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REVIEW

New challenges in perioperative management of pancreatic cancer

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Abstract

Pancreatic ductal adenocarcinoma (PDAC) is the fourth leading cause of cancer-related death in the industrialized world. Despite progress in the understanding of the molecular and genetic basis of this disease, the 5-year survival rate has remained low and usually does not exceed 5%. Only 20%-25% of patients present with potentially resectable disease and surgery represents the only chance for a cure. After decades of gemcitabine hegemony and limited therapeutic options, more active chemotherapies are emerging in advanced PDAC, like 5-Fluorouracil, folinic acid, irinotecan and oxaliplatin and nab-paclitaxel plus gemcitabine, that have profoundly impacted therapeutic possibilities. PDAC is considered a systemic disease because of the high rate of relapse after curative surgery in patients with resectable disease at diagnosis. Neoadjuvant strategies in resectable, borderline resectable, or locally advanced pancreatic cancer may improve outcomes. Incorporation of tissue biomarker testing and imaging techniques into preoperative strategies should allow clinicians to identify patients who may ultimately achieve curative benefit from surgery. This review summarizes current knowledge of adjuvant and neoadjuvant treatment for PDAC and discusses the rationale for moving from adjuvant to preoperative and perioperative therapeutic strategies in the current era of more active chemotherapies and personalized medicine. We also discuss the integration of good specimen collection, tissue biomarkers, and imaging tools into newly designed preoperative and perioperative strategies.

Key words: Neoadjuvant chemotherapy; Biomarkers; Preoperative strategies; Pancreatic ductal adenocarcinoma; Personalized medicine

Core tip: Adoption of preoperative treatment strategies in

management of pancreatic ductal adenocarcinoma has the potential to increase resection rates and reduce relapse rates by targeting residual tumor cells and micrometastases early. The use of new, more active chemotherapy regimens such as 5-Fluorouracil, folinic acid, irinotecan and oxaliplatin and nab-paclitaxel plus gemcitabine in the neoadjuvant setting may offer an opportunity to downstage patients with borderline resectable or locally advanced disease to true curative intent R0 resection candidates. A more personalized approach in the setting of a neoadjuvant research platform, using tissue biomarkers and advanced imaging techniques to monitor treatment response could help improve our understanding of tumor biology and ultimately identify patients who could benefit from curative surgery.

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INTRODUCTION

Clinical landscape of pancreatic cancer and the challenges facing clinicians and researchers

Pancreatic ductal adenocarcinoma (PDAC) is one of the most lethal and aggressive malignancies and is the fourth leading cause of cancer-related death in industrialized countries[1]. Despite progress in our understanding of the molecular and genetic basis of this disease, 5-year survival rates have remained low and usually do not exceed 5%. This is due to the fact that PDAC presents as locally advanced or metastatic disease in most patients and only 20%-25% present with potentially resectable disease. However, even in these patients, the 5-year survival rate after a curative intent resection (R0) is approximately 15%-20%[2]. Survival rates for patients who undergo a margin-positive resection (R1 or R2) are similar to those with locally advanced disease[3-5].

Most drugs and other therapeutic strategies have shown little impact on disease course and prognosis in PDAC. This is likely due to a combination of late diagnosis, complex tumor biology, genetic heterogeneity, and the active role that the stroma appears to play in precluding intratumoral drug delivery[6]. Surgery still remains the only curative option and there has been no clear impact of perioperative strategies on outcomes. Moreover, clinical trials in PDAC, built too often around the empiric assessment of only one target or one drug in large phase Ⅲ studies, could also explain, in part, why the prognosis for PDAC patients has not dramatically changed as it has for other cancers.

When presented with localized disease, it is essential to clearly establish resectability at the time of initial evaluation in order to avoid unnecessary and ineffective surgery in patients with rapidly evolving metastatic disease and to focus efforts on increasing the rate of true R0 resection with effective preoperative therapy. In addition, moving toward preoperative treatment in PDAC could offer a unique opportunity to study the effects of interventional therapies on tumor biology and response and may represent the best approach for improving the prognoses in this devastating disease.

This review aims to provide an overview of the current knowledge and available data on adjuvant and neoadjuvant treatment in PDAC and to discuss the basic and clinical rationale for moving to preoperative and perioperative therapeutic strategies in the current era of more active chemotherapies and personalized medicine. We will also discuss new challenges in this setting with a special emphasis on new strategies and trials that integrate translational biomarker and imaging research.

DEFINITION AND STAGING OF RESECTABLE, BORDERLINE RESECTABLE, AND LOCALLY ADVANCED DISEASE

Definitions used in the literature have often been heterogenous or difficult to interpret, making data comparisons between trials challenging. It is thus essential to carefully define these three entities for the purposes of this discussion.

Multidetector computed tomography (CT) with three-dimensional (3-D) reconstruction is the modality of choice for preoperative staging of pancreatic cancer. The American Joint Committee on Cancer (AJCC) staging system for PDAC defines criteria for resectability on the basis of radiographic findings, the presence/absence of metastases, and the tumor's association with blood vessels. PDAC is defined as resectable if tumor extension to the celiac and superior mesenteric artery is absent, superior mesenteric and portal veins are patent, and there are no distant metastases[7]. However, with the development of more sophisticated imaging tools and surgical techniques, more patients have been included in a growing category of borderline resectable disease[8,9]. A universally accepted set of criteria to define borderline resectable disease does not exist. Efforts to standardize the definition of borderline resectability were undertaken by the American Hepato-Pancreato-Biliary Association (AHPBA) in 2009. At this consensus conference, expert participants expanded the venous involvement criteria to allow tumor abutment of the superior mesenteric vein/portal vein with or without impingement and narrowing of the lumen (in addition to venous encasement or short segment occlusion)[10]. This definition has been adopted into the National Comprehensive Cancer

Table 1 Comparison of American Hepatopancretobiliary Association/Society for Surgery of the Alimentary Tract/Society of Surgical Oncology, MD Anderson Cancer Center, and National Comprehensive Cancer Network definitions of borderline resectable pancreatic cancer

	AHPBA/SSO/SAT	MDACC	NCCN 2012
SMV-PV	Abutment, encasement or occlusion	Short segment occlusion	Abutment with impingement or narrowing
SMA	Abutment	Abutment	Abutment
CHA	Abutment or short segment encasement	Abutment or short segment encasement	Abutment or short segment encasement
Celiac trunk	No abutment or encasement	Abutment	No abutment or encasement

AHPBA/SSO/SSAT: American Hepatopancretobiliary Association/Society of Surgical Oncology/Society for Surgery of the Alimentary Tract; MDACC: MD Anderson Cancer Center; NCCN: National Comprehensive Cancer Network; SMV: Superior mesenteric vein; PV: Portal vein; SMA: Superior mesenteric artery; CHA: Common hepatic artery; Abutment: Tumor-vessel interface less than 180° of vascular circumference; Encasement: Tumor-vessel interface at least 180° of vascular circumference.

Table 2 Major phase Ⅲ trials of adjuvant therapy for resected Pancreatic ductal adenocarcinoma

Ref.	Year	*n*	Treatment arms	OS (mo)	*P* value	5-yr OS (%)
GITSG[15]	1985	21	CRT[1]/5-FU then 5-FU maintenance for 2 yr	20.0	0.035	19
		22	Observation	10.9		5
EORTC[16]	1999	60	[2]CRT/5-FU	17.1	0.09	20
		54	Observation	12.6		10
ESPAC-1[18]	2004	145	[1]CRT/5-FU +/- 5-FU/FA bolus for 6 cycles	15.9	0.05	10
		144	No CRT	17.9		20
CONKO-001[14]	2007	179	Gem 6 cycles	22.8	0.005	20.7
		175	Observation	20.2		10.4
RTOG 97-04[22]	2008	187	Gem 3 wk, CRT/5-FU, Gem 3 mo	20.5	0.09	22
(pancreatic head only)		194	5-FU 3 wk, CRT/5-FU, 5-FU 3 mo	17.1		18
ESPAC-3[21]	2010	551	5-FU/FA for 6 cycles	23.0	0.53	NA
		537	Gem for 6 cycles	23.6		NA

[1]CRT:20 Gy + 5-FU bolus days 1-3 x 2; [2]20 Gy + 5-FU continous infusion x 2. CRT: Chemoradiotherapy; 5-FU: 5-Fluorouracil; FA: Folinic acid; Gem: Gemcitabine; OS: Overall survival; NA: Not available.

Network (NCCN) guidelines[11]. Another commonly cited definition is that proposed by the MD Anderson Cancer Center. They expanded the concept of borderline resectability, taking into consideration tumor biology and the patient's general condition, defining 3 subgroups: type A patients with anatomically-defined borderline resectability; type B patients with findings suspicious of extra-pancreatic involvement; type C patients with contraindication to major abdominal surgery[8]. Table 1 shows existing criteria for borderline resectable pancreatic cancer.

Good preoperative staging is essential because of the poor prognosis associated with pancreatic cancer with involved or resected vessels. In a systematic review and meta-analysis on arterial resection (AR) during pancreatectomy by Mollberg *et al*[12], AR was associated with poor short- and long-term outcomes. However, pancreatectomy with AR may be justified in highly selected patients taking into account the potential survival benefit compared to patients without resection. These patients should be treated and prospectively included in clinical trials to assess outcomes after AR in the era of modern pancreatic surgery and multimodal therapy.

ADJUVANT THERAPY

Due to high rates of up to 80%-85% for metastasis and local relapse after tumor resection[13,14], surgery alone is inadequate as the only therapeutic option in resectable PDAC. Several randomized trials have investigated adjuvant treatment in PDAC patients. Major adjuvant approaches include: systemic chemotherapy, fluorouracil-based chemoradiation, and chemoradiation plus chemotherapy. Table 2 summarizes the major reported adjuvant Phase Ⅲ trials and Table 3 summarizes the ongoing phase Ⅲ trials.

In 1985, the Gastrointestinal Tumor Study Group (GITSG) reported increased survival among patients treated with 5-fluorouracil (5-FU) bolus with concurrent 5-FU and a split course of radiotherapy followed by maintenance 5-FU weekly for 2 years or until tumor recurrence as compared with observation[15]. Although the GITSG study was considered the pivotal study justifying the use of adjuvant chemoradiotherapy (CRT) as the standard of care, the patient numbers for a phase Ⅲ study were small by current standards (n = 49) and the benefit may have been derived from the systemic therapy and not from the CRT. Despite these important limitations, this study has led to the adoption of CRT as the main adjuvant treatment in resected PDAC in the United States. The utility of radiotherapy has never been addressed in any of the United States trials conducted since the GITSG trial while these findings were not confirmed in the

Table 3 Major phase Ⅲ ongoing adjuvant/neoadjuvant trials

Sponsor/study name	Treatment arms	Primary outcome	Clinicaltrial.gov No.	EudraCT number
Unicancer	Gemcitabine *vs* folfirinox	DFS	NCT01526135	
Celgene corporation	Nab-paclitaxel + gem *vs* gem	OS	NCT01964430	
Radiation therapy Oncology group	Pre and post CRT 5-FU *vs* pre and post CRT gem	OS, DFS	NCT00003216	
National cancer institute	Gem *vs* gem + erlotinib, followed by CT *vs* CRT with capecitabine or 5-FU	OS	NCT01013649	
EORTC trial 40084 - 22084	Gem *vs* gem + erlotinib followed or not by CRT with capecitabine or 5-FU	OS		2011-000618-20
CONKO 005	Gem *vs* gem + erlotinib	DFS		2007-003813-15

FOLFIRINOX: 5-Fluorouracil, folinic acid, irinotecan and oxaliplatin; 5-FU: 5-Fluorouracil; FA: Folinic acid; Gem: Gemcitabine; OS: Overall survival; DFS: Disease free survival.

European Organisation for Research and Treatment of Cancer (EORTC-40891) and European Study Group for Pancreatic Cancer (ESPAC-1) trials in Europe.

The EORTC conducted a multicenter prospective randomized phase 3 trial of adjuvant CRT *vs* observation. No difference was found in overall median survival between the CRT group and the observation group[16]. A recent report on the long-term outcome of patients from this trial reaffirmed no difference in overall survival (OS)[17].

In the ESPAC-1 trial, patients were randomized after resection to one of four treatment arms: adjuvant chemotherapy with 5-FU and folinic acid (FA), CRT, a sequence of CRT and chemotherapy, and observation. Authors pooled patients who received CRT according to GITSG regimen or a sequence of CRT plus chemotherapy and compared them with patients not assigned to CRT. Patients receiving CRT had a significantly worse outcome[18].

This trial has been criticized for methodological and statistical issues. Only 88% of patients in the CRT group actually received radiation therapy and only 70% of patients received the planned 40 Gy radiation. In addition, the present standards for radiation therapy have changed from the original GITSG protocol which used a split-course of radiation and a bolus application of 5-FU. Considering modern radiation techniques and application of 5-FU by continous infusion, a different outcome might be achieved today[19].

From 1998 to 2004, Oettle *et al*[14] conducted a large multicenter phase 3 randomized trial to determine the influence of adjuvant gemcitabine chemotherapy after resection of pancreatic cancer on disease-free survival (CONKO-001). Significantly longer disease-free survival (DFS) and OS were reported in patients receiving gemcitabine compared to observation. A recent report on long-term outcomes of the CONKO-001 trial confirmed the benefit of adjuvant gemcitabine for 6 mo *vs* observation[20].

The ESPAC-1 and CONKO-001 trials established the survival advantage of adjuvant chemotherapy with 5-FU plus FA or gemcitabine as compared to no chemotherapy.

The international multicenter phase 3 ESPAC-3 trial compared 5-FU plus FA *vs* gemcitabine in the adjuvant setting. A total of 1088 patients were randomly assigned to receive 6 cycles of 5-FU/FA or gemcitabine. No differences were found between groups in median survival time, progression-free survival (PFS) or quality of life. However, gemcitabine was associated with significantly fewer serious adverse events[21].

To date, the use of adjuvant CRT (intended to reduce local recurrence by administering radiation to the pancreatic bed with concomitant 5-FU) is still a matter of debate. While it is the standard of care in the United States, this adjuvant strategy is not recommended in Europe as a standard of care[22,23].

This recommendation is supported by the results of a recent Bayesian network meta-analysis of 9 randomized controlled trials that compared treatments in terms of overall survival and grade 3-4 toxicity[24]. After adjusting for positive lymph node status, results suggest that adjuvant chemotherapy with 5-FU [hazard ratio (HR) = 0.65] or gemcitabine (HR = 0.59) provides an overall survival advantage over observation or chemoradiation, whereas chemoradiation is associated with poorer overall survival compared with 5-FU (HR = 1.69) and gemcitabine (HR = 1.86). Chemoradiation plus chemotherapy with 5-FU or gemcitabine did not provide a survival benefit but increased grade 3-4 toxicity. In this meta-analysis, adjuvant chemotherapy reduced mortality after resection of PDAC by about one-third and prolonged overall survival with a better toxicity profile.

RATIONALE FOR MOVING FROM ADJUVANT TO NEOADJUVANT TREATMENT IN PDAC

Recent reports of the high revisitation rates associated with true R1 resections after standardized inking of the resected specimen should prompt us to change the way we treat pancreatic cancer even if the disease is judged resectable by high-quality imaging[25]. Vascular involvement or a clear circumferential margin less than 1.5 mm dramatically impacts survival and preoperative therapy may be indicated in this case to reduce the

influence of these factors.

Definition of neoadjuvant vs induction therapy and the rationale for pre-operative therapy

Neoadjuvant treatment is by definition intended to be administered to patients with resectable disease. However, patients with borderline resectable and locally advanced disease have often been included in neoadjuvant trials. Neoadjuvant treatment in these settings has the intent of tumor downstaging to improve both resection and true R0 resection rates. While patients with borderline resectable PDAC still have the option to undergo resection, those with locally advanced pancreatic cancer (LAPC) in the strictest sense do not have the option of upfront surgery. In the case of LAPC, neoadjuvant chemotherapy is thus intended as an induction therapy to downstage the disease, allowing for the possibility of resection in the event of tumor shrinkage. In the literature, the term neoadjuvant has been widely applied to patients with LAPC. For this reason, in this review we will always specify the stage of the disease after using the term neoadjuvant.

Several clinical arguments have been proposed that justify and advocate the use of chemotherapy or chemoradiation before curative intent surgery. Furthermore, the latest basic and genomic research in PDAC biology has provided further rationale to support clinical arguments and justify the use of upfront chemotherapy.

Clinical rationale

PDAC should, in most cases, be considered a systemic/generalized disease due to the high frequency of micro-metastatic disease in lymph nodes and other organs. These micro-metastases are involved in early relapse (local or metastatic) after curative resection. The administration of pre-operative chemotherapy can target occult disease and avoid the delay between diagnosis, surgery, and adjuvant chemotherapy. This delay, which is generally at least 2 mo, usually occurs due to surgical waiting lists and the need for postoperative patient recovery[26]. The initiation of adjuvant chemotherapy is frequently delayed due to surgical complications, comorbidity, and prolonged recovery after pancreaticoduodenectomy, and delay occurs in up to one-fourth of eligible patients[16,27]. Therefore, a higher proportion of patients may receive pre-operative treatment compared to treatment in the adjuvant setting, and pre-operative treatment may be better tolerated, resulting in higher rates of treatment compliance[28-30]. In addition, pre-operative treatment strategies may reduce intraoperative peritoneal tumor seeding, potentially reducing the risk of early local relapse.

Pre-operative therapies also provide a time-window in which patients who progress or develop distant metastases during treatment can be identified and, therefore, avoid unnecessary surgery. Pre-operative chemotherapy may also potentially enhance the true R0 resection rate, especially in patients with borderline resectable disease and vascular involvement, and may improve survival which is dramatically reduced when retroperitoneal margins are < 1.5 mm.

Basic/genomic rationale

Recent genomic analyses have suggested that patients with very small or clinically undetectable primary tumors still have a high risk of developing metastases[31-33]. Using a mathematical modeling approach with radiological and pathological data from pancreatic cancer patients who underwent autopsy, Haeno *et al*[31] proposed that PDAC grows in an exponential manner. Researchers were able to predict that even a patient with a tumor of 1 cm in diameter had a 28% probability of harbouring microscopic metastases at presentation. The probability of metastasis increased to 94% for a tumor size of 3 cm in diameter at presentation. They added a genomic rationale in favour of upfront systemic chemotherapy that may provide improved outcomes for patients who present with such "early stage" disease. The autopsy series also revealed that only a few patients (14/101) died with non-metastatic disease, suggesting that there may be some patients who lack pro-metastatic factors and who carry non-metastatic genomic features, or have good responses to systemic therapies. Findings from this study suggest that targeting tumour cells as they are growing rapidly is crucial, and the need to avoid any delay in chemotherapy could outweigh the benefit of surgically removing the primary tumour. Rapid administration of systemic treatment might, therefore, result in a survival benefit by reducing the number of exponentially growing cancer cells, whereas interventions that postpone chemotherapy (such as surgery or radiotherapy) could be detrimental[34].

Recent findings on the multiple crucial roles of the stroma also support comprehensive neoadjuvant approaches. Anti-stromal drugs such nab-paclitaxel may be combined with chemotherapy and radiation therapy to potentiate their effects on cancer cells after stromal reduction[35,36]. Other mediators, like chemokines, that play a role in the enrichment of cancer stem cells can also be targeted in future perioperative strategies.

PREOPERATIVE THERAPY: CURRENT SITUATION AND ISSUES

Resectable disease

Several phase Ⅱ neoadjuvant trials in resectable pancreatic cancer have been published during the past two decades, but, to date, there has been no completed randomized trial that directly compared neoadjuvant treatment followed by surgery *vs* up-front surgery. One such trial is ongoing, and is comparing

4 cycles of gemcitabine plus oxaliplatin (GEMOX) chemotherapy *vs* upfront surgery (NEOPAC study, NCT01314027).

Chemoradiation is the most frequently used modality in these phase Ⅱ PDAC trials and different administration schemes and doses of radiation and chemotherapy have been used. In all the trials published, the definition of resectable disease remained constant[37-41]. Overall, these trials showed that patients whose disease did not progress at re-staging after neoadjuvant chemoradiation had higher R0 resection rates, lower local recurrence rates, and increased survival rates compare to historical data. Most importantly, response to neoadjuvant chemoradiation helped to select patients who were unlikely to benefit from upfront surgery. Up to 26% of initially resectable patients could not be resected 4-6 wk after completion of their neoadjuvant chemotherapy treatment[42]. However, as we are currently lacking valid prognostic biomarkers, the testing of which should be integrated into future trials, we do not know if this percentage of patients with progressive disease despite neoadjuvant treatment is representative of those patients who would not have benefited from upfront surgery. In two meta-analyses on neoadjuvant treatment, resection rates and survival outcome following neoadjuvant therapy were similar in patients with initially resectable tumors compared to those patients with primarily resected tumors followed by adjuvant therapy[42,43]. However, these meta-analyses suffered from a number of limitations in the available literature on neoadjuvant treatment in pancreatic cancer: (1) the definition of resectability varied widely between studies; (2) there was heterogeneity in treatment regimens, often with old drugs or obsolete radiotherapy regimens; and (3) patient inclusion in these trials was challenging because of the need for histologic proof of pancreatic cancer, which is sometimes difficult to obtain for small pancreatic lesions.

Despite the theoretical advantages that it potentially offers, there is no current evidence to support the routine clinical use of neoadjuvant therapy in resectable PDAC outside of a clinical trial[11,44].

Borderline resectable and locally advanced disease

Patients with borderline resectable disease represent a subset of patients with a low probability of R0 resection if immediate surgery is performed. Preoperative therapy in this setting has the theoretical potential to downstage the disease and increase the chance of achieving an R0 resection. However, the available literature does not allow for formation of a definitive conclusion because of the heterogeneity of resectability definitions and therapeutic regimens, and the low number of patients included in the reported studies[45-48]. The number of patients included in these heterogenous trials who underwent surgical resection ranged from 33% to 64% and in these selected patients, R0 resection rates were high, ranging from 87% to 100%.

Katz *et al*[9] retrospectively assessed the benefit of neoadjuvant chemotherapy in patients with borderline resectable disease at MD Anderson Cancer Center. In this study, 160 (7%) of 2,454 patients were classified as borderline resectable and 125 (78%) completed a course of preoperative therapy and were re-staged. Sixty-three percent (79 of 125) of patients proceeded to surgery and 53% (66 of 125) of patients underwent pancreatectomy. Vascular resection was required in 18 (27%) of 66 patients, and 62 (94%) underwent a margin-negative pancreatectomy. Of all 160 patients with borderline resectable disease, the median survival was 18 mo and 5-year survival was 18%. Median survival was 40 mo for the 66 patients who completed all therapy and 13 mo for the 94 patients who did not undergo pancreatectomy ($P < 0.001$)[9].

In addition, results of systematic reviews and meta-analyses suggest that neoadjuvant treatment appears to have some activity in patients with borderline resectable/unresectable PDAC. Nearly one-third of tumors considered marginal for resection at initial evaluation were ultimately resected after neoadjuvant treatment[42,43].

As in the case of borderline resectable disease, the aim of upfront treatment in LAPC may be to convert the tumor to resectability. As mentioned before, a more appropriate definition of this strategy should be "induction" therapy.

Studies over the past three decades have assessed this strategy in the locally advanced setting[49-54]. In a systematic review and meta-analysis of response and resection rates after preoperative/neoadjuvant therapy[43], a total of 111 trials (n = 4394) were analyzed. Studies were subdivided into group 1 (initially resectable tumors) and group 2 (initially non-resectable: both borderline resectable/unresectable). Neoadjuvant therapy included chemotherapy in 96% and radiation therapy in 94% of studies. In group 1, estimated resectability was 73.6% compared to only 33.2% in group 2. Furthermore, higher resection-associated morbidity and mortality rates were observed in group 2 *vs* group 1 (26.7% *vs* 39.1%; and 3.9% *vs* 7.1%). Combination chemotherapies resulted in higher estimated response and resection probabilities for patients with initially non-resectable tumors compared to monotherapy. Estimated median survival following resection was 23.3 mo for group 1 and 20.5 mo for group 2 patients.

In conclusion, while for those patients with initially resectable tumors, resection frequencies and survival after neoadjuvant therapy are similar to those for patients with primarily resected tumors and adjuvant therapy, one-third of initially staged non-resectable tumor patients would be expected to have resectable tumors following preoperative therapy, with overall

survival comparable to what was observed in primarily resected PDAC patients. Thus, patients with locally non-resectable tumors should be included in well-defined induction protocols and subsequently re-evaluated for resection.

Use of new active chemotherapies for downstaging PDAC

Most of the previous studies reported the use of 5-FU- or gemcitabine-based chemoradiation or chemotherapy combinations with limited activity. Recently, combination therapies with FOLFIRINOX (5-FU, leucovorin, irinotecan, oxaliplatin) or gemcitabine plus nab-paclitaxel have been shown to significantly increase median OS and tumor response rates (11.1 mo *vs* 6.8 mo, $P < 0.001$; 8.5% *vs* 6.7%, $P < 0.0001$) in metastatic disease[45,56]. These regimens, providing higher objective response rates of 31% and 29% (67% of metabolic response), respectively, may be applied as a neoadjuvant/induction treatment. The Medical College of Wisconsin Pancreatic Cancer Program group first reported its initial experience of induction chemotherapy with FOLFIRINOX followed by chemoradiation in 18 patients with borderline resectable PDAC[55]. This report suggests very high adherence to therapy, a higher resection rate (67%), and longer survival in patients who underwent surgery. However, the apparent safety of FOLFIRINOX followed by chemoradiation and the high resection rate (with vascular resection and reconstruction in 83% of patients) in this report may not be transferable to centers with limited experience in the management of patients with PDAC. A prospective trial is ongoing (ALLIANCE).

Similarly, preliminary data exploring preoperative gemcitabine and nab-paclitaxel administration have shown tumoral response and downstaging associated with stromal reduction[35].

Today, the available literature does not support any particular treatment strategy over another, and prospective trials based on well-standardized definitions of resectability and evaluation of feasibility of different strategies with clearly established end-points are highly desirable. The aim of the newly designed ESPAC-5 trial is to assess the feasibility of randomizing patients to a neo-adjuvant trial as previous trials have failed to recruit. This trial will compare upfront surgery followed by adjuvant chemotherapy with 3 different neoadjuvant regimens: gemcitabine-capecitabine chemotherapy *vs* FOLFIRINOX *vs* capecitabine-based chemoradiation prior to surgery. Combination chemotherapies seem to be associated with higher response and resection probability. The efficacy of new, more active combination regimens like FOLFIRINOX or gemcitabine plus nab-paclitaxel, which are increasingly used since they have been proved to be highly effective in the metastatic setting, remain to be investigated in controlled trials specifically designed in these settings[45,56]. Table 4 summarizes a non-exhaustive list of ongoing neoadjuvant/preoperative trials registered at clinicaltrials.gov before January 2014.

INTEGRATING BIOMARKER AND IMAGING TOOLS INTO NEWLY DESIGNED PREOPERATIVE AND PERIOPERATIVE STRATEGIES AND RESEARCH PLATFORMS

Developing perioperative strategies is of the utmost interest for curative management of pancreatic cancer. Recent progress made in the understanding of the complex biology and molecular heterogeneity of PDAC offers opportunities to identify new targets, explore relevant pathways involved in pancreatic carcinogenesis, and find predictive/prognostic biomarkers. In addition, during the time interval between diagnosis and planned surgery, the administration of a neoadjuvant therapy could allow early evaluation of treatment effects by dynamic imaging such as dynamic contrast-enhanced/diffusion weighted-magnetic resonance imaging (DCE/DW-MRI) or positron emission tomography-computed tomography (PET-CT) and may constitute a relevant test for subsequent adjuvant chemotherapy benefit.

Tissue biomarkers and preoperative tissue sampling

To date, no predictive biomarkers for treatment response in PDAC have entered into clinical practice. However, great progress has been made in understanding the genetic complexity of PDAC. With "OMICS" techniques becoming more and more available and cheaper, it will hopefully soon be possible to predict which therapies will benefit each individual patient[56].

The one predictive biomarker in PDAC that is supported by evidence in the literature is the human equilibrative nucleotide transporter 1 (hENT1), the major mediator of gemcitabine uptake in pancreatic cancer cells[57-59]. Data from multiple retrospective studies have shown that only patients with high expression of hENT1 seem to benefit from adjuvant gemcitabine chemotherapy after curative intent resection[60-63].

Although these results have not been validated in a prospective trial, they might be transferable in neoadjuvant settings to guide the choice of gemcitabine-based chemotherapy *vs* other drugs.

In an autopsy study, the loss of SMAD/DPC4 expression was observed in only 22% of LAPC patients, compared with 73% of patients with metastatic disease[64]. *SMAD4* gene inactivation was also associated with poorer prognosis in patients with surgically-resected adenocarcinoma of the pancreas[65] and correlated with a local pattern of disease pro-

Table 4 Selected ongoing neoadjuvant/preoperative trials registered at clinicaltrial.gov before January 2014

Clinicaltrial.gov No.	Type of cancer	Intervention	Design	Primary outcome	Biomarker
NCT01771146	Locally advanced	FOLFIRINOX	Phase Ⅱ Single arm	PFS	No
NCT01458717	Borderline resectable	Gemcitabine and CRT *vs* uprfont surgery	Phase Ⅱ/Ⅲ Randomized trial	2-yr OS	No
NCT01065870	Locally advanced	gemcitabine, capecitabine and docetaxel +/- RT with gemcitabine and capecitabine	Phase Ⅱ/Ⅲ Non randomized	2-yr OS	No
NCT01314027	Resectable	Neoadjuvant gemcitabine/ oxaliplatin *vs* adjuvant CT with gemcitabine	Phase Ⅲ randomized multicenter trial	PFS	No
NCT01521702	Resectable	Neoadjuvant gemcitabine/ oxaliplatine *vs* surgery and adjuvant gemcitabine	Phase Ⅲ Randomized Multicenter trial	PFS	No
NCT00536874	Resectable	Gemcitabine and oxaliplatine	Phase Ⅱ Single arm	OS 18 mo	Yes (proteomic profiling, laboratory biomarker analysis)
NCT01661088	Borderline resectable	FOLFIRINOX, gemcitabine during and after radiation therapy	Phase Ⅱ Single arm	R0 resection rate	No
NCT00609336	Resectable	Gemcitabine, docetaxel, capecitabine, RT and surgery	Phase Ⅱ Single arm	OS	No
NCT00869258	Locally advanced	Gemcitabine, docetaxel and capecitabine followed by RT with gemcitabine	Phase Ⅱ Single arm	Conversion rate	No
NCT00557492	Resectable	Bevacizumab with gemcitabine and radiation therapy	Phase Ⅱ Single arm	R0 resection rate	Yes (not specified)
NCT01298011	Resectable	Gemcitabine and nab-paclitaxel	Phase Ⅱ Single arm	Histological response	Yes (SPARC expression in the tumor)
NCT01359007	Borderline resectable Locally advanced	FOLFIRINOX	Phase Ⅰ Single arm	R0 resection rate	No
NCT01470417	Resectable Borderline resectable	Nab-paclitaxel and gemcitabine Nab-paclitaxel and gemcitabine with CT	Phase Ⅱ Not randomized	Biochemical and pathologic response rate R0 resection rate	Yes (biochemical radiographic, and pathologic factors)
NCT01494155	Resectable	Capecitabine, Hydroxychloroquine and proton RT	Phase Ⅱ Single arm	PFS	Yes (autophagy)
NCT00733746	Resectable	Gemcitabine and erlotinib	Phase Ⅱ Single arm	OS	Yes (gene expression, polymorphism and laboratory biomarker analysis)
NCT01726582	Resectable Borderline resectable	Targeted CT prior and after surgery guided by molecular profiling CRT before surgery	Phase Ⅱ Single arm	R0 resection rate	Yes (see: www.mcw.edu/surgery/patientinfo/Pancreatic-Cancer-Trial.htm)
NCT01150630	Resectable	Adjuvant *vs* neoadjuvant Capecitabine, cisplatine, epirubicine and gemcitabine	Phase Ⅱ/Ⅲ Multicenter randomized trial	Event-free survival at 1 yr	No

FOLFIRINOX: 5-Fluorouracil, folinic acid, irinotecan and oxaliplatin; CRT: Chemoradiation therapy; CT: Chemotherapy; RT: Radiation therapy; PFS: Progression free survival; OS: Overall survival.

gression[66] while loss of *SMAD4* expression was not correlated with recurrence pattern but was shown to be predictive for adjuvant chemotherapy benefit in another large study[67]. A subclassification of PDAC into three subtypes (classical, quasi-mesenchymal, and exocrine-like) based on gene expression profiling has been proposed with evidence of a differing response to chemotherapy in cell lines with the same expression profile[68].

Prospective validation of these data in larger cohorts of resectable and unresectable patients is needed as well as their integration into neoadjuvant trials. In this setting, obtaining pre-therapeutic tissue represents a key step in such protocols by adequately using endoscopic ultrasound fine needle aspiration (EUS-FNA) sampling not only for diagnosis of PDAC but also for molecular staging and characterization. Therefore, effort should be focused on good pre-operative tissue acquisition and on addressing standard protocols for molecular biology. On the other hand, the use of liquid biopsies from circulating tumor DNA to characterize mutational panels and monitor response seems to be very promising[69,70].

Imaging tools to monitor treatment response and tumor downstaging

The most important issues in preoperative strategy are (1) the evaluation of treatment efficacy and tumor response, preferably as early as possible to adapt therapy; and (2) the re-staging of the tumor in

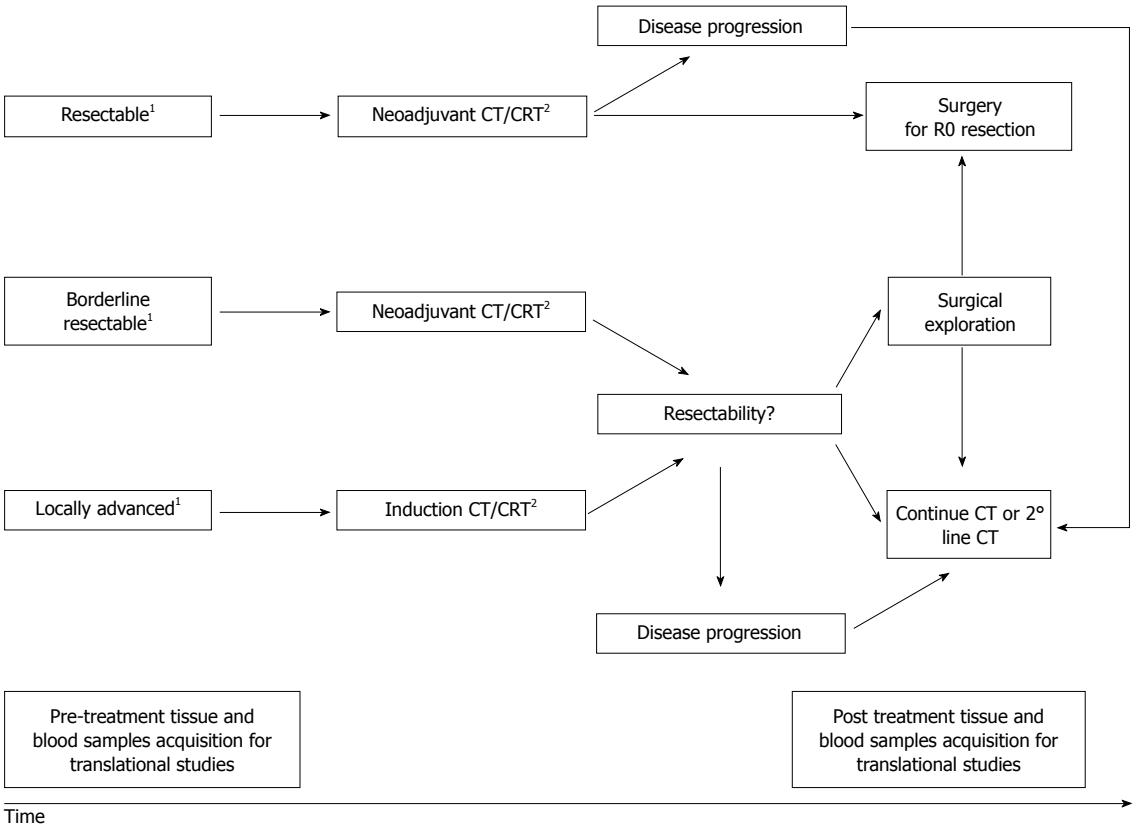

Figure 1 Proposed pre-operative strategies to integrate biomarkers into clinical trials. [1]Patients' selection based on predictive and prognostic biomarker; [2]Functional imaging assessment. CT: Computed tomography; CRT: Chemoradiotherapy.

terms of resectability. One limitation is the difficulty associated with evaluating morphologic response in a pancreatic tumour mass. Some authors have shown that response of borderline resectable pancreatic cancer to preoperative therapy is rare and is not reflected by radiographic indicators[71]. Therefore, RECIST criteria are probably inadequate for detection of tumoral changes and objective response may not be an effective treatment endpoint for patients with borderline resectable pancreatic cancer. Detecting differences between fibrotic and neoplastic tissue is virtually impossible with classic abdominal imaging and the additional value of dynamic imaging like DW/DCE-MRI or metabolic PET-CT imaging should be evaluated for identifying responders *vs* non-responders.

DCE-MRI provides a quantitative estimation of physiologic parameters related to perfusion and/or permeability *in vivo*. Previous publications have reported that quantitative DCE-MRI parameters are correlated with fibrosis and microvascular density in pancreatic tumoral and non-tumoral lesions and its utility in monitoring treatment response in non-resectable PDAC[72-74].

A recent study assessed PET scan response in advanced PDAC patients treated with gemcitabine plus nab-paclitaxel for the first time. Results showed that a complete loss of ^{18}F-fluorodeoxyglucose uptake was associated with improved overall survival[36].

There is a need for further validation of these promising functional imaging techniques for the evaluation of early tumor response.

PERSPECTIVES TOWARD A PERSONALIZED APPROACH IN PDAC

In Figure 1, we propose pre-operative strategies to integrate translational research into clinical trials with particular emphasis on biobanking and imaging tools to monitor response. New strategies should initially stage and categorize tumor and patients, not only clinically but also based on specific biomarkers that are capable of predicting tumor behavior and response to selected therapies. Moreover, one of the most attractive therapeutic strategies is to target the stroma and microenvironment of the tumor to decrease the desmoplastic resistant compartment and to increase intratumoral delivery of cytotoxics. Hopefully, with the use of new, more active regimens like combinations of gemcitabine plus nab-paclitaxel, and FOLFIRINOX$^{+/-}$ new therapies in borderline resectable or locally advanced pancreatic cancer, we may improve the percentage of patients who could benefit from curative R0 resection, thus improving PDAC management and outcomes. This underlines the importance of response monitoring and iterative tumor re-staging in the preoperative period.

Future research and trials should therefore focus

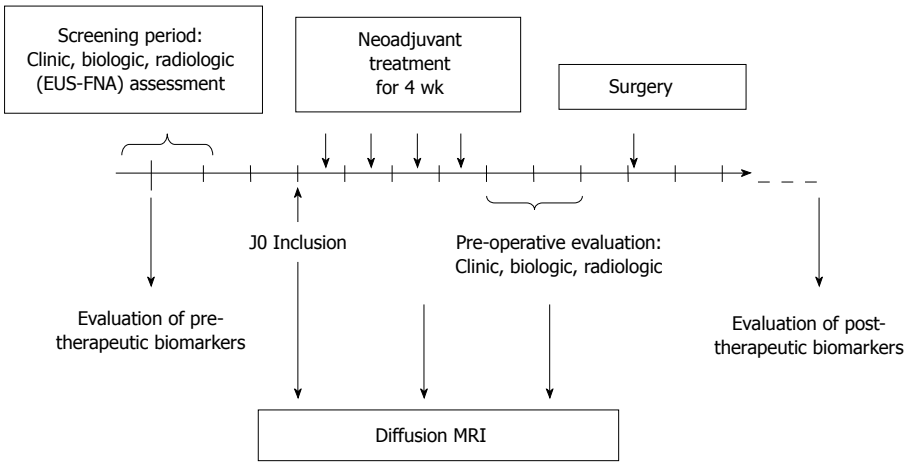

Figure 2 Proposed "neoadjuvant short window protocol" integrating tissue biomarker and dynamic imaging to monitor early response. EUS-FNA: Endoscopic ultrasound fine needle aspiration; MRI: Magnetic resonance imaging.

on exploratory early proof-of-concept studies based on predictions of response derived from dynamic imaging and molecular tools. This will permit the selection of the most active drugs and the best therapeutic approaches to move forward into phase Ⅲ trials where survival benefit will remain the final judge. Thus, a short window neoadjuvant protocol could represent an excellent *in vivo* model to understand and monitor treatment effects on the tumor and to determine predictive tools and markers for treatment-derived survival benefit without delaying surgical resection (Figure 2).

The list of ongoing neoadjuvant protocols shown in Table 4, although not exhaustive, deserves some remarks. There are a lot of phase Ⅱ studies and only a few phase Ⅲ studies in the list. This, together with the fact that several studies have been withdrawn due to lack of recruitment, reflects the difficulties, especially for monocentric studies, in enrolling well-selected patients. Some trials are still mixing resectable/borderline resectable/LAPC, underlining the need for a well-standardized and universally-accepted definition for these three entities for future clinical trials. In addition, there is too much heterogeneity in primary outcomes, ranging from R0 resection rate to DFS/PFS, or OS. This underlines the need for good selection of clear primary endpoints to address clinical questions and allow comparisons between studies. Finally, only a few studies incorporate translational biomarkers research into the trial design. This reflects difficulties in tissue acquisition especially in the setting of non-resectable pancreatic cancer and should prompt us to push efforts in standardization of tissue sampling and processing.

CONCLUSION

The only chance of a cure for PDAC remains surgery. Despite more than 20 years of effort, adjuvant therapeutic strategies in resectable PDAC still add limited benefit. Neoadjuvant strategies in borderline resectable or locally advanced pancreatic cancer may improve outcomes and there is an emerging and recent trend toward a neoadjuvant approach in potentially resectable PDAC. After decades of gemcitabine hegemony, more active chemotherapies like FOLFIRINOX and nab-paclitaxel plus gemcitabine have emerged and have shown survival advantage in metastatic settings. Incorporation of tissue biomarker testing and imaging techniques into preoperative strategies should allow clinicians to identify patients who may ultimately achieve curative benefit from surgery. Neoadjuvant strategies can provide the best model to monitor molecular changes and early response to allow for better selection of patient treatments.

Molecular studies may transform the way that we think about pancreatic cancer and provide the opportunity to refocus and prioritize our efforts toward a more personalized approach in order to improve outcomes. This is the great challenge of the modern oncologic approach to pancreatic cancer.

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