Adjuvant Treatment of Surgically Resectable Pancreatic Ductal Adenocarcinoma

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Abstract: Pancreatic ductal adenocarcinoma (PDAC) is the third-leading cause of cancer-related mortality in the United States. Surgical resection of early and localized disease provides the only chance for a cure; however, the majority of patients who have PDAC present with advanced disease that cannot be removed surgically. In the minority of patients who undergo surgical resection, there is a high rate of disease recurrence that eventually leads to death. The use of systemic therapy improves the outcome of patients who undergo surgery by targeting early micrometastatic disease. This review focuses on the medical management (both chemotherapy and radiation therapy) of surgically resectable pancreatic cancer, including the findings of recent practice-changing clinical trials that favor combination chemotherapy for adjuvant treatment and neoadjuvant chemoradiation therapy. The review also highlights important ongoing trials that aim to improve outcomes in patients with resectable pancreatic cancer.

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is the major form of cancer that arises in the pancreas, accounting for more than 90% of cases. An estimated 55,440 new cases of PDAC were diagnosed in the United States in 2018, causing 44,330 deaths.[1] Worldwide, PDAC is the 12th-most-common cancer, with approximately 458,918 new cases diagnosed in 2018. The highest incidence is reported in North America and Europe. An estimated 432,242 deaths from PDAC occurred globally in 2018.[2] In the United States, PDAC is currently the third-leading cause of cancer-related mortality and is projected to become the second-leading cause of cancer mortality by 2020.[1,3] The 5-year overall survival (OS) rate of patients with PDAC in the United States was 3% in the period from 1975 to 1977, which marginally improved to 9% in the period from 2007 to 2013.[4]

Surgical Treatment of Pancreatic Ductal Adenocarcinoma

Surgical resection with negative margins is the only treatment option that has the potential to cure PDAC. In the absence of a formal

Table 1. Consensus Criteria for Surgical Resectability in Nonmetastatic PDAC

Vasculature Involved	Resectable PDAC	Borderline-Resectable PDAC	Unresectable PDAC
SMA	No involvement	<180°	>180°
Celiac trunk	No involvement	<180°	>180°
CHA	No involvement	Reconstructible	Unreconstructible
PV	<180°	>180° or reconstructible	Unreconstructible
SMV	<180°		
Aorta	No involvement	No involvement	Involvement
Resection rate	Frequent	>50%	<5%

CHA, common hepatic artery; PDAC, pancreatic ductal adenocarcinoma; PV, portal vein; SMA, superior mesenteric artery; SMV, superior mesenteric vein.

Sources: Katz MH et al. *Ann Surg Oncol*. 2013;20(8):2787-2795; Al-Hawary MM et al. *Radiology*. 2014;270(1):248-260.[9,10]

screening strategy and without clinical symptoms or signs leading to early detection, fewer than 20% of patients present with disease that can be treated surgically up front.[5,6] The Whipple procedure (pancreaticoduodenectomy) is performed for tumors in the head or neck of the pancreas, which account for 60% to 70% of all PDACs,[7] whereas distal pancreatectomy is done for tumors in the body or tail of the pancreas.

In nonmetastatic disease, resectability is assessed by triple-phase contrast-enhanced computed tomography or magnetic resonance imaging to evaluate the anatomic relationship of the tumor to nearby vasculature.[8] Table 1 summarizes the consensus radiologic criteria for surgical resectability in nonmetastatic PDAC.[9,10] In most patients treated with surgical resection, disease recurs after surgery, with the worst outcomes seen in patients who have positive margins or lymph node metastases.[11-15] A small number of patients present with borderline-resectable disease. With no single widely accepted definition, the term *borderline-resectable PDAC* denotes disease in which the likelihood of a microscopically margin-positive (R1) resection is significant. This category has been the focus of research on neoadjuvant chemotherapy and radiation therapy.

Given the high frequency of disease recurrence following surgical resection of PDAC, multiple studies have shown the benefit of adjuvant medical treatment, which is discussed below. Guidelines from both the American Society of Clinical Oncology (ASCO) and the European Society for Medical Oncology strongly recommend adjuvant chemotherapy following surgery for all patients who did not receive preoperative chemotherapy, including those with T1N0 disease. ASCO recommends that adjuvant treatment begin within 8 weeks of surgery and that chemotherapy last for 6 months.[8,16,17] However, the optimal timing, duration, regimen, and strategy (chemotherapy vs radiation therapy) have not been well established, partly because of evolving standards of regimens.

Postsurgical Treatment for Pancreatic Ductal Adenocarcinoma

Adjuvant Chemotherapy Regimens

In the pivotal phase 3 CONKO-001 (Charité Onkologie 001) trial of adjuvant chemotherapy with gemcitabine, 368 patients who had PDAC were randomly assigned either to gemcitabine (1000 mg/m^2 intravenously [IV] on days 1, 8, and 15 every 28 days for 6 months) or to observation following surgical resection. Median disease-free survival (DFS) was significantly longer with gemcitabine than with observation alone (13.4 vs 6.7 months; P<.001). Median OS also was significantly better with gemcitabine than with observation alone (22.8 vs 20.2 months; P=.01)[18,19] As a result, gemcitabine became the standard of care for the adjuvant treatment of resected PDAC and was generally well-tolerated by treated patients.

The third trial from the European Study Group for Pancreatic Cancer (ESPAC-3) was a phase 3 trial that was published in 2010. Researchers randomly assigned 1088 patients either to 6 months of adjuvant gemcitabine at 1000 mg/m^2 once a week for 3 of every 4 weeks or to 6 months of adjuvant 5-fluorouracil (5-FU) plus leucovorin (5-FU given as a 425-mg/m^2 IV bolus; leucovorin given as a 20-mg/m^2 IV bolus) on days 1 to 5 every 28 days. Median OS times were similar in the 2 study arms: 23.6 months with gemcitabine vs 23.0 months with 5-FU. However, the incidence of grade 3/4 gastrointestinal adverse events was slightly higher in the 5-FU arm.[20] Adjuvant chemotherapy with gemcitabine and adjuvant chemotherapy with 5-FU were both recommended by the National Comprehensive Cancer Network with a category 1 level of evidence.[21]

ESPAC-4, reported in 2017, randomly assigned 732 patients with resected PDAC to receive adjuvant gemcitabine alone (1000 mg/m^2 once a week for 3 of every 4 weeks) or in combination with capecitabine

(830 mg/m^2 orally twice daily on days 1-21 of a 28-day cycle) for 6 cycles. Median OS with the combination was superior to median OS with gemcitabine alone (28.0 vs 22.5 months; hazard ratio [HR], 0.82; 95% CI, 0.68-0.98; *P*=.032). The 5-year OS rate also was higher in the combination arm than in the gemcitabine-alone arm (28.8% vs 16.3%). The benefit from the combination treatment was seen in patients with microscopically margin-negative (R0) resections (median OS, 39.5 vs 27.9 months; *P*<.001) vs those with R1 resections (23.7 vs 23.0 months; *P*>.05). Although the rates of collective grade 3/4 adverse events were similar in the 2 arms, slightly higher rates of grade 3/4 diarrhea (5% vs 2%; *P*=.008), neutropenia (38% vs 24%; *P*<.001), and hand-foot syndrome (7% vs 0%; *P*<.001) were seen in the combination arm. On the basis of this study, the combination of gemcitabine and capecitabine for 6 months became a newer standard of adjuvant chemotherapy.[22]

The phase 3 JASPAC 01 study (Japan Adjuvant Study Group of Pancreatic Cancer), which was reported in 2016, randomly assigned 385 patients to receive 6 months of either gemcitabine at 1000 mg/m^2 on days 1, 8, and 15 every 4 weeks or S-1 (40-60 mg on the basis of body surface area orally twice daily, 4 weeks on and 2 weeks off). Median OS was significantly longer in the patients treated with S-1 than in those treated with gemcitabine (46.5 vs 25.5 months; HR, 0.57; 95% CI, 0.44-0.72; *P*<.0001). The frequency of grade 3/4 leukopenia, neutropenia, and transaminase elevations was higher with gemcitabine than with S-1. Given the ethnic homogeneity of the study population (Japanese), it is difficult to conclude that S-1 is universally superior to gemcitabine.[23]

Most recently and on the basis of a prior smaller pilot study,[24] the phase 3 PRODIGE 24 study (Trial Comparing Adjuvant Chemotherapy With Gemcitabine Versus mFOLFIRINOX to Treat Resected Pancreatic Adenocarcinoma) compared modified leucovorin, 5-FU, irinotecan, and oxaliplatin (mFOLFIRINOX) vs single-agent gemcitabine in the treatment of PDAC after surgical resection. A total of 493 patients with good performance status were randomly assigned either to 6 months of gemcitabine alone (28-day cycles of gemcitabine at 1000 mg/m^2 on days 1, 8, and 15) or to mFOLFIRINOX (oxaliplatin at 85 mg/m^2 IV, leucovorin at 400 mg/m^2 IV, irinotecan at 150 mg/m^2 after initial dose of 180 mg/m^2, and 5-FU at 2400 mg/m^2 IV over 46 hours) given every 2 weeks. Preliminary results reported at the 2018 American Society of Clinical Oncology (ASCO) annual meeting showed that at a median follow-up of 30.5 months, the primary endpoint of median DFS was nearly doubled with mFOLFIRINOX (21.6 vs 12.8 months; HR, 0.59; 95% CI, 0.47-0.74), and a major improvement in median OS (54.4 vs 34.8 months, HR, 0.66; 95% CI, 0.49-0.89) was noted. More grade 3/4 adverse events occurred with mFOLFIRINOX than with gemcitabine, including diarrhea (19% vs 4%), sensory neuropathy (9% vs 0%), fatigue (11% vs 5%), and vomiting (5% vs 1%).[25]

Given the superior survival outcomes with combination chemotherapy vs single-agent chemotherapy, combination chemotherapy (mFOLFIRINOX or gemcitabine plus capecitabine) is now the new standard of care for the adjuvant treatment of PDAC. In patients with a favorable performance status, who recover well from their surgery, the magnitude of benefit may favor the use of mFOLFIRINOX. However, because no study has compared mFOLFIRINOX vs the combination of gemcitabine and capecitabine, it is difficult to determine which regimen is better than the other, and it should be kept in mind that patient selection partly explains the apparent superior outcome with mFOLFIRINOX. Drawing from the toxicity profiles of these regimens, it is likely that the 2-drug regimen of gemcitabine and capecitabine is better tolerated by patients with less favorable performance status and/or with comorbidities, such as pre-existing neuropathy, or even by older patients. The authors would prefer to use mFOLFIRINOX in patients with favorable performance status and a minimal comorbidity profile. In contrast, in patients with borderline performance status or an unfavorable medical profile that makes combination chemotherapy difficult, single-agent treatment with gemcitabine or a fluoropyrimidine for 6 months would be a reasonable option. Table 2 summarizes the landmark trials that defined the adjuvant chemotherapy regimens for PDAC. The findings of practice-changing clinical trials of adjuvant chemotherapy are summarized in the Figure.

Adjuvant Chemoradiation Therapy

The legacy of the original Gastrointestinal Tumor Study Group (GITSG) trials and the patterns of locoregional recurrence after resection pushed the argument for the use of adjuvant chemoradiation therapy. The morbidity of local recurrence is of major concern. Local recurrence in the surgical bed has been reported in autopsy series of patients with stage I or II PDAC, with only local recurrence in 15% of patients and both local and systemic recurrence in approximately 65% of patients.[26] Additionally, the rate of only local recurrence at first disease progression in patients enrolled in the Multidisciplinary Oncology Cooperative Group (GERCOR) postoperative trial of gemcitabine alone vs gemcitabine-based chemoradiotherapy was significantly lower in the chemoradiotherapy arm than in the chemotherapy-alone arm (11% vs 24%).[27]

Although a clear survival benefit from the use of adjuvant chemotherapy has been shown, as discussed above, an unequivocal survival benefit from the addition

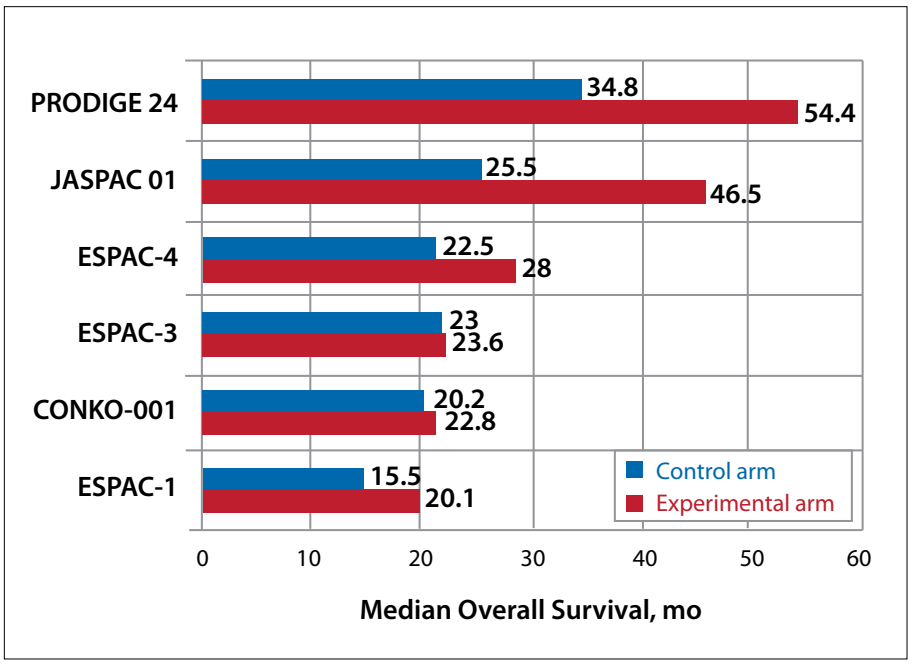

Figure. Best median overall survival outcomes in adjuvant chemotherapy–based trials for pancreatic ductal adenocarcinoma.

Sources: Oettle H et al. *JAMA*. 2013;310(14):1473-1481; Oettle H et al. *JAMA*. 2007;297(3):267-277; Neoptolemos JP et al. *JAMA*. 2010;304(10):1073-1081; Neoptolemos JP et al. *Lancet*. 2017;389(10073):1011-1024; Uesaka K et al. *Lancet*. 2016;388(10041):248-257; Conroy T et al. ASCO abstract LBA4001; *J Clin Oncol*. 2018;36(18)(suppl); Neoptolemos JP et al. *N Engl J Med*. 2004;350(12):1200-1210.[18-20,22,23,25,31]

of radiation therapy to the adjuvant treatment of PDAC has not yet been seen. A regional pattern of use remains, with chemoradiation used more often in the United States than in Europe. Below, we review the pivotal studies that explored the role of adjuvant chemoradiation in resected PDAC.

The GITSG trial reported in 1985 randomly assigned 43 patients with resected PDAC to observation or to external beam radiotherapy (total of 40 Gy) with concurrent bolus 5-FU (500 mg/m^2 per day on the first 3 and last 3 days of radiotherapy) followed by maintenance 5-FU at 500 mg/m^2 per day for 3 days monthly for 2 years or until disease recurrence. The study was closed early owing to poor accrual. Despite the low dose of radiation compared with today's standards, the median OS was 20 months for patients in the treatment arm vs 11 months for those in the observation arm (P=.03). Only 14% of the treated patients had grade 3 leukopenia, and otherwise the treatment was well tolerated.[28] Enrollment of an additional 30 patients yielded a comparable median OS of 18 months.[29] On the basis of subsequent studies, discussed below, it is likely that the major benefit seen in DFS and OS was a consequence of the use of systemic therapy rather than of the radiation treatment itself.

The phase 3 European Organisation for Research and Treatment of Cancer (EORTC) study reported in 1999 randomly assigned 114 patients with resected pancreatic cancer to postoperative concurrent 5-FU (25 mg/kg per day by continuous infusion) plus external beam radiotherapy (40 Gy in split courses) or to observation. Contrary to the findings of the GITSG study, no significant improvement in survival was noted for chemoradiotherapy (2-year survival, 26% vs 34%; P=.099). Additionally, the locoregional recurrence rates in the 2 arms did not differ.[30]

The 2004 phase 3 ESPAC-1 trial used a 2 × 2 factorial design and randomly assigned 289 patients with resected pancreatic cancer to one of 4 groups: adjuvant chemotherapy, chemoradiation, chemoradiation followed by chemotherapy, or observation. Additional randomization schemes were added to increase patient accrual, complicating the design of the study and its interpretation. Chemoradiation consisted of concurrent 20-Gy external beam radiation therapy administered in 10 daily fractions over 2 weeks and bolus 5-FU (500 mg/m^2 IV on days 1-3), repeated after a 2-week break. In the chemotherapy arm, patients received leucovorin at 20 mg/m^2 IV followed by bolus 5-FU at 425 mg/m^2 IV on days 1-5 every 28 days for 6 months. In an intention-to-treat analysis, survival outcome was better in the patients who received postoperative chemotherapy alone than in those who did not receive chemotherapy (median OS, 20.1 vs 15.5 months; P=.009). The survival outcome of the patients who received chemoradiation was numerically worse, although the difference was not statistically significant, than that of the patients who did not receive chemoradiation (median OS, 15.9 vs 17.9 months; P=.05). When the arms were compared, median OS was best in the chemotherapy-alone arm (21.6 months), second-best with chemoradiation followed by chemotherapy (19.9 months), third-best with observation (16.9 months), and fourth-best with chemoradiation alone (13.9 months).[31] The study was criticized for multiple reasons, such as the

Table 2. Summary of Landmark Trials for Adjuvant Chemotherapy in PDAC

Study (Year)	Patients, No.	Experimental Arm vs Control Arm	R0 Resection Rate, %	Median DFS, mo	Median OS, mo	Primary Endpoint
ESPAC-1 (2004)[31]	289	5-FU vs observation	82	–	21.6	OS
CONKO-001 (2007)[18,19]	368	Gemcitabine vs observation	83	13.4	22.8	DFS
RTOG 9704 (2008)[33]	451	Gemcitabine vs 5-FU before and after chemoradiation	42	11.4	20.5	OS
ESPAC-3 (2010)[20]	1088	Gemcitabine vs 5-FU	65	14.3	23.6	OS
ESPAC-4 (2017)[22]	732	Gemcitabine/capecitabine vs gemcitabine	40	13.9	28.0	OS
JASPAC 01 (2016)[23]	385	S-1 vs gemcitabine	87	22.9	46.5	OS
PRODIGE 24 (2018)[25]	493	mFOLFIRINOX vs gemcitabine	60	21.6	54.4	DFS

5-FU, 5-fluorouracil; DFS, disease-free survival; mFOLFIRINOX, modified leucovorin, 5-FU, irinotecan, and oxaliplatin; mo, months; OS, overall survival; PDAC, pancreatic ductal adenocarcinoma.

experimental design and suboptimal quality control. The interpretation of the results of this trial as indicating a negative effect of radiation therapy on survival influenced the standard of care, especially in European countries but also to some degree in the United States. However, the need for an answer to the radiation question in a better-controlled study led to the launch of the Radiation Therapy Oncology Group (RTOG) 0848 phase 3 trial, discussed below.

The phase 2 EORTC-40013 study investigated the relative benefits of adding chemoradiotherapy to systemic chemotherapy. A total of 90 patients with resected pancreatic cancer were randomly assigned to systemic chemotherapy (2 cycles of gemcitabine at 1000 mg/m^2 weekly for 3 of 4 weeks) followed by chemoradiotherapy (weekly gemcitabine at 300 mg/m^2, 50.4 Gy of radiotherapy in 28 daily fractions of 1.8 Gy) or to 4 cycles of gemcitabine alone (1000 mg/m^2 weekly for 3 of 4 weeks in a 4-week cycle). The addition of chemoradiation to adjuvant chemotherapy was not deleterious, with comparable median OS times in the 2 arms (24 months). Although the rates of local recurrence appeared to be lower in the chemoradiation arm, the rates of systemic recurrence were similar in the 2 arms.[27]

An open-label phase 3 trial of adjuvant concurrent chemoradiation vs adjuvant 5-FU, reported in 2012, showed no difference in survival between adjuvant chemoradiation and 5-FU chemotherapy. In the chemoradiation arm, patients received a total dose of external beam radiation of 50.4 Gy; this was combined with a concurrent infusion of 5-FU at 200 mg/m^2 IV daily, cisplatin at 30 mg/m^2 IV per week, and 3 million units of interferon alfa-2b 3 times weekly, followed by 2 cycles of daily 5-FU. The chemotherapy-only arm received bolus leucovorin at 20 mg/m^2 IV and 5-FU at 425 mg/m^2 IV on days 1-5 every 28 days for 6 cycles.[32]

The phase 3 RTOG 9704 study (A Phase III Study of Pre and Post Chemoradiation 5-FU vs. Pre and Post Chemoradiation Gemcitabine for Postoperative Adjuvant Treatment of Resected Pancreatic Adenocarcinoma), which was completed in 2008, randomly assigned 451 patients in a 1:1 ratio to infusional 5-FU or to gemcitabine for 3 weeks before and 12 weeks after chemoradiation (50.4 Gy with a daily concurrent infusion of 5-FU at 250 mg/m^2 IV). No differences in DFS and OS were found between the 2 arms of the study. This trial does not answer the question of how much benefit radiation therapy adds to systemic chemotherapy in patients who are treated surgically.[33]

A 2013 network meta-analysis of 9 published randomized trials (including ESPAC-1, ESPAC-3, RTOG 9704, EORTC-40891, JSAP-02, and CONKO-001) compared 6 different adjuvant strategies—observation alone, 5-FU alone, gemcitabine alone, chemoradiotherapy alone, chemoradiotherapy followed by 5-FU, and chemoradiotherapy followed by gemcitabine.

Compared with observation, the HRs for death after adjustment for lymph node involvement were 0.65 (95% CI, 0.49-0.84) for 5-FU and 0.59 (95% CI, 0.41-0.83) for gemcitabine. In contrast, survival was worse with chemoradiation than with 5-FU alone (HR, 1.69; 95% CI, 1.12-2.54) or gemcitabine alone (HR, 1.86; 95% CI, 1.04-3.23). The HR for death was 1.61 (95% CI, 0.11-19.85) with chemoradiation plus 5-FU vs 5-FU, and was 11.22 (95% CI, 0.12-687.5) with chemoradiation plus gemcitabine vs gemcitabine alone. The meta-analysis

showed clear benefit from adjuvant chemotherapy with 5-FU or gemcitabine for PDAC. Chemoradiation plus chemotherapy is less effective in prolonging survival and is more toxic than chemotherapy.[34]

A meta-analysis of 875 patients from 5 randomly assigned trials showed an OS benefit with chemotherapy overall, but chemoradiation was more effective in patients who had R1 resections.[35] A retrospective analysis of more than 6000 patients in the National Cancer Database revealed a median OS benefit of chemoradiation compared with chemotherapy alone, irrespective of resection margin status and nodal status (22.3 vs 20.0 months; $P<.001$). On subgroup analysis, patients with R1 resections and nodal involvement derived more benefit than did those with R0 resections and no nodal involvement.[36]

The studies discussed above show that the effect of adding chemoradiation to adjuvant chemotherapy with a single agent (5-FU or gemcitabine) is neutral at best and may even be harmful in unselected patients. However, in the patients with R1 resections and nodal involvement, the addition of chemoradiation could offer some benefit. The phase 3 RTOG 0848 trial of 950 patients with resected PDAC (pancreatic head only) and no progression of disease after 5 months of adjuvant chemotherapy is randomly assigning patients in a 1:1 ratio to 1 more cycle of chemotherapy or to 1 more cycle of chemotherapy plus chemoradiation with either 5-FU or capecitabine (NCT01013649). Upon completion, the results of this trial may shed light on the additional benefit of adjuvant chemoradiation following chemotherapy. Table 3 summarizes key ongoing trials for surgically treatable PDAC.

Perioperative Treatment for Potentially Surgically Resectable PDAC

The concept of neoadjuvant or perioperative therapy for patients with localized and especially resectable pancreatic cancer has gained momentum in recent years. Although there is enough consensus to support its use in borderline-resectable disease, full agreement on its use in resectable PDAC has not be reached. Despite an absence of trials to support the superiority of neoadjuvant or perioperative treatment, especially in terms of OS, perioperative therapy is being used increasingly for patients with resectable PDAC, especially in high-volume institutions. Proponents of neoadjuvant therapy base their argument on 3 advantages: (1) delivering effective systemic therapy to treat micrometastatic disease early and without the constraints of delaying such therapy and/or limiting its delivery in sufficient dose intensity and duration in the face of unpredictable postoperative recovery; (2) downsizing the disease to facilitate R0 resection; and (3) testing the tumor for biological behavior affecting the long-term benefit of radical surgery. At present, neoadjuvant therapy for patients with resectable disease should preferably be offered in the context of a prospective clinical trial.

The National Comprehensive Cancer Network recommends neoadjuvant therapy for patients with resectable PDAC in the presence of high-risk features, such as highly elevated CA19-9 levels, large primary tumors, large regional nodes, and severe disease-related symptoms.[21] ASCO guidelines recommend neoadjuvant chemotherapy for patients with resectable PDAC who cannot undergo surgery up front owing to reversible comorbid conditions.[8]

Evidence for Perioperative Chemotherapy

No prospective phase 3 randomized trial has compared perioperative therapy with traditional postoperative adjuvant treatment in patients who have resectable pancreatic cancer. A randomized phase 2 trial assigned 88 patients to adjuvant treatment with 6 months of gemcitabine; adjuvant treatment with a combination of cisplatin, epirubicin, gemcitabine, and capecitabine; or perioperative chemotherapy with the same combination regimen. DFS and the R0 resection rate with perioperative treatment were superior to those with the 2 adjuvant regimens. This study highlights the feasibility and efficacy of such an approach vs traditional adjuvant treatment.[37]

In another small pilot study of 21 patients who had resectable disease treated with neoadjuvant leucovorin, 5-FU, irinotecan, and oxaliplatin (FOLFIRINOX), 76% of the patients had R0 resections.[38] In the 2016 single-arm, phase 2 AGITG GAP study (A Phase II Study of Perioperative Nab-Paclitaxel and Gemcitabine for Resectable Pancreatic Ductal Adenocarcinoma), 42 patients received 2 cycles of neoadjuvant therapy and 4 cycles of adjuvant therapy consisting of gemcitabine plus nab-paclitaxel (Abraxane, Celgene). A total of 38% of patients had R0 resections, and their median recurrence-free survival was 17.7 months.[39]

A retrospective analysis of a prospectively maintained database of patients with PDAC was published in 2017.[40] Following multidisciplinary tumor board discussion, the patients with resectable or borderline-resectable disease were offered neoadjuvant chemotherapy followed by chemoradiation to a total dose of 50.4 Gy. A total of 85 patients were analyzed, of whom 76.5% were treated with FOLFIRINOX and 23.5% with gemcitabine/capecitabine. After systemic chemotherapy, only 20% had surgical resection and 39% had further disease progression. The remaining 41% (35 patients) received further treatment with concurrent chemoradiation therapy; of these, 51% had disease progression and 49% underwent surgery. Although retrospective, this study highlights the low success rate of disease downstaging in PDAC with

Table 3. Summary of Key Ongoing Trials for PDAC

Trial	Patients, No.	Phase	Regimens	Strategy Tested	Primary Outcome	Identifier
NEOPAC	310	3	Neoadjuvant gemcitabine/oxaliplatin and adjuvant gemcitabine or adjuvant gemcitabine	Neoadjuvant and adjuvant vs adjuvant	PFS	NCT01521702
NEONAX	162	2	Neoadjuvant (2) and adjuvant (4) gemcitabine/nab-paclitaxel vs adjuvant gemcitabine/nab-paclitaxel (6)	Neoadjuvant vs adjuvant combination chemotherapy	18-mo DFS	NCT02047513
Prep-02/JSAP-05	280	2/3	Neoadjuvant gemcitabine/S-1 and adjuvant S-1 vs adjuvant S-1	Neoadjuvant vs adjuvant combination chemotherapy	OS	UMIN000009634
NEPAFOX	126	2/3	Neoadjuvant (6) and adjuvant (6) FOLFIRINOX vs adjuvant gemcitabine	Perioperative chemotherapy regimens	OS	NCT02172976
SWOG S1505	112	2	Split neoadjuvant and adjuvant gemcitabine/nab-paclitaxel vs split neoadjuvant and adjuvant mFOLFIRINOX	Perioperative gemcitabine/nab-paclitaxel vs mFOLFIRINOX regimens	OS	NCT02562716
APACT	800	3	Gemcitabine/nab-paclitaxel vs gemcitabine	Adjuvant chemotherapy option	DFS	NCT01964430
GIP-2	310	3	FOLFOXIRI vs gemcitabine	Adjuvant chemotherapy option	DFS	NCT02355119
RTOG 0848	950	3	Chemotherapy (gemcitabine, mFOLFIRINOX, or gemcitabine-based combo) with or without chemoradiation	Adjuvant chemotherapy with/out adjuvant chemoradiation therapy	OS	NCT01013649

5-FU, 5-fluorouracil; DFS, disease-free survival; FOLFIRINOX, leucovorin, 5-FU, irinotecan, and oxaliplatin; FOLFOXIRI, leucovorin, 5-FU, oxaliplatin, and irinotecan; mFOLFIRINOX, modified leucovorin, 5-FU, irinotecan, and oxaliplatin; IMRT, intensity-modulated radiation therapy; mo, month; OS, overall survival; PDAC, pancreatic ductal adenocarcinoma; PFS, progression-free survival; RT, radiation therapy; XRT, external radiation therapy; y, year.

chemotherapy alone, which was improved with the addition of chemoradiation therapy.

Maintenance Therapy After Completion of Perioperative Chemotherapy

A significant number of patients will have disease relapse despite surgical resection and additional medical treatment, a problem that highlights the need for more effective treatment. There is evidence to suggest that PDAC is a systemic disease even if it is radiographically localized.[41] This has led to the hypothesis that maintenance treatment could provide additional benefit to patients who have undergone surgery and completed their adjuvant treatment. The patients treated in the GITSG study received chemotherapy with a maintenance approach in which bolus 5-FU was continued for up to 2 years.[28] In a retrospective analysis, maintenance capecitabine in patients who had completed prescribed adjuvant gemcitabine after surgical resection was shown to improve OS compared with no maintenance capecitabine (median OS, >48 vs 22 months; P<.001).[42] It is unclear whether maintenance chemotherapy provides any additional benefit, especially following the more effective combination chemotherapy regimens. A prospective study of maintenance chemotherapy, especially following a more modern combination adjuvant chemotherapy regimen, could help shed light on this question.

Benefit of Preoperative Chemoradiation Therapy

Retrospective population-based studies had shown possible benefit from neoadjuvant radiation therapy in patients with resectable PDAC.[43,44] The recently completed phase 3

PREOPANC-1 study (Preoperative Chemoradiotherapy Versus Immediate Surgery for Resectable and Borderline Resectable Pancreatic Cancer) provides the strongest evidence to support the neoadjuvant use of chemoradiation therapy in patients with resectable or borderline-resectable PDAC within the context of gemcitabine-based adjuvant treatment. Nearly half of the patients had resectable PDAC. A total of 246 patients were randomly assigned to immediate surgery or to preoperative chemoradiotherapy, both followed by adjuvant gemcitabine chemotherapy. Preoperative chemoradiotherapy (2.4 Gy × 15) was given with gemcitabine at 1000 mg/m^2 on days 1, 8, and 15 and was preceded and followed by a cycle of gemcitabine. The researchers found that median OS was significantly better in the preoperative treatment arm than in the immediate-surgery arm (17.1 vs 13.5 months; HR, 0.71; *P*=.047). In addition, the R0 resection rate was better in the preoperative treatment arm than in the up-front surgery arm (65% vs 31%; *P*<.001).[45]

Various smaller studies have shown that neoadjuvant gemcitabine, alone or in combination with a platinum agent, chemoradiation, or adjuvant gemcitabine, results in R0 resection rates ranging from 36% to 64%.[46-49]

Ongoing Studies for the Perioperative Treatment of PDAC

Multiple studies of the optimal medical treatment of surgically resectable PDAC are evaluating various regimens, the sequencing of chemotherapy and chemoradiation therapy, and the timing of such interventions in relation to surgical treatment. Several important studies are highlighted below. The results of these trials will likely shape the medical treatment of patients with surgically treated PDAC.

The NEOPA trial (Neoadjuvant Treatment in Resected Pancreatic Cancer), which planned to enroll 410 patients to study the role of neoadjuvant gemcitabine and chemoradiation therapy in addition to surgery and adjuvant gemcitabine in resectable PDAC, was closed owing to recruitment failure (NCT01900327).

The NEOPAC trial (Neoadjuvant Gemcitabine/Oxaliplatin Plus Adjuvant Gemcitabine in Resectable Pancreatic Cancer) has randomized 310 patients to study the role of neoadjuvant chemotherapy (gemcitabine/oxaliplatin) followed by adjuvant gemcitabine after surgery vs up-front surgery followed by adjuvant gemcitabine in resectable pancreatic head adenocarcinoma.[50] The phase 2/3 Prep-02/JSAP-05 trial (Randomized Phase II/III Trial of Neoadjuvant Chemotherapy With Gemcitabine and S-1 Versus Surgery-First for Resectable Pancreatic Cancer) has randomized 280 patients to study the neoadjuvant chemotherapy regimen of gemcitabine and S-1 followed by adjuvant S-1 after surgery vs up-front surgery followed by adjuvant S-1 in resectable PDAC.[51] In patients with resectable PDAC, preoperative FOLFIRINOX followed by postoperative FOLFIRINOX is being compared with up-front surgery followed by adjuvant gemcitabine in the NEPAFOX trial (Randomized Multicenter Phase II/III Study With Adjuvant Gemcitabine Versus Neoadjuvant/Adjuvant FOLFIRINOX for Resectable Pancreas Carcinoma).[52] The Southwest Oncology Group (SWOG) S1505 trial (A Randomized Phase II Study of Perioperative mFOLFIRINOX vs. Gemcitabine/Nab-Paclitaxel as Therapy for Resectable Pancreatic Adenocarcinoma)is comparing regimens for the perioperative treatment of resectable PDAC, given as 3 cycles of preoperative chemotherapy followed by 3 cycles of postoperative chemotherapy; 112 patients have been randomly assigned in a 1:1 ratio to mFOLFIRINOX or to gemcitabine plus nab-paclitaxel. The study is closed to accrual, and results are being awaited.[53] The ongoing NEONAX trial (Neoadjuvant Plus Adjuvant or Only Adjuvant Nab-Paclitaxel Plus Gemcitabine for Resectable Pancreatic Cancer) is studying the optimal way to give perioperative gemcitabine/nab-paclitaxel to patients with surgically resectable PDAC; patients have been randomized to receive chemotherapy for 2 cycles preoperatively followed by 4 cycles postoperatively or to total adjuvant treatment for 6 cycles.[54] Table 3 summarizes key ongoing trials for surgically treatable PDAC.

Conclusions

Although the medical management of surgically resectable PDAC has evolved over the years, PDAC continues to be a deadly disease, even after successful R0 resection. Combination chemotherapy regimens (mFOLFIRINOX or gemcitabine/capecitabine) have been shown to be more effective than single-agent chemotherapy in the adjuvant treatment of PDAC. Because the toxicity profiles of these combination regimens are higher than those of single-agent gemcitabine, they may be poorly tolerated by patients with marginal performance status, who may benefit from the single-agent approach. The role of chemoradiation therapy in the adjuvant treatment of PDAC is not yet a settled matter. It may help to reduce local recurrence rates in patients with higher-risk features, such as R1 resection or positive lymph nodes. Given the concern regarding the detrimental effects of radiation in the adjuvant setting, such treatment must be considered on a case-by-case basis following a multidisciplinary discussion. Neoadjuvant chemotherapy in patients with surgically resectable PDAC has not been well defined; ongoing studies are expected to help clarify its role. Neoadjuvant concurrent chemoradiation in surgically resectable PDAC has been shown to achieve higher R0 resection rates, and

the PREOPANC study found improved OS. No medical treatment for surgically resectable PDAC is tailored to the tumor molecular profile at this time.

Disclosures

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