Neoadjuvant therapy in resectable pancreatic cancer—is this the way forward?—a narrative review

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Objective: To confront the current dilemma with regard to resectable pancreatic cancer treatment paradigm and preoperative therapeutic strategies.

Background: Pancreatic cancer represents a systemic disease, and its treatment ideally includes the administration of systemic therapy regardless of its anatomical stage. While preoperative therapy has recently become the new standard for borderline resectable stages, adjuvant therapy after surgery remains the current standard of care for resectable disease. However, to deliver systemic therapy in the postoperative setting implies that a significant subset of patients, not fully recovering after a pancreatectomy, will never receive appropriate treatment. Administration of chemotherapy before pancreatectomy may represent the only way to assure optimal treatment, simultaneously selecting patients for surgery according to tumor biology. For these reasons, many high-volume centers for pancreatic surgical oncology are increasingly considering this strategy also for patients with resectable disease.

Methods: In this brief narrative review, the most recent literature will be highlighted, together with updates, new perspectives on the topic, and the author's own personal view.

Conclusions: Available data to support this paradigm shift are still germinal, and the optimal modalities and timing of preoperative therapy are eagerly debated as well.

Keywords: Resectable; pancreatic cancer; pancreatic ductal adenocarcinoma (PDAC); neoadjuvant; preoperative

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Introduction

Pancreatic ductal adenocarcinoma (PDAC) has recently become the 3rd cause of cancer-related mortality in the United States (1). PDAC remains associated with a dismal prognosis, considering that the 5-year overall survival is still of less than 8% (2) and approximately two-third of the patients present with metastatic—therefore inoperable—disease. Primary oncologic resection, the only potentially curative treatment, is consequently possible in less than 20% of patients. When the disease is localized to the pancreas, PDAC can be classified as resectable, borderline resectable, or locally advanced (unresectable) (3). In all patients undergoing surgery, systemic therapy is considered ideal for optimizing outcomes. It dramatically improves survival outcomes, and is classically administered in the adjuvant setting as the standard of care (4,5). Recently, with the intent of better selection, and to increase the number of potential candidates for surgery, the treatment paradigm has rapidly evolved towards preoperative treatment strategies (*Figure 1*). Nowadays, preoperative therapy has become the new standard for borderline resectable PDAC, according to expert opinions and consensus statements (3,6). However, available data to support preoperative therapy in resectable

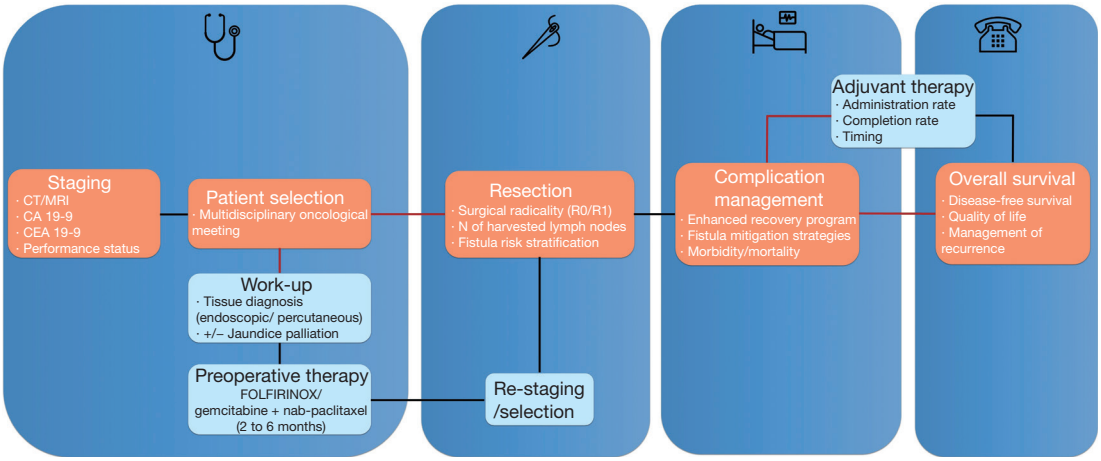

Figure 1 Authors proposal for algorithms of treatment strategies (including preoperative therapy only; adjuvant therapy only, or both) and outcome parameters for resectable pancreatic cancer. CT, computed tomography; MRI, magnetic resonance imaging; CA 19-9, carbohydrate antigen 19.9; CEA, carcinoembryonic antigen; FOLFIRINOX, folinic acid, 5-fluorouracil, irinotecan, oxaliplatin; R0/1, negative/microscopically positive tumor margins.

stages are still germinal, and the optimal sequence of systemic and surgical treatment is eagerly debated. In this brief narrative review, the most recent literature will be highlighted together with updates, new perspectives on the topic, and authors own personal views and opinions. We present the following article in accordance with the Narrative Review reporting checklist (available at https://dx.doi.org/10.21037/cco-21-51).

Current definitions of "resectable" PDAC

The itself definition of "resectable" PDAC evolved together with the definition of "borderline resectable" PDAC. Originally, resectable PDAC was defined as a tumor localized to the pancreas not infiltrating the major mesenteric vessels. However, it eventually become clearer that a microscopically complete (R0) resection was among the most important indicators of a favorable long-term prognosis (7-9). Therefore, the notion of "borderline resectable" PDAC was further developed (in addition to "resectable" and "unresectable" disease) to characterize tumors that are considered technically resectable (with or without vascular resection), but that are at high risk for positive surgical margins when pancreatectomy is performed upfront. The National Comprehensive Cancer Network (NCCN) adopted the first official definition of BR PDAC in 2006 (10). Since then, several other definitions have been proposed, all aiming to define objective radiographic criteria and guide the multidisciplinary teams in treatment strategies (11-13). In the current NCCN definition of radiographically borderline resectable PDAC, the interface between the tumor and adjacent blood vessels (i.e., superior mesenteric artery/vein, portal vein, celiac trunk, common hepatic artery) is described as the degree of contact between the tumor and each vessel defined as <180° or ≥180°, providing greater uniformity and standardization of reporting (3). While the radiographic tumor anatomy remains fundamental in the definition of borderline resectable PDAC, any comprehensive definition of "resectability" must also consider both the anticipated biologic aggressiveness of the tumor and the supposed capacity of the patient to withstand the burden of surgery. The MD Anderson Cancer Center group addressed these critical aspects categorizing patients with borderline resectable PDAC using not only anatomic (A), but also biologic (B) (a high serum cancer antigen 19-9 level or radiologically suspected metastases) and conditional (C) (comorbidities and physiologic derangements that confer higher risk for surgery) criteria. The B and C criteria were later incorporated into international consensus guidelines on definitions and criteria of borderline resectable PDAC (13,14).

The rationale behind preoperative therapy

The primary expected benefits of preoperative therapy are represented by: (I) early selection of patients with aggressive

biology, sparing them a futile operation; (II) treatment of occult systemic disease before surgery, in order to prolong survival especially in patients who are going to experience postoperative morbidity, and possibly; (III) reduction of tumor's size and anatomic extent, to increase the likelihood of a microscopically radical resection (15-17). An evaluation of the American College of Surgeons and the National Cancer Data Base demonstrated that in up to 58% of patients undergoing upfront surgery adjuvant therapy is omitted due to postoperative complications (18). Given that all three aforementioned benefits are theoretically valid also in resectable stages, many high-volume centers for pancreatic surgical oncology are increasingly delivering preoperative therapy to these patients as well. Patients undergoing surgery after preoperative therapy also exhibited reduced incidence of POPF, despite having increased clinical burden in case of its occurrence (19). However, over a third of patients incur grade 3 or greater toxicities and may not complete treatment, while other may suffer disease progression prior to their anticipated operation. Likewise in the adjuvant setting, not all patients undergoing chemotherapy with a neoadjuvant intent eventually undergo surgery when outcomes are analyzed in an intention-to-treat fashion. On the other hand, early progression during systemic therapy may be interpreted as synonymous with aggressive tumor biology. Presumptively, those patients would not derive benefit from pancreatectomy as well, experiencing early disease recurrence due to aggressive tumor biology. One major limitation to the extensive use of preoperative therapy for resectable PDAC is currently represented by the frequent need for biliary stenting, to decompress possible biliary obstruction prior to therapy. Most patients with PDAC present with jaundice, and routine biliary stenting compared to upfront surgery delays treatment and increase the risk of perioperative infections (20). However, a recent study suggests that a prolonged period of time elapsed from the time of biliary stenting to pancreatectomy may reduce morbidity and post-operative complications (21). Finally, evaluation of response to preoperative therapy for patients with PDAC is challenging. Preoperative regimens are selected on baseline data such as radiographic stage and serum CA 19-9 level and then administered for pre-specified durations (typically 3 or 6 months). Absence of disease progression, rather than evidence for tumor response, usually drives the decision for resection following preoperative therapy (16,22). A more granular and precise assessment of response to therapy is needed especially in case of resectable disease, to inform decision making and treatment sequencing based on reliable indicators of biologic response and to avoid failure to treat (23).

Preoperative therapy: evidence from clinical trials

Preoperative chemotherapy is now considered by current guidelines as the preferred strategy for patients with locally advanced or borderline resectable PDAC (3,6). However, its use continues to be debated as high-level data supporting this strategy are few and relatively recent. To date, there are no randomized controlled trials comparing adjuvant and neoadjuvant chemotherapy for resectable PDAC head-to-head. In general, the vast majority of reports consists of retrospective single-institutional series. Overall, improved patient survival is shown when patients are treated with preoperative therapy compared to those who are treated with upfront pancreatectomy. However, these findings appear limited by high heterogeneity in patient cohorts, stage definitions, and treatment strategies (24-27). In particular, it is fundamental to highlight that, unless presented in an intention to treat fashion, data regarding survival after preoperative therapy and pancreatectomy may be too optimistic, not reflecting the real-life outcomes due to selection bias. A recent large retrospective study from MD Anderson Cancer Center showed an overall resection rate of only 22% after induction therapy with either FOLFIRINOX or gemcitabine + nab-paclitaxel for all stages of disease (40% for resectable PDAC) (28). Notably, reported resection rates are consistent with those reported in another large analysis of patients treated at Verona University Hospital (27). Efficacy and safety of preoperative treatment of borderline resectable PDAC has been explored by several clinical trials. The Alliance for Clinical Trials in Oncology A021101 study randomized patients with borderline resectable PDAC to receive preoperative FOLFIRINOX followed by conventional capecitabine-based radiotherapy. Sixty-eight per cent of patients eventually underwent pancreatectomy with R0 resection in 93% of cases and a median overall survival of 21.7 months (29). The role for radiation in the preoperative setting remains as well controversial (30). Two different trials aimed to assess the efficacy of perioperative radiotherapy, one from Korea (NCT01458717) and one from the Netherlands (PREOPANC-1). Borderline resectable patients (and resectable patients in case of PREOPANC-1) were randomized to either gemcitabine-based chemo-radiation or surgery (31,32). Both trials showed

Table 1 Ongoing RCTs for resectable pancreatic adenocarcinoma

RCT Name	ID[a]	Country	Phase	Size[b]	Completion[b]	Arms	Status
NiTRO (37)	NCT03528785	Italy	2	67	2021	Preoperative nal-IRI, Oxaliplatin, LV, 5-FU	Recruiting
NEONAX (38)	NCT02047513	Germany	2	162	2021	Perioperative [2/4] *vs.* adjuvant [6] gemcitabine + nab-paclitaxel	Active/not recruiting
PANACHE01 (39)	NCT02959879	France	2	160	2021	Perioperative FOLFOX [2/4] *vs.* mFOLFIRINOX [2/4]	Recruiting
NorPACT-1 (40)	NCT02919787	Norway	2–3	130	2021	Perioperative *vs.* adjuvant mFOLFIRINOX	Recruiting
PREOPANC-2 (41)[c]	NTR7292	Netherlands	3	368	2021	Neoadjuvant mFOLFIRINOX [4] *vs.* preoperative gemcitabine/CRT [1.5] + postoperative gemcitabine [4]	Recruiting
Alliance A021806 (42)	NCT04340141	US/Canada	3	352	2026	Perioperative [4/2] *vs.* adjuvant [6] mFOLFIRINOX	Recruiting

[a], trials registered in ClinicalTrials.gov, clinicaltrialsregister.eu, and trialregister.nl; [b], estimated; [c], the PREOPANC-2 trial57 includes patients with upfront resectable and borderline resectable pancreatic cancer. RCT, randomized clinical trials; LV, leucovorin; 5-FU, 5-FluoroUracil; CRT, chemoradiation therapy (2.4 Gy × 15 fractions); FOLFOX, fluorouracil, leucovorin calcium, and oxaliplatin; mFOLFIRINOX, modified fluorouracil, leucovorin, irinotecan hydrochloride, and oxaliplatin; nal-IRI, nanoliposomal irinotecan.

a more favorable R0 resection rate and overall survival among patients who received preoperative therapy. However, both studies compared surgery de novo to radiation alone, not in association with induction systemic chemotherapy (which represents the current standard of treatment). More recently, Alliance for Clinical Trials in Oncology A021501 study randomized patients with borderline resectable PDAC to receive either eight cycles of modified FOLFIRINOX (mFOLFIRINOX) or seven cycles of mFOLFIRINOX followed by stereotactic body radiotherapy (33). Neoadjuvant mFOLFIRINOX was associated with a median overall survival of 31 months, consolidating mFOLFIRINOX as the reference regimen in this setting, while mFOLFIRINOX with hypo-fractionated RT did not improve OS compared to historical data. Which one is the most effective preoperative chemotherapy regimen/modality, and which is the appropriate length of treatment, still represent open questions? The MD Anderson large retrospective series found no significant differences between FOLFIRINOX and gemcitabine + nab-paclitaxel in terms of overall survival for all stage of disease, despite more favorable response and resection rates after FOLFIRINOX (28). PREOPANC-2 (to be completed within 2022) is designed to identify the best preoperative treatment for resectable and borderline resectable PDAC, randomizing patients to either receive preoperative FOLFIRINOX (eight cycles) alone or preoperative gemcitabine-based chemo-radiotherapy (three cycles) and subsequent adjuvant treatment (34). The recent SWOG S1505 was the first trial to enroll exclusively patients with resectable PDAC (35). A total of 102 patients were randomized to preoperative therapy with either mFOLFIRINOX or gemcitabine + nab-paclitaxel. Of them, respectively 84% and 85% completed preoperative chemotherapy, 73% and 70% underwent resection, and 49% and 40% completed all treatment. Two-year OS was 47% for mFOLFIRINOX and 48% for gemcitabine + nab-paclitaxel, with a median overall survival of 23 months for both regimens. Notably, 25% of the eligible patients did not proceed to surgery, most commonly because of progression of disease and chemotherapy-related toxic effects; patients who proceeded to surgery did not undergo a resection because of metastatic disease or complications. While this important phase 2 clinical trial did not demonstrate an improved survival after perioperative chemotherapy compared with historical data from adjuvant trials in resectable pancreatic cancer, it demonstrated adequate safety and high resectability rates (36). Several trials examining preoperative therapy for resectable PDAC are currently ongoing (*Table 1*), and will add some new evidence to this ever-changing landscape (37-42).

Preoperative therapy for resectable PDAC: truly the way forward?

In recent years, it has become clearer how PDAC represents a systemic disease at the time of diagnosis, regardless of its radiographic anatomic stage. Therefore, its treatment ideally includes the administration of systemic therapy, also

when surgical resection is performed, as pointed out by the dismal median disease-free survival of 6 months observed in the control group of an historical adjuvant trial (43). To deliver systemic therapy in the adjuvant setting implies that a significant subset of patients, who do not fully recover after a pancreatectomy, will never receive the standard of care for PDAC treatment. For this reason, to administrate systemic therapy before pancreatectomy is seen by many as the only way to assure optimal treatment to each patient (besides reaching a utopian near-zero complication rate after surgery). However, the dilemma in a real-life scenario is not only represented by mere treatment sequencing (neoadjuvant *vs.* adjuvant), but the uncertain results of an intention-to-treat approach with neoadjuvant therapy compared to surgery first, as many patients undergoing chemotherapy with a neoadjuvant intent eventually never undergo surgery.

On the other hand, to date preoperative therapy for resectable PDAC still presents major flaws, several unknows, and lack of proof of hypnotized benefits. Current available first-line regimens, such as mFOLFIRINOX and gemcitabine + nab-paclitaxel, have relatively low response rates at the price of moderate toxic effects (28,36). Available data from randomized trials (both for adjuvant and neoadjuvant treatment) come from highly selected subsets of patients, with outcomes that may be not completely generalizable due to selection bias, intrinsic flaws of primary endpoints (overall and disease-free survival), and high variability of treatment schedules and modalities. Additionally, outcomes of neoadjuvant and adjuvant treatments have never been compared directly in resectable stage. Further enrollment of patients with resectable PDAC in clinical trials is essential to address many open questions. However, probably a "one-size-fits-all" approach is destined to fail in real-life clinical practice, as anatomically resectable PDAC represents a spectrum of disease with heterogeneous biological behavior. Hopefully, in the future there will be some progress towards the only "way forward": precision oncology for PDAC, including the possibility of accurate identification of biologically aggressive disease through reliable biomarkers, and individualization of therapy through genomic/transcriptomic characterization and targeting (44,45). To this extent, anatomical resectability may ideally become an obsolete concept, and patients will be selected for surgical resection only according to individualized biological traits of their disease.

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Footnote

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