

# Neoadjuvant therapy for localized pancreatic cancer: guiding principles

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**Abstract:** The management of localized pancreatic cancer (PC) remains controversial. Historically, patients with localized disease have been treated with surgery followed by adjuvant therapy (surgery-first approach) under the assumption that surgical resection is necessary, even if not sufficient for cure. However, a surgery-first approach is associated with a median overall survival of only 22-24 months, suggesting that a large proportion of patients with localized PC have clinically occult metastatic disease. As a result, adjuvant therapy has been recommended for all patients with localized PC, but in actuality, it is often not received due to the high rates of perioperative complications associated with pancreatic resections. Recognizing that surgery may be necessary but usually not sufficient for cure, there has been growing interest in neoadjuvant treatment sequencing, which benefits patients with both localized and metastatic PC by ensuring the delivery of oncologic therapies which are commensurate with the stage of disease. For patients who have clinically occult metastatic disease, neoadjuvant therapy allows for the early delivery of systemic therapy and avoids the morbidity and mortality of a surgical resection which would provide no oncologic benefit. For patients with truly localized disease, neoadjuvant therapy ensures the delivery of all components of the multimodality treatment. This review details the rationale for a neoadjuvant approach to localized PC and provides specific recommendations for both pretreatment staging and treatment sequencing for patients with resectable and borderline resectable (BLR) disease.

**Keywords:** Pancreatic cancer (PC); neoadjuvant therapy

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## Introduction

Pancreatic cancer (PC) is a rising public health threat and is anticipated to account for over 48,000 cancer-related deaths by 2020—a death rate which will only be surpassed by lung cancer (1). In an era when the oncologic treatments of many solid organ cancers have made significant advances, it is sobering that the survival of patients with PC remains largely unchanged (2). Over the past 30 years, even among patients with localized PC who were managed with immediate surgery (surgery-first), the median survival rate is, at best, only 24 months (3). The majority of patients developed systemic recurrence even after margin negative

(R0) resections, suggesting that PC is a systemic disease, even in the absence of radiographic evidence of distant metastases (4-6). Despite current practice guidelines, which recommend a surgery-first approach for localized PC, the application of a local therapy, such as surgery, for the treatment of a systemic disease is in contradiction with accepted oncologic principles of stage-specific treatment (7). An alternative approach is to administer early systemic therapy prior to surgery (neoadjuvant therapy) for the management of systemic disease that is suspected but not radiographically confirmed. Patients who have aggressive tumor biology and develop disease progression during neoadjuvant therapy can be spared an operative

**Table 1** Prospective randomized trials of adjuvant therapy for PC

Study, year	Pt No.	Was it standardized?			Chemotherapy	Outcome
		Pathology review	Pre-Rx Imaging	XRT QA/QC		
GITSG (11), 1985	43	No	No	No	Bolus 5-FU	Improved median survival for those who received adjuvant therapy (20 vs. 11 mo). Two-yr OS 42% vs. 15%
EORTC (12), 1999	114	Yes	No	No	5-FU infusion	No statistically significant difference in survival (17.1 vs. 12.5 mo)
ESPAC1 (13), 2004	541	No	No	No	Bolus 5-FU	Improved median survival for chemotherapy alone (19.4 mo). No benefit for XRT
RTOG 9704 (14), 2006	442	Yes	Yes	Yes	Gemcitabine vs. 5-FU infusion	Nonsignificant trend favoring gemcitabine before and after chemoXRT
CONKO-001 (15), 2007	354	No	No	N/A	Gemcitabine	Improved median disease free survival (13.4 vs. 6.9 mo)
ESPAC3 (16), 2010	1,088	No	No	N/A	Bolus 5-FU vs. gemcitabine	No difference in DFS or OS between 5-FU and gemcitabine

PC, pancreatic cancer.

intervention with limited oncologic benefit. In this review, we will highlight the current status of PC staging, delineate recommendations for stage-specific treatment sequencing, and highlight important time points in clinical decision-making during therapy.

### Limitations of current staging of PC

The foundation of modern oncology is the utilization of stage-specific therapies in order to maximize survival and quality of life for all treated patients. The success of achieving this goal is dependent on the ability to accurately discriminate between different disease stages. The staging of PC was once defined by operative exploration and the surgeon's intraoperative assessment of resectability. However, the current staging of PC is now based on the pre-operative, objective radiologic classification of critical tumor-vessel relationships and the presence/absence of extrapancreatic disease (8). Although contrast enhanced computed tomography (CT) provides highly accurate assessments of such tumor-vessel relationships, the detection of metastatic disease is imperfect and approximately 10-20% of PC patients are discovered to have unanticipated metastases at the time of laparoscopy or laparotomy (9,10). Furthermore, over 76% of patients who undergo surgical resection will develop metastatic disease as the first evidence of disease recurrence (5,6). Therefore, the majority of patients with presumed localized PC have clinically occult

metastatic disease at the time of diagnosis, and current imaging modalities cannot discriminate between patients who have microscopic metastatic disease and patients who may truly have localized disease.

Given the high likelihood of disease recurrence after resection, multiple randomized clinical trials have assessed the benefit of adjuvant chemotherapy or chemoradiation in an effort to improve survival in patients with localized PC. *Table 1* summarizes the key adjuvant studies which provide a reference to which neoadjuvant therapy must be compared. Although the trials cannot be directly compared to one another due to differences in treatment design, staging requirements, and patient characteristics, it is important to note that the median overall survival for all trials was consistently between 20-24 months (11-13,15). In addition, all trials reported a significant proportion (a minimum of 30-45%) of patients who failed to receive all intended adjuvant treatment and highlight the difficulty in administering adjuvant therapy after pancreatectomy (17). Inherent in the design of adjuvant trials is a selection bias which excludes patients who experience significant surgical morbidity or mortality from surgery. These patients do not experience an adequate recovery to be considered for trial enrollment. When these additional patients are taken into consideration, approximately 50% of patients who undergo pancreatectomy for PC will not receive adjuvant therapy (18). Given the high risk of patients with localized PC who develop systemic disease recurrence, a reliance

**Table 2** Potential advantages of neoadjuvant therapy**Benefits of neoadjuvant therapy**

- The ability to deliver systemic therapy to all patients
- Identification of patients with aggressive tumor biology (manifested as disease progression) at the time of post-treatment, preoperative restaging who thereby avoid the toxicity of surgery
- Increased efficacy of radiation therapy; free radical production in a well oxygenated environment
- Decreased radiation induced toxicity to adjacent normal tissue as the radiated field is resected at the time of pancreatectomy
- Decreased rate of positive resection margins; SMA margin in particular
- Decreased rate of pancreatic fistula formation
- Potential for the downstaging of borderline resectable tumors to facilitate surgical resection

**Disadvantages of neoadjuvant therapy**

- Potential for complications from pre-treatment endoscopic procedures
- Biliary stent related morbidity; stent occlusion during neoadjuvant therapy
- Disease progression obviating resectability; loss of a “window” of resectability which may occur (rarely) in the borderline resectable patient
- Physicians have to work together during the preoperative phase; discrete handoff from surgeon to medical oncologist to radiation oncologist is not possible in the neoadjuvant setting (as occurs with adjuvant therapy)

on adjuvant therapy to treat micrometastatic disease is troublesome when it can only be successfully administered to half of the at-risk population.

### Rationale for neoadjuvant treatment sequencing

To address the limitations of adjuvant therapy, a growing interest has emerged in alternative treatment sequencing. Neoadjuvant therapy for PC has several theoretical advantages over adjuvant therapy (summarized in *Table 2*). In contrast to an adjuvant approach, neoadjuvant therapy ensures the delivery of all components of multimodality treatment to all patients who undergo a potentially curative pancreatectomy. Importantly, since neoadjuvant therapy offers an “induction” phase lasting approximately 2-3 months, individuals with unfavorable tumor biology who develop early metastatic disease are identified prior to surgery. Importantly, in the subset of patients (up to 20-30%) who are found to have disease progression after induction therapy (before surgery), the morbidity of an operation is avoided. When chemoradiation is utilized in neoadjuvant therapy, the delivery of chemoradiation in a well-oxygenated environment improves the efficacy of radiation and decreases the toxicity to adjacent normal tissue (19,20). The addition of radiation has important pathologic implications with several series reporting decreased rates of positive margins (R1 or R2) and node positive disease (21-23).

When neoadjuvant therapy was first introduced as an

alternative to a surgery-first approach, several concerns were raised by the surgical community pertaining to safety and feasibility. Foremost was the concern that the patients with localized PC may develop local disease progression which would prevent potentially curative surgical resection; the “window of opportunity” for surgery could be lost. Over the last decade as the experience with neoadjuvant therapy has developed, concerns regarding local disease progression have not been realized. In the largest combined experience with neoadjuvant therapy for patients with resectable PC (a broad definition of resectable used in these studies), less than 1% of eligible patients were found to have isolated local disease progression at the time of re-staging after neoadjuvant therapy (before planned surgery) (24,25). Disease progression during or after neoadjuvant therapy, if it occurs, is usually seen at distant sites such as the liver, peritoneum, and lung. In addition, theoretical concerns over the toxicity of neoadjuvant therapy and the impact of treatment-related side effects on operative morbidity and mortality were also not observed (24-26). In fact, the incidence of pancreatic fistula, the most frequent serious complication associated with pancreatectomy, has been demonstrated to be reduced after neoadjuvant therapy as the treated pancreas becomes more firm with a decrease in enzyme production (21-23). With regard to overall complications, a recent analysis of the NSQIP database demonstrated no differences in 30-day mortality and postoperative morbidity rates among patients

**Table 3** Definition of resectability used by the multidisciplinary PC working group at the Medical College of Wisconsin

<b>Resectable</b>
Tumor-artery relationship: no radiographic evidence of arterial abutment (celiac, SMA, or hepatic artery)
Tumor-vein relationship: tumor-induced narrowing $\leq 50\%$ of SMV, PV, or SMV-PV
<b>Borderline resectable</b>
Artery: tumor abutment ( $\leq 180^\circ$ ) of SMA or celiac artery. Tumor abutment or short segment encasement ( $>180^\circ$ ) of the hepatic artery
Vein: tumor induced narrowing of $>50\%$ of SMV, PV, or SMV-PV confluence. Short segment occlusion of SMV, PV, SMV-PV with suitable PV (above) and SMV (below) to allow for safe vascular reconstruction
Extrapancreatic disease: CT scan findings suspicious, but not diagnostic of, metastatic disease (for example, small indeterminate liver lesions which are too small to characterize)
<b>Locally advanced</b>
Artery: tumor encasement ( $>180^\circ$ ) of SMA or celiac artery
Vein: occlusion of SMV, PV, or SMV-PV without suitable vessels above and below the tumor to allow for reconstruction (no distal or proximal target for vascular reconstruction)
Extrapancreatic disease: no evidence of peritoneal, hepatic, extra-abdominal metastases
<b>Metastatic</b>
Evidence of peritoneal or distant metastases
PC, pancreatic cancer.

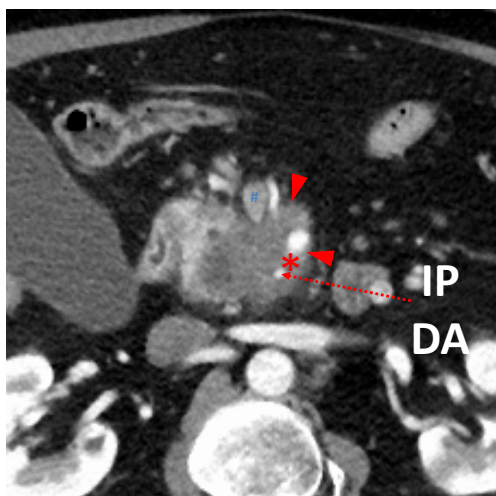
treated with neoadjuvant therapy as compared to patients who received surgery-first (27).

Importantly, the multidisciplinary care is the cornerstone of successful administration of neoadjuvant therapy. The scope of the multidisciplinary team is vast and includes medical, surgical, and radiation oncologists, diagnostic radiologists, advanced endoscopists, genetic counselors, dietitians, and endocrine specialists. Before embarking on a neoadjuvant approach, all patients should have the benefit of having their case reviewed in a multidisciplinary conference where the optimal treatment plan can be established and the course of treatment outlined prior to the initiation of any therapy. We have found that when all members of the treatment team are engaged and aligned with basic treatment principles (detailed below), the patients' care and treatment experience are optimized.

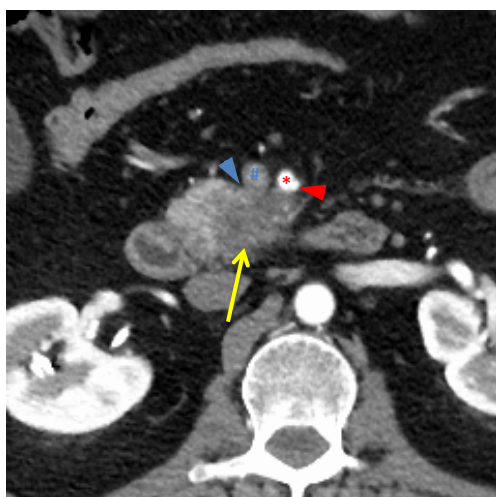
### **Principle #1: radiographic determination of clinical stage of disease**

The first and most critical step in the management of PC is the determination of the clinical stage of disease and establishment of a histologic diagnosis. All disease-specific and stage-specific treatment planning is predicated on this step. With PC, it is critically important to use standardized,

objective radiologic criteria for clinical staging. Modern imaging techniques have revolutionized the clinical staging of PC. Before the development of multidetector CT, up to 30% of patients with presumed resectable PC were found, at the time of operation, to have either metastatic disease or local tumor-associated vascular invasion which precluded resection (28). Currently, precise and objective anatomic radiographic criteria are used to determine the extent of the tumor-vascular relationship and to categorize clinical staging (Table 3). PC can be broadly divided into patients with inoperable disease (metastatic or locally advanced) and operable disease [borderline resectable (BLR) or resectable]. The majority of patients will present with metastatic disease, as evidenced by ascites/peritoneal implants, liver, or lung metastases. In the absence of metastatic disease, the clinical stage is determined by the relationship of the primary tumor to adjacent vasculature. As a general rule, any tumor abutment ( $\leq 180$  degree tumor-vessel interface) or encasement ( $>180$  degree) of the celiac axis, common hepatic artery, or SMA should be considered a contraindication to immediate surgery. A patient is deemed to have locally advanced, unresectable disease when: (I) the tumor encases the SMA or celiac axis, as defined by  $>180$  degrees of the circumference of the vessel; or (II) there is occlusion of the SMPV confluence without the possibility



**Figure 1** Locally advanced PC. SMA is labelled with \* and arrows define the hypodense tumor which encases (>180 degrees) of the SMA. PC, pancreatic cancer.



**Figure 2** BLR PC. SMV is labelled with # and SMA is labelled with \*. Note the hypodense tumor which abuts both the SMV and SMA. BLR, borderline resectable; PC, pancreatic cancer.

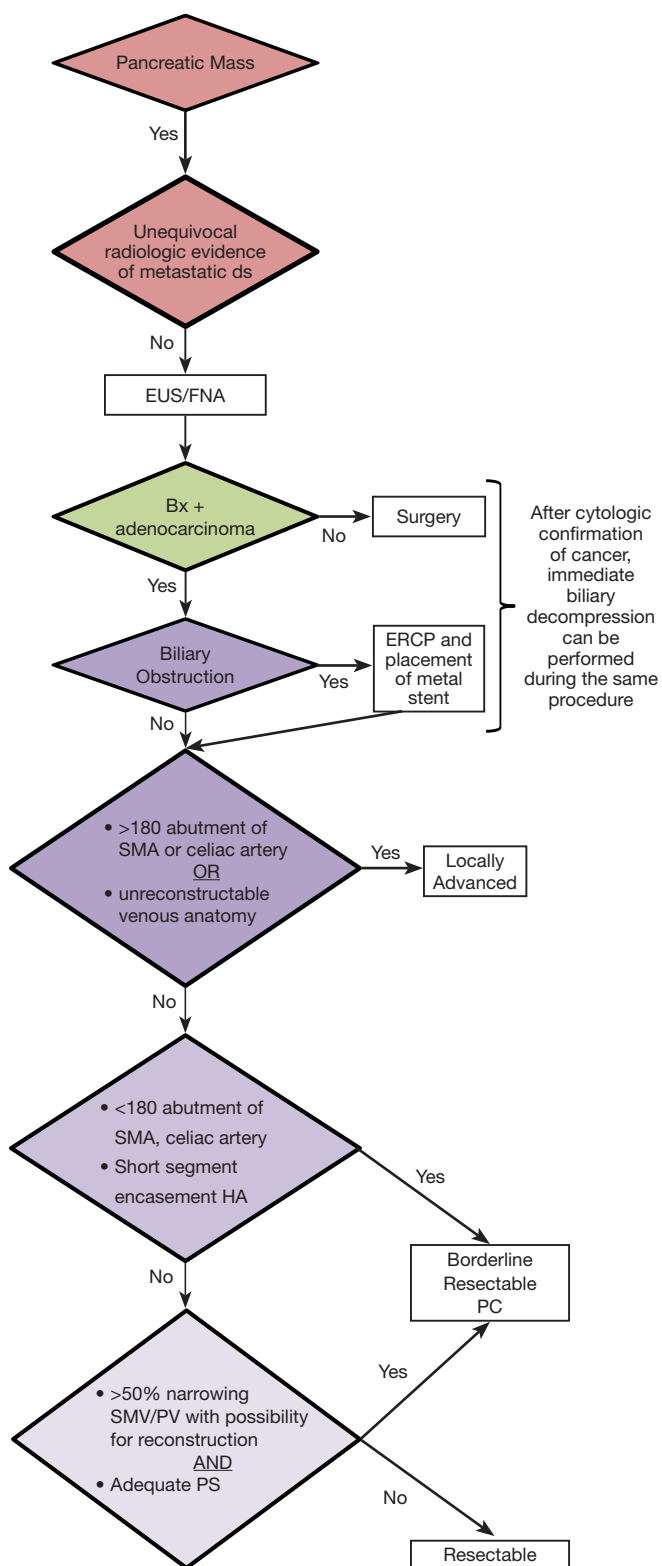
for venous reconstruction (*Figure 1*). Patients who have tumor abutment, without encasement, of the SMA or celiac axis, or short segment encasement of the hepatic artery are considered to have BLR PC (*Figure 2*) (29). In addition, patients with tumors that cause >50% narrowing or short segment occlusion of the SMV/PV that may be amenable to reconstruction are also considered to be BLR. There is emerging consensus that even more subtle tumor-



**Figure 3** Resectable PC. SMV is labelled with # and SMA is labelled with \*. A hypodense tumor is present in the pancreatic head with preservation of the fat plane between the pancreas and the SMV. No tumor abutment of the SMA. PC, pancreatic cancer.

vein abutment may be best considered BLR, especially with respect to the use of neoadjuvant therapy rather than surgery-first (30). Finally, patients who have radiographic lesions which are indeterminate for metastases (usually too small to accurately characterize), even in the absence of SMA abutment or venous narrowing, are also considered by some institutions to have BLR PC (31). Radiographic findings of a resectable PC are (I) the absence of tumor-arterial abutment or encasement; and (II) <50% narrowing of the SMV/PV (*Figure 3*).

Our preferred algorithm for the initial diagnostic work-up and management of suspected PC is summarized in *Figure 4*. The single most important imaging tool for the detection and staging of PC is a CT scan. Current multi-detector protocols utilize dual-phase technique, with the acquisition of arterial phase images at 30 seconds after IV injection of contrast and portal venous images approximately 1 minute after injection. A rapid injection of intravenous contrast allows for the maximal enhancement of the pancreas and mesenteric vasculature (10). At least two phases of contrast-enhanced helical scanning are required. The first (arterial) phase is performed from the diaphragm through the horizontal portion of the duodenum in order to define the relationship of the tumor to the adjacent arteries and to determine the presence or absence of aberrant arterial anatomy. The arterial phase images are used for visualization of the primary tumor and optimal assessment of the tumor-artery relationships. Arterial phase images allow low-density adenocarcinomas to be distinguished from pancreatic neuroendocrine tumors, which are classically hypervascular in the arterial phase. The second (venous)



**Figure 4** Algorithm for determining clinical disease stage in PC. PC, pancreatic cancer.

phase is performed to define the relationship of the tumor to the surrounding venous structures (SMV, portal vein, and splenic vein) and to uncover metastases to locoregional lymph nodes and distant organs (particularly to the liver). Multidetector contrast enhanced CT provides the most comprehensive evaluation for clinical staging; we reserve additional imaging studies such as magnetic resonance imaging or positron emission testing for indeterminate lesions which are suspicious for metastatic disease.

One non-anatomic consideration which has profound implications for survival, and therefore staging, is the patient's performance status. Especially among PC patients, striking differences in survival can be observed based on performance status alone (32-34). In a study which examined over 3,000 advanced PC patients who were treated with variety of new investigational drugs, the median survival of patients with a Karnofsky performance status (KPS) <70% was 2.4 months as compared with 5.5 months in patients with a KPS ≥70% (34). The median time to disease progression was greater in patients with a KPS score ≥70%. These findings were corroborated in the CALGB 80303 study, where PC patients with an Eastern Cooperative Oncology Group (ECOG) performance status of 0-1 experienced a median survival of 4.8-7.9 months as compared to 2.9 months in patients with an ECOG performance status of 2 (32). Because decreased performance status correlates with an increased risk of disease progression and death, performance status has been proposed as an additional criterion for BLR clinical status, even in the presence of an anatomically resectable PC (31).

**Principle #2: coordination of endoscopic procedures and establishment of durable biliary drainage**

Confirmation of malignancy is required in all patients prior to treatment with systemic therapy or radiotherapy. For patients with localized disease which may be amenable to surgical resection, we prefer EUS-guided FNA biopsy. The sensitivity of EUS-FNA is in range of 85% to 90% with potential false negative results of up to 15% based on tumor size and the experience of the endoscopist. False negative results can be minimized by having a cytopathologist present at the time of EUS to ensure that a cytologic diagnosis is made before the termination of the procedure. When FNA material is examined by an experienced cytopathologist, false-negative biopsies are rare, but can occur, especially when the tumors are small. Therefore, negative results from

EUS-guided FNA should not be considered as proof that a malignancy does not exist, and repeat EUS-guided FNA may improve the yield of positive results in those patients with suspected malignancy. If the patient is jaundiced and EUS fails to identify a mass, an ERCP with biliary brushing may be performed followed by placement of a plastic stent (we prefer an easily removable stent when a tissue diagnosis of malignancy is not readily obtained). Importantly, high-quality CT imaging should be performed before any endoscopic intervention (EUS or ERCP) is attempted because of the risk of biopsy-induced pancreatitis, which may distort the pancreatic and peripancreatic anatomy and result in overstaging of the disease.

Although not essential for staging purposes, patients who present with jaundice will require an ERCP for biliary decompression prior to the initiation of neoadjuvant therapy. Biliary drainage and resolution of hyperbilirubinemia is required to maintain adequate liver function which is necessary for the use of several chemotherapeutic agents (25). In most cases, if on-site cytopathologic confirmation of cancer can be performed at the time of EUS, immediate ERCP can be performed with placement of a metal stent to provide more durable biliary decompression. With regards to the latter concern, large single institution experiences have demonstrated that self-expanding metal stents do not compromise future surgical resections (35). In addition, metal stents have demonstrated superior durability during neoadjuvant therapy with only a 7% rate of stent occlusion as compared to polyethylene (plastic) stents where stent occlusion has been reported in up to 45% of patients (36).

### **Principle #3: defining clinically important treatment responses**

After accurate determination of the clinical stage, the assignment of type(s) of neoadjuvant therapy and the duration of therapy is developed with the intent to both treat radiographically occult micrometastatic disease (present in the majority of patients) and to maximize local control. Importantly, the assessment of treatment response is critically important and should be performed following the completion of any treatment modality. In patients with localized PC, defining treatment response to therapy can be particularly challenging as, by definition, measurable extrapancreatic disease does not exist. At the Medical College of Wisconsin, treatment response is assessed using three critically important criteria: (I) the presence or absence of clinical benefit (for example, the

resolution of pain); (II) CT findings to suggest stable or responding disease *vs.* disease progression (change in cross-sectional diameter of the tumor); and (III) the decrease or increase in serum level of carbohydrate antigen 19-9 (CA19-9). Clinical benefit and CA19-9 response are used as surrogate markers of response under the assumption that extrapancreatic micrometastatic disease has likely responded to therapy if the condition of the patient improves and the level of CA19-9 declines. Although modern chemotherapy regimens such as FOLFIRINOX (5-fluorouracil, oxaliplatin, irinotecan, and leucovorin) and gemcitabine/nab-paclitaxel have been associated with 30-40% response rates among patients with more advanced disease, the majority of patients with localized PC are likely to have minimal to modest changes in tumor size (9,37-39). Moreover, although tumors may demonstrate a decrease in overall size, the relationship of the tumor to adjacent vessels generally does not change. A change in clinical stage, reflecting a change in local tumor-vessel anatomy, in response to neoadjuvant therapy has been reported to occur in less than 1% of cases (37). Therefore, the utilization of restaging imaging should primarily be performed to: (I) identify disease progression, whether it be local or distant, which would alter clinical management and; (II) facilitate operative planning. Importantly, careful attention to radiographic findings allows for a detailed preoperative plan, especially when vascular reconstruction is anticipated. It is especially important that vascular resections occur as planned events rather than an emergent response to vascular injury, as unexpected vascular injuries can ultimately compromise the completeness of the resection resulting in a positive margin (40,41).

CA19-9 has been demonstrated to be a useful prognostic marker in patients with PC. Among patients with localized PC, a decrease in CA19-9 in response to neoadjuvant therapy has previously been reported to correlate with overall survival. A greater than 50% reduction in CA19-9 levels in response to neoadjuvant therapy has been associated with an improved overall survival (42,43). Importantly, among patients who undergo neoadjuvant therapy and pancreatic resection, the normalization of CA19-9 in response to therapy has been a highly favorable prognostic factor and has been associated with a median survival of 46 months. Equally important is the recognition that an increase in CA19-9 level after therapy correlates with disease progression. Although the majority of patients will experience a decline in CA19-9 in response to neoadjuvant therapy, approximately 20% of patients will have an increase in CA19-9, and among these patients,

metastatic disease was detected in 50% of cases (44). Therefore, clinicians should have a low threshold for expanding the diagnostic workup (MRI of liver or PET) prior to surgery in patients who have a rising CA19-9 after neoadjuvant therapy.

#### **Principle #4: development of a stage-specific treatment plan**

##### ***Resectable PC***

Outside of a clinical trial, neoadjuvant treatment of resectable PC may consist of chemotherapy alone or chemoradiation. If chemoradiation is used, gemcitabine combined with external-beam radiation therapy is favored (*Figure 5A*). This regimen is a slight modification of the neoadjuvant treatment schema reported by Evans and colleagues and includes a standard fractionation course of radiation therapy (1.8 Gy/day, M-F, 28 fractions) to a total dose of 50.4 Gy, with concurrent weekly gemcitabine given on day 1 (day -2 to +1) at a dose of 400 mg/m<sup>2</sup> at fixed dose rate over 40 minutes (25). This program resulted in a median survival of almost 3 years in those patients who completed all therapy to include surgery (24). Restaging with pancreatic protocol CT imaging is completed 4 weeks after the last radiation treatment and in the absence of disease progression, patients are then brought to surgery. The recent reports of both FOLFIRINOX and gemcitabine/nab-paclitaxel, which demonstrated efficacy in patients with advanced disease (38,39), have generated enthusiasm for their use in patients with localized disease, especially those with BLR disease (26,45,46). Acknowledging that the use of chemoradiation remains controversial, neoadjuvant FOLFIRINOX or gemcitabine/nab-paclitaxel delivered over approximately 2 months also represents a logical treatment alternative for patients with resectable disease.

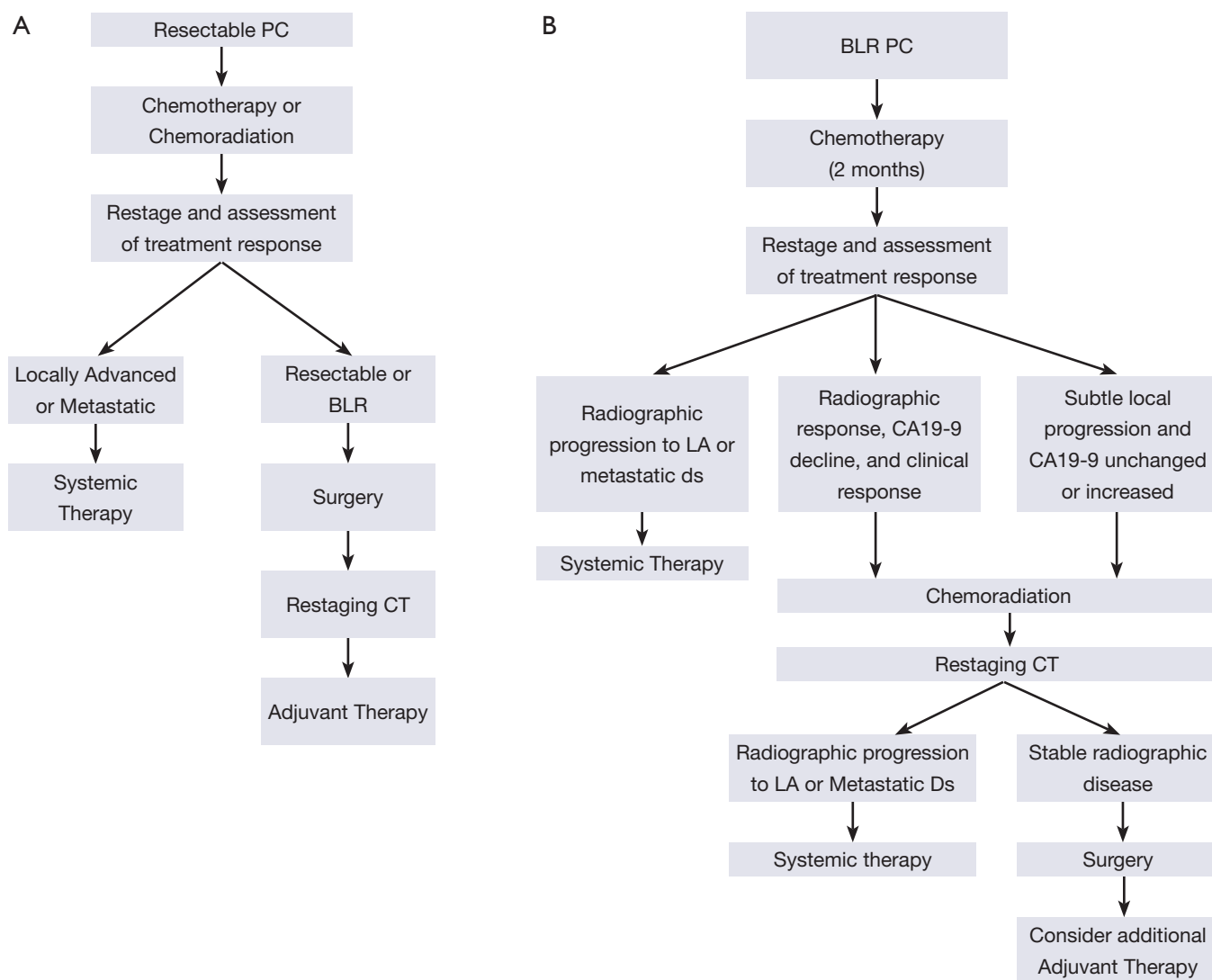
##### ***BLR PC***

Patients with BLR PC are fundamentally different from those with resectable disease in that they are: (I) at higher risk for harboring radiographically occult distant metastatic disease; (II) at the highest possible risk for a positive margin of resection due to tumor-artery abutment; (III) require a more complex operation usually involving vascular resection and reconstruction, and therefore; (IV) there is a greater possibility that, despite the best efforts of the physician

team, a surgical procedure may yield no oncologic benefit for the patient. For these reasons, investigators have applied a more robust level of selection consisting of a longer period of induction therapy, often including chemotherapy followed by chemoradiation prior to considering surgery. The chemoradiation portion of induction therapy has been thought to be particularly important for those patients with arterial abutment in the hope of sterilizing at least the periphery of the tumor and thereby preventing a positive margin of resection.

Our preferred off-protocol neoadjuvant treatment schema for patients with BLR PC consists of an initial two months of systemic therapy followed by chemoradiation (*Figure 5B*). The choice of systemic agents for initial treatment has evolved from gemcitabine-based therapies to consideration of FOLFIRINOX, GTX, gemcitabine/nab-paclitaxel, or other combination therapies (26,39,47-50). After the delivery of systemic therapy, patients are restaged with particular attention to treatment response indicators (clinical, radiographic, biochemical). Importantly, in the absence of a robust response to chemotherapy alone (and assuming no evidence of distant disease), it is our practice to proceed directly to chemoradiation (as discussed above) to minimize the risk of local disease progression after chemotherapy. Treatment sequencing in patients with BLR PC aims to both treat presumed (radiographically occult) systemic disease without the delay imposed by a surgery-first treatment approach—while also avoiding local disease progression which may sacrifice a window of opportunity for surgical resection of the primary tumor. Patients who have stable disease following two months of chemotherapy [no change on CT imaging and a modest decline (or no decline) in CA19-9] should transition to chemoradiation rather than second line systemic therapy which may increase the risk for local disease progression. As therapies evolve and therapeutic options increase, this recommendation may change. Importantly, we may be entering a new era in the management of localized PC, where small but clinically significant advances in systemic therapies improve control of distant metastases and patient survivals to the extent that more patients survive long enough to experience challenging symptoms of local-regional disease recurrence/progression for which we have little contemporary experience. The importance of local disease control, especially in patients with potentially operable disease, cannot be overstated—as clinically significant local-regional disease recurrence may be preventable with an optimal operation and the consistent delivery of multimodality therapy to include chemoradiation





**Figure 5** Treatment sequencing in (A) resectable and (B) BLR PC. CA19-9, carbohydrate antigen 19-9; BLR, borderline resectable; PC, pancreatic cancer.

either before or after surgery.

#### **Principle #5: avoid high risk operations in high risk patients**

Following the completion of neoadjuvant therapy, at the time of restaging prior to surgery, it is important that a careful assessment of the patient's performance status and medical comorbidities be re-evaluated. Several studies have demonstrated that patients with poor performance status or uncontrolled comorbidities are likely to experience postoperative morbidity and mortality (51-53). The physiologic stress associated with preoperative therapy

has the potential to identify/expose patients with poor physiologic reserve who may not tolerate a large operation. If a given patient cannot tolerate induction therapy, they are unlikely to tolerate five to seven hours of surgery and recover to their pre-diagnosis level of independence with self-care. Identification of such patients at the time of diagnosis without the "stress test" of induction therapy may be difficult—a surgery-first treatment approach may incur a higher morbidity and mortality in the absence of the selection advantage afforded neoadjuvant treatment sequencing. During and after induction therapy, physicians can more accurately assess the physiologic tolerance of an individual patient to undergo major surgery. Perhaps even

more importantly, after neoadjuvant therapy, the patient and their family have an improved understanding of the disease, are much better informed (than within one to two weeks following diagnosis) and evolve a much more educated opinion regarding their physicians' recommendation for or against an operation.

In our recent experience, among older patients who completed neoadjuvant therapy but did not undergo surgery (due to either disease progression seen on restaging or a decline in performance status due to the combination of treatment toxicity and underlying comorbidities), the median overall survival was the same regardless of why surgery was not performed. A decline in performance status due to evolving medical comorbidities or the failure to recover from treatment-related toxicity was just as powerful a predictor of poor outcome as was the development of metastatic disease. This confirms previous reports of the powerful impact of performance status on response to anticancer therapy and overall survival in patients with solid tumors (54).

## Conclusions

In contrast to many other solid organ tumors, treatment sequencing for patients with localized PC remains highly controversial. The limited (and clinically insignificant) gains in survival for patients with localized PC over the past three decades have been due, in part, to the current inability of physician teams to accurately stage patients. This has resulted in the overuse of surgery in patients with locally advanced and metastatic disease. In contrast to a surgery-first strategy, neoadjuvant treatment sequencing will guide the selection of patients for surgery and help to identify those patients with progressive disease for whom an operation has little oncologic benefit. Considering that surgery has a modest impact on the natural history of PC in most patients, a neoadjuvant approach to treatment sequencing is gaining support from clinicians of all specialties and will form the backbone for most future studies of multimodality therapy in localized PC.

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