

Adjuvant or Neoadjuvant Therapy in the Treatment in Pancreatic Malignancies

Where Are We?



Robert A. Wolff, MD

KEYWORDS

- Resectable pancreatic cancer • Borderline resectable pancreatic cancer
- Locally advanced pancreatic cancer • Adjuvant therapy • Neoadjuvant therapy
- Preoperative therapy • Chemotherapy • Resection

KEY POINTS

- Up-front surgery is considered the standard of care for resectable pancreatic cancer despite modest improvements in median overall survival observed over time.
- With few exceptions, surgery first is widely endorsed in the oncology community and this will not change without randomized trials comparing up-front surgery/adjuvant therapy with neoadjuvant therapy/subsequent surgery.
- Until definitive results from these trials are reported, up-front surgery will be used to select patients for adjuvant therapy.
- This strategy places patients at risk for positive surgical margins, poor recovery, and rapid relapse, limiting the delivery of adjuvant therapy.

INTRODUCTION

Ever since A.O. Whipple reported on a 2-stage surgical procedure for removal of ampullary and periampullary neoplasms, variations of the Whipple procedure (pancreaticoduodenectomy) have been widely used for surgical resection of malignant neoplasms of the pancreatic head. By the 1960 to 1970s, it became clear that, despite surgical resection, adenocarcinoma of the pancreas had a propensity to recur locally and metastasize. Early efforts at adjuvant therapy culminated in the report of a randomized trial comparing combined modality therapy with observation after surgery in patients with resected pancreatic cancer. The results, published in 1985, began the era of modern adjuvant therapy for resected pancreatic cancer. In the intervening 30 years, adjuvant

Disclosure: The author has nothing to disclose.

Department of Gastrointestinal Medical Oncology, University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard-Unit 421, Houston, TX 77030, USA

E-mail address: rwolff@mdanderson.org

Surg Clin N Am 98 (2018) 95–111

<https://doi.org/10.1016/j.suc.2017.09.009>

0039-6109/18/© 2017 Elsevier Inc. All rights reserved.

surgical.theclinics.com

therapy has been refined, but improvements in overall survival after surgery have been modest. Moreover, longer survival durations after surgery and adjuvant therapy observed over time are likely partially explained by the availability of newer systemic regimens at the time of relapse. Furthermore, despite improvements in mortality related to pancreatic cancer surgery, it is estimated that only 50% to 60% of patients undergoing surgery with curative intent subsequently receive adjuvant therapy.

In this article, results from modern trials of adjuvant therapy are summarized and followed by a discussion of the flaws in the paradigm of up-front surgery followed by adjuvant therapy. Thereafter, the rationale for preoperative therapy is described with some clinical results. In addition, given the growing appreciation for 3 distinct subsets of localized, nonmetastatic pancreatic cancer (resectable, borderline resectable [BR], and locally advanced [LA] disease), the benefits of a neoadjuvant therapy for these subsets are proposed.

RATIONALE FOR ADJUVANT THERAPY AFTER SURGERY FOR PANCREATIC CANCER

As surgery for carcinoma of the pancreas became widely adopted, postoperative mortality began to decrease and it became increasingly evident that most patients who survived surgical resection ultimately died of disease recurrence. Over time, it became clear that pancreatic cancer had the propensity to recur locally and spread to distant sites. In a review of the experience of the Massachusetts General Hospital (MGH), Tepper and colleagues¹ reported the local failure rate after surgery to be almost 50%, with metastatic disease being observed with less frequency. Hence, early trials of adjuvant therapy were developed using initial chemoradiation, with 5-fluorouracil (5FU) as a radiosensitizer and, in some reports, subsequently delivering 5FU as systemic therapy.

CONFLICTING EARLY EVIDENCE WITH ADJUVANT CHEMORADIATION

In a landmark trial spearheaded by the Mayo Clinic, patients who had undergone complete resection of an adenocarcinoma of the pancreatic head, and who had adequate recovery from surgery, were randomized 1:1 to receive 5FU-based chemoradiation followed by weekly 5FU for up to 2 years, or to undergo observation alone after surgery.² Among the 21 patients randomized to chemoradiation, median overall survival was 20 months, whereas the survival for the 22 patients in the observation arm was only 11 months ($P = .03$). The results from this trial could not be confirmed in a subsequent trial performed by the European Organization for Research and Treatment of Cancer (EORTC).³ Median survival was 17 months for 60 patients with resected pancreatic cancer randomized to receive chemoradiation and 12 months for the 54 patients undergoing observation ($P = .09$). Critics have argued that this was an underpowered positive trial, supporting the role of chemoradiation therapy, whereas others argued against chemoradiation as adjuvant therapy.

The role of chemoradiation in adjuvant therapy was further disputed after the results of the European Study of Pancreatic Cancer showed that the delivery of radiation to adjuvant therapy after surgery led to inferior survival compared with treatment with chemotherapy alone.⁴

Table 1 summarizes the results of several trials in which chemoradiation was a component of therapy.^{2–5} Despite efforts spanning more than 20 years, there is no compelling evidence that chemoradiation provides any advantage compared with systemic therapy alone. Of note, the largest ongoing trial of chemotherapy and chemoradiation versus chemotherapy alone has been accruing patients since 2014 and does not expect to reach target accrual of 950 patients until 2020.

Table 1
Select trials with chemoradiation as a component of adjuvant therapy

Study/Year	Number of Patients	R1 Resection Rate (%)	Adjuvant Chemoradiation Median Survival (mo)
GITSG 1985	21	0	20
EORTC 1999	60	22	17
ESPAC 2004	280	18	15
RTOG 9704 2008	451	>35	17–20

Abbreviations: EORTC, European Organization for Research and Treatment of Cancer; ESPAC, European Study Group for Pancreatic Cancer; GITSG, Gastrointestinal Tumor Study Group; RTOG, Radiation Therapy Oncology Group.

THE EMERGENCE OF SYSTEMIC THERAPY AS ADJUVANT THERAPY FOR PANCREATIC CANCER

Although progress in adjuvant therapy has been slow, there is now evidence that systemic therapy is superior to observation alone after resection with curative intent, as shown in [Table 2](#).^{6–10} These results show that (1) chemotherapy improves survival more than observation after surgery, and (2) there is no clear advantage of gemcitabine compared with 5FU when these drugs are given as single agents. However, the combination of gemcitabine with the oral fluoropyrimidine, capecitabine, has recently been reported as superior to gemcitabine alone for resected pancreatic cancer.⁹ Thus, the standard of care for patients who undergo up-front surgery with curative intent is gemcitabine and capecitabine given over 24 weeks. This treatment is expected to result in a median overall survival of 28 months with approximately 20% of patients surviving for 5 years.

On first glance at [Table 2](#), it seems that adjuvant therapy is improving. Early trials with gemcitabine alone led to overall median survivals of 22 months, whereas the most recent trial shows an improvement in survival to 28 months when gemcitabine and capecitabine are combined. Note that the median survival of patients who receive gemcitabine monotherapy has also steadily increased from 22 months to 25 months. This improvement is possibly explained by better patient selection and improvements

Table 2
Randomized trials of systemic therapy as adjuvant therapy for resected pancreatic cancer

Study	Year	Number of Patients	R1 Resection Rate (%)	Control Arm Median Survival (mo)	Experimental Arm Median Survival (mo)	P	Available Second-Line Therapy
CONKO 001	2007	368	18	Observation 20.2	Gem 22.1	.06	5FU or gemcitabine
ESPAC 1 and ESPAC 3 (v1)	2009	458	25	Observation 16.8	5FU + Leucovorin 23.2	.003	Gemcitabine
ESPAC 3 v2	2010	1088	35	5FU + Leucovorin 23	Gem 23.6	.39	5FU/oxaliplatin cape/ oxaliplatin
ESPAC 4	2017	730	60	Gem 25.5	Gem + Cape 28	.032	Gem/nab-p or FOLFIRINOX

Abbreviations: cape, capecitabine; gem, gemcitabine; nab-p, nab-paclitaxel.

in perioperative care. However, overall survival may also be influenced by additional anticancer therapy after relapse. In the late 1990s and early 2000s, there was no clear evidence that second-line therapy had any impact on survival for those patients who presented with metastatic disease. With the advent of oxaliplatin, which became available in 2003, investigators have shown some activity of this agent in the second-line setting when combined with 5FU/folinic acid (FOLFOX [folinic acid, 5FU, oxaliplatin] or OFF [oxaliplatin, folinic acid, 5FU]) or capecitabine (XELOX [Xeloda, oxaliplatin]/CapOx [capecitabine, oxaliplatin]).^{11,12} Since that time, 2 newer regimens for advanced pancreatic cancer have been approved. The combination of 5FU, folinic acid, irinotecan, and oxaliplatin (FOLFIRINOX) was accepted as a standard front-line therapy in 2011.¹³ In addition, gemcitabine and nab-paclitaxel was subsequently approved in by the US Food and Drug Administration in 2013¹⁴ (both of these regimens showed superiority compared with single-agent gemcitabine in large randomized trials in metastatic pancreatic cancer). Because the options for second-line therapy have expanded over time and were available during the conduct of the recently reported European Study Group for Pancreatic Cancer (ESPAC) 4 trial, some of the incremental prolongation of survival now observed after up-front surgery and adjuvant therapy may therefore be explained by the availability of newer regimens for use at the time of relapse.

In summary, the combination of gemcitabine and capecitabine delivered over 6 months is considered the new standard adjuvant regimen for those patients with adequate recovery from surgery with curative intent. This regimen is expected to result in a median survival of 28 months with a 5-year survival rate of 20%.

THE FLAWED STRATEGY OF UP-FRONT SURGERY AND ADJUVANT THERAPY

Many pancreatic cancer experts continue to endorse the paradigm of up-front surgery followed by adjuvant therapy with continued trials of newer systemic therapies in an effort to make incremental progress. However, data from several sources, including results from the adjuvant trials already reported, suggest that up-front surgery for resectable pancreatic cancer is a flawed strategy and one that hampers more rapid progress for patients. Furthermore, this strategy may limit the number of patients who will benefit from initial surgery.

Ignoring the Denominator

One of the most striking things common to reports of prospective adjuvant therapy trials after initial surgery is the absence of the denominator from which the study population was derived; of the patients taken to the operating room for curative surgery, not all undergo adjuvant therapy. Present estimates from several studies reveal that only 50% to 60% of patients who undergo surgical resection ultimately receive

Table 3 The proportion of patients receiving adjuvant therapy after surgical resection			
Data Source	Year	Number of Patients Resection Type	Patients Receiving Adjuvant Therapy (%)
Johns Hopkins	2008	368 R0/R1	53
Mayo Clinic	2008	472 R0 only	60
Medicare/SEER	2011	396 R0/R1	47
NCDB	2014	2047 R0/R1	58

Abbreviations: NCDB, National Cancer Data Base; SEER, Surveillance, Epidemiology and End Results.

adjuvant therapy. **Table 3** summarizes the data in this regard. For example, in a study reported by the group at the Johns Hopkins Hospital (JHH), among 870 patients who underwent an R0 or R1 resection, only 53% underwent adjuvant therapy.¹⁵ The Mayo Clinic also reported their experience for patients who underwent R0 resection; 58% of them received adjuvant therapy.¹⁶ In a more recent analysis derived from the American College of Surgeons (ACS) National Surgical Quality Improvement Program and the National Cancer Data Base (NCDB), among 2047 patients undergoing pancreatic cancer resection, the receipt of subsequent adjuvant therapy was similarly limited to 58%.¹⁷ Other results come from Surveillance, Epidemiology and End Results(SEER)/Medicare data. Among 396 Medicare beneficiaries, adjuvant therapy was given to 47% of resected patients.¹⁸

Thus, despite the recognition that surgical resection must be linked to the subsequent delivery of adjuvant therapy, a large subset of patients (40%–50%) never receive it. The main factors, discussed in more detail later, are likely related to the complexity of the surgery and resultant complications, potential for early relapse, and postoperative death.

Postoperative Complications Hamper the Delivery of Adjuvant Therapy

Median age of onset for pancreatic cancer is 70 years. Known risk factors for pancreatic cancer include a history of tobacco use, obesity, long-standing diabetes, and metabolic syndrome. Thus, many surgical candidates are of advanced age and often have comorbidities increasing their risk of surgical complications. In the aforementioned analysis from the ACS National Surgical Quality Improvement Program and the NCDB, the rate of serious postoperative complications was 23%; this affected the likelihood of receiving adjuvant therapy. For those patients experiencing at least 1 serious complication, the rate of adjuvant therapy delivery was only 44%. Among those patients with no serious complications, adjuvant therapy was given to 62%. Furthermore, even when adjuvant therapy was ultimately delivered, it was more likely to be delayed by greater than 70 days in patients with serious complications.¹⁷

Pancreatic Cancer Resections Result in Postoperative Death

Since the early reports of the Whipple procedure, 30-day mortality has steadily declined from around 30% to less than 3% in high-volume centers. However, a recent report shows that this operation remains risky. Among 15,000 patients undergoing resections in centers around the United States, although 30-day mortality was only 3.4%, 90-day mortality was double, increasing to 7.5%.¹⁹

Pancreatic Cancer Is Locally Invasive

Even before cross-sectional imaging became widely available, it was known that pancreatic cancer has a propensity to recur locally. Similar to the experience at MGH, investigators at the Bethesda Naval Hospital reported a local recurrence rate of 47%, with confirmation based on autopsy or surgical exploration.²⁰ More recent autopsy data show that local recurrence occurs more frequently than had been estimated through clinical, surgical, or radiographic means. In a rapid autopsy program established at JHH, among 22 patients who died after potentially curative surgery, more than 80% had evidence for local recurrence.²¹ Of note, 59% of these patients received chemoradiation as a component of adjuvant therapy.

Furthermore, achieving microscopically negative surgical margins (R0) is increasingly recognized as having more favorable prognosis compared with resections that have microscopically positive margins (R1). Data from several single-institution reports and larger multicenter trials have clearly shown that R1 resections confer worse

prognosis compared with R0 resections.^{8,9,22} Importantly, evaluation of microscopic margins requires a collaborative approach between the pathologist and the surgeon and methods for rigorous assessment of surgical margins have been developed and published by several groups. This requirement likely explains the increase in the frequency of positive surgical margins reported in adjuvant trials over time, as shown in **Tables 1** and **2**.

Although high-quality dynamic phase cross-sectional imaging has provided the means to characterize tumors as resectable, BR, or LA, even when tumors are radiographically defined as potentially resectable, R1 resections occur frequently.

Verbeke and colleagues²³ suggested that the biology of invading pancreatic cancer cells is distinct from other malignancies in which negative resection margins are also critical for long-term survival. They evaluated the peripheral zone of pancreatic resection specimens, compared them with resected rectal cancers, and found that pancreatic cancer cells were more widely dispersed at the periphery of the tumor compared with resected specimens of rectal cancer. This finding shows one of the insurmountable flaws of up-front surgery, achieving R0 resections based on imaging studies that only provide information at a macroscopic level. It is difficult to imagine that the resolution of future body imaging will become so precise as to allow the visualization of the boundary of the diffusely dispersed and infiltrating border of a pancreatic carcinoma. It is therefore naive to believe that, based on imaging and intraoperative evaluation of the tumor mass, clinicians will observe any meaningful decrease in positive surgical margins with surgery as the first anticancer intervention. Furthermore, if up-front surgery results in an R1 resection, there is no salvage strategy in the postoperative period that offers a significant chance at long-term survival. This flaw in the up-front surgery paradigm is critical, and the “If in doubt, take it out” approach to localized pancreatic cancer is dooming a sizable proportion of patients to inferior survival.

Pancreatic Cancer Is a Systemic Disease

Although many patients present with seemingly localized disease, most harbor microscopic metastases. The rapid autopsy program described earlier found that, among the 22 patients who underwent surgery with curative intent, 88% had metastases at the time of autopsy.²¹ However, it is not always appreciated that overt metastatic disease may develop within weeks of presentation with potentially resectable disease. In an analysis of several preoperative trials among patients who were thought to have localized, resectable disease and in whom treatment was initiated with preoperative therapy, 16% developed radiographically evident metastases within 6 to 12 weeks.²² In another study, the likelihood of encountering unanticipated metastases at the time of surgical exploration increased quickly with every week after preoperative imaging.²⁴ If only 1 week had passed between the imaging and surgical exploration, 12% of patients had unanticipated metastases, whereas 35% had metastases if the imaging was 6 weeks old.

It is therefore reasonable to expect that, among patients who undergo up-front surgery for resectable disease, at least 15% to 20% will develop clinically evident metastatic disease within the recovery period. No one could argue for up-front surgical intervention as beneficial for this subgroup of patients.

Pancreatic Surgery Is Immunosuppressive

The immunosuppressive nature of major surgical procedures is increasingly recognized and the biological basis of this immunosuppression is currently being elucidated. Recent animal studies show that the stress of major intra-abdominal surgery leads to higher levels of circulating tumor cells compared with levels found in animals undergoing sham procedures.²⁵ In addition, natural killer cell and antitumor

T-lymphocyte functions are dysregulated after major surgical stress.^{26,27} The roles of inflammatory cytokines, coagulation, angiogenic factors, and catecholamines are also thought to play an important role in promoting tumor metastases after resection of the primary tumor.²⁸ Although surgery after neoadjuvant therapy would also be expected to promote metastases, given the prior delivery of anticancer therapy, the overall microscopic tumor burden may be reduced by preoperative treatment.

In summary, up-front surgery for pancreatic cancer:

- Often leads to incomplete resection of the primary tumor (R1)
- Is sufficiently complex to prevent sufficient recovery to receive adjuvant therapy
- Does not identify patients with aggressive tumor biology who will not benefit from resection
- Can be fatal
- May promote the metastatic compartment by immunosuppressing the patient or through other mechanisms

Thus, up-front surgery is being used to select patients for adjuvant therapy, which is necessary to improve long-term outcomes. Presently, adjuvant therapy is received by only 50% to 60% of patients who undergo surgery as initial therapy, and many of these have undergone an incomplete resection or harbor a higher metastatic tumor burden based on the need to recover for weeks and the immunosuppressive effects of surgery. These circumstances are not optimal for successful delivery of adjuvant therapy.

RATIONALE FOR NEOADJUVANT THERAPY

Taken together, the flaws inherent in up-front surgery as initial cancer therapy argue for the adoption of an alternative approach for the treatment of localized pancreatic cancer.

There are several advantages to the delivery of neoadjuvant therapy rather than up-front surgery.

First, it allows for the delivery of anticancer therapy to patients who have not been physiologically compromised by a major surgical procedure. Second, it provides a period of time to uncover aggressive tumor biology with identification of those patients who have interval development of metastatic disease, contraindicating surgery. This time interval can also reveal underlying patient frailty given the relative rigors of preoperative chemotherapy or chemoradiation. Such patients are likely at higher risk for surgical complications and prove themselves to be unattractive for surgical intervention, something that is not possible with up-front surgery.

From a biological perspective, treatment with chemotherapy or chemoradiation provides early treatment of micrometastatic disease without waiting for recovery from surgery, which is likely to increase the underlying micrometastatic burden. With the primary intact, the tumor mass is also well perfused and the cytotoxic effects of chemotherapy and/or radiation are not compromised by the creation of a more hypoxic, inflammatory, and fibrotic surgical bed. Furthermore, preoperative therapy has the potential to destroy tumor cells, particularly in the periphery of the tumor mass, thereby improving the likelihood of an ultimate R0 resection.

EARLY RESULTS WITH PREOPERATIVE THERAPY

In a series of trials conducted at the University of Texas MD Anderson Cancer Center (UTMDACC), strict radiographic criteria were used to define potentially resectable disease. These criteria, combined with other inclusion and exclusion criteria used consistently over time, have allowed the enrollment of a fairly homogenous patient populations into sequential neoadjuvant trials (Table 4). The initial 3 trials were designed

Table 4 Sequential neoadjuvant trials for resectable pancreatic cancer performed at University of Texas MD Anderson Cancer Center 1992 to 2008					
Author, Year	Number of Patients	Regimen	Resection Rate (%)	R1 Resection Rate (%)	Median Survival, Resected (mo)
Evans et al, ²⁹ 1992	28	5FU + 50.4 Gy	61	18	Not Stated
Pisters et al, ³⁰ 1998	35	5FU + 30 Gy	57	10	25
Pisters et al, ³¹ 2002	35	Paclitaxel + 30 Gy	57	32	19
Evans et al, ³⁴ 2008	86	Gemcitabine + 30 Gy	74	11	34
Varadhachary et al, ³⁵ 2008	90	Gem/cis then Gem + 30 Gy	58	4	31

Abbreviation: cis, cisplatin.

using a platform of neoadjuvant chemoradiation with either 5FU or paclitaxel as radiosensitizers.^{29–31} The resection rate after preoperative therapy ranged from 57% to 61% with median overall survival for eventually resected patients ranging from 19 to 25 months. These survival durations were similar to those among patients who underwent initial surgery and subsequent adjuvant therapy. However, approximately 40% of enrolled patients were spared the morbidity of surgery based on the discovery of metastatic disease before surgery or intraoperatively. Of note, the results published from UTMDACC were superior to results from a multicenter cooperative group trial conducted through the Eastern Cooperative Oncology Group.³² The trial enrolled 53 patients and only 45% underwent surgery, with a median survival of 15.7 months.

GEMCITABINE-BASED PREOPERATIVE THERAPY

After gemcitabine showed superiority to weekly bolus 5FU and leucovorin in the treatment of advanced pancreatic cancer, investigators at the University of Michigan reported on the potent radiosensitizing properties of gemcitabine.³³ Our group therefore performed an initial trial of neoadjuvant gemcitabine-based chemoradiation for patients with resectable pancreatic cancer, with a subsequent trial of systemic gemcitabine and cisplatin followed by gemcitabine-based chemoradiation. The results of these trials are also summarized in [Table 4](#).^{34,35}

Several conclusions can be drawn from these 2 trials. First, gemcitabine-based chemoradiation led to resection rates between 57% and 75%, equivalent to or higher than the rate of delivery of adjuvant therapy after up-front surgery (50%–60%). Second, R0 resection rates were high at approximately 90%. Third, overall median survival for patients undergoing resection was higher than survival durations reported using up-front surgery and adjuvant therapy. These two reports, with a combined enrollment of 176 patients, were published in 2008. Although other groups have reported on their experience using neoadjuvant therapy, smaller numbers of patients have been enrolled in these studies. For example, in a trial of neoadjuvant therapy using gemcitabine and cisplatin without radiation, only 35 patients were enrolled, and 60% were ultimately resected with an 80% R0 resection rate.³⁶ Median follow-up in this trial was limited but the disease-free and overall survival durations were described as promising.

Nevertheless, results using neoadjuvant therapy in resectable pancreatic cancer remain encouraging. In a prospective analysis of 69 patients treated outside of a clinical trial in the interval from 2004 to 2010 by the group at the Medical College of Wisconsin, the resection rate was 87% and the R0 rate was 97%.³⁷ The median overall survival for all patients was 31.5 months and the median overall survival for resected patients was 44.9 months.

However, many reports of preoperative therapy have enrolled heterogeneous populations of patients with some having resectable disease, others having BR pancreatic cancer, and others still having LA disease. Under these circumstances, results are more challenging to interpret given the small numbers of patients in each category.

EVIDENCE FOR TREATMENT EFFECT USING NEOADJUVANT THERAPY

Although neoadjuvant therapy followed by surgery has not been shown to be clearly superior to up-front surgery and adjuvant therapy, there is evidence for a treatment effect with the delivery of neoadjuvant therapy.

In reports from several institutions, T stage and N stage are reduced with the delivery of neoadjuvant therapy.^{38–40} In addition, overall treatment effect shows that preoperative therapy can result in pathologic complete response or near-complete responses.⁴¹ Such responses are associated with longer survival compared with patients whose resected tumors show lesser degrees of treatment effect.⁴² In addition, virtually all reports of preoperative therapy show high rates of R0 resection among the patients who ultimately undergo surgical resection. Moreover, local recurrence after resection may be significantly reduced with the delivery of neoadjuvant therapy.

OTHER LINES OF EVIDENCE SUPPORTING THE DELIVERY OF NEOADJUVANT THERAPY

Using large data sets, several groups have used propensity matching to compare outcomes of patients undergoing neoadjuvant therapy with those of patients undergoing up-front surgery and adjuvant therapy. In at least 3 analyses, neoadjuvant therapy has been shown to be superior to up-front surgery and adjuvant therapy.^{43–45} However, in one of these studies among patients with clinical stage I disease, the differences in survival between patients treated with preoperative therapy and surgery and those treated with up-front surgery and adjuvant therapy were not significant.⁴⁴ Nevertheless, this same report showed progressive superiority to neoadjuvant therapy for patients with clinical stage II and III pancreatic cancer. Furthermore, neoadjuvant therapy was compared with adjuvant therapy using a Markov decision analysis of 22 studies.⁴⁶ Neoadjuvant therapy led to longer life expectancy and longer quality-adjusted life expectancy.

In addition, others have performed cost-analyses comparing neoadjuvant therapy with up-front surgery, showing that the delivery of neoadjuvant therapy is more cost-effective.⁴⁷

In summary, the delivery of preoperative therapy before surgical resection in potentially resectable pancreatic cancer has a sound rationale; has led to high rates of R0 resections; has shown treatment effect that includes complete pathologic responses; and has shown survival durations for resected patients to be at least equivalent, if not superior, to those reported in studies investigating up-front surgery and adjuvant therapy. Furthermore, it provides a selection mechanism to spare patients with unfavorable tumor biology the morbidity of pancreatic cancer surgery.

THE ROLE OF NEOADJUVANT THERAPY IN BORDERLINE RESECTABLE PANCREATIC CANCER

As our group at UTMDACC was conducting studies of preoperative therapy in those patients strictly defined as having potentially resectable disease, we also encountered patients who did not meet our radiographic criteria for resectability based on encasement of the common hepatic artery, significant involvement of the superior mesenteric vein or superior mesenteric-portal venous confluence, or tumor abutment along the superior mesenteric artery or celiac trunk. Nonetheless, we found that, after delivery of multimodality preoperative therapy, a subset of these patients had some evidence of response to treatment without interval development of metastatic disease. Some of these patients were able to undergo R0 or R1 resections, with encouraging survival durations. Based on this experience, we proposed a definition for BR disease and presented 4 cases of patients who were initially considered to have BR tumors and ultimately underwent surgical resection after a period of multimodal therapy.⁴⁸

Importantly, the concept of BR disease was not unique to our group. During this time frame, an appreciation for the distinction between tumors that would now be considered borderline or marginally resectable was emerging.⁴⁹ For example, one of the earliest reports using preoperative therapy to downstage what is now known as BR disease was conducted at Stanford University and reported by Mehta and colleagues.⁵⁰ The investigators reported on 15 patients they described as having marginally resectable adenocarcinoma of the pancreas, defined as tumors having portal vein, superior mesenteric vein, or artery involvement. These patients were treated with infusional 5-FU and external beam radiation therapy (EBRT) to doses ranging from 50.4 to 56 Gy. Nine patients (60%) underwent surgical resection with negative surgical margins and 2 of 9 (22%) had a complete pathologic response to preoperative treatment. Furthermore, there was a striking difference in overall survival between those patients who did undergo surgical resection and those who did not (30 vs 8 months, respectively).

Thereafter, the authors reported on a series of 160 patients we defined as having BR disease seen at UTMDACC from 1999 to 2006.⁵¹ Of these, 125 (78%) completed preoperative therapy and restaging, and 66 (41%) underwent pancreatectomy with an R0 resection rate of 94%. Median survival was 40 months for the 66 patients who completed all therapy and 13 months for the 94 patients who did not undergo pancreatectomy ($P < .001$).

Other groups are now reporting their single-institutional experiences with BR disease and, depending on the series, resection rates after preoperative therapy range from about 40% to 60%, with most resections classified as R0.^{52,53}

Recently, the Alliance for Clinical Trials in Oncology reported on a prospective multicenter pilot trial of induction FOLFIRINOX followed by capecitabine-based chemoradiation in 23 patients deemed to have BR pancreatic cancer.⁵⁴ The overall resection rate was 68%, and R0 resections were achieved for 93%. The median overall survival for the population was 21.7 months, and 21.7 months for the resected patients.

The next Alliance trial is being designed as a randomized trial to investigate whether radiation therapy is a necessary component of neoadjuvant therapy for BR disease. Eligible patients with BR tumors will be randomized to receive 8 doses of FOLFIRINOX or 7 doses of FOLFIRINOX followed by radiation therapy.

In the United States, although many centers do not endorse preoperative therapy for potentially resectable disease, there is a growing consensus about the use of

neoadjuvant therapy for patients defined as having BR disease. In the National Comprehensive Cancer Network Pancreatic Cancer Subcommittee, there was lack of consensus in this regard in 2006. However, by 2013, most participating centers endorsed neoadjuvant therapy for patients with BR disease.⁵⁵ This position is not shared by an expert group of pancreatic cancer specialists in Europe who recommend a neoadjuvant approach to BR disease only in the context of a clinical trial.⁵⁶

NEOADJUVANT THERAPY FOR LOCALLY ADVANCED DISEASE

Although reports have been limited, there have been efforts to downstage LA disease using neoadjuvant therapy. One of the earliest trials reported modest success using infusional 5FU with EBRT in 16 patients with LA disease.⁵⁷ Although only 2 (12.5%) were able to undergo surgery with curative intent, the survival of these 2 patients was comparable with that of patients with resectable pancreatic cancer treated with up-front surgery and adjuvant therapy. In a larger trial, the group at Duke University reported on 111 patients treated with preoperative chemoradiation from 1995 to 2000 and included patients with resectable ($n = 53$) or LA ($n = 58$) disease.⁵⁸ The overall resection rate was superior for patients defined as having resectable disease (53%) compared with the rate for patients with LA disease (19%), with an overall R0 resection rate of 70%.

These and other reports have suggested that, for a subset of patients with pancreatic cancer not initially considered resectable, neoadjuvant therapy could provide sufficient tumor destruction or downstaging to proceed with surgical resection (Fig. 1). However, the resection rates reported after neoadjuvant therapy have varied widely from as low as 1% to 60%, with most studies reporting resection rates ranging between 20% and 40%.^{51,52,59,60} Patients reported in these studies likely represented a heterogeneous population composed of some having tumor with complete vascular encasement and others having some degree of tumor-vessel contact without encasement.

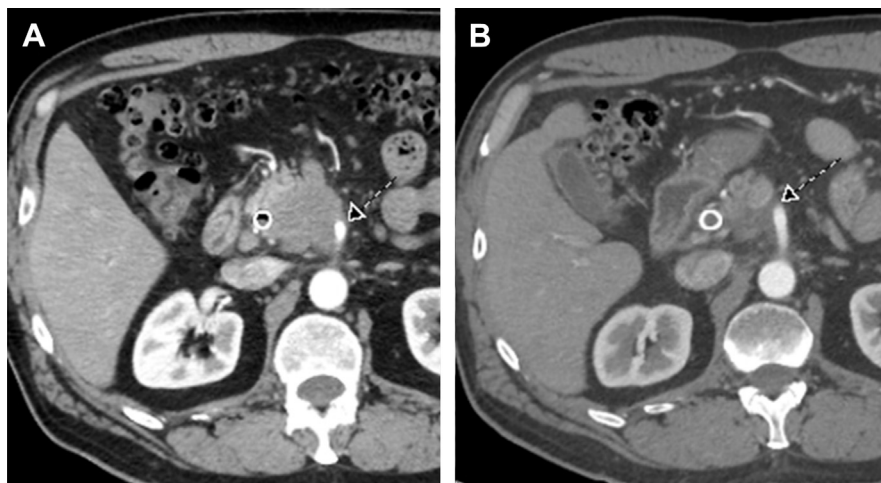


Fig. 1. (A) Pretreatment computed tomography (CT) imaging of a locally advanced pancreatic cancer with tumor along the right side of the superior mesenteric artery and extending to the contralateral side. (B) Posttreatment CT image of the tumor mass after FOLFIRINOX for 6 doses and capecitabine-based chemoradiation. The residual tumor was resected with skeletonization of the superior mesenteric artery. Histopathology showed a complete pathologic response to neoadjuvant therapy. Arrow in (A) and (B) depicts the direct contact of tumor with the superior mesenteric artery.

NEOADJUVANT THERAPY AT MD ANDERSON OVER 25 YEARS

Members of our multidisciplinary pancreatic cancer team at UTMDACC have been avid supporters of neoadjuvant therapy for years. Over the past 25 years, we have made an effort to conduct clinical trials in localized pancreatic carcinoma that have used surgical resection as a later step in our patients' anticancer therapy. Using a prospectively collected database, we have tracked patients who have undergone surgery after neoadjuvant therapy either as part of a clinical trial or off protocol. Earlier this year, we published our 25-year experience with surgical resection after neoadjuvant therapy.⁶¹ During the period 1999 to 2014, surgical resections for BR and LA tumors increased. The use of induction systemic chemotherapy and the delivery of postoperative chemotherapy also increased. In addition, R0 resection rates and vascular resection rates increased overall. Despite the increase in resections for patients initially considered to have BR or LA tumors, locoregional recurrence rates remained similar over time, and overall survival improved significantly from a median of 24.1 months in the early 2000s to 43.4 months by 2014 ($P < .0001$). Although the results reported by our group should not be construed as typical, they do represent what is possible using a multidisciplinary approach, and interest in pursuing a neoadjuvant platform in localized pancreatic cancer is growing.

In general, UTMDACC patients defined as having potentially resectable pancreatic cancer are treated on prospective clinical trials whenever available. For those who do not wish to participate, or do not meet eligibility criteria, neoadjuvant therapy with chemoradiation is often advised. For those with BR disease, our approach has been to deliver systemic therapy for 2 to 3 months and if, on restaging, there is no evidence of metastatic disease, we usually recommend a course of chemoradiation. Decisions about patients' surgical candidacy are then made after restaging and formal review in a multidisciplinary pancreatic cancer conference.

THE FUTURE OF ADJUVANT AND NEOADJUVANT THERAPY

There is no definitive evidence supporting the use of postoperative radiation as a component of adjuvant therapy after up-front surgery. Thus, efforts to improve adjuvant therapy have focused on the investigation of combination systemic therapy. At present, there are 2 ongoing randomized trials in this area. The first is comparing gemcitabine with gemcitabine and nab-paclitaxel in the adjuvant setting.⁶² In addition, modified FOLFIRINOX is being compared with gemcitabine as systemic adjuvant therapy.⁶³ Given the survival benefit shown by adding capecitabine to gemcitabine, these 2 trials are likely to be amended to allow gemcitabine/capecitabine as the control arm for both. In neoadjuvant therapy, in which gemcitabine/nab-paclitaxel and FOLFIRINOX are already being used, more novel approaches designed to affect the tumor microenvironment or enhance the patient's immune response are now being investigated.^{64,65}

In addition, our group has reported on imaging characteristics of pancreatic adenocarcinoma and has classified primary tumors in the pancreatic parenchyma as either stromal rich or stromal poor.⁶⁶ This characterization seems to provide prognostic information, with stromal-poor tumors conferring a worse prognosis for patients after conventional neoadjuvant therapy. In the future, without the need for ample biopsies for molecular interrogation, the ability to tailor neoadjuvant therapy based on imaging characteristics may be feasible.⁶⁷

In summary, neoadjuvant therapy:

- Allows early delivery of cytotoxic therapy before patients are compromised by the stress of a major surgical procedure

- Provides an interval of time to identify aggressive tumor biology and frail patients
- Delivers treatment to tumors that are intact and not altered by surgery with resultant local hypoxia, inflammation, and fibrosis
- Has potential to decrease or even eliminate microscopic metastatic tumor burden
- Can generate treatment effect that increases R0 resection rates and has prognostic significance
- Can expand the population of patients who may ultimately benefit from resection

SUMMARY

Up-front surgery is considered the standard of care for resectable pancreatic cancer despite modest improvements in median overall survival observed over time (20 months in 1985, 28 months in 2017). Nevertheless, with few exceptions, surgery first is widely endorsed in the oncology community and will not change without randomized trials comparing up-front surgery/adjuvant therapy with neoadjuvant therapy/subsequent surgery. Randomized trials of neoadjuvant versus adjuvant therapy are currently enrolling patients.⁶⁸ Until definitive results from these trials are reported, up-front surgery will be used to select patients for adjuvant therapy. This strategy places patients at risk for positive surgical margins, poor recovery, and rapid relapse, limiting the delivery of adjuvant therapy.

In contrast, our 25-year experience has shown that neoadjuvant therapy can lead to greater incremental improvements in survival compared with up-front surgery and adjuvant therapy over the same time period. Although there has been a general lack of interest in neoadjuvant therapy for resectable disease, there is growing enthusiasm for neoadjuvant therapy in patients with BR tumors and, in some centers, LA disease. As systemic therapies, radiation techniques, and other locally ablative techniques evolve, resection rates and survival for patients with BR and LA pancreatic cancer are expected to improve.

In addition, for patients undergoing up-front surgery resulting in positive surgical margins, median survival is less than 2 years.⁹ Given the demonstrated treatment effect of neoadjuvant therapy, newer drug regimens, and an expanding array of locally ablative and radiation techniques, growing numbers of patients with BR or LA pancreatic cancer are more likely to become surgical candidates with curative potential after application of preoperative therapy.

REFERENCES

1. Tepper J, Nardi G, Sutt H. Carcinoma of the pancreas: review of MGH experience from 1963 to 1973. Analysis of surgical failure and implications for radiation therapy. *Cancer* 1976;37:1519–24.
2. Kalser MH, Ellenberg SS. Pancreatic cancer. Adjuvant combined radiation and chemotherapy following curative resection. *Arch Surg* 1985;120:899–903.
3. Klinkenbijl JH, Jeekel J, Sahnoud T, et al. Adjuvant radiotherapy and 5-fluorouracil after curative resection of cancer of the pancreas and periampullary region: phase III trial of the EORTC gastrointestinal tract cancer cooperative group. *Ann Surg* 1999;230:776–82.
4. Neoptolemos JP, Dunn JA, Stocken DD, et al. Adjuvant chemoradiotherapy and chemotherapy in resectable pancreatic cancer: a randomised controlled trial. *Lancet* 2001;358:1576–85.
5. Regine WF, Winter KA, Abrams RA, et al. Fluorouracil vs gemcitabine chemotherapy before and after fluorouracil-based chemoradiation following resection

- of pancreatic adenocarcinoma: a randomized controlled trial. *JAMA* 2008;299:1019–26.
6. Oettle H, Post S, Neuhaus P, et al. Adjuvant chemotherapy with gemcitabine vs observation in patients undergoing curative-intent resection of pancreatic cancer: a randomized controlled trial. *JAMA* 2007;297:267–77.
 7. Neoptolemos JP, Stocken DD, Tudur Smith C, et al. Adjuvant 5-fluorouracil and folinic acid vs observation for pancreatic cancer: composite data from the ESPAC-1 and -3(v1) trials. *Br J Cancer* 2009;100:246–50.
 8. Neoptolemos JP, Stocken DD, Bassi C, et al. Adjuvant chemotherapy with fluorouracil plus folinic acid vs gemcitabine following pancreatic cancer resection: a randomized controlled trial. *JAMA* 2010;304:1073–81.
 9. Neoptolemos JP, Palmer DH, Ghaneh P, et al. Comparison of adjuvant gemcitabine and capecitabine with gemcitabine monotherapy in patients with resected pancreatic cancer (ESPAC-4): a multicentre, open-label, randomised, phase 3 trial. *Lancet* 2017;389:1011–24.
 10. Oettle H, Neuhaus P, Hochhaus A, et al. Adjuvant chemotherapy with gemcitabine and long-term outcomes among patients with resected pancreatic cancer: the CONKO-001 randomized trial. *JAMA* 2013;310:1473–81.
 11. Pelzer U, Schwane I, Stieler J, et al. Best supportive care (BSC) versus oxaliplatin, folinic acid and 5-fluorouracil (OFF) plus BSC in patients for second-line advanced pancreatic cancer: a phase III-study from the German CONKO-study group. *Eur J Cancer* 2011;47:1676–81.
 12. Xiong HQ, Varadhachary GR, Blais JC, et al. Phase 2 trial of oxaliplatin plus capecitabine (XELOX) as second-line therapy for patients with advanced pancreatic cancer. *Cancer* 2008;113:2046–52.
 13. Conroy T, Desseigne F, Ychou M, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *N Engl J Med* 2011;364:1817–25.
 14. Von Hoff DD, Ervin T, Arena FP, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. *N Engl J Med* 2013;369:1691–703.
 15. Herman JM, Swartz MJ, Hsu CC, et al. Analysis of fluorouracil-based adjuvant chemotherapy and radiation after pancreaticoduodenectomy for ductal adenocarcinoma of the pancreas: results of a large, prospectively collected database at the Johns Hopkins Hospital. *J Clin Oncol* 2008;26:3503–10.
 16. Corsini MM, Miller RC, Haddock MG, et al. Adjuvant radiotherapy and chemotherapy for pancreatic carcinoma: the Mayo Clinic experience (1975-2005). *J Clin Oncol* 2008;26:3511–6.
 17. Merkow RP, Bilimoria KY, Tomlinson JS, et al. Postoperative complications reduce adjuvant chemotherapy use in resectable pancreatic cancer. *Ann Surg* 2014;260:372–7.
 18. Lim JE, Chien MW, Earle CC. Prognostic factors following curative resection for pancreatic adenocarcinoma: a population-based, linked database analysis of 396 patients. *Ann Surg* 2003;237:74–85.
 19. Swanson RS, Pezzi CM, Mallin K, et al. The 90-day mortality after pancreatectomy for cancer is double the 30-day mortality: more than 20,000 resections from the national cancer data base. *Ann Surg Oncol* 2014;21:4059–67.
 20. Johnstone PA, Sindelar WF. Patterns of disease recurrence following definitive therapy of adenocarcinoma of the pancreas using surgery and adjuvant radiotherapy: correlations of a clinical trial. *Int J Radiat Oncol Biol Phys* 1993;27:831–4.
 21. Iacobuzio-Donahue CA, Fu B, Yachida S, et al. DPC4 gene status of the primary carcinoma correlates with patterns of failure in patients with pancreatic cancer. *J Clin Oncol* 2009;27:1806–13.

22. Wolff RA, Varadhachary GR, Evans DB. Adjuvant therapy for adenocarcinoma of the pancreas: analysis of reported trials and recommendations for future progress. *Ann Surg Oncol* 2008;15:2773–86.
23. Verbeke CS, Knapp J, Gladhaug IP. Tumour growth is more dispersed in pancreatic head cancers than in rectal cancer: implications for resection margin assessment. *Histopathology* 2011;59:1111–21.
24. Glant JA, Waters JA, House MG, et al. Does the interval from imaging to operation affect the rate of unanticipated metastasis encountered during operation for pancreatic adenocarcinoma? *Surgery* 2011;150:607–16.
25. Menges P, Klocker C, Diedrich S, et al. Surgical trauma leads to a shorter survival in a murine orthotopic pancreatic cancer model. *Eur Surg Res* 2015;54:87–94.
26. Tai LH, Zhang J, Auer RC. Preventing surgery-induced NK cell dysfunction and cancer metastases with influenza vaccination. *Oncoimmunology* 2013;2:e26618.
27. Ananth AA, Tai LH, Lansdell C, et al. Surgical stress abrogates pre-existing protective T cell mediated anti-tumor immunity leading to postoperative cancer recurrence. *PLoS One* 2016;11:e0155947.
28. Neeman E, Ben-Eliyahu S. Surgery and stress promote cancer metastasis: new outlooks on perioperative mediating mechanisms and immune involvement. *Brain Behav Immun* 2013;30(Suppl):S32–40.
29. Evans DB, Rich TA, Byrd DR, et al. Preoperative chemoradiation and pancreaticoduodenectomy for adenocarcinoma of the pancreas. *Arch Surg* 1992;127:1335–9.
30. Pisters PW, Abbruzzese JL, Janjan NA, et al. Rapid-fractionation preoperative chemoradiation, pancreaticoduodenectomy, and intraoperative radiation therapy for resectable pancreatic adenocarcinoma. *J Clin Oncol* 1998;16:3843–50.
31. Pisters PW, Wolff RA, Janjan NA, et al. Preoperative paclitaxel and concurrent rapid-fractionation radiation for resectable pancreatic adenocarcinoma: toxicities, histologic response rates, and event-free outcome. *J Clin Oncol* 2002;20:2537–44.
32. Hoffman JP, Lipsitz S, Pisansky T, et al. Phase II trial of preoperative radiation therapy and chemotherapy for patients with localized, resectable adenocarcinoma of the pancreas: an Eastern Cooperative Oncology Group Study. *J Clin Oncol* 1998;16:317–23.
33. Shewach DS, Lawrence TS. Radiosensitization of human solid tumor cell lines with gemcitabine. *Semin Oncol* 1996;23(5 Suppl 10):65–71.
34. Evans DB, Varadhachary GR, Crane CH, et al. Preoperative gemcitabine-based chemoradiation for patients with resectable adenocarcinoma of the pancreatic head. *J Clin Oncol* 2008;26:3496–502.
35. Varadhachary GR, Wolff RA, Crane CH, et al. Preoperative gemcitabine and cisplatin followed by gemcitabine-based chemoradiation for resectable adenocarcinoma of the pancreatic head. *J Clin Oncol* 2008;26:3487–95.
36. Heinrich S, Pestalozzi BC, Schafer M, et al. Prospective phase II trial of neoadjuvant chemotherapy with gemcitabine and cisplatin for resectable adenocarcinoma of the pancreatic head. *J Clin Oncol* 2008;26:2526–31.
37. Christians KK, Heimler JW, George B, et al. Survival of patients with resectable pancreatic cancer who received neoadjuvant therapy. *Surgery* 2016;159:893–900.
38. Roland CL, Yang AD, Katz MH, et al. Neoadjuvant therapy is associated with a reduced lymph node ratio in patients with potentially resectable pancreatic cancer. *Ann Surg Oncol* 2015;22:1168–75.

39. Townend P, de Reuver PR, Chua TC, et al. Histopathological tumour viability after neoadjuvant chemotherapy influences survival in resected pancreatic cancer: analysis of early outcome data. *ANZ J Surg* 2017. [Epub ahead of print].
40. Schorn S, Demir IE, Reyes CM, et al. The impact of neoadjuvant therapy on the histopathological features of pancreatic ductal adenocarcinoma - A systematic review and meta-analysis. *Cancer Treat Rev* 2017;55:96–106.
41. Zhao Q, Rashid A, Gong Y, et al. Pathologic complete response to neoadjuvant therapy in patients with pancreatic ductal adenocarcinoma is associated with a better prognosis. *Ann Diagn Pathol* 2012;16:29–37.
42. Lee SM, Katz MH, Liu L, et al. Validation of a proposed tumor regression grading scheme for pancreatic ductal adenocarcinoma after neoadjuvant therapy as a prognostic indicator for survival. *Am J Surg Pathol* 2016;40:1653–60.
43. Mokdad AA, Minter RM, Zhu H, et al. Neoadjuvant therapy followed by resection versus upfront resection for resectable pancreatic cancer: a propensity score matched analysis. *J Clin Oncol* 2017;35:515–22.
44. Mirkin KA, Hollenbeak CS, Wong J. Survival impact of neoadjuvant therapy in resected pancreatic cancer: a prospective cohort study involving 18,332 patients from the National Cancer Data Base. *Int J Surg* 2016;34:96–102.
45. Sharma G, Whang EE, Ruan DT, et al. Efficacy of neoadjuvant versus adjuvant therapy for resectable pancreatic adenocarcinoma: a decision analysis. *Ann Surg Oncol* 2015;22(Suppl 3):S1229–37.
46. de Geus SW, Evans DB, Bliss LA, et al. Neoadjuvant therapy versus upfront surgical strategies in resectable pancreatic cancer: a Markov decision analysis. *Eur J Surg Oncol* 2016;42:1552–60.
47. Abbott DE, Tzeng CW, Merkow RP, et al. The cost-effectiveness of neoadjuvant chemoradiation is superior to a surgery-first approach in the treatment of pancreatic head adenocarcinoma. *Ann Surg Oncol* 2013;20(Suppl 3):S500–8.
48. Varadhachary GR, Tamm EP, Abbruzzese JL, et al. Borderline resectable pancreatic cancer: definitions, management, and role of preoperative therapy. *Ann Surg Oncol* 2006;13:1035–46.
49. Wolff RA. Neoadjuvant chemoradiation for localized adenocarcinoma of the pancreas: great logic, grim reality. *Ann Surg Oncol* 2001;8:747–8.
50. Mehta VK, Fisher G, Ford JA, et al. Preoperative chemoradiation for marginally resectable adenocarcinoma of the pancreas. *J Gastrointest Surg* 2001;5:27–35.
51. Katz MH, Pisters PW, Evans DB, et al. Borderline resectable pancreatic cancer: the importance of this emerging stage of disease. *J Am Coll Surg* 2008;206:833–46.
52. Christians KK, Tsai S, Mahmoud A, et al. Neoadjuvant FOLFIRINOX for borderline resectable pancreas cancer: a new treatment paradigm? *Oncologist* 2014;19:266–74.
53. Takahashi H, Ohigashi H, Gotoh K, et al. Preoperative gemcitabine-based chemoradiation therapy for resectable and borderline resectable pancreatic cancer. *Ann Surg* 2013;258:1040–50.
54. Katz MH, Shi Q, Ahmad SA, et al. Preoperative modified FOLFIRINOX treatment followed by capecitabine-based chemoradiation for borderline resectable pancreatic cancer: alliance for clinical trials in oncology trial A021101. *JAMA Surg* 2016;151:e161137.
55. Tempero MA, Malafa MP, Behrman SW, et al. Pancreatic adenocarcinoma, version 2.2014: featured updates to the NCCN guidelines. *J Natl Compr Canc Netw* 2014;12:1083–93.

56. Bockhorn M, Uzunoglu FG, Adham M, et al. Borderline resectable pancreatic cancer: a consensus statement by the International Study Group of Pancreatic Surgery (ISGPS). *Surgery* 2014;155:977–88.
57. Jessup JM, Steele G Jr, Mayer RJ, et al. Neoadjuvant therapy for unresectable pancreatic adenocarcinoma. *Arch Surg* 1993;128:559–64.
58. White RR, Hurwitz HI, Morse MA, et al. Neoadjuvant chemoradiation for localized adenocarcinoma of the pancreas. *Ann Surg Oncol* 2001;8:758–65.
59. Kim HJ, Czischke K, Brennan MF, et al. Does neoadjuvant chemoradiation down-stage locally advanced pancreatic cancer? *J Gastrointest Surg* 2002;6:763–9.
60. Gillen S, Schuster T, Meyer Zum Buschenfelde C, et al. Preoperative/neoadjuvant therapy in pancreatic cancer: a systematic review and meta-analysis of response and resection percentages. *PLoS Med* 2010;7:e1000267.
61. Cloyd JM, Katz MH, Prakash L, et al. Preoperative therapy and pancreatoduodenectomy for pancreatic ductal adenocarcinoma: a 25-year single-institution experience. *J Gastrointest Surg* 2017;21(1):164–74.
62. Available at: <https://clinicaltrials.gov/ct2/show/NCT01964430>.
63. Available at: <https://clinicaltrials.gov/ct2/show/results/NCT01526135>.
64. Sherman MH, Yu RT, Engle DD, et al. Vitamin D receptor-mediated stromal reprogramming suppresses pancreatitis and enhances pancreatic cancer therapy. *Cell* 2014;159:80–93.
65. Azad A, Yin Lim S, D'Costa Z, et al. PD-L1 blockade enhances response of pancreatic ductal adenocarcinoma to radiotherapy. *EMBO Mol Med* 2017;9:167–80.
66. Koay EJ, Truty MJ, Cristini V, et al. Transport properties of pancreatic cancer describe gemcitabine delivery and response. *J Clin Invest* 2014;124:1525–36.
67. Koay EJ, Amer AM, Baio FE, et al. Toward stratification of patients with pancreatic cancer: past lessons from traditional approaches and future applications with physical biomarkers. *Cancer Lett* 2016;381(1):237–43.
68. Versteijne E, van Eijck CH, Punt CJ, et al. Preoperative radiochemotherapy versus immediate surgery for resectable and borderline resectable pancreatic cancer (PREOPANC trial): study protocol for a multicentre randomized controlled trial. *Trials* 2016;17:127.