Review Article

Neoadjuvant therapy in upfront resectable pancreatic cancer: current evidence and future considerations

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Abstract: Neoadjuvant therapy represents an increasingly recognized strategy in the management of radiographically resectable pancreatic cancer. The rationale behind neoadjuvant therapy includes the potential to increase the likelihood in achieving margin-negative resections, completing multimodality therapy, improving cost-effectiveness, and identifying poor candidates for surgery. In this review, we highlight current data from prospective clinical trials describing the feasibility and efficacy of neoadjuvant therapy in resectable pancreatic cancer. We end with a discussion on future considerations and unanswered questions important in establishing neoadjuvant therapy as part of the standard treatment paradigm for upfront resectable pancreatic cancer.

Keywords: Neoadjuvant; resectable; pancreatic; adenocarcinoma; gastrointestinal (GI)

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Introduction

Pancreatic cancer remains the fourth leading cause of cancer death in both men and women in the U.S. with a dismal 5-year survival rate of 8% across all stages (1). Pancreatic ductal adenocarcinoma (PDAC) comprises approximately 80% of all pancreatic cancers, and surgical resection remains the only potential cure for this lethal malignancy in the <20% of patients that present with resectable disease (2). The median survival is 17–27 months in those with resected pancreatic cancer and the current standard of care following surgery in this population is adjuvant chemotherapy or chemoradiation (3).

However, disease recurrence occurs in 66–92% of patients within 2 years of resection with local recurrence rates of 35–60% and systemic recurrence rates as high as 80–90% (3). Patients who undergo successful surgical resection with microscopically negative margins (R0) and node-negative disease have historically shared a more favorable prognosis than those with microscopically (R1) or macroscopically (R2) positive margins and node-positive disease (4). Accordingly, therapies that can optimize R0 resection rates, decrease local recurrence, and reduce systemic recurrence represent potential strategies to improve outcomes in the subset of pancreatic cancer patients with resectable disease that are most likely to survive.

Neoadjuvant or preoperative therapy has recently been the subject of growing clinical investigation in the treatment paradigm of upfront resectable pancreatic cancer. In this review, we highlight recent findings from prospective clinical trials investigating the efficacy of neoadjuvant therapy in radiographically resectable pancreatic cancer. We provide a critical appraisal of the current state of neoadjuvant therapy in the management of initially

Table 1 Phase I clinical trials investigating neoadjuvant therapy in resectable pancreatic cancer

Study design, n; year	Regimen	Resection rate (%)	Response (%)	Median OS (mo)	Ref.
Phase I, 44; 2007	Chemo: gemcitabine 1 g/m^2 + oxaliplatin 40, 55, 70, or 85 mg/m^2 IV RT: 27 Gy in 1.8 Gy fractions	NA	NA	NA	(5)
Phase I, 13; 2013	Chemo: S-1 ×14 consecutive with gemcitabine 1,000 mg/m^2: 20, 30 and 40 mg/day for levels 0, 1 and 2	100	18% partial response	NA	(6)
Phase I, 26; 2013	RT: 5% incremental increase from 30 to 36.8 Gy	81	4% partial response	1-, 3-, and 5-year OS: 81%, 52%, and 52% respectively	(7)
Phase I, 10 (target accrual 12); 2014	Chemo: Capecitabine 1,650 mg/m^2 once weekly ×2 doses RT: photon beam: dose level I: 3 Gy ×10; dose level 2: 5 Gy ×5 (every other day); dose level 3: 5 Gy ×5 (daily)	80	NA—study closed prematurely	NA—study closed prematurely	(8)

OS, overall survival; 5-FU, 5-fluorouracil; IV, intravenous; d, day; MMC, mitomycin C; RT, radiation therapy; Chemo, chemotherapy; Gy, gray; R0, negative margins; S-1, tegafur, gimeracil, oteracil; NA, not available.

resectable pancreatic cancer. We also discuss the potential advantages and disadvantages to a neoadjuvant or upfront surgery approach and review ongoing clinical trials seeking to provide further clarity on the utility of neoadjuvant therapy.

Search criteria

A literature search using the keywords "neoadjuvant" and "pancreatic cancer" was conducted through MEDLINE to include published studies up to March 10, 2018. The search returned a total of 1,368 hits. Limiting the search to clinical studies of prospective design, English language, and involving neoadjuvant therapy in resectable pancreatic cancer, a final 29 studies were included in this review (*Tables 1*,*2*).

Clinical trials of neoadjuvant therapy in resectable pancreatic cancer

Phase I trials

Preoperative therapy (primarily radiation therapy or RT-based modalities) in pancreatic cancer was first investigated more than 2 decades ago with the intent to improve rates of local control, resectability, and distant metastases (35,36). A phase I study enrolled 44 patients with 12 patients with resectable pancreatic adenocarcinoma to determine the dose-limiting toxicity (DLT) of biweekly oxaliplatin and gemcitabine with concurrent RT (5). Ten DLTs were observed including grade 3 platelet disorder (n=4), decline in functional status (n=2), gastrointestinal (GI) bleed (n=2), and GI toxicity (n=2). The study concluded that biweekly oxaliplatin 85 mg/m^2 with full-dose gemcitabine and concurrent RT is well tolerated. One phase I study involving 11 patients evaluated the DLTs and MTD of neoadjuvant gemcitabine plus oral S-1 in resectable pancreatic adenocarcinoma (6). The authors observed a 100% rate of resectability with 22% of patients demonstrating a partial response (PR). However, the treatment regimen was not well-tolerated due to grade ≥3 toxicities including liver dysfunction, neutropenia, and anorexia.

A separate phase I study involving 26 patients sought to determine the recommended dose of carbon-ion radiotherapy needed to reduce the risk of postoperative local recurrence in patients with resectable pancreatic adenocarcinoma (9). All patients completed the scheduled treatment course without treatment breaks, and no DLT was observed (*Table 1*). Another phase I study investigated the feasibility and tolerability of neoadjuvant short course radiotherapy (SC-CRT) delivered with photon RT concurrent with capecitabine in patients with resectable pancreatic adenocarcinoma (10). The intended accrual for the study was 12 patients; however, the study was closed prematurely due to unexpected intraoperative complications. Specifically, the main surgical complication

Table 2 Phase I/II clinical trials investigating neoadjuvant therapy in resectable pancreatic cancer

Study design, n; year	Regimen	Resection rate (%)	Response (%)	Median OS (mo)	Ref.
Phase II, 28; 1993	Chemo: 5-FU 300 mg/m^2 per day RT: 50.4 Gy in 1.8 Gy fractions	61%, 82% R0	No partial responses	NA	(9)
Phase II, 26; 1993	Chemo: 5-FU 1,000 mg/m^2 daily continuous IV ×4 (d2–5, 28–32) + MMC 10 mg/m^2 IV bolus (d2) RT: 50.4 Gy in 1.8 Gy fractions	38%, all R0	20% clinical response including duodenal carcinomas defined as ≥25% size reduction of sum of diameters	12	(10)
Phase II, 39; 1996	Chemo: 5-FU 300 mg/m^2 RT: 30.0 or 50.4 Gy; intraoperative EBRT 10 Gy	100%, 7 (18%) R1	NA	19	(11)
Phase II, 53; 1998	Chemo: MMC 10 mg/m^2 (d2) and 5-FU 1,000 mg/m^2/d continuous IV (d2–5, 29–32) RT: 50.4 Gy in 1.8 Gy fractions	45%, R0 45.8%	8% partial response	9.7 overall, 15.7 after resection	(12)
Phase II, 35; 1998	Chemo: 5-FU 300 mg/m^2 daily 5 days per week ×2 weeks RT: 30 Gy in 3 Gy fractions, EB-IORT with pancreaticoduodenectomy	57%, R0 90%	96% minor response	25	(13)
Phase II, 19; 2002	Chemo: 5-FU 650 mg/m^2 (d1–5 and d21–25) + Cisplatin 80 mg/m^2 d2 and 22 RT: 30 Gy split course RT or 45 Gy standard fractionation RT	79%, 3/15 (20%) R1	37% partial response	20	(14)
Phase II, 35; 2002	Chemo: Paclitaxel 60 mg/m^2 weekly ×3 weeks RT: 30 Gy in 3 Gy fractions, EB-IORT with pancreatectomy	57%, 68% R0	96% partial response	12	(15)
Phase I-II, 28; 2004	Chemo: gemcitabine, tested at 3 dose levels: 20, 50, and 100 mg/m^2 RT: 50.4 Gy in 1.8 Gy fractions	71%	NA	25	(16)
Phase II, 41; 2006	Chemo: 5-FU 300 mg/m^2 day ×5 weeks and cisplatin 20 mg/m^2 (d1–5 and d29–33) RT: 50 Gy in 2 Gy fractions	63%, R0 80%	10% partial response	9.4	(17)
Phase II, 20; 2006	Chemo: gemcitabine 1,000 mg/m^2 intravenously (d1, d8, and d15) RT: 36 Gy in daily 2.4-Gy fractions	85%, R0 94%	15% partial response	26	(18)
Phase II, 50; 2007	Arm 1 (n=24): gemcitabine 1,000 mg/m^2 every 7 days for 43 days Arm 2 (n=26): gemcitabine 1,000 mg/m^2 and cisplatin 25 mg/m^2 every 7 days for 43 days (omission on d22)	54%, 6/24 (25%) R1; 38% in arm 1 *vs.* 70% in arm 2	4% partial response from combined therapy	9.9 *vs.* 15.6	(19)
Phase II, 86; 2008	Chemo: Gemcitabine 400 mg/m^2 weekly RT: 30 Gy in 3 Gy fractions	74%, R0 89%	NA	22.7	(20)

Table 2 *(continued)*

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Study design, n; year	Regimen	Resection rate (%)	Response (%)	Median OS (mo)	Ref.
Phase II, 28; 2008	Chemo: Gemcitabine 1,000 mg/m^2 twice weekly + cisplatin 50 mg/m^2	89%, R0 80%	4% partial response	26.5	(21)
Phase II, 90; 2008	Gemcitabine 750 mg/m^2 and cisplatin 30 mg/m^2 ×2 weeks (4 doses) → gemcitabine 400 mg/m^2 + 30 Gy in 3 Gy fractions	58%, R0 96%	NA	17.4	(22)
Phase II, 41; 2009	Chemo: 5-FU 300 mg/m^2 day ×5 weeks and cisplatin 20 mg/m^2 (d1–5 and d29–33) RT: 50 Gy in 2 Gy fractions	63%, R0 80.7%	65% stable disease	9.4	(23)
Phase II, 101; 2009	Chemo: 5-FU 650 mg/m^2 (d1–5 and d21–25) and cisplatin 80 mg/m^2 (d2 and 22) RT: 45 Gy in 1.8 Gy fractions	61%, 20/61 (33%) R1	NA	17, 23 with resection	(24)
Phase II, 34; 2010	Chemo: Docetaxel 30 mg/m^2 weekly RT: 45 Gy in 25 fractions	50%, all R0	9% partial response	32	(25)
Phase II, 33; 2012	Chemo: Cetuximab load 400 mg/m^2 followed by cetuximab 250 mg/m^2 weekly + gemcitabine 50 mg/m^2 twice weekly RT: 54Gy	76%, 92% R0	30% partial response	24.3	(26)
Phase II, 68; 2013	Chemo: two 28-day cycles of gemcitabine (1 gm/m^2 on d1, 8, and 15) and oxaliplatin (85 mg/m^2 on d1 and 15) RT: 30 Gy in 2 Gy fractions	63%, 84% R0	7% partial response and 28% minor response (10–29% decrease in tumor longest diameter)	18.2	(27)
Phase II, 35; 2013	Chemo: gemcitabine 1,000 mg/m^2 (d1, d8) + S-1 40 mg/m^2 twice daily for first 14 consecutive days followed by 7-day rest	86%, R0 87%	19% partial response	19.7	(28)
Phase II, 59; 2013	Chemo: gemcitabine 1,500 mg/m^2 + bevacizumab 10 mg/kg every 2 weeks ×3 cycles RT: 30 Gy in 3 Gy fractions	74%, R0 88%	NA	16.8, 19.7 months with resection	(29)
Phase I-II, 50; 2014	Chemo: capecitabine 1,650 mg/m^2 divided twice daily RT: 5×5 Gy equivalents in 1 week	77%, 36/37 (97%) R1	NA	17	(30)
Phase II, 35; 2014	Chemo: gemcitabine 1,000 mg/m^2 + oxaliplatin 80 mg/m^2 every 2 weeks and adjuvant gemcitabine 1,000 mg/m^2 ×5 cycles	71%	10.5% partial response	27.2	(31)
Phase II, 38 (target accrual 64); 2015	Arm A: surgery alone (n=20) Arm B: gemcitabine 50 mg/m^2 twice weekly with 45 Gy + 9 Gy boost on the pancreatic lesion (n=18) Both arms received adjuvant chemotherapy according to the CONKO-001 study protocol (adjuvant gemcitabine 1 gm/m^2)	75% *vs.* 61.1%, R0 25.0 *vs.* 38.9% (P=0.489)	5.6% complete response, 22.2% partial response	19.5 *vs.* 22.4	(32)

Table 2 *(continued)*

Table 2 *(continued)*

Study design, n; year	Regimen	Resection rate (%)	Response (%)	Median OS (mo)	Ref.
Phase II, 66 (target accrual 254); 2015	Arm A: surgery (n=33) Arm B neoadjuvant gemcitabine 300 mg/m^2 and cisplatin 30 mg/m^2 (d1, 8, 22, and 29) + RT + surgery (n=33) Both arms received adjuvant chemotherapy according to the CONKO-001 study protocol (adjuvant gemcitabine 1 gm/m^2)	70% *vs.* 58% patients, R0 48% *vs.* 52% (P=0.81)	4 patients with partial response	14.4 *vs.* 17.4 (P=0.96)	(33)
Phase II, 57; 2017	Chemo: S-1 60 mg/m^2 RT: 30 Gy in 10 fractions	96%, R0 98%	7% with partial response	1- and 2-year OS: 91% and 83%, respectively	(34)

OS, overall survival; 5-FU, 5-fluorouracil; IV, intravenous; d, day; MMC, mitomycin C; RT, radiation therapy; Gy, Gray; R0, negative margins; R1, microscopic residual tumor; EB-IORT, electron beam intraoperative radiation therapy; EBRT, external beam radiation therapy; CONKO-001, Charité Onkologie 001; S-1, tegafur, gimeracil, oteracil; NA, not available.

encountered was increased intraoperative radiation fibrosis reported by surgeons, which ultimately translated to increased mean operative time. No patients had surgery delayed because of acute treatment-related toxicities.

Phase II trials

A number of phase II trials have been conducted over the past 2 decades to further explore the potential role of neoadjuvant chemoradiation in patients with pancreatic adenocarcinoma (*Table 2*). Among the first prospective clinical trials incorporating chemotherapy and RT was a phase II study involving 26 patients with biopsy-proven localized pancreatic cancer treated with neoadjuvant RT concurrent with 5-flourouracil (5-FU) and mitomycin C (within 24 hours of starting RT) that produced a 38% resectability rate (10). Including the cohort of duodenal cancers, all but 2 patients were able to complete the planned preoperative chemoRT (1 biliary catheter-related sepsis and 1 myelosuppression). A number of other phase II studies have assessed the safety and efficacy of 5-FU-based chemoradiotherapy to treat patients with resectable pancreatic adenocarcinoma (9-14,17,23,24). Resectability rates varied from 45–100% with rates of R0 resections ranging from 45.8–100%. No complete responses (CRs) were observed. The median overall survival (OS) ranged from 9.4–24 months. Overall, neoadjuvant therapies were well tolerated with no delay in surgery from treatment-related toxicities reported.

Gemcitabine is well-known to be a potent radiosensitizer that has shown clinical superiority compared to 5-FU in the treatment of advanced pancreatic cancer (*Table 2*). A number of phase II studies have sought to evaluate its potential role in neoadjuvant therapy for patients with resectable pancreatic adenocarcinoma (16,18). One study was stopped prematurely for poor accrual rate (32). Rates of resection varied from 61–85% with R0 resection rates varying from 40–90% (*Table 2*). Other studies have further expanded the use of gemcitabine with the addition of cisplatin because the two agents have differing mechanisms of action and lack of cross-resistance (19-22,33). Resectability rates ranged from 58–89% with R0 resection rates varying from 52–96% (*Table 2*). One randomized-controlled trial had promising results demonstrating improved resection rates and encouraging survival with use of combination therapy (19). However, one study suggested that the combination did not enhance survival beyond that achieved with neoadjuvant gemcitabine-based chemoradiotherapy alone (22). Another study has suggested there was an improvement in quality-of-life and improvement in nutritional status with combination gemcitabine and cisplatin (21). A separate randomized-control trial reportedly ended prematurely for slow accrual (33). In that study, combination therapy was well-tolerated, however no CRs were observed. Other combination therapies with gemcitabine include oxaliplatin and S-1 with trials demonstrating promising R0 resection rates (27,28,31).

Other promising agents have also been explored in

phase II trials (*Table 2*). Two taxane-based regimens were studied and demonstrated resection rates ranging from 50–57% with R0 resection rates varying from 68–100% (15,25). Median OS ranged from 12–32 months. Overall the regimens were well-tolerated. A study evaluating the use of cetuximab given prevalence of EGFR overexpression in pancreatic adenocarcinomas was able to achieve a 76% rate of resection (26). Another study explored the use of bevacizumab given its potential synergism with gemcitabine (29). While the regimen was well-tolerated and achieved a rate of surgical resection of 74%, the rate of complete pathologic response was not superior to other regimens.

Given concern for the metastatic propensity of pancreatic adenocarcinoma, there has been a strong interest to reduce the duration of RT. A phase I-II trial utilized a 2-week proton-based radiation with capecitabine and was able to demonstrate the regimen was well tolerated with a 4.1% grade 3 toxicity rate (30). Another phase II trial utilizing hypo-fractionated RT with S-1 demonstrated a 96% rate of resectability with the authors attributing the high resection rate to the short 2-week treatment duration (34).

Meta-analyses of clinical studies on neoadjuvant therapies in resectable pancreatic cancer

Given the growing body of evidence concerning neoadjuvant therapy in resectable pancreatic cancer, several meta-analyses have recently been conducted to further clarify on the benefit of this approach. Gillen *et al.* identified 111 retrospective and prospective studies involving 4,394 patients between 1980 to 2009 to assess tumor response, resection rates, survival rate, and toxicities in resectable, borderline, and unresectable pancreatic cancer (37). The most common chemotherapeutic regimens included gemcitabine, 5-FU, platinum-based regimens, and mitomycin C within the studies identified. For patients with resectable disease, a resectability rate of 73.6% [95% confidence interval (CI): 65.9–80.6%] was achieved. The authors observed CR and PR rates of 3.6% (95% CI: 2–5.5%) and 30.6% (95% CI: 20.7–41.4%), respectively, and the median OS after resection was 23.3 (range, 12–54) months. Because the rates of resection in this analysis were similar to the rates published in the literature of patients who did not receive neoadjuvant therapy, the authors questioned the utility of neoadjuvant therapy in patients with resectable pancreatic cancer.

Assifi *et al.* identified 14 prospective phase II trials that were predominantly single-arm studies comprising 536 patients and evaluated the role of neoadjuvant chemoradiotherapy in both resectable, borderline, and unresectable pancreatic cancer (38). In patients with resectable disease, resectability after chemoradiation was 65.8% (95% CI: 55.4–75.6%) with an 85.1% R0 resection rate. There was a large proportion of SD (73.9%, 95% CI: 63.2–83.3%) compared to PRs (9.5%, 95% CI: 2.9%–19.4%). In addition, the median OS was 23.0 months (range, 11.7–34 months). Given these results, the authors concluded that the role and impact of neoadjuvant therapy within resectable disease remains unclear given similar outcomes reported in the literature in patients who do not receive neoadjuvant therapy.

Andriulli *et al.* identified 20 prospective phase I–II studies involving 707 patients utilizing neoadjuvant gemcitabine-based therapy with or without radiation in patients with localized pancreatic cancer (39). Including both resectable and unresectable cases, the CR and PR rates were 12% (95% CI: 4–23%) and 27% (95% CI: 18–38%), respectively. In patients with resectable disease, a resectability rate of 91% (95% CI: 83–97%) was achieved with 89% R0 resections (95% CI: 83–94%). The median OS was 18.7 months (95% CI: 9–32%). However, with a treatment-related grade 3–4 toxicity of 29% (95% CI: 14–47%) and lingering questions regarding whether survival is enhanced by neoadjuvant therapy, the authors concluded there is marginal support for the benefits of neoadjuvant therapies in patients with potentially resectable disease.

D'Angelo *et al.* identified 16 randomized controlled trials between 1985 and 2015 focusing on adjuvant and neoadjuvant therapy to evaluate OS and protocol achievement in resectable pancreatic cancer (40). In the neoadjuvant setting, the OS varied between 9.9 and 19.4 months, 12.5–29.8 months with adjuvant therapy, and 11 and 20.2 months with surgery only. Protocol achievement ranged between 18.18% and 70.00% for patient treated with neoadjuvant therapy. Given these findings, the authors believe adjuvant therapy should still remain the standard of care. In addition, the authors advocate for studies to determine whether neoadjuvant therapy can enhance patient outcomes in patients who adjuvant therapy instead of designing trials to compare neoadjuvant *vs.* adjuvant therapy. Verma *et al.* included 30 prospective phase II trials to assess the postoperative morbidity and mortality in patients with pancreatic cancer who received

neoadjuvant chemotherapy or chemoradiotherapy (41). Common postoperative complications in patients with resectable or borderline disease who received neoadjuvant chemoradiotherapy included delayed gastric emptying (6–15%), pancreatic leaks (3–7%), sepsis (3–19%), hemorrhage (2–13%), and fistula formation (2–3%). 9/13 studies demonstrated a mortality of 4%. Patients who received neoadjuvant chemotherapy demonstrated comparable complications with pancreatic leaks (3–11%), fistula rates (3–4%), sepsis (3–7%) and mortality (0–4%). The rates of complications were similar to patients who received surgery only. Hence, the authors concluded that neoadjuvant chemotherapy or chemoradiotherapy is safe based on post-operative outcomes.

D'Angelo *et al.* included 12 prospective studies from 2008 to 2015 comprising 624 patients with resectable, borderline, and locally advanced disease to evaluate the rate of protocol achievement and OS (42). The most common chemotherapeutic agent used was gemcitabine. The authors reported a pooled protocol achievement rate of 65% (95% CI: 62–67%) with a 94% R0 resection rate. The OS from patients with resectable disease who eventually received resection was not significantly different in comparison to the survival rate within the total cohort [20.87 (95% CI: 17.97–23.82 months) *vs.* 22.78 months (95% CI: 20.42–25.16 months)]. Given the lack of strong evidence, the authors believe that further studies with randomized trials to clarify the benefits of neoadjuvant therapy are needed. While previous meta-analyses are plagued by heterogeneity in anatomic definitions for PDACs, there have been significant advances to standardize the definitions with release of expert consensus criteria in 2009. In one meta-analysis, Dhir *et al.* evaluated 96 retrospective and prospective phase I–II studies from 2009 involving 5,520 patients with resectable (n=1,056), borderline (n=935), and unresectable (n=1,840) pancreatic cancer treated with neoadjuvant therapy (43). While there have been concerns in regards to disease progression during neoadjuvant therapy, the incidence of progression was rare (11%). In patients with resectable disease, the authors reported a resectability rate of 76% with a R0 resection rate of 63%. A PR rate of 11% was observed. In patients with resectable disease who underwent surgery, the median OS was 30 months. Grade ≥3 toxicity was observed in 36% of the patients (95% CI: 27–45%) with 91% able to complete planned therapy. In short, the authors concluded these results demonstrate neoadjuvant therapy as a potential avenue for treatment in patients with resectable PDAC.

Zhan *et al.* identified 39 prospective studies involving 1,458 patients with 14 studies specifically focusing on evaluating the safety and efficacy of neoadjuvant therapy in patients with resectable pancreatic disease (44). The authors observed a resectability rate of 73% with a R0 resection rate of 84.2%. The CR and PR rate was 1.8% and 14.6%, respectively. OS was 17.76 months without resection and 24.24 months with resection. The incidence of grade ≥3 toxicities was 11.3%. Given these findings, neoadjuvant therapy has yet to demonstrate clinical superiority. In addition, considering the risk of disease progression, the authors concluded that neoadjuvant chemotherapy may not be beneficial in patients with resectable disease.

Discussion

The incorporation of systemic therapies ± RT with surgery have afforded improvements in survival in patients with resectable pancreatic cancer (3,4). However, there is a growing debate as to whether neoadjuvant or adjuvant therapy represents the appropriate management approach to optimize survival in resectable disease—the only potentially curable population of pancreatic cancer patients. Some have criticized that not all patients who undergo potentially curative resection receive adjuvant therapy (contemporary estimates of 40–50% of patients receive adjuvant therapy after surgery) (45). Furthermore, postoperative complications and mortality can impede delivery of adjuvant therapy. R0 resections confer more favorable prognosis than non-R0 resections; by virtue of the limits of preoperative imaging in detecting microscopic disease, upfront surgical approaches prohibit the ability to achieve meaningful decreases in tumor reduction or identify patients with aggressive disease who would otherwise not benefit from surgery. Lastly, pancreatic surgery has been shown to be immunosuppressive and may promote metastases that may otherwise be reduced by preoperative therapy.

Proponents of neoadjuvant therapy in upfront resectable pancreatic cancer have argued that this approach: (I) increases the chances for R0 resection; (II) increases the likelihood to complete multimodality therapy; (III) minimizes pancreatic leak; (IV) increases the efficacy of RT; (V) improves cost-effectiveness; and (VI) identifies poor candidates for surgery including either those with poor performance status, aggressive tumor biology, or unanticipated metastases (46). There is a growing body of

evidence to support the feasibility of neoadjuvant therapy in radiographically resectable pancreatic cancer (*Tables 1,2*). Many studies have demonstrated that preoperative therapy produces survival durations for resected patients that are often equivalent, if not superior, to outcomes with upfront surgery and adjuvant therapy (45). Other studies, however, have shown mixed results with respect to a neoadjuvant approach. Furthermore, neoadjuvant therapy does carry its own set of risks including disease progression during preoperative therapy for disease that was initially resectable and potentially curable and the lack of large, prospective randomized phase III trials with level 1 evidence to support this approach over adjuvant therapy (4,46).

Several major guidelines currently recognize neoadjuvant therapy as an option within the treatment paradigm for resectable pancreatic cancer (47,48). In short, neoadjuvant therapy can be considered in select patients with technically resectable disease and high-risk features including: markedly elevated CA 19-9 levels or radiographic findings suspicious but not diagnostic of metastatic disease, poor performance status or comorbidities rendering the patient not fit for major abdominal surgery, large primary tumors, large regional lymph nodes, excessive weight loss, or extreme pain. The American Society of Clinical Oncology (ASCO) posits that neoadjuvant therapy can be offered as an alternative strategy for patients who meet criteria for upfront resectable disease (47). However, the National Comprehensive Cancer Network (NCCN) does not recommend neoadjuvant therapy for clearly resectable pancreatic cancer without high-risk features as such an approach in this setting should take place in the context of a clinical trial (48).

These recommendations have been put forth with the understanding that although benefits may outweigh harms for a neoadjuvant approach, the quality of evidence supporting this strategy is low. Beyond the need for high-level evidence from larger, prospective randomized clinical trials supporting a neoadjuvant approach, there still remains several questions to this treatment strategy in resectable pancreatic cancer. For one, it is unclear which modality represents the optimal strategy in a neoadjuvant approach: chemotherapy, RT, or combined modality? Furthermore, in patients who have received preoperative therapy for localized pancreatic cancer, what is the role of adjuvant therapy (49,50)? With the understanding that there are no data from randomized clinical trials to answer this question, major guidelines recommend a total of 6 months of adjuvant therapy (including the duration of the neoadjuvant regimen) as extrapolated from adjuvant therapy trials (47). This decision should be based on multidisciplinary review and the choice of adjuvant regimen should be based on response to the neoadjuvant regimen and anticipated tolerability; adjuvant therapy should only be administered in those without evidence of recurrent or distant disease and who have recovered from surgery (ideally within 4–8 weeks) (48).

Additionally, are there evidence-based criteria or definitive predictors to guide selection of candidates who would benefit most from neoadjuvant therapy? One phase I/II trial associated *KRAS*^{G12D} mutation status and high CXCR7, CEA, CA 19-9, and HGF levels to worse survival in patients treated with neoadjuvant chemoradiation (30). A separate group identified a 6-gene signature that predicts survival in localized PDAC and could potentially be used to select candidates for neoadjuvant therapy (51). Higher levels of tumor-infiltrating lymphocytes and a higher ratio of CD8/FOXP3 lymphocytes were associated with improved OS in PDAC patients treated with neoadjuvant therapy (52). Lastly, hENT1, TS/DPD, EGFR, SPARC, and SMAD4 are among the growing list of potential biomarkers that may guide selection of patients with resectable pancreatic cancer who would benefit most from neoadjuvant therapy (46). Reassuringly, there are several ongoing phase II and III trials that may potentially address several questions that remain unanswered in the neoadjuvant treatment of resectable pancreatic cancer (*Table 3*). Results from these studies are eagerly awaited to see if neoadjuvant therapy is truly primed to establish itself as an integral component of the treatment paradigm for localized resectable pancreatic cancer.

Conclusions

Evidence is accumulating to support the feasibility and efficacy of neoadjuvant therapy in radiographically resectable pancreatic cancer. Several major national guidelines now recognize neoadjuvant therapy as an option in the treatment of resectable pancreatic cancer. Nevertheless, high-level evidence is lacking to guide the selection of patients who would benefit most from neoadjuvant therapy, choice of optimal modality in a neoadjuvant strategy, and need for adjuvant therapy following neoadjuvant therapy. Results from ongoing, randomized prospective clinical trials may provide further clarity to several questions remaining unanswered in the neoadjuvant treatment of resectable pancreatic cancer.

Table 3 Ongoing phase II–III clinical trials investigating neoadjuvant therapy in resectable pancreatic cancer

Study	n (patients needed)	Design	Regimen	Primary outcome
NCT01900327	410	Phase III	Gemcitabine-based chemoRT → adjuvant gemcitabine *vs.* adjuvant gemcitabine	3-year OS
NCT02047513 (NEONAX)	166	Phase II	Gemcitabine + nab-paclitaxel → adjuvant gemcitabine + nab-paclitaxel *vs.* adjuvant gemcitabine + nab-paclitaxel	18-month DFS
NCT01771146	100	Phase II	Neoadjuvant FOLFIRINOX	PFS
NCT01521702 (NEOPAC)	310	Phase III	Neoadjuvant FOLFIRINOX → adjuvant gemcitabine *vs.* adjuvant gemcitabine	5-year PFS
NCT01314027 (NEOPAC)	350	Phase III	Neoadjuvant gemcitabine/oxaliplatin + adjuvant gemcitabine *vs.* adjuvant gemcitabine	PFS
NCT01150630	370	Phase II/III	Adjuvant gemcitabine vs Adjuvant PEXG *vs.* neoadjuvant and adjuvant PEXG	1 year event-free survival
NCT00727441	87	Phase II	GM-CSF Secreting Allogeneic Pancreatic Cancer Vaccine +/– IV or oral cyclophosphamide → adjuvant gemcitabine + CRT	Safety, feasibility, and immune response
NCT00733746 (ACOSOG-Z5041)	123	Phase II	Neoadjuvant gemcitabine + erlotinib	2-year OS
NCT02178709	48	Phase II	Neoadjuvant FOLFIRINOX	Pathologic complete response
NCT01389440 (GEMCAD1003)	24	Phase II	Neoadjuvant gemcitabine + erlotinib	R0 resection rate
NCT02562716	112	Phase II	Neoadjuvant and adjuvant mFOLFIRINOX *vs.* neoadjuvant and adjuvant gemcitabine and nab-paclitaxel	OS
NCT02030860	15	Pilot	Neoadjuvant nab-paclitaxel and gemcitabine +/– paricalcitol	Number of adverse events
NCT02305186	56	Randomized phase Ib/II	Neoadjuvant CRT (capecitabine) ± pembrolizumab	Safety and immune response
NCT02919787 (NorPACT)	90	Phase III	Neoadjuvant 5-FU + oxaliplatin + irinotecan followed by adjuvant gemcitabine + capecitabine	OS
NCT02047513 (NEONAX)	166	Phase II	Neoadjuvant and adjuvant nab-paclitaxel/gemcitabine *vs.* adjuvant nab-paclitaxel/gemcitabine	DFS
NCT02305186 (UVA-PC-PD101)	56	Phase Ib/II	Neoadjuvant CRT (capecitabine) + pembrolizumab *vs.* neoadjuvant CRT (capecitabine)	Safety and immune response
NCT01470417 (GAIN-1)	10	Phase II	Neoadjuvant nab-paclitaxel + gemcitabine *vs.* nab-paclitaxel + gemcitabine + CRT	Biochemical response rate, radiographic response rate, pathologic downstaging and margin status
NCT00536874	39	Phase II	Neoadjuvant Gemcitabine + oxaliplatin	OS
NCT02243358	20	Phase II	Neoadjuvant FOLFOX + CRT (gemcitabine)	Tumor response
NCT02723331	50	Phase II	Neoadjuvant and adjuvant Nab-paclitaxel and gemcitabine + SBRT with resectable disease *vs.* Neoadjuvant and adjuvant Nab-paclitaxel and gemcitabine + SBRT with borderline resectable disease	R0 resection rates

Table 3 *(continued)*

Table 3 *(continued)*

Study	n (patients needed)	Design	Regimen	Primary outcome
NCT01298011	25	Phase II	Neoadjuvant Gemcitabine and Nab-paclitaxel	Grade III/IV histological response
NCT00557492	59	Phase II	Neoadjuvant bevacizumab and gemcitabine + RT	R0 resection rate and pathologic complete response
NCT02172976	126	Phase II/III	Adjuvant gemcitabine *vs.* neoadjuvant and adjuvant FOLFIRINOX	OS
NCT01494155	50	Phase II	RT with proton or photon RT + capecitabine and hydroxychloroquine	PFS
NCT01660711	21	Phase II	Neoadjuvant and adjuvant mFOLFIRINOX	Tolerability
NCT00609336	35	Phase II	Induction gemcitabine + docetaxel + capecitabine PO + neoadjuvant capecitabine/oxaliplatin + RT → adjuvant gemcitabine oxaliplatin	OS
NCT00313560	52	Phase II	Neoadjuvant erlotinib + adjuvant capecitabine + RT *vs.* neoadjuvant placebo + adjuvant capecitabine + RT	Pharmacodynamics of neoadjuvant erlotinib
NCT02047474	46	Phase II	Neoadjuvant/adjuvant mFOLFIRINOX	PFS
NCT02427841	44	Phase II	Neoadjuvant nab-paclitaxel + gemcitabine and adjuvant nab-paclitaxel + gemcitabine	R0 resection rate
NCT01360593	50	Phase II	Induction Gemcitabine/Capecitabine → SBRT	PFS
NCT01150630	98	Phase II-III	Adjuvant PEXG *vs.* neoadjuvant/adjuvant PEXG *vs.* adjuvant gemcitabine	Event-free survival

RT, radiation therapy; CRT, chemoradiation; OS, overall survival; DFS, disease-free survival; PFS, progression-free survival; PEXG, gemcitabine hydrochloride with cisplatin, epirubicin hydrochloride, and capecitabine; SBRT, stereotactic body radiation therapy; mFOLFIRINOX, modified 5-fluorouracil, irinotecan, oxaliplatin; FOLFIRINOX, folinic acid, 5-FU, irinotecan, oxaliplatin; R0, microscopically negative margins.

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Footnote

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