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EDITORIAL

# Neoadjuvant treatment for resectable pancreatic adenocarcinoma

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## Abstract

Pancreatic adenocarcinoma is the fourth leading cause of cancer mortality in the United States in both men and women, with a 5-year survival rate of less than 5%. Surgical resection remains the only curative treatment, but most patients develop systemic recurrence within 2 years of surgery. Adjuvant treatment with chemotherapy or chemoradiotherapy has been shown to improve overall survival, but the delivery of treatment remains problematic with up to 50% of patients not receiving postoperative treatment. Neoadjuvant therapy can provide benefits of eradication of micrometastasis and improved delivery of intended treatment. We have reviewed the findings from completed neoadjuvant clinical trials, and discussed the ongoing studies. Combinational cytotoxic chemotherapy such as fluorouracil, leucovorin, irinotecan, and oxaliplatin and gemcitabine plus nanoparticle albumin-bound (nab)-paclitaxel, active in the metastatic setting, are being studied in the neoadjuvant setting. In addition, novel targeted agents such as inhibitor of immune checkpoint are incorporated with cytotoxic chemotherapy in early-phase clinical trial. Furthermore we have explored the utility of biomarkers which can personalize treatment and select patients for target-driven therapy to improve treatment outcome. The treatment of resectable pancreatic adenocarcinoma requires multidisciplinary approach and novel strategies including innovative trials to make progress.

**Key words:** Pancreatic cancer; Resectable pancreatic adenocarcinoma; Neoadjuvant treatment; Biomarkers; Chemotherapy; Surgery



**Core tip:** The treatment of resectable pancreatic adenocarcinoma requires multidisciplinary approach and novel strategies including innovative trials to make progress. Data from completed neoadjuvant clinical trials are reviewed, and important ongoing studies are presented. Biomarkers for patient selection and personalized medicine are discussed.

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## INTRODUCTION

Pancreatic cancer can arise from either the exocrine or endocrine cells. Cancer of the endocrine pancreas, also known as pancreatic neuroendocrine tumor, is uncommon and has a relatively better prognosis than pancreatic adenocarcinoma (cancer of the exocrine pancreas). In the United States, approximately 48960 people are diagnosed with cancer of the exocrine pancreas each year, and an estimated 40560 people will die from their disease; it is the fourth leading cause of cancer mortality in men and women[1]. Globally, it is the seventh leading cause of cancer mortality in men and women, causing more than 300000 deaths annually[2]. Most patients with pancreatic adenocarcinoma will die within two years of diagnosis, and the 5-year survival rate is less than 5%[3]. The lack of a low cost screening test with high sensitivity and specificity contributes to most cases being diagnosed at an advanced stage.

Staging of pancreatic adenocarcinoma is usually done with tri-phasic pancreatic-protocol computed tomography scan of abdomen and pelvis and chest imaging. Based upon imaging, the tumor is classified as resectable, borderline resectable, locally advanced, or metastatic. Approximately 15% to 20% of patients are diagnosed with resectable disease and 45%-55% of patients are diagnosed with metastatic disease[4]. Appropriate staging allows the selection of patients who will have the best chance for curative intent resection (R0). Patients with borderline resectable disease are often given neoadjuvant treatment for tumor down-staging to render resection afterwards. Up to about one-third of patients with borderline-resectable tumors could have resectable disease after neoadjuvant treatment[5]. However, the role of neoadjuvant treatment for resectable pancreatic cancer remains unclear.

Surgical resection remains the only curative treatment for pancreatic cancer. A tumor is considered resectable if there is no arterial tumor contact [celiac axis (CA), superior mesenteric artery (SMA), common hepatic artery] and there is no tumor contact with the superior mesenteric vein (SMV) or portal vein (PV) or ≤ 180-degrees contact without vein contour irregularity on imaging study[6]. A tumor is considered unresectable if there is distant metastasis or unreconstructible SMV/PV due to tumor; if the tumor involves the pancreatic head it is unresectable if there is more than 180-degree encasement of the SMA or CA; a tumor of the pancreatic body or tail is unresectable if there is more than 180-degree encasement of the SMA or CA or tumor contact with the CA and aortic involvement[6].

Surgical management may include pancreaticoduodenectomy or pancreatectomy. It has been shown that pancreatic cancer patients undergoing surgery have better outcomes at high-volume hospitals, and the multidisciplinary approach and experienced surgeon seem to contribute most to the outcome of patients receiving pancreatic surgery[7]. The incomplete resection with positive surgical margins is frequent, reported 40% to 50% in most series[8]. The survival rate for patients with positive surgical margins is similar to that of patients who have locally-advanced disease[9]. The long-term survival after surgery remains low due to high rate of systemic recurrence: About 10% for node-positive disease and about 25% to 30% for node-negative disease[10-13]. Adjuvant treatment has been shown to improve survival as demonstrated in studies such as ESPAC-1, CONKO-001, ESPAC-3, RTOG 9704, and GITSG[14]. However, the delivery of postoperative treatment can be problematic with up to 50% of patients not receiving the intended treatment due to post-operative complications[15,16]. About 15% of patients may develop overt metastatic disease during postoperative recovery period, therefore early initiation of adjuvant chemotherapy within 20 d after surgery has been shown to improve disease-free and overall survival[8,17].

## COMPLETED NEOADJUVANT TREATMENT STUDIES FOR RESECTABLE PANCREATIC CANCER

Due to the high rate of micrometastasis with systemic recurrence and difficulty in achieving R0 resection and delivering adjuvant therapy in time, neoadjuvant therapy has been studied to seek improvement in resection and survival. Potential benefits include early treatment of micrometastatic disease, tumor shrinkage for complete resection, and better tumor oxygenation plus drug delivery during chemoradiotherapy. It can also facilitate patient selection for surgery since those patients with disease progression at restaging would likely not benefit from resection.

Currently there is no data that clearly demonstrates improved resectability or survival with neoadjuvant treatment compared with initial surgery followed by adjuvant therapy. The National Comprehensive Cancer Network suggests not administering neoadjuvant therapy outside of a clinical trial. There have been several meta-analyses that have examined the benefit of neoadjuvant therapy. One analysis of 4394 patients in 111 phase Ⅰ/Ⅱ studies with about 1120 patients with resectable disease in 35 studies found no difference in overall survival between neoadjuvant and adjuvant treatment[5]. A meta-analysis of 19 studies in neoadjuvant chemoradiation showed that patients receiving neoadjuvant chemoradiotherapy were less likely to have a positive resection margin but they had an increased risk of perioperative death[18]. Another study of 536 patients in 14 phase Ⅱ studies concluded that patients with locally advanced

**Table 1 Selected published neoadjuvant phase Ⅱ trials in resectable pancreatic adenocarcinoma between 2006-2015**

| Trial/reference published year | Trial phase/patient number | Treatment regimen | Primary endpoint | Result |
|---|---|---|---|---|
| NCT00335543/2015[63] | Ⅱ, randomized/66 (254 planned) | Upfront surgery *vs* chemoradiation with gemcitabine/cisplatin and radiotherapy of 55.8 Gy | Median survival | Median survival: 14.4 mo *vs* 17.4 mo ($P$ = 0.96). Overall R0: 48% *vs* 52% ($P$ = 0.81) |
| NCT00536874/2014[64] | Ⅱ/38 | Gemcitabine and oxaliplatin | 18-mo overall survival | 18-mo overall survival: 63%. Median overall survival: 27.2 mo. Resection rate was 71%, and 74% of resection was R0 |
| NCT00490360/2008[20,65] | Ⅱ/28 | Gemcitabine and cisplatin | Resectability rate ⩾ 70% | Resection rate was 89%, and 80% of resection was R0. Overall survival was 26.5 mo |
| Evans *et al*[21] | Ⅱ/86 | Chemoradiation with gemcitabine and radiotherapy of 30 Gy (in 10 fractions) for pancreatic head cancer | Clinical outcome | Overall R0: 74%. Median overall survival was 22.7 mo with a 5-yr survival of 27% (36% in R0) |
| Varadhachary[22] | Ⅱ/90 | Gemcitabine and cisplatin followed by chemoradiation with gemcitabine and radiotherapy of 30 Gy for pancreatic head cancer | Clinical outcome | Overall R0 was 58%. Additional chemotherapy did not improve clinical outcome |
| Palmer *et al*[66] | Ⅱ, randomized/50 | Gemcitabine *vs* gemcitabine and cisplatin | Resection rate | Resection rate was 54%: 9 (38%) in the gemcitabine arm and 18 (70%) in the combination arm |

pancreatic cancer would benefit from neoadjuvant treatment[19]. Of note, some trials included in these analyses used older generation of chemotherapy and chemoradiation regimens such as 5-fluorouracil, cisplatin and mitomycin-C. Additionally, not only perspective studies, but retrospective cohort studies and case reports were also included in these meta-analyses, which are subjective to confounding and bias errors. Therefore, we have summarized the 6 published phase Ⅱ trials with gemcitabine-based regimen in the last 10 years (Table 1). Most of these trials have shown overall R0 rate around 50%. Two studies, neoadjuvant chemotherapy with gemcitabine and cisplatin reported by Heinrich *et al*[20], and neoadjuvant chemoradiation with gemcitabine reported by Evans *et al*[21], have demonstrated overall R0 rate of more than 70%. However, adding chemotherapy with gemcitabine and cisplatin before gemcitabine-based chemoradiation did not improve clinical outcome including overall R0 and survival rate[22].

Barbour *et al*[23] reported the result of GAP study: Phase Ⅱ study of gemcitabine and nab-paclitaxel for resectable pancreas cancer, a muticenter study conducted in Australia in 2015 ASCO Gastrointestinal Cancers Symposium. Patients in this study received 2 mo of pre-operative chemotherapy with gemcitabine and nab-paclitaxel, then underwent surgical resection. Patients received post-operative treatment based on their resection status (R0 *vs* R1). The primary endpoint was to examine the rate of R0 resection with all margins microscopically clear (minimum distance from tumor to resection margin ⩾ 1.0 mm), with a planned enrollment of 50 patients to aim for R0 rate of 85% or greater. However, this study was stopped after enrolling 42 patients due to a review by Independent Data and Safety Monitoring Committee showing the primary endpoint could not be met.

The ACOSOG Z5041 (NCT00733746) is a phase Ⅱ study in United States investigating overall survival at 2 years in patients receiving perioperative gemcitabine and erlotinib[24]. Erlotinib, an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor, has been shown to deliver statistically significant but marginal benefit in overall survival when adding to gemcitabine compared to gemcitabine alone as first-line treatment in patients with advanced pancreatic cancer[25]. The ACOSOG Z5041 met the accrual goal of 123 patients at end of 2013, and the result of the study is highly anticipated. The ACOSOG Z5041 will address the benefit of erlotinib as an adjunct to gemcitabine given perioperatively in resectable setting[26]. Additionally, this study will explore the biomarkers for response to erlotinib, such as E-cadherin whose expression is lost during epithelial-mesenchymal transition (EMT) contributing to cellular insensitivity to EGFR inhibition[27]. The NEOPAC (NCT01521702) is a phase Ⅲ randomized study in Europe comparing adjuvant gemcitabine *vs* neoadjuvant gemcitabine and oxaliplatin plus adjuvant gemcitabine[28]. The primary endpoint is progression-free survival, and the study has been terminated after enrolling about 25% of planned accrual.

## ONGOING NEOADJUVANT TREATMENT STUDIES FOR RESECTABLE PANCREATIC CANCER

The landscape of systemic treatment in metastatic pancreatic cancer has changed significantly since 2011. Conroy *et al*[29] have shown FOLFIRINOX (5-fluorouracil plus leucovorin, irinotecan and oxaliplatin) delivered significant improvement of median overall survival when compared to gemcitabine alone in a randomized phase Ⅲ study enrolling 342 patients [11.1 mo *vs* 6.8 mo ($P$ < 0.001)]. Of note, this study excluded patients

**Table 2 Selected ongoing neoadjuvant trials for resectable pancreatic cancer**

| Trial | Trial phase | Treatment regimen | Primary endpoint | Planned accrual (patients) |
|---|---|---|---|---|
| NCT01900327 (NEOPA) | Ⅲ | Chemoradiation with gemcitabine and radiotherapy of 50.4 Gy *vs* upfront surgery | 3 yr survival rate | 410 |
| NCT02172976 | Ⅱ/Ⅲ | Perioperative FOLFIRINOX *vs* adjuvant gemcitabine | Median overall survival | 126 |
| NCT02047513 (NEONAX) | Ⅱ | Perioperative nab-paclitaxel/gemcitabine *vs* adjuvant nab-paclitaxel/gemcitabine | Disease free survival | 166 |
| NCT02305186 | Ⅰ/Ⅱ | Neoadjuvant pembrolizumab plus chemoradiation with capecitabine and radiotherapy of 50.4 Gy *vs* neoadjuvant chemoradiation | Dose limiting toxicities; # of tumor infiltrating lymphocytes per high power field in resected tissue | 56 |

with suboptimal performance status (ECOG 2 and beyond) or ages older than 76 years old. Von Hoff and colleagues[30] reported increased median overall survival with nab-paclitaxel plus gemcitabine compared to gemcitabine alone in a randomized phase Ⅲ study with 861 patients [8.5 mo *vs* 6.7 mo ($P < 0.001$)]. Therefore both FOLFIRINOX and nab-paclitaxel/gemcitabine have become preferred regimens in advanced pancreatic cancer, and are currently explored in the neoadjuvant setting (Table 2).

The NEPAFOX is a phase Ⅱ/Ⅲ multicenter study (NCT02172976) conducted in Germany with primary endpoint being median overall survival that has started recruiting patients with resectable or borderline resectable pancreatic cancer since November 2014. The phase Ⅱ study will randomize 126 patients to either surgery followed by 6 mo of gemcitabine or perioperative FOLFIRINOX (3 mo before surgery and 3 mo after surgery). After an interims analysis, the trial can be continued as phase Ⅲ to enroll 310 patients[31].

The NEONAX study (AIO-PAK-0313, NCT02047513) is a phase Ⅱ study conducted in Germany that has started recruiting patients with resectable pancreatic cancer since April 2015. This trial will randomize 166 patients to either perioperative treatment with nab-paclitaxel and gemcitabine (2 mo before surgery and 4 mo after surgery) or adjuvant treatment with nab-paclitaxel and gemcitabine. The primary outcome measure is disease-free survival, and aims to improve the disease-free survival rate at 18 mo in at least one arm to ⩾ 55%. This study will conduct biomarker study by collecting tumor tissue for exome sequencing, and circulating tumor DNA for biocorrelate and pharmacogenomic study[32,33].

The NEOPA study (NCT01900327; Neoadjuvant Treatment in Resectable Pancreatic Cancer) is an ongoing phase Ⅲ study in Germany that will randomize 410 patients to neoadjuvant gemcitabine-based chemoradiation *vs* upfront surgery[34]. Both groups will receive post-operative adjuvant treatment with gemcitabine. The primary endpoint is 3-year survival rate. This study is to examine the hypothesis that neoadjuvant gemcitabine-based chemoradiation increases the three-year overall survival by 12% compared to upfront surgery for resectable pancreatic cancer.

The Prep-02/JSAP05 study is a prospective randomized phase Ⅱ/Ⅲ trial conducted in Japan since January 2013 (clinical trial information: UMIN000009634)[35]. This study plans to enroll 360 patients with resectable pancreatic cancer, and randomizes them to either surgery followed by adjuvant chemotherapy with S1 for 6 mo or 2 mo of neoadjuvant chemotherapy with gemcitabine and S1 followed by surgery then 6 mo of adjuvant chemotherapy with S1. The primary study endpoint is resection rate for phase Ⅱ and overall survival for phase Ⅲ. This study plans to have 40 patients in each arm of the phase Ⅱ part, and moves on to phase Ⅲ if there are no more than 14 cases of non-resection in each arm of phase Ⅱ study. S-1 is an oral fluorinated pyrimidine, containing tegafur, 5-chloro-2,4-dihydroxypyridine and potassium oxonate at a molar ratio of 1:0.4:1[36]. Tegafur is a pro-drug of 5-fluorouracil, and S1 has been shown to deliver higher 5-fluorouracil levels in the plasma and the tumor tissue. The safety and efficacy of combination chemotherapy with gemcitabine and S1 for resectable pancreatic cancer have been reported in pilot study[37].

The UVA-PC-PD101 study (NCT02305186; Safety and Immunological Effect of Pembrolizumab in Resectable or Borderline Resectable Pancreatic Cancer) is a phase Ⅰb/Ⅱ multicenter study in patients with resectable or borderline resectable pancreatic cancer. This study will randomize 56 subjects in 2:1 to the experimental arm with pembrolizumab given concurrently with chemoradiation or control arm receiving chemoradiation only. Patients in both arms will receive surgery and adjuvant chemotherapy with gemcitabine. The primary outcome measures are to determine the safety of neoadjuvant chemoradiation with capecitabine in combination with pembrolizumab, and to examine and compare the difference in the number of tumor infiltrating lymphocytes (TILs) in resected pancreatic tissue between experimental and control arms[38]. The investigators hypothesize chemoradiation recruits TILs to the microenvironment of pancreatic cancer causing overexpression of programmed death-ligand 1 (PD-L1). PD-L1 binds to PD-1 on T-cells, and suppress cytotoxic T-cells. Pembrolizumab is a monoclonal antibody that targets the PD-1, and release the inhibition on cytotoxic T-cells. Therefore, it is expected that there are more immune effects at tumor tissues in the experimental arm than control arm. It will be interesting to see if this will

translate into improved clinical outcome.

## BIOMARKERS IN RESECTABLE PANCREATIC CANCER

At this time there are no validated biomarkers for early pancreatic cancer. Carbohydrate antigen 19-9 (CA-19-9) is currently used as a marker for following patients during treatment for pancreatic cancer but it is non-specific and can be positive in other conditions such as cirrhosis of the liver, pancreatitis, cholangitis, and other GI cancers. Presence of circulating tumor cells in the peripheral blood has been found to be a negative prognostic factor in pancreatic cancer and potentially may have a role in patient selection for neoadjuvant treatment[39].

Whole exome sequencing in pancreatic cancer demonstrated four frequently mutated genes: *KRAS*, *TP53*, *CDKN2a/p16*, and *SMAD4/DPC4*. KRAS was found to be mutated in virtually all pancreatic cancer patients but genetic alterations in the other three genes were found to be associated with malignant behavior and may be a prognostic tool[40]. The inflammatory markers ferritin and C-reactive protein (CRP) have also been studied for prognostic and predictive value in advanced pancreatic cancer. The study demonstrated that patients with elevation in both biomarkers had a notable decrease in overall survival, and can possibly be a clinically useful tool[41].

The expression of E-cadherin, a calcium-dependent adhesion molecule, is frequently suppressed or lost during EMT of solid tumor malignancy including non-small cell lung and pancreatic cancers, which renders invasiveness and drug resistance[42,43]. Several retrospective studies in pancreatic cancer have shown poorer clinical outcome with decreased expression of E-cadherin[44-46]. Furthermore, E-cadherin interacts with EGFR, and down-regulation of E-cadherin contributes to decreased response and survival in patients receiving EGFR inhibitors for non-small cell lung cancer[47,48]. Ko *et al*[49] have recently reported the result of a phase Ⅱ study with combined inhibitors of EGFR, and MEK which is a key downstream effector of EGFR signaling, in advanced pancreatic cancer. They have found patients with tumors exhibiting an epithelial phenotype (demonstrated by high level of E-cadherin expression) were more likely to be sensitive to study treatment. The planned correlative investigation of ACOSOG Z5041 (NCT00733746), a completed perioperative phase Ⅱ study of gemcitabine and erlotinib for resectable pancreatic cancer, will provide further information on the interaction between EMT marker status and overall/progression-free survival after treatment.

Gemcitabine is a prodrug that is taken into cells *via* a nucleoside transporter[50]. The human equilibrative nucleoside transporter 1 (hENT1) has been studied as a predictive marker for treatment response, and there is data that hENT1 expression may correlate with response to gemcitabine[51-53]. These findings were not able to be validated in the metastatic setting in the LEAP trial[54].

The PD-1 is encoded by the *PDCD1* gene. It is primarily expressed by activated T-cells as negative co-stimulatory receptor; binding of PD-1 to its ligands, PD-L1 and PD-L2, downregulates T-cells and the immune system[55,56]. Many tumor cells express PD-L1 and PD-L2 which is a mechanism which allows escape from immune destruction of the tumor cells. Pembrolizumab is an anti-PD-1 antibody that is approved for use in metastatic melanoma and metastatic non-small cell lung cancer and is currently under study for other malignancies, and PD-L1 expression may be a potential marker for efficacy of anti-PD-1 studies for pancreatic cancer.

Elevated CRP levels in the plasma, a well-established marker of inflammation, at diagnosis correlate with higher tumor stage and grading and poorer clinical outcome in pancreatic cancer[57]. Patients with CRP greater than 13 mg/L had improved survival with ruxolitinib and capecitabine compared to capecitabine and placebo in a randomized phase Ⅱ study also known as the RECAP study enrolling 127 patients with metastatic pancreatic cancer (median overall survival of 83 d *vs* 55 d, $P = 0.01$)[58]. The CRP level could be a useful marker for patient stratification in the management of pancreatic cancer, and the JAK inhibitor ruxolitinib may improve clinical outcome in patients with elevated CRP. An ongoing phase Ⅲ study, known as JANUS 2, is examining these promising leads as a second-line setting in patients with advanced pancreatic cancer[59].

There is high prevalence of BRCA1/2 mutations in Ashkenazi Jewish with pancreatic cancer[60]. The *BRCA1* and *BRCA2* gene encodes large proteins that coordinate the homologous recombination repair double strand breaks (DSBs) pathway. Poly ADP-ribose polymerases (PARP) are a family of nuclear enzymes that regulates the repair of DNA single-strand breaks through the base-excision repair (BER) pathway. Since BRCA1/2-mutated tumors cannot utilize homologous recombination to repair DSBs, exposing these cells to PARP inhibitor, which shuts down BER rescue pathway, will lead to accumulation of DNA damage, genomic instability and cell death, also known as synthetic lethality[61]. Investigators from Memorial Sloan-Kettering Cancer Center have reported high response rate with combination of gemcitabine, cisplatin and veliparib, a PARP inhibitor, as first-line treatment in patients with andvanced pancreatic cancer and mutant BRCA[62]. Ongoing phase Ⅱ randomized study comparing gemcitabine and cisplatin with and without veliparib is currently underway (NCT01585805). This study will most likely provide us the information on using BRAC mutation as a biomarker for personalized treatment.

## CONCLUSION

The need for more effective treatment regimens for resectable pancreatic cancer is highlighted by the

continued relatively low survival even in patients who receive surgical resection. Several studies utilizing more active chemotherapy regimens are pending results, and additional studies are ongoing. There also remains the need for accurate and cost-effective biomarkers to aid in the management of pancreatic cancer.

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