcomes. Currently, clinicaltrials.gov lists over 3000 registered PDAC trials, with 1099 in phase I, 1441 in phase II, and 306 in phase III. Among them, 254 trials are neoadjuvant, of which 23 are in phase III. The EU Clinical Trials Register shows 487 PDAC trials, with 87 in phase III, including 10 neoadjuvant trials.

Given the vast amount of information available, the focus should be on well-conducted phase II/III randomized trials that include appropriate control arms. Combination chemotherapy remains the mainstay of systemic treatment for PDAC with no role for chemoradiation regarding survival, at least in the adjuvant setting. Interestingly, only a relatively small number of agents and combinations have demonstrated sufficient efficacy to gain regulatory approval or become standard-of-care options [3]. An overview of adjuvant, neoadjuvant, and induction chemotherapy based on empirical staging is illustrated in Fig. 3.

Empirical resectable PDAC

The standard of care for EmR PDAC remains upfront resection followed by 6 months of adjuvant

Table 2 Selected randomized trials of adjuvant and neoadjuvant treatment for resectable pancreatic cancer

Trial	Recruitment period	Treatment arms	Number of patients	Median overall survival (months)	5-year overall survival (%)	Comments
2.1 Adjuvant treatment for resectable pancreatic cancer						
GITSG 9173 [33]	1974–1982	CRT + 5FU Observation	21 22	21 10.9 ($p = 0.03$)	19 5	R0 only
Norway multi-center [34]	1984–1987	5FU/DOX/MMC Observation	30 31	23 11 ($p = 0.04$)	4 8	Includes 14 patients with ampullary cancer
Japan multi-center [35]	1986–1992	MMC/Oral 5-FU Observation	81 77	17.1 12.6 (n.s.)	11.5 18	Includes patients with metastases
EORTC 40891 [36, 37]	1987–1995	CRT Observation	60 54	24.5 19 ($p = 0.099$)	20 10	T1-2, N0-1a, M0 pancreatic head cancer
ESPAC-1 [8], All patients and early follow-up of 2 × 2 factorial	1994–2000	No CRT CRT	178 175	16.1 15.5 ($p = 0.24$)	19.5 10.3	Significant for chemotherapy overall but not 2 × 2 factorial. Not significant
		No chemotherapy 5FU/FA	235 238	14 19.7 ($p = 0.0005$)	9.9 23.3	–
ESPAC-1 [9], 2 × 2 factorial, final follow-up	1994–2000	No CRT CRT	144 145	17.9 15.9 ($p = 0.05$)	19.6 10.8	ECOG 0-2, R0/R1
		No chemotherapy vs. 5FU/FA	142 147	15.5 20.1 ($p = 0.009$)	8.4 21.1	–
		Observation	69	16.9	10.7	–
		CRT	73	13.9	7.3	–
		5FU/FA	75	21.6	29	–
		CRT + 5FU/FA	72	19.9	13.2	–
CONKO-001 [10, 38]	1998–2004	GEM Observation	179 175	22.1 20.2 ($p = 0.01$)	22.5 11.5	–
RTOG 9704 [39, 40]	1998–2002	5FU/FA + 5FU-RT + 5FU/FA GEM + 5FU-RT + GEM	230 221	– – $p = 0.34$	– –	–
ESPAC-3 [11]	2000–2007	5FU/FA GEM	551 537	23 23.6 ($p = 0.39$)	15.9 17.5	ECOG 0-2, R0/R1
JSAP-02 [41]	2002–2005	GEM (+ IORT in 27) Observation (+ IORT in 47)	58 60	22.3 18.4 ($p = 0.19$)	23.9 10.6	Karnofsky > 50
CapRI [42]	2004–2007	5FU + cisplatin + IFNα2b + RT + CI 5FU 5FU/FA	64 68	32.1 25.5 ($p = 0.49$)	25 25	ECOG 0-2, R0/R1
JASPAC-01 [43]	2007–2010	GEM S-1	190 187	25.2 46.5 ($p < 0.0001$)	24.4 44.1	ECOG 0 = 69%, postop CA19-9 > 37 kU/L = 21, R1+ = 31%, LN+ = 63%
CONKO-005 [44]	2008–2013	GEM GEM + erlotinib	217 219	26.2 24.5 ($p = 0.061$)	20 25	R0 only, Karnofsky PS ≥ 60%
CONKO-006 [45]	2008–2013	GEM GEM + sorafenib	65 57	17.1 18.2 ($p = 0.94$)	– –	R1 only, Karnofsky PS ≥ 60%

Table 2 (Continued)

Trial	Recruitment period	Treatment arms	Number of patients	Median overall survival (months)	5-year overall survival (%)	Comments
ESPAC-4 [12]	2008–2014	GEM GEM-CAP	366 365	25.5 28 (P = 0.032)	16.3 28.8	R0/R1, no restrictions
NRG Oncology/RTOG 0848 [46] NCT01013649	2009–2014	1st randomization GEM GEM + erlotinib	163 159	29.9 28.1 (p = 0.62)	– –	Postop CA 19-9 < 180 kU/L, 2nd randomization to CRT reports Q4 2023
PRODIGE-24 [13, 47]	2012–2016	GEM vs. mFOLFIRINOX	246 vs. 247	35 vs. 54.4 (p = 0.003)	–	ECOG 0/1, post-OP CA 19-9 < 180 kU/L, < 80 years
APACT [48, 49]	2014–2018	GEM vs. GEM-NabP	434 vs. 432	37.7 vs. 41.8 (p = 0.0090). Not primary end point	31 vs. 38	ECOG 0-1, post-OP CA 19-9 < 100 kU/L, primary endpoint (DFS) not met: 18.0 vs. 19.4 months (p = 0.18)
2.2 Neoadjuvant treatment for resectable pancreatic cancer						
Germany multi-center [56]	*2003–2009*	CRT + surgery + GEM Surgery + GEM	33 33	17.4 14.4 (p = 0.79)	– –	Terminated due to slow recruitment
Bologna [57]	2007–2014	CRT + surgery Surgery	18 20	19.5 22.4	–	Terminated due to slow recruitment, not significant
PACT-15 [58]	2010–2015	PEXG + surg + PEXG Surgery + GEM Surgery + PEXG	26 30 32	– – –	– – –	≤ 75 years, stage I-II, protocol event-free at 1 year: 6 (23%, 95% CI: 7–39) of 30; 15 (50%, 32–68) of 30; 19 (66%, 49–83) of 29
Prep-02/JSAP-05 [59]	2013–2016	GEM + S1 + surg + S1 Surgery + S1	182 (not resected = 42) 180 (not resected = 51)	36.7 26.6 (p = 0.015)	– –	ECOG = 0/1, < 80 years, cf. JASPAC-01 median survival for adjuvant S1 = 46.5 months vs. 26.6 months in JSAP-05
PREOPANC1 [60, 61]	2013–2017	CRT = GEM + surg + GEM Surgery + GEM	65 68	14.6 15.6 (p = 0.83)	– –	–
SWOG S1505, [62] NCT02562716	2015–2018	mFOLFIRINOX + surg + mFOLFIRINOX GEM-NabP + surg + GEM-NabP	55 47	23.2 23.6	– –	Primary endpoint > 2-year OS of 40%: 47% (95% CI: 31–61) for arm 1 and 48% (31–63) for arm 2, neither was significant
NEONAX-AIO-PAK-0313 [63]	2015–2021	GEM-NabP + surg + GEM-NabP Surgery + GEM	63 (not resected = 18) 64 (not resected = 13)	25.2 16.7 (n.s.)	– –	Planned 166 patients. Primary endpoint median DFS rate of 55% at 18 months double negative result: neoadjuvant 32.2%: adjuvant 41.4%
PANACHE01-PRODIGE48, [64] NCT02959879	2017–2020	mFOLFIRINOX + surg + CTX FOLFOX + surg + CTX Surgery + CTX	70 50 26	30.6 31.3 36 (n.s.)	– – –	CTX = Initially GEM, 5FU, and GEMCAP, but latterly and mostly mFOLFIRINOX
NORPACT-1, [65] NCT02919787	2017–2021	FOLFIRINOX + surg + mFOLFIRINOX Surg + mFOLFIRINOX	77 63	25.1 38.5 (p = 0.096)	–	Alive at 1 year: neoadj = 60% vs. adj = 73%, upfront surgery had longer survival

CRT chemoradiotherapy, *RT* radiotherapy, *CTX* chemotherapy, *CI* continuous infusion, *5FU* 5-fluorouracil, *DOX* doxorubicin, *MMC* mitomycin C, *FA* folinic acid, *GEM* gemcitabine, *CAP* capecitabine, *IORT* intraoperative radiotherapy, *mFOLFIRINOX* modified folinic acid (FA), 5-fluorouracil (5FU), irinotecan (IR) and oxaliplatin (OX), *NabP* nab-paclitaxel, *SBRT* stereotactic body radiotherapy, *DFS* disease-free survival, *OS* overall survival

chemotherapy but there is no survival advantage to using chemoradiotherapy, resulting only in additional toxicity (Table 2, 2.1). A ceiling in optimal survival has now been reached with combination chemotherapies and is unlikely to be improved without radically new effective therapies, and/or more intelligent utilization of existing cytotoxic drugs based on the actual biology of the tumor at the point of treatment. When comparing the overall survival outcomes of adjuvant trials it is very important to consider the different selection eligibility criteria as well as the toxicity of each regimen [50]. The APACT study (which failed its primary endpoint and hence adjuvant GEM-NabP is not approved by the FDA) only included patients with an Eastern Cooperative Oncology Group performance status of ≤1 and a serum 19-9 level of <100 kU/L and PRODIGE24 was restricted to patients ≤79 years, with a WHO performance score of 0/1, no significant cardiovascular disease, and a serum CA19-9 level of <180 kU/L, whereas ESPAC4 had none of these restrictions [12, 23, 44]. These discrepancies are reflected in the notable differences in overall survival for the same gemcitabine control arms used in these studies with overall median (95% CI) survival rates of 37.7 months (range: 31.1–40.5) for APACT, 35.0 months (range: 28.7–43.9) for PRODIGE24, and 25.5 months (range: 22.7–27.9) for ESPAC4 [12, 23, 44]. Thus, the APACT trial had the most favorable selection criteria leading to longer overall survival irrespective of the type of intervention. It is also noteworthy that both ESPAC4 and PRODIGE24 had an absolute increase in 5-year overall survival in the experimental arms by 12% but only 7% in the APACT trial compared to the control gemcitabine arms [12, 23, 44].

Although a considerable number of patients with pancreatic cancer initially have surgically resectable disease, a significant portion of them eventually experience distant recurrences [51, 52]. The promising outcomes seen with adjuvant chemotherapy have led to the investigation of the same drug regimens in the neoadjuvant and perioperative settings for EmR disease. Strong arguments for the use of neoadjuvant therapy have been put forward, but the randomized evidence clearly shows a lack of survival advantage in this setting (Table 2, 2.2; [3, 53–55]).

The combination of resectable (EmR) and borderline resectable (EmBR) populations in several of the clinical trials created some confusion, at least at first, in understanding the outcome data. Some early trials, like those led by Golcher et al. and Casadei et al., had to be closed prematurely due to slow patient accrual during a period when neoadjuvant therapy was less accepted [56, 57]. The Prep-02/JSAP-05 trial claimed an improvement in median overall survival for the neoadjuvant group (neoadjuvant gemcitabine and S1 followed by resection then adjuvant S1) at 36.7 months compared to 26.6 months in the upfront resection group (adjuvant S1; [59]). This was a problematic study, however, (only ever published as an abstract), as in the phase III JASPAC-01 trial, patients who had received adjuvant S1 had a median overall survival of 46.5 months, surpassing the adjuvant gemcitabine group with an overall survival of 25.5 months [43, 59]. The trial, however, did not lead to a change in practice (in Japan) as recommended by the Clinical Practice

Table 3 Selected randomized trials of adjuvant and neoadjuvant regimens for borderline-resectable pancreatic cancer

Trial	Recruitment period	Treatment arms	Number of patients	Median overall survival (months)	5-year overall survival (%)	Comments
Korea multicenter [67]	2012–2014	CRT + GEM + surg + GEM + CRT Surgery + GEM + CRT	27 (8) 23 (6)	21 12 (1-sided $p = 0.028$)	– –	Target = 110, premature as interim analysis plan at 50% enrolment, only 1-sided $\alpha = 0.05$; only 8 and 6, respectively, had protocol treatment, pre-planned p value not valid
PREOPANC1 [60, 61]	2013–2017	CRT + GEM + surg + GEM Surg + GEM	54 59	15.7 14.3 ($p = 0.029$)	– –	–
ESPAC5 [27]	2014–2018	Surgery + adj GEM-CAP + surg + adj FOLFIRINOX + surg + adj CRT + surg + adj	32 20 20 16	1-year OS: 42 (27, 64) % 79 (62, 100) % 84 (70, 100) % 64 (43, 95) % ($p = 0.002$)	– – – –	Neoadj GEMCAP and FOLFIRINOX similar, both superior to neoadj CRT and upfront surgery, no difference in resection rates
NUPAT-01 [68]	2015–2020	FOLFIRINOX + surg + CTX GEM-NabP + surg + CTX	26 25	–	3-year OS 55.3% vs. 54.4% (n. s.)	Primary endpoint R0 resection rate: 73.1% for FOLFIRINOX, 56.0%for Gem-NabP
Alliance A021501, [28] NCT02839343	2016–2019	mFOLFIRINOX + surg mFOLFIRINOX + SBRT + surg	54 56	29.8 17.1	– –	18 months OS: 66.7 vs. 47.3

CRT chemoradiotherapy, *RT* radiotherapy, *CTX* chemotherapy, *CI* continuous infusion, *5FU* 5-fluorouracil, *DOX* doxorubicin, *MMC* mitomycin C, *FA* folinic acid, *GEM* gemcitabine, *CAP* capecitabine, *IORT* intraoperative radiotherapy, *mFOLFIRINOX* modified FA/5FU + IR + 5-FU/FA, *NabP* nab-paclitaxel, *SBRT* stereotactic body radiotherapy, *DFS* disease-free survival, *OS* overall survival, *surg* surgery, *neoadj* neoadjuvant

Guidelines for Pancreatic Cancer 2019 of the Japan Pancreas Society [66].

The NORPACT-1 is the latest multicenter trial to report the results of short-course neoadjuvant FOLFIRINOX versus upfront surgery for EmR pancreatic head cancer, which again does not support the use of neoadjuvant therapy for EmR [65]. In this study 140 patients were randomly assigned to neoadjuvant chemotherapy, ($n=77$) or upfront surgery ($n=63$) with a median (95% CI) survival that was actually less for the neoadjuvant group (25.1 [17.2–34.9] months) than for upfront surgery (38.5 months [27.6–not reached]) although not statistically significant ($p=0.096$; [65]).

Empirical borderline-resectable PDAC

The PREOPANC1 and ESPAC5 trials now provide strong evidence for the use of neoadjuvant chemotherapies for EmBR PDAC while the Alliance A021501 trial suggests that stereotactic body radiotherapy added to neoadjuvant chemotherapy adds to toxicity and may also depress survival (Table 3; [27, 28, 60, 61]). In the PREOPANC1 trial, patients with EmBR had a significant survival impact with neoadjuvant therapy (chemoradiation plus gemcitabine and then adjuvant gemcitabine compared to upfront surgery and adjuvant gemcitabine; [60, 61]). The role of chemoradiation in this context remains unproven especially since survival rates were poor in both groups and the control arm employed mono-gemcitabine, which is no longer the standard of care. In the Alliance A021501 phase II study for EmBR, patients were randomized to receive neoadjuvant mFOLFIRINOX with or without 33–40 Gy hypofractionated radiation therapy, and both groups received adjuvant 5-FU and oxaliplatin (mFOLFOX6) after resection. The median overall survival was 29.8 months for chemotherapy alone versus 17.1 months for chemotherapy plus radiotherapy [28]. Similarly, the ESPAC5 study for EmBR PDAC found that neoadjuvant chemotherapy with randomization to either FOLFIRINOX or GEMCAP resulted in superior survival compared to upfront surgery, while neoadjuvant 50.4-Gy capecitabine-based chemoradiotherapy did not show the same benefit [27]. The ESPAC5 trial is the only randomized trial that has a head-to-head comparison between FOLFIRINOX and GEMCAP, which demonstrated similar survival outcomes but with less toxicity for GEMCAP.

In the PREOPANC1 trial, the resection rates for EmBR were 52% for the neoadjuvant group and 64% for the upfront surgery group, while the R0 resection rates were 79% and 13%, respectively [60]. In the ESPAC5 trial, the resection rates in the three neoadjuvant arms were 65% after FOLFIRINOX, 85% after GEMCAP, and 80% after chemoradiotherapy, with a resection rate of 75% for upfront surgery. The R0 resection rates after neoadjuvant therapy were 12% with FOLFIRINOX, 15% with GEMCAP, and 30% with chemoradiotherapy, compared to 11% with upfront surgery [27]. In the Alliance A021501 trial, the resection rates were 35% with neoadjuvant chemotherapy followed by radiotherapy and 49% with neoadjuvant chemotherapy only (without radiotherapy; [28]). The R0 resection rates were 74% after neoadjuvant chemotherapy followed by radiotherapy and 88% after neoadjuvant chemotherapy only [28]. Thus, for EmBR, neoadjuvant chemotherapy favors overall survival but resection rates and R-status do not predict survival, while the role of neoadjuvant radiation therapy is not proven.

Table 4 Selected randomized trials of induction regimens for unresectable pancreatic cancer

Trial	Recruitment period	Treatment arms	Number of patients	Median overall survival (months)	5-year overall survival (%)	Comments
LAP-07 [69]	2008–2011	1st randomization GEM vs. GEM + erlotinib	223 vs. 219	13.6 vs. 11.9 ($p=0.09$)	–	Resection rate = 18/449 (4.0%)—not an endpoint
		2nd randomization GEM vs. CRT	136 vs 133	16.5 vs. 15.2 ($p=0.83$)	–	–
CONKO-007, [70] NCT01827553	2013–2021	mFOLFIRINOX + surg vs. GEM + surg vs.	140 27 CTX-resect = 60	CTX-surg = 15	4.3	Primary endpoint was altered to R0, 525: surg $n=122$ (median OS 19 months, 5-year OS = 17.5%), non-surg = 214 (median OS = 14 months, 5-year OS = 0%, $p<0.001$), resection 122/525 = 23.2%
		mFOLFIRINOX + CRT + surg vs. GEM + CRT + surg	147 22 CRT-resect = 62	CRT-surg = 15 ($p=0.71$)	9.6	
NEOLAP, [71] NCT02125136	2014–2018	FOLFIRINOX + surgery GEM-NabP + surg	85 85	20.7 18.5 ($p=0.53$)	– –	Primary endpoint resection rate, 168 registered, 165 induction GEM-NabP, 130 randomized to further induction CTX. Median OS with resection (52) = 27.5 months vs. no-resection (113) = 13.9 months, $p<0.0001$. Overall resection rate 52/168 = 31%
NEOPAN, [72]	2015–2027	FOLFIRINOX GEM	85 86	– –	– –	Primary endpoint was PFS PFS 9.7 vs. 7.5 ($p=0.03$), OS 15.1 vs. 15.6 ($p=0.5$)

CRT chemoradiotherapy, *RT* radiotherapy, *CTX* chemotherapy, *CI* continuous infusion, *5FU* 5-fluorouracil, *DOX* doxorubicin, *MMC* mitomycin C, *FA* folinic acid, *GEM* gemcitabine, *CAP* capecitabine, *IORT* intraoperative radiotherapy, *mFOLFIRINOX* modified FA/5FU + IR + 5-FU/FA, *NabP* nab-paclitaxel, *SBRT* stereotactic body radiotherapy, *DFS* disease-free survival, *OS* overall survival, *surg* surgery

Empirical locally advanced, unresectable PDAC

Induction chemotherapy

According to NCCN guidelines, selected patients without systemic metastases are recommended to receive 4–6 months of induction combination chemotherapy, followed by chemoradiation or stereotactic body radiation therapy. Surgical resection should be considered if feasible after induction therapy, with adjuvant chemotherapy as clinically indicated [21]. Among the various induction therapy regimens, FOLFIRINOX is the preferred choice for patients with favorable performance status, while gemcitabine with nab-paclitaxel (GEM-NabP) is an alternative (Table 4). The CONKO-007 included 495 patients who received 3 versus 6 months of either FOLFIRINOX or gemcitabine, with or without chemoradiation, followed by surgical exploration (if technically resectable; [70]). The primary endpoint of overall survival was later amended to R0 resection due to delayed patient accrual. The study showed no significant difference in overall survival between the groups, indicating that the addition of radiation during induction therapy did not provide a survival benefit. Importantly, however, this prospective study showed that a resection rate of 23.2% was achieved in EmUR PDAC after induction chemotherapy.

The NEOLAP trial treated EmUR patients with two cycles of induction GEM-NabP, and those without progression were randomized to receive four cycles of FOLFIRINOX or two additional cycles of GEM-NabP [71]. The study found no statistically significant difference in resection rates (the primary endpoint) between the two groups, with both showing overall median survival rates of around 20 months, but importantly again demonstrated in this prospective study an overall reaction rate of 31% [71]. A decade ago, none of these patients would have even been considered for surgical resection.

Surgical exploration after induction chemotherapy

Determining resectability is based on the expertise of the center and surgeon's experience. Surgical exploration should be undertaken if resection and vascular reconstruction seem feasible, as conventional cross-sectional imaging may not accurately reflect response to induction therapy or the likelihood of resection [2, 3, 73]. A decrease in serum CA19-9 levels after induction therapy is associated with an increase in successful resections [74–77]. Different surgical techniques, such as "artery first," "triangle resection," and "arterial divestment," should be considered to optimize resection rates [78–82]. A clean dissection of lymphatic and neural tissue structures in the anatomical triangle bordered by the SMA, celiac axis, and portal vein is crucial for a successful operation (Fig. 2d,e; [81]). The periarterial divestment technique aims to achieve radical tumor clearance without the need for arterial dissection (Fig. 2f; [78, 79, 82, 83]). In a retrospective analysis of EmUR patients who had R0 portal venous resections, the median overall survival was 24 months with a 5-year overall survival of 20% [84].

Empirical oligometastatic disease PDAC

Patients with limited metastases can be considered for resection of the primary tumor and simultaneous metastasectomy achieving median overall survival of 12.3–14.5 months in selected patients [3, 84, 85]. In the largest recent series, in patients with a good pathological response at metastatic sites (ypM0) a median overall survival of 25.5 months was achieved, which increased to 29.0 months with further adjuvant chemotherapy [86]. Patients with lung metastases generally seem to survive longer than those with liver metastases, and moreover pulmonary resection can result in a median survival of 29.2 months from the time of diagnosis of disease recurrence compared with 19.6 months in those with unresected lung metastases [87, 88].

Adjuvant therapies after neoadjuvant treatment

It remains unclear whether patients who have undergone pancreatectomy for localized PDAC after neoadjuvant treatment still benefit from adjuvant chemotherapy. In a retrospective study, adjuvant chemotherapy was found to offer no survival benefit in this setting [89]. By contrast, adjuvant chemotherapy has been found to be associated with improved survival after adjustment for treatment and tumor characteristics in multivariable analyses in a comprehensive analysis of the National Cancer Database [90].

In a multicenter, retrospective study, patients with localized PDAC (EmR, EmBR und EmUR) who underwent pancreatic surgery after at least two cycles of neoadjuvant FOLFIRINOX chemotherapy were retrospectively analyzed. In patients with node-positive disease, adjuvant chemotherapy after neoadjuvant FOLFIRINOX treatment and resection was associated with significantly improved median overall survival of 26 vs. 13 months, respectively [91]. However, adjuvant chemotherapy did not show a significant survival benefit in patients with node-negative disease with a median overall survival of 38 vs. 54 months, respectively [91]. A National Cancer Database study showed that the associated survival was significantly improved in patients who has received adjuvant chemotherapy after neoadjuvant treatment and resection compared with neoadjuvant treatment alone [92]. Furthermore, the survival benefit of additional adjuvant chemotherapy remained significant for those with node-negative disease, a lymph node ratio of <0.15, low-grade tumor histology, and negative resection margin status [92]. A separate National Cancer Database analysis revealed that additional adjuvant chemotherapy was significantly associated with substantially bet-

ter median overall survival of 26.6 vs. 21.2 months, with a varied benefit by age, tumor stage, and tumor differentiation [93]. These findings suggest that patients with localized PDAC may benefit from additional adjuvant chemotherapy to achieve prolonged survival after multiagent neoadjuvant or induction chemotherapy and surgical resection. Patients receiving FOLFIRINOX are more prone to greater cumulative toxicity than with other regimens; thus, for example, GEMCAP followed by, for instance, gemcitabine monotherapy could be given for many more cycles, but what is really needed right now is more evidence from well-designed randomized trials.

Targeted therapies

The development of cytotoxic therapies for different stages of pancreatic cancer has primarily relied on empirical approaches. Reductionist attempts to develop treatments by targeting key pathogenic gene alterations have seen limited success, with most targets having a prevalence ranging from 0.1% to 5%, and the survival advantage provided by these agents being only a few months, despite the frequency of altered mutational pathways [94, 95]. The Know Your Tumor Registry represents the largest pancreatic cancer targeted therapy program. Out of 1856 referred patients, 282 (15.2%) had actionable mutations, but only 46 (2.5%) received matched therapy [7]. Survival since diagnosis varied among patients, with a median overall survival of 1.3 years for those with no actionable alteration, 1.5 years for patients with actionable mutations who received unmatched therapy, and 2.6 years for those who had matched therapy [7]. Maintenance therapy with the poly(adenosine diphosphate-ribose) polymerase (PARP) inhibitor olaparib improved progression-free survival from 3.8 to 7.4 months in patients with metastatic pancreatic cancer and germline mutations in the *BRCA1/2* genes, provided they had not progressed after at least 4 months of platinum-based first-line chemotherapy [96]. The potential fraction of PDAC patients with druggable driver alterations may significantly increase if novel KRAS inhibitors, targeting the G12D mutation present in about 40% of PDAC patients, prove successful in clinical trials [97].

Drug-resistant persisters in PDAC

In the evolution of PDAC, acquired genomic mutations accumulate in pancreatic exocrine cells leading to increasing dysplastic pancreatic intraepithelial neoplasia, PanIN1 and PanIN2, then carcinoma in situ PanIN3 before progressing to invasion [98]. Low-grade PanIN1A consists of a flat to papillary ductal epithelium with abundant supranuclear mucin and loss of polarity while high-grade PanIN3 is characterized by cytonuclear atypia, dysplasia, or carcinoma in situ with a more complex papillary architecture, nuclear hyperchromatism, and pleomorphism. Telomere shortening and oncogenic KRAS activation are initiating events followed by hypermethylation and/or intragenic mutations and/or loss of heterozygosity of CDKN2A/p16, and mutational activation and or/loss of TP53, as well as homozygous loss or intragenic mutation and second allele loss of DPC4/SMAD4 [99].

Loss of TP53 enables a deterministic pattern of genome evolution in PDAC, suggesting that TP53 mutations are associated with heterogeneous gains in KRAS, MYC, and GATA6, which can further drive metastasis and/or influence PDAC subtypes [100]. The development of PDAC toward greater genomic diversity offers proof that subclonal heterogeneity probably contributes to the unsatisfactory reactions to therapy in PDAC. Within this framework, the simultaneous development of distinct subclones in the

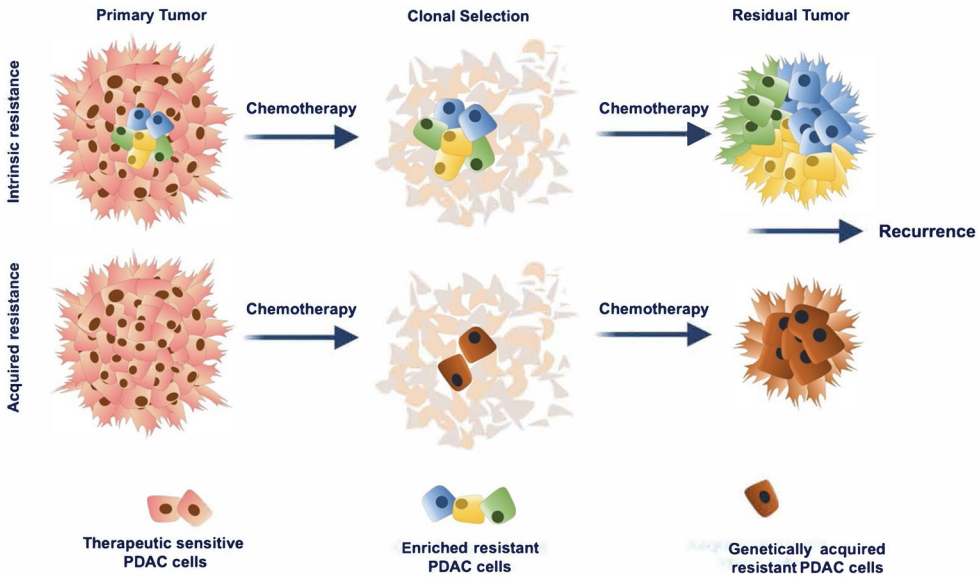

Fig. 4 Resistance mechanisms developing during the evolution of pancreatic cancer may be broadly classified into (1) intrinsic mechanism due to enrichment of persister cells with specific resistance features and (2) acquired resistance over time due to new genetic mutations and structural chromosomal changes

identical tumor and at varying stages along a set pathway might clarify the prevalent incidence of varied therapy responses in PDAC. Although these findings propose a traditional model of step-by-step genomic evolution in therapy resistance, mounting proof proposes that non-genetic priming or adjustment significantly adds to therapy resistance [101].

Emerging findings from our research laboratory indicate that intrinsic drug-tolerant cells, often referred to as "persisters," have the capacity to arise from a preexisting subset of cancerous cells subsequent to neoadjuvant chemotherapy (Fig. 4; [95, 101–103]). These persister-like cells adapt to the impact of chemotherapy by enhancing the expression of genes such as *CYP3A5* and other co-expressed drug-metabolizing genes. These genes are responsible for metabolizing irinotecan, a constituent of FOLFIRINOX, into forms that lack therapeutic activity. Cancer persister cells can enter a state of dormancy or quiescence, rendering them impervious to the effects of chemotherapy and/or chemoradiotherapy. Consequently, while chemotherapy might effectively eliminate the majority of cancer cells, it could falter in eradicating a minor subset of persister cells, which manage to endure and subsequently repopulate the tumor. Within this conceptual framework, the persister cell state mirrors the notion of minimal residual disease, potentially leading to relapse if treatment discontinues. Accordingly, the identification and comprehensive understanding of persister cells could potentially pave the way for innovative strategies to combat drug-resistant forms of cancer [103].

Molecular classifications and personalized therapy of PDAC

Pancreatic ductal adenocarcinomas exhibit genetic and biological heterogeneity. The simplest molecular classification includes basal-like and classic-like subtypes, which vary across different disease stages and respond differently to various treatments (Fig. 1; [14–17, 95, 104]). Classic-like subtypes define well-differentiated tumors that tend to be associated with better outcomes and expression of the key pancreatic-specific transcription factors GATA6, HNF1A, and PDX. Basal-like subtypes are less differentiated tumors with mesenchymal characteristics, including upregulated expression of ΔNP63 and TGFβ-signaling and tend to be associated with poor prognosis [104]. While current subtyping schemas can identify prognostic subgroups among patients with resectable tumors, they are less effective in those with advanced-stage disease.

Different molecular subtypes also respond differently to chemotherapies [14–17, 95, 104]. Basal-like PDACs show poor response to chemotherapy in locally advanced or metastatic PDAC [14, 15]. The utility of the classic and basal-like subtypes for predicting survival and response to two major first-line schemes—mFOLFIRINOX and gemcitabine nab-paclitaxel—in advanced PDAC was assessed in the COMPASS study (NCT02750657; [105]). There was a nearly 4-month longer overall survival for patients with classic-like than for those with a basal-like phenotype [105]. Additionally, patients with high expression of the classic-like marker GATA6 had 2 months longer survival than those with GATA6 low expression. Patients with the classic-like subtype who had mFOLFIRINOX had longer survival than those with the basal-like subtype [105]. Collectively, these findings suggest that GATA6-low and basal-like subtype may be associated with poor response to mFOLFIRINOX.

Intratumor heterogeneity is linked to stromal heterogeneity, leading to various tumor microenvironment programs, including "reactive," "intermediate," and "deserted" cellular and transcriptomic subtypes [24]. A deserted-like microenvironment is found in untreated tumors and has been associated with poor treatment response in patients. Drug-tolerant persister cells, arising from different tumor cell lineages during first-line and/or second-line therapy, contribute to disease relapse. Both FOLFIRINOX and chemoradiation therapy have been reported to induce phenotype switching from classic-like to basal-like subtypes, resulting in greater chemoresistance and reduced survival [95, 103–105]. What may be of more importance is the acquisition of hybrid molecular phenotypes with both classic- and basal-like characteristics and persister cell type features. Understanding and addressing post-therapy cellular plasticity and persister cell enrichment will require well-designed clinical trials with multidimensional omics analysis approaches.

New trials

Several studies are exploring the use of transcriptomic profiling in the clinical trial setting. The PANCREAS study (PurIST Classification-Guided Adaptive Neoadjuvant Chemotherapy by RNA Expression Profiling of EUS Aspiration Samples) aims to enroll 41 patients, determining the PurIST molecular subtypes in tumor samples obtained by endoscopic ultrasound fine-needle aspiration (EUS/FNA) to establish the pancreatic cancer subtype (NCT04683315). Therapy is directed on the basis of molecular subtype (classic vs. basal). Patients with the classic subtype will receive mFOLFIRINOX and patients with the basal subtype will receive neoadjuvant Gem-NabP. The primary outcome measure is the number of patients who receive PurIST classification-directed therapy and have a treatment response following 12 weeks of therapy—but the stage of disease is not specified.

PASS-01 (Pancreatic Adenocarcinoma Signature Stratification for Treatment) is a randomized phase II trial that will enroll 150 patients with PDAC of any stage to receive either mFOLFIRINOX or Gem-NabP

Table 5 Selected ongoing perioperative and molecular studies for localized pancreatic cancer and oligometastatic disease

Trial Name	Identifier	Population	Number	Phase	Interventions (number of chemotherapy cycles)	Primary endpoint
PREOPANC-2	EudraCT 2017-002036-17	Resectable and borderline resectable	368	III	Neoadjuvant FOLFIRINOX (8) vs. neoadjuvant gemcitabine-based chemoradiotherapy plus adjuvant gemcitabine (4)	Overall survival
PREOPANC-3	NCT04927780	Resectable	378	III	Neoadjuvant (8) plus adjuvant (4) mFOLFIRINOX vs. adjuvant FOLFIRINOX (12)	Overall survival
ALLIANCE A021806	NCT04340141	Resectable	352	III	Neoadjuvant (8) plus adjuvant mFOLFIRINOX (4) vs. adjuvant mFOLFIRINOX (12)	Overall survival
HOLIPANC	NCT04617457	Oligo-metastatic	150	II	Induction NAPOX (4) stage + (4) restage. Adjuvant chemotherapy discretionary. Non-randomized	Overall survival
METAPANC	AIO-PAK-0219	Oligo-metastatic	272	III	Induction mFOLFIRINOX (8) + NO SURGERY + maintenance FOLFIRI or capecitabine (3 months) vs. mFOLFIRINOX (8) + surgery + adjuvant FOLFIRI or capecitabine (3 months)	Overall survival
ESPAC-6	NCT05314998	Resected	394	III	Adjuvant mFOLFIRINOX (12) or GEM-CAP (6) based on transcriptomic signature vs. adjuvant mFOLFIRINOX (12)	Disease-free survival
ESPAC-7	n.a.	Locally advanced	196	II	Induction mFOLFIRINOX or GEM + NabP based on transcriptomic signature vs. mFOLFIRINOX	Resection rate

mFOLFIRINOX modified FA/5FU + IR + 5-FU/FA, *NAPOX* liposomal IR + OX + 5-FU/FA, *FOLFIRI* 5-FU/FA, *IR* (1 cycle = 14 days), *n.a.* not available

(NCT04469556). The primary outcome measure is progression-free survival, and it is the first randomized trial to have a head-to-head comparison of these two regimens. Important secondary outcome measures include overall survival associated with treatment-specific signatures, and GATA6 concordance between organoid transcriptomic profiles and patient transcriptomic profiles.

The ESPAC6 trial (NCT05314998) will randomize resectable (EmR) patients 1:1 to an experimental arm in which patients will receive either adjuvant mFOLFIRINOX or GEMCAP based on the ESPAC transcriptomic treatment-specific signature or to the control arm in which all patients will receive adjuvant mFOLFIRINOX. The primary endpoint is disease-free survival, with multiple secondary endpoints in transcriptomic and genomic analyses. The ESPAC7 is similarly designed for patients with EmUR locally advanced PDAC tumors, with the primary endpoint in this case being the rate of resection.

Several standard clinical trials are comparing neoadjuvant and adjuvant alternatives in EmR and EmBR settings (Table 5). The Phase III Alliance 21806 trial is evaluating perioperative mFOLFIRINOX (eight cycles neoadjuvant and four cycles adjuvant) compared to adjuvant mFOLFIRINOX (12 cycles). The PREOPANC-3 trial in The Netherlands is evaluating the same treatment regimens. PREOPANC-2 is also evaluating neoadjuvant mFOLFIRINOX (eight cycles) compared to neoadjuvant gemcitabine-based chemoradiotherapy, with both groups receiving four cycles of adjuvant gemcitabine in the borderline and resectable PDAC populations.

Further evidence on the role of surgical resection in patients with EmOm is expected from several ongoing studies. The non-randomized single-arm, phase II HOLIPANC study will enroll 150 patients with hepatic oligometastatic PDAC to receive induction therapy with liposomal irinotecan, oxaliplatin, and 5-FU/FA (NAPOX) followed by surgical exploration and synchronous resection of both primary and metastatic lesions if feasible.

The METAPANC study will randomize 272 patients with EmOm to receive either FOLFIRINOX until disease progression or surgery after at least eight cycles of FOLFIRINOX.

Conclusion

The personalized treatment in localized pancreatic cancer is now firmly established based on the empirical system of staging. For locally resectable (EmR), this requires primary resection followed by adjuvant combination chemotherapy, utilizing either mFOLFIRINOX for patients aged 79 or younger with good performance status and no significant cardiovascular issues, or GEMCAP in other cases. For borderline resectable (EmBR), a neoadjuvant chemotherapy regimen followed by adjuvant therapy, particularly FOLFIRINOX or GEMCAP, is favored. For individuals initially diagnosed with unresectable (EmUR) disease, a 3–6-month induction course of combination chemotherapy, preferably mFOLFIRINOX, is recommended. A similar approach may be taken in selected patients with EmOm. The total number of cycles and dosing when both pre- and postoperative chemotherapy is administered needs to be evaluated in future trials. Chemoradiotherapy in the adjuvant setting is not supported, while its role in the neoadjuvant and induction settings is questioned by a number of studies (Lap-07, Alliance A021501, and ESPAC5). Surrogate markers in outcome evaluation in neoadjuvant and induction strategies are not supported by the evidence, requiring disease-free and overall survival as the primary endpoints. Real progress is now dependent on integrating the empirical staging sys-

tems with a deeper understanding of tumor plasticity according to tumor evolution with resistance mechanism based on acquired mutations and the selection of cell persister populations with intrinsic resistance mechanisms. Several key studies that are ongoing are designed to do precisely this, notably PASS-01, ESPAC6, and ESPAC7.

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Conflict of interest J.P. Neoptolemos, K. Hu, P. Bailey, C. Springfeld, B. Cai, Y. Miao, C. Michalski, C. Carvalho, T. Hackert and M.W. Büchler declare that they have no competing interests.

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