REVIEW

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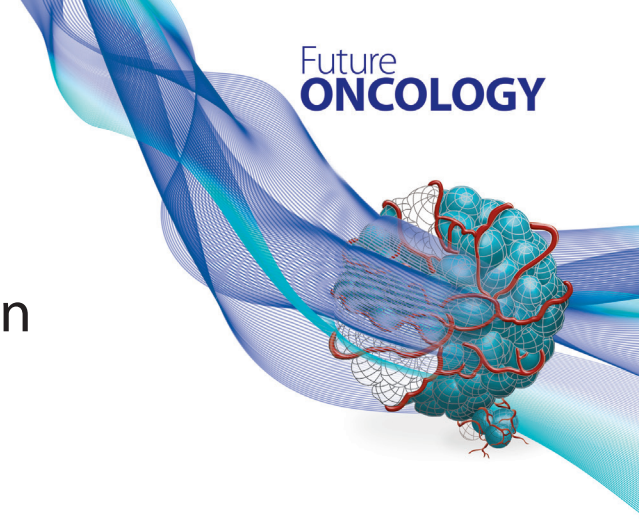

# The role of neoadjuvant therapy in pancreatic cancer: a review

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Controversy remains regarding neoadjuvant approaches in the treatment of pancreatic cancer. Neoadjuvant therapy has several potential advantages over adjuvant therapy including earlier delivery of systemic treatment, *in vivo* assessment of response, increased resectability rate in borderline resectable patients and increased margin-negative resection rate. At present, there are no randomized data favoring neoadjuvant over adjuvant therapy and multiple neoadjuvant approaches are under investigation. Combination chemotherapy regimens including 5-fluorouracil, irinotecan and oxaliplatin, gemcitabine with or without abraxane, or docetaxel and capecitabine have been used in the neoadjuvant setting. Radiation and chemoradiation have also been incorporated into neoadjuvant strategies, and delivery of alternative fractionation regimens is being explored. This review provides an overview of neoadjuvant therapies for pancreatic cancer.

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**KEYWORDS**
• 5-fluorouracil • abraxane • capecitabine • chemotherapy • docetaxel • gemcitabine • irinotecan • oxaliplatin • pancreatic cancer • radiation • surgery

Pancreatic adenocarcinoma is considered one of the most aggressive malignancies. Most patients are diagnosed with advanced stage disease and only 15–20% of patients are considered candidates for curative resection. An additional 5–10% is diagnosed with borderline resectable or locally advanced disease. Although surgical resection is considered the only potentially curative treatment, resection alone results in low cure rates with median overall survival (OS) rates of approximately 20 months [1,2]. Pancreatic cancer is biologically aggressive and lacks therapeutic agents that are effective against micrometastases. Even in patients who undergo complete surgical resection followed by adjuvant chemotherapy with or without radiation, the risk for systemic recurrence can be as high as 77%, and may be either locoregional or distant in nature [3].

Response rates to adjuvant therapies are variable and there is no reliable method to identify which patients will respond to treatment. Nonetheless, some randomized studies demonstrate OS and disease-free survival advantages associated with adjuvant therapies for resectable pancreatic cancer [4,5].

Unlike adjuvant therapy, a neoadjuvant treatment approach potentially allows for *in vivo* assessment of tumor response. In addition, the use of early systemic therapy prior to surgery allows treatment of radiographically undetectable metastatic disease in some patients. It has been reported that

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disease progression occurs in 45–74% following neoadjuvant chemoradiation [6–9] and 30–78% following neoadjuvant chemotherapy [10]. Noncurative surgery and its associated risks can be avoided in patients who demonstrate disease progression following neoadjuvant therapy.

Neoadjuvant treatment also has the potential to improve compliance [11] as adjuvant therapy is frequently delayed due to recovery from surgery. It is estimated that approximately 25% of patients undergoing curative resection for pancreatic cancer do not receive the planned postoperative treatment due to surgical complications, refusal, early disease recurrence and poor performance status [12,13]. In the CONKO-001 trial, only 63% of patients received the planned adjuvant treatment [14]. In the neoadjuvant setting, however, 73–100% of patients are reported to complete the majority of the treatment [6,10,15–19].

One of the most promising advantages of neoadjuvant therapy in pancreatic cancer is the potential to increase the number of operative candidates by converting initially borderline or locally unresectable tumors to resectable. This was confirmed in a meta-analysis where approximately a third of patients with tumors initially deemed unresectable were converted to operative candidates following neoajuvant therapy. Furthermore, those patients who converted to operative candidates enjoyed similar survival rates as patients with initially resectable tumors [15]. Neoadjuvant therapy has also been associated with improved margin-negative resection (R0) for patients with initially unresectable tumors [6,16,20–22]. Original concerns over theoretical increases in operative morbidity and mortality have been disputed in a meta-analysis showing no differences in patients who received neoadjuvant therapy compared with those treated with upfront surgery [20]. In fact, a decreased incidence of anastomotic fistulas has been reported for patients receiving neoadjuvant treatments, probably because radiation causes a firmer pancreas which is less likely to leak [20,23–24].

Lastly, there are data to suggest an economic advantage associated with the use of neoadjuvant strategies compared with upfront surgery. A recent study examining the ACS-NSQIP, the American College of Surgeons National Cancer Database and MD Anderson Cancer Center (MDACC) databases developed a model evaluating costs and survival for pancreatic cancer patients undergoing different treatments. This study demonstrated that the use of neoadjuvant chemoradiation resulted in improved survival (quality-adjusted life months) and cost savings (~US$10,000 per patient-case) compared with the surgery-first approach [25].

In this review, we provide an overview of existing data on neoadjuvant approaches for pancreatic cancer.

## Methods

A PubMed online search was performed using the following search keywords alone or in combination: 'pancreatic cancer', 'adenocarcinoma', 'neoadjuvant', 'preoperative', 'radiation', 'chemotherapy' and 'chemoradiation'. All studies from 1995 to 2015 were reviewed for inclusion in this manuscript. Meta-analyses were included, but review articles, opinion articles and case reports were excluded. An attempt to sort the data into resectable, borderline and locally advanced pancreatic cancer was made, however many of the publications included data not limited to one subtype. We did not restrict our search based on tumor location or operative techniques as the purpose of this review was to provide an overview of current data for neoadjuvant therapy in the treatment of pancreatic cancer and new developments and future directions for this approach.

## Preoperative staging & surgical resectability

It is recognized that the lack of a standard definition of surgical resectability has confounded outcome data for many pancreatic cancer treatment studies. The ability to accurately stage patients is essential for the development and evaluation of stage-specific therapies to maximize outcome and quality of life for all patients. Surgical staging was once considered standard for pancreatic cancer and intraoperative assessment defined resectability.

The definition of a resectable tumor has been clarified in parallel with the definition of borderline resectable and unresectable tumors. The concept of a borderline resectable patient population first proposed by Katz *et al.* was defined by radiographic features, biopsy-proven regional lymph nodes, suspicion of distant metastases and questionable performance status [26]. More recently, preoperative staging evaluating the relationship of tumor to vessel and presence or absence of extrapancreatic disease is accomplished with high-quality cross-sectional

imaging, and parameters of accurate imaging acquisition [27,28]. **Table 1** describes current definitions of potentially resectable, borderline resectable and unresectable locally advanced pancreatic cancer use in the recent ALLIANCE A021101 trial [29]. The American Joint Committee on Cancer staging system has similarly been revised to emphasize the importance of resectability focusing on defining the relationship of tumor to vessels and on identifying and predicting the ability to perform margin-negative resection. Stages I and II, and the subset of borderline resectable patients with stage III cancer are defined as resectable [30] where borderline resectable is defined as abutment of the celiac axis (celiac, common hepatic arteries of superior mesenteric artery of <180° [27]). In the absence of metastatic disease, patients with uninvolved or focal involvement of the superior mesenteric and portal veins confluence are considered resectable. More extensive involvement or encasement of the superior mesenteric and portal veins confluence constitutes stage III disease. Contrast-enhanced computed tomography (CT) is useful in evaluating location of tumor with respect to vascular structures and predicting R0 resections in 73% of cases [31]. Current staging techniques are limited in detection of metastatic disease, however, with approximately 10–20% found to have unanticipated metastases at the time of laparoscopy or laparotomy [32] and approximately 75% developing distant metastases following surgical resection [33].

## Limitations of available data

A number of publications include patients with resectable, borderline resectable, and locally-advanced unresectable tumors rendering the results difficult to interpret. In addition, interpretations of data from early studies are limited by use of older chemotherapy regimens, monochemotherapy or radiation alone in addition to small sample size. More recent studies have limited patient inclusion criteria defined by radiographic criteria and have incorporated more aggressive modern combination chemotherapy protocols and chemoradiation strategies.

Early studies conducted prior to the gemcitabine era examined 5-fluorouracil (5-FU)-based neoadjuvant chemoradiation regimens [34]. The first study incorporated 5-FU and concurrent radiation in 28 patients [35]. This regimen was poorly tolerated due to gastrointestinal toxicity requiring hospitalization in 32%. Despite the toxicity, 61% underwent curative surgery [35]. A subsequent study from the same institution evaluated a rapid fractionation chemoradiation treatment regimen consisting of 5-FU at the same dose and concurrent radiation delivered over 2 weeks to reduce time to surgery [36]. This modified regimen was better tolerated with 9% experiencing grade 3–4 toxicity and 57% of

**Table 1. ALLIANCE A-021101 definitions of potentially resectable, borderline resectable and unresectable pancreatic cancer as defined by computed tomography/MRI.**

| Anatomic structure | Potentially resectable | Borderline resectable | Unresectable and/or locally advanced |
|---|---|---|---|
| SMV and portal vein | Tumor–vessel interface <180° of vessel wall circumference | Tumor–vessel interface ≥180° of vessel wall circumference, and/or short segment occlusion amenable to resection or reconstruction with normal vein proximal and distal to interface | Occlusion of the SMV or portal vein without sufficient cuff or normal vein above or below the interface for venous reconstruction |
| SMA | No radiographic interface between tumor and artery | Tumor–vessel interface <180° of vessel wall circumference | Tumor interface ≥180° of vessel wall circumference |
| Aorta | No radiographic interface between tumor and aorta | | Interface between tumor and aorta |
| Celiac axis | No radiographic interface between tumor and celiac axis | | |
| Nodes | Absence of suspicious lymph nodes outside of surgical field | | |
| Hepatic artery | No radiographic interface between tumor and artery | Reconstructable short segment interface of any degree between tumor and vessel wall with normal artery proximal and distal to interface | Long-segment interface of any degree or major tributaries with insufficient artery proximal or distal to the interface for reconstruction |

Presence of distant (including nonregional lymph nodes – aortocaval, distant abdominal) or ascites defines metastatic disease.
SMA: Superior mesenteric artery; SMV: Superior mesenteric vein.
Data taken from [28,29].

patients were able to undergo definitive surgery, similar to the previous study. Another Phase II study included 26 patients with pancreatic cancer and five patients with duodenal cancer treated with neoadjuvant concurrent 5-FU and mitomycin C with radiation. Approximately a third of patients were found to have progressive disease prior to surgery and the resection rate was 38%, resulting in 5-year survival rates of 58% [37]. Subsequently, the Eastern Cooperative Oncology Group conducted a Phase II trial using this same treatment regimen [7]. Similar to previous findings, only 45% of patients were able to undergo surgical resection and median OS for patients who had curative surgery was only 9.7 months, inferior to historic controls for patients treated with surgery alone [7]. Another neoadjuvant treatment strategy incorporating 5-FU, cisplatin and concurrent radiation has been reported in several retrospective studies [9,17–18,34,38–39]. The results of these studies have been disappointing as they do not appear to be significantly improved over those using adjuvant therapies, and efforts to improve on these outcomes have led to studies evaluating neoadjuvant chemoradiation with other agents.

Initial interest in gemcitabine in the neoadjuvant setting was inspired by the sentinel study demonstrating noninferiority to 5-FU-based treatment and improved quality of life in patients with advanced pancreatic cancer [40]. Gemcitabine is a known radiosensitizer [41] and incorporation of gemcitabine-based chemoradiation into neoadjuvant strategies for pancreatic adenocarcinoma appears to be associated with improved tolerance and longer survival rates compared with 5-FU-based chemoradiation. However, there are no randomized trials comparing the two approaches. Subsequently, a variety of radiation fractionation regimens (30–50.4 Gy) and chemotherapy regimens have resulted in resection rates ranging from 45 [12] to 85% [42].

## Resectable disease

No clear advantage has been demonstrated favoring neoadjuvant treatment over adjuvant therapy for patients with clearly resectable disease as data have been conflicting.

### • Neoadjuvant chemoradiation for resectable disease

Investigators from MDACC have generated the most data using neoadjuvant therapy in the treatment of resectable pancreatic cancer in a series of Phase II trials for resectable tumors, where the definition was clearly defined and remained the same for all studies [6,16,35–36,43]. All these trials demonstrated that patients who completed neoadjuvant chemoradiation and were without radiographic evidence of progression prior to surgery had a higher chance of achieving R0 resection when compared with historical surgical data, and those that underwent surgical resection demonstrated higher median and OS rates. It should be recognized that although the surgical management of these patients was consistent across this series, a review of 132 patients receiving neoadjuvant chemoradiation revealed that 43% required vascular resection [44], which may be considered inoperable in other institutions. The investigators reported a median OS of 21 months for patients using this aggressive neoadjuvant followed by surgery approach [44]. Greer *et al.* confirmed these findings in a retrospective review of 102 patients when they reported lower recurrence, improved survival and higher R0 resection rates for patients who received neoadjuvant chemoradiation compared with patients who received immediate surgery followed by adjuvant therapy, even though there was a selection bias where patients were more likely to have locally advanced disease in the preoperative therapy group [45].

In addition to the MDACC data, a retrospective review reported data for 236 radiographically resectable pancreatic head cancers of which 144 received preoperative chemoradiation and 92 proceeded straight to surgery. Tumors treated with neoadjuvant therapy tended to be slightly larger or have more venous abutment. Nonetheless, 53% underwent resection, with 12% found to have unresectable disease and 19% with metastatic disease at the time of surgery. Similarly, of those who underwent immediate surgery, 74% underwent resection, 9% were found to have unresectable disease and17% had metastatic disease. At the time of surgery, patients who received neoadjuvant chemoradiation had smaller tumor size and lower incidence of positive lymph nodes than the surgery first group but no difference in positive margins or need for vascular resection. A median OS advantage was demonstrated for resected patients who received neoadjuvant therapy compared with those who did not (27 vs 17 months; p = 0.04) [46]. Another retrospective study compared preoperative

versus postoperative chemoradiation in patients treated with curative intent in 142 patients with resectable pancreatic or periampullary cancer. Patients with biopsy confirmation of adenocarcinoma and a low-density mass in the pancreatic head underwent preoperative chemoradiation. Patients without a mass on CT or in whom biopsy was negative underwent immediate surgery followed by adjuvant chemoradiation. Intraoperative radiation was also delivered as a 'boost' in 68% of cases. A total of 91 patients received neoadjuvant chemoradiation using 5-FU and concurrent radiation and none experienced delay in surgery due to toxicity, but 24% of those undergoing immediate surgery did not receive postoperative chemoradiation because of delayed recovery. Similar to the previous studies, the rate of pancreaticoduodenectomy was low with only 57% patients receiving curative resection following neoadjuvant therapy [12]. There was no difference in survival between patients receiving neoadjuvant chemoradiation followed by surgery and patients completing surgery followed by chemoradiation [12]. The largest retrospective study from the Californian Cancer Surveillance Program reported results from 458 patients with resectable pancreatic cancer in which 8.5% received neoadjuvant therapy. In this study, those who received neoadjuvant therapy demonstrated improved survival and a lower rate of lymph node involvement [47,48]. Similarly, a questionnaire-based study demonstrated higher R0 resection rates associated with preoperative compared with no neoadjuvant therapy in patients with resectable tumors [49].

To date, no prospective randomized studies have reported data comparing the efficacy of neoadjuvant therapy compared with adjuvant treatment in patients with initially resectable pancreatic cancer.

### • Neoadjuvant chemotherapy (without radiation) for resectable disease

Early trials explored neoadjuvant chemotherapy without radiation to treat occult metastatic disease prior to surgery with an attempt to identify patients with disease that will progress despite aggressive surgery. In a randomized Phase II trial, patients with resectable pancreatic cancer received either preoperative gemcitabine alone or in combination with cisplatin. Only 38% of patients in the gemcitabine cohort underwent curative resection compared with 70% in the gemcitabine-cisplatin cohort, without differences observed in surgical complications. Median OS was poor for both arms; 9.9 and 15.6 months, in the gemcitabine only and combination chemotherapy arms, respectively [10]. Another single-arm Phase II trial included 28 patients with resectable pancreatic cancer who received four cycles of twice weekly gemcitabine and cisplatin followed by surgery. In this study, 71% underwent R0 resection. Although most of the patients were able to undergo planned surgery, the median OS for the entire cohort was 26.5 months [50]. Numerous studies have not shown an advantage with neoadjuvant therapy. Heinrich *et al.* demonstrated that neoadjuvant gemcitabine and cisplatin did not impair resectability rates over a surgery first approach in a prospective Phase II trial of 28 patients with initially resectable disease [50]. Another study compared neoadjuvant gemcitabine and oral S-1 to upfront resection and found no difference in resectability or survival rates between groups [51].

In a meta-analysis of 111 studies incorporating neoadjuvant therapy strategies in pancreatic cancer (including those with initially resectable disease), better response rates were observed in patients treated with chemoradiation compared with chemotherapy alone, but resection rates did not differ between those patients with resectable tumors who received neoadjuvant therapy compared with those treated with adjuvant therapy [15]. Another meta-analysis including 20 prospective studies evaluated the benefit of gemcitabine-based neoadjuvant regimens and found only marginal survival benefits for patients with resectable cancer whether they received radiation or not [23].

**Table 2** summarizes published neoadjuvant therapy trials that included patients with initially resectable tumors. In conclusion, there is no clear advantage supporting the routine use of neoadjuvant therapy in patients with initially resectable pancreatic cancer who have been properly staged using current accepted definitions for resectablility.

## Borderline resectable disease

Borderline resectable pancreatic cancer is fundamentally different from initially resectable pancreatic cancer in that there is a higher risk for positive resection margin due to tumor-vascular abutment, more complex surgical resection which may include vascular resection and reconstruction, and presence of occult distant metastatic disease. For these

**Table 2. Summary of neoadjuvant trials including patients eligible for upfront resection.**

| Study (year) | Patients (n) | Regimen | Resection rate (%) | R0 rate (% of resected) | Median OS (months) | Ref. |
|---|---|---|---|---|---|---|
| Palmer randomized Phase II (2007) | 24 | Gem | 38 | 25 | 45 R | [10] |
| | 26 | Gem + Cis | 69 | 46 | 7 UR, 10 all | |
| Heinrich Phase II (2008) | 28 | Gem + Cis | 93 | 80 | 19 R, 26.5 all | [50] |
| Tajima Phase I (2012) | 34 | Gem + S-1 | 100 | 85 | 56% at 2 years | [51] |
| O'Reilly Phase II (2014) | 38 | Gem + Ox | 71 | 74 | 27 (all) | [52] |
| Faris retrospective (2013) | 35 | FOLFIRINOX only in 2 + CRT in 20 without response | 55 | 42 | NR | [53] |
| Evans prospective (1992) | 28 | 5-FU + RT (50.4 Gy) + IORT | 61 | 50 | 18 (R), 4 (UR) | [35] |
| Pisters prospective (1998) | 35 | 5-FU+ RT (30 Gy) + IORT | 57 | 51 | 25 (R), 7 (UR) | [36] |
| Pisters prospective (2002) | 35 | Paclitaxel RT + (30 Gy) + IORT | 57 | 34 | 19 (R), 10 (UR) | [43] |
| Turrini Phase II (2010) | 34 | Tax + RT (45 Gy) | 50 | 100 | 32 (all) | [54] |
| Evans Phase II (2008) | 86 | Gem + RT (30 Gy) | 74 | 89 | 22.7 (all), 34 (R), 7 (UR) | [6] |
| Varadhachary Phase II (2008) | 90 | Gem + Cis + GemRT (30 Gy) | 66 | 96 | 17.4 (all), 31 (R) | [16] |
| Sho (2013) | 61 | Gem + RT (50.4–54 Gy) | 97 | 92 | NR | [55] |
| Van Buren Phase II (2013) | 59 | Fixed dose rate Gem + Bev + RT (30 Gy) | 73 | 88 | 16.8 (all), 19.7 (R) | [48] |
| Kim Phase II (2013) | 23 R, 39 BR, 6 UR | Gem + Ox + RT (30 Gy) | 63 | 84 | 18.2 (all), 27.1 (R), 10.9 (UR) | [56] |
| Pipas Phase II (2012) | 4 R, 23 BR, 6 UR | Gem + cetuximab + RT (54 Gy) | 100 R 76 (all) | 92 (all) | 24.3 (all) | [57] |
| Faris retrospective (2013) | 22 | FOLFIRINOX ± CRT | 55 | 42 | NR | [53] |
| Shinoto Phase I (2013) | 26 | 30.0–36.8 GyE carbon-ion RT | 81 | 90 | 18.6 (all) | [58] |

5-FU: 5 fluorouracil; Bev: Bevacizumab; BR: Borderline resectable; Cis: Cisplatin ; CRT: Chemoradiation; FOLFIRINOX: 5-fluorouracil, oxaliplatin, irinotecan, and leucovorin; Gem: Gemcitabine; Gy: Gray; NR: Not reported; Ox: Oxaliplatin; R: Resectable; RT: Radiotherapy; S1: Pral 5-fluorouracil; Tax: Docetaxel; UR: Unresectable.

reasons, surgery may not yield benefit for this subset of patients. The most significant factor predicting long-term survival in pancreatic cancer patients is an R0 resection and it has been demonstrated that resection with positive margin is independently associated with prognosis similar to inoperable disease [2,21–22,59–62]. Neoadjuvant therapy with the intent of sterilizing the margin could be considered in patients with vascular involvement, with particular attention to restaging to tailor surgical recommendations. Several studies suggest that neoadjuvant chemoradiation may enhance margin-negative resectability rates and improve local control [37,56–57,63–77]. Unfortunately, many of the studies are confounded by inclusion of patients with locally advanced unresectable tumors and lack of strict definition of borderline resectable disease. **Table 3** reviews data from prospective neoadjuvant trials using chemoradiation strategies including patients with borderline resectable or locally advanced unresectable disease.

### • Neoadjuvant chemoradiation for borderline resectable disease

Use of aggressive gemcitabine-based neoadjuvant chemoradiation regimens has been pursued in patients with more advanced pancreatic cancer in an attempt to increase R0 resection and survival rates. Data from prospective trials containing patients with borderline resectable disease demonstrate that the surgical resection rate ranges from 24 to 64%, and the R0 resection rate ranges from 87 to 100% [56–57,63–77]. Although most of these studies are small, neoadjuvant chemoradiation appears to be associated with good potential for downstaging and R0 resection in this population, which may be in part due to careful patient selection with adequate staging studies, and strict adherence to the definition of borderline resectable. The benefit of neoadjuvant therapies in 160 patients with borderline resectable tumors was retrospectively reviewed by Katz *et al* [26]. The patients included in this review were treated with 2–4 months of neoadjuvant chemoradiation with

5-FU, gemcitabine, capecitabine or paclitaxel from 1999 and 2006. Of these, 78% completed preoperative therapy and restaging, and 41% underwent surgery, with 27% requiring vascular resection/revision. The R0 resection rate was 94% and median OS was 40 months for patients who underwent surgery compared with 13 months for those who did not undergo pancreatectomy ($p < 0.001$). Unfortunately, 59% of the resected patients ultimately recurred with median time to progression of 24 months; 45% distant recurrence, 9% local recurrence and 11% peritoneal or regional nodal recurrence, overall indicating the need to improve the efficacy of neoadjuvant strategies [26].

Currently, investigations of more aggressive neoadjuvant systemic treatment regimens are underway in an attempt to improve upon the

**Table 3. Summary of neoadjuvant trials using chemoradiation strategies including patients with borderline resectable or locally advanced disease.**

| Study (year) | Patients (n) | Regimen | Resection rate (%) | R0 rate (% of resected) | Median OS (months) | Ref. |
|---|---|---|---|---|---|---|
| Kim Phase II (2013) | 23 R, 39 BR, 6 UR | Gem + Ox + RT (30 Gy) | 63 | 84 | 18.2 (all), 27.1 (R), 10.9 (UR) | [56] |
| Pipas Phase II (2012) | 4 R, 23 BR, 6 UR | Gem + cetuximab + RT (54 Gy) | 100 R, 76 (all) | 92 (all) | 24.3 (all) | [57] |
| Landry (2010) randomized Phase II | 21 BR | Gem + RT (50.4 Gy)<br>Gem + RT (50.4 Gy) vs Gem + Cis + 5-FU + RT (50.4 Gy) | 30<br>22 | 33<br>50 | 19.4 (all)<br>13.4 (all), 26.3 (R) | [63] |
| Katz retrospective (2012) | 129 BR | Gem then Gem + RT (30 Gy) vs Gem + Cis + 5-FU + RT (50.4 Gy) | 84<br>78 | 95 | 33 (all) | [78] |
| Barugola retrospective (2012) | 362 BR | Gem then Gem + RT vs Gem alone | NR | NR | NR | [79] |
| Kang retrospective (2012) | 202 BR | Gem + RT | 91 | 87 | 26.3 (all) | [80] |
| McClaine retrospective (2010) | 109 BR | Gem + RT | 46 | 67 | 23.3 (all) | [81] |
| Turrini retrospective (2009) | 160 BR | 5-FU + Cis + RT (45 Gy) | 18 | 100 | 24 (all) | [34] |
| Stokes (2011) | 40 BR | Cape + RT (50.4 Gy) | 40 | 88 | 23 (R), 12 (all) | [68] |
| Patel (2011) | 17 BR | GTX + IMRT (45 Gy micro, 50 Gy gross) | 64 | 89 | 15 (all) | [66] |
| Small (2008) | 9 BR ,16 R | Gem + RT (26 Gy) | 33 borderline | 94 (all) | NR | [67] |
| Massucco (2006) | 10 BR, 18 UR | Gem ± Ox + RT (45 Gy) | 39 borderline | 87 (all) | 21 (R), 10 (UR), 15.4 (all) | [64] |
| Mehta (2001) | 15 BR | 5-FU + RT (50.4–56 Gy) | 60 | 100 | 30 (R), 8 (UR) | [65] |
| Chuong (2013) | 73 | Gem then SBRT | 56 | 96 | 16.4 (all) | [82] |
| Shinchi prospective (2002) | 31 UR | 5-FU ± RT (50.4 Gy) | NR | NR | 13.3 (RT), 6.4 (no RT) | [76] |
| Tinkl prospective (2009) | 120 UR | Gem + RT (50.4–55.8 Gy) | 31.6 | 92 | 25 (all) | [72] |
| Kim Phase I (2013) | 38 UR | Gem + Ox + RT (27 Gy) | 28.9 | 64 | 12.5 (all) | [56] |
| Huguet Phase II and III (2007) | 167 | FOLFUGEM, Gem + Ox, Gem then Gem + RT (55 Gy)<br>Gem + Ox | NR | NR | 13.1 (all) | [69] |
| Krishnan prospective (2007) | 247 UR<br>76 | Gem then Gem + RT (30–55 Gy)<br>5-FU, Gem, Cape | NR | NR | 9.1 (all) | [70] |
| Mukhergee (2013) randomized Phase II | 74 UR, 38 UR | Gem or Cape then Gem or Cape + RT (58 Gy)<br>Gem or Cape | NR | NR | 15.2 (Gem), 13.4 (Cape) | [72] |
| Leone prospective (2013) | 15 BR, 24 UR | Gem + Ox then Gem + RT (50.4 Gy) | 28.2 | 100 | 27.8 (BR), 13.3 (UR) | [71] |
| Polistina prospective (2010) | 33 UR | Gem then Gem + SBRT (30 Gy, 3 fractions) | 8 | 66 | 10.6 (all) | [73] |

5-FU: 5 fluorouracil; Bev: Bevacizumab; BR: Borderline resectable; Cape: Capecitabine; Cis: Cisplatin ; FOLFIRINOX: 5-fluorouracil, oxaliplatin, irinotecan, and leucovorin; Gem: Gemcitabine; GTX: Gemcitabine, docetaxel and capecitabine; Gy: Gray; IMRT: Intensity-modulated radiation therapy; IORT: Intraoperative radiation therapy; NR: Not reported; Ox: Oxaliplatin; R: Resectable; RT: Radiotherapy; S1: Pral 5-fluorouracil; SBRT: Stereotactic body radiotherapy; Tax: Docetaxel; UR: Unresectable.

distant failure rate [83]. Since it is often difficult for patients to tolerate aggressive chemotherapy combined with radiation, incorporating neoadjuvant chemotherapy followed by chemoradiation has been explored. The potential benefit of this method is the ability to deliver systemic doses of cytotoxic therapy to address occult micrometastatic disease early in the treatment, followed by additional local therapy for those patients who do not progress during chemotherapy. A Phase II trial exploring this approach evaluated three cycles of induction full-dose gemcitabine with an accelerated radiation fractionation treatment delivered during the second cycle. Results were encouraging with an 85% resection rate and median OS and 2-year OS rates of 26 months and 61%, respectively, for those undergoing surgery [42].

Others have investigated the incorporation of highly targeted radiation delivery approaches in the neoadjuvant setting in attempt to deliver more biologically effective doses of radiation while reducing toxicities of surrounding normal tissues. Given the close proximity of the pancreas to the stomach and small bowel, the predominant high-grade toxicity that can result from pancreatic stereotactic body radiotherapy (SBRT) is gastrointestinal. The major advantage of proton beam over conventional radiation is that the energy distribution of protons can be directed and deposited in tissue volumes designated by the physicians in a 3D pattern. Investigators from Massachusetts General Hospital first reported the results of a Phase I/II study of preoperative short-course proton beam radiation with capecitabine as neoadjuvant treatment for pancreatic cancer [84,85]. These results were especially promising when compared with a similar study using the same dose escalation schema and photon radiation in which unexpected intraoperative complications occurred (63 vs 27%, respectively) [86]. Although the safety of this approach was established in patients with 'resectable' pancreatic cancer, clinical trials are underway investigating the use of neoadjuvant proton beam radiation in patients with borderline, locally advanced unresectable or medically inoperable pancreatic cancer [87].

SBRT is a technology that allows for the precise and focused delivery of a few fractions of radiation in the ablative dose range. By ensuring accurate radiation targeting using image guidance, as well as highly conformal radiation dose distribution with a steep gradient, it is possible to deliver high doses of radiation to the pancreas while limiting dose to surrounding normal tissue. The first studies of pancreatic SBRT were conducted in patients with locally advanced disease and attempted to define the optimal radiation dose and delivery method to maximize tumor control while minimizing gastrointestinal toxicity. An early study of 77 patients treated with SBRT (25 Gy in a single fraction) resulted in a 1-year OS of 21% and locoregional control of approximately 90% [88]. Using this high dose of radiation, the late >grade 3 toxicity rate was 9% and consisted mainly of gastrointestinal ulceration and bleeding. To improve upon these results, a Phase II multi-institutional study delivered 33 Gy in 5 fractions to 49 patients after gemcitabine therapy [89]. Patients treated using this fractionated approach had a 1-year OS of 59%, locregional recurrence rate of 78% and a lower rate of severe late gastrointestinal toxicity (6%) [89]. Neoadjuvant SBRT has been studied in patients with borderline resectable pancreatic cancer, with the goal of downstaging the tumor to improve R0 resection rates and local-regional control. A retrospective study included 110 patients with borderline resectable and 49 with locally advanced pancreatic cancer treated with various chemotherapy regimens followed by SBRT using a dose-painting technique to deliver 30 Gy in 5 fractions to the entire tumor while escalating dose to regions of vascular abutment/encasement to 40 Gy [90]. The intention behind delivering a higher dose at the tumor–vascular interface was to increase regression of tumor away from the vessel. Patients underwent restaging studies and were considered for surgery 4 weeks after SBRT. The results of this approach are promising; 51% of borderline resectable patients underwent surgery and 96% had an R0 resection. One study reported data from 21 patients with borderline resectable (48%) and locally advanced unresectable (52%) tumors who received FOLFIRNOX (median: 4.7 cycles) followed by SBRT. Dose reductions for FOLFIRINOX were required in 29% of patients and 9% were unable to tolerate treatment. Disappointingly, 14% had disease progression following chemotherapy and 33% proceeded to surgery, with an additional 28% found to be unresectable at the time of procedure [91]. While there are no randomized trials to compare neoadjuvant chemotherapy alone versus chemotherapy and SBRT

for borderline resectable and locally advanced pancreatic cancer, a retrospective study suggests that the addition of SBRT may improve R0 resection rates [92]. Neoadjuvant systemic chemotherapy followed by SBRT remains an attractive and promising approach for the management of patients with nonmetastatic pancreatic cancer and continues to be a subject of clinical investigation [93].

### • Neoadjuvant chemotherapy (without radiation)

Some investigators believe that radiation does not produce a significant enough response and have investigated more aggressive systemic neoadjuvant chemotherapy regimens without concurrent radiation. This strategy maximizes systemic therapy dosing without added toxicity, theoretically leading to more effective elimination of distant micrometastasis and potentially improved long-term outcome. To date, no clinical trial has compared neoadjuvant chemotherapy to chemoradiation.

Sahora *et al.* conducted two Phase II gemcitabine-based neoadjuvant trials in patients with borderline resectable or unresectable pancreatic cancer. The gemcitabine and oxaliplatin as neoadjuvant therapy for locally advanced, nonmetastatic pancreatic cancer trial (NeoGemOx) included 15 patients with borderline resectable tumors and 18 with unresectable tumors resulting in a 39% resection rate, R0 resection rate of 69% and median OS of 22 months for those who underwent resection compared with 12 months for those who did not [74]. The gemcitabine and oxaliplatin as neoadjuvant therapy for locally advanced, nonmetastatic pancreatic cancer trial (NeoGemTax) treated a similar population of 12 borderline resectable and 13 unresectable patients and a similar 32% resection rate was observed. The R0 resection rate was 87% and a median OS of 16 months was observed for those who underwent resection compared with 12 months for those who did not [75]. Despite a lack of radiation and inclusion of patients with locally advanced unresectable disease in these trials, the overall resection and R0 resection rates were high, indicating that chemotherapy alone has a role in the neoadjuvant setting.

Since FOLFIRINOX is superior to gemcitabine in good performance status patients [4] with metastatic pancreatic cancer, several retrospective studies have evaluated the use of this regimen in the neoadjuvant setting reporting resection rates ranging from 33 to 42% and R0 resection rates from 55 to 92% [21,53,91,94–96]. Since there is significant toxicity associated with this regimen, investigators are exploring a modified FOLFIRINOX dose schedule as neoadjuvant therapy [95]. A recently published meta-analysis including 13 studies and 253 patients with initially resectable, borderline resectable and unresectable disease reported a 39% resection rate and 85% R0 resection rate. Of particular interest, 64% of patients with borderline resectable tumors underwent R0 resections compared with 23% of those with initially unresectable tumors [96]. **Table 4** summarizes trials that have utilized neoadjuvant chemotherapy strategies (without radiation) in the treatment of borderline resectable or locally advanced unresectable pancreatic cancer. We await the results of prospective trials and longer follow-up for survival outcomes associated with this approach.

## Locally advanced unresectable disease

As previously noted, many of the early studies included both patients with borderline resectable and locally advanced unresectable pancreatic cancer. An early study from Duke including 25 patients with locally advanced pancreatic cancer treated with neoadjuvant chemoradiation found that only a small percent were downstaged, with 27.3% with decreased size of the primary tumor and 13.6% meeting criteria for radiographic regression [97]. In a subsequent report including 53 patients with potentially resectable and 58 with locally advanced unresectable pancreatic cancer who received neoadjuvant chemoradiation, only 19% of those with locally advanced disease underwent resection, with 11% radiographically downstaged from locally advanced to potentially resectable by neoadjuvant [8]. Memorial Sloan–Kettering reported the largest study including 87 patients locally advanced pancreatic cancer who received neoadjuvant therapy. In this study, only 3.4% had significant radiographic response leading to surgical exploration [98]. These studies indicate that a small population of locally advanced unresectable pancreatic cancer patients is downstaged following preoperative therapy, however, radiographic downstaging may not be adequate to determine which patients may benefit from neoadjuvant therapy. Development of treatment response indicators (clinical, radiographic,

**Table 4. Summary of neoadjuvant trials using chemotherapy (without radiation) in patients with borderline resectable or locally advanced disease.**

| Study (year) | Patients (n) | Regimen | Resection rate (%) | R0 rate (% of resected) | Median OS (months) | Ref. |
|---|---|---|---|---|---|---|
| Lee Phase II (2008) | 18 BR<br>25 UR | Gem + Cape | 61 BR<br>24 UR | 82 BR<br>83 UR | 32 R<br>13 UR | [24] |
| Sahora Phase II (2011) | 18 BR<br>15 UR | Gem + Ox | 39 | 69 | 22 R<br>12 UR | [74] |
| Sahora Phase II (2011) | 12 BR<br>13 UR | Gem + Tax | 32 | 87.5 | 16 (all) | [75] |
| Hosien retrospective (2012) | 14 BR<br>4 UR | FOLFIRINOX only in 8 + CRT in 9 without response | 88<br>33 | 71<br>100 | 16 R (all) | [21] |

BR: Borderline resectable; Cape: Capecitabine; CRT: Chemoradiation; FOLFIRINOX: 5-fluorouracil, oxaliplatin, irinotecan, and leucovorin; Gem: Gemcitabine; Ox: Oxaliplatin; R: Resectable; Tax: Docetaxel; UR: Unresectable.

biochemical) will be important in tailoring prospective validation studies and patient selection for subsequent surgical exploration.

In the Gillen meta-analysis, approximately a third of all initially unresectable tumors (including borderline and locally advanced cancers) proceeded to surgery following neoadjuvant treatment [15]. Similar results were reported in another meta-analysis including 14 studies and 536 patients [99]. Andriulli *et al.* reported a small benefit to the use of neoadjuvant therapy in patients with unresectable pancreatic cancer [23]. To date, no Phase III trials directly comparing neoadjuvant therapies to adjuvant therapies have been published. However, multiple Phase I and II clinical trials have evaluated the role of neoadjuvant radiation, chemotherapy and chemoradiation regimens in pancreatic cancer. In conclusion, numerous studies suggest that many patients with borderline resectable and fewer patients with locally advanced unresectable pancreatic cancer who receive neoadjuvant therapy may benefit from an improved probability of R0 resection, resulting in similar outcomes as patients who present with initially resectable disease [15].

## Radiologic assessment of response to neoadjuvant therapy

The optimal way to monitor a response to neoadjuvant therapy has not been established. Typically, patients undergo serial imaging by CT to evaluate response and resectability. However, there are inconsistent data surrounding radiological response following neoadjuvant therapy. In a retrospective review of 16 patients treated with radiation, cisplatin, IFN-α and 5-FU on a treatment protocol for locally advanced pancreatic cancer, no patient demonstrated regression of abutment or encasement of originally involved vessels on reimaging. In addition pre- and post-treatment tumor densities were not statistically different [100]. It is important to point out, however, that these treatments are not the most standardly used in the neoadjuvant setting. Other investigators reported similar observations for 50 patients with borderline resectable pancreatic cancer who underwent neoadjuvant chemoradiation. In spite of the fact that comparisons of pre- and post-treatment CT images demonstrated no significant change in tumor size or degree of tumor–vessel involvement in the majority of patients, 58% underwent resection with 93% R0 rate, 72% node-negative rate and 54% with moderate pathologic response [101]. A larger retrospective study reported that use of contrast-enhanced CT demonstrated rare downstaging after neoadjuvant therapy using the modified Response Evaluation Criteria in Solid Tumors tool for 129 patients with borderline resectable pancreatic cancer, and should not be used for evaluation of treatment-related end points in this setting [78].

A more recent study prospectively evaluated the ability of contrast-enhanced CT to evaluate tumor response and predict resectability after neoadjuvant chemotherapy and radiation therapy in 47 patients with locally advanced pancreatic cancer. In this study, 33 patients underwent R0 resection and 14 had R1 resection or no resection at all. Partial regression of superior mesenteric vein–portal vein contact was observed in ten cases and was associated in all cases with R0 resection. Partial regression of any peripancreatic vascular axis was observed in 22 patients and was associated with R0 resection in 91% of cases. Persistence of superior mesenteric

vein–portal vein stenosis after chemoradiation was not predictive of R1 resection. The authors concluded that partial regression of tumor–vessel contact indicates suitability for surgical exploration, independent of decrease in tumor size or amount of residual vascular involvement [102].

Functional imaging modalities such as PET to follow tumor response to neoadjuvant therapy may be considered and are a focus of current investigation [103]. Others have proposed incorporation of biomarkers in the reassessment of patients with pancreatic cancer who undergo preoperative therapy. One study demonstrated that normalization of CA 19-9 (<40 U/ml) is an independent prognostic factor for OS for both unresected (15 months for normalization of CA19-9 vs 11 months) and resected (38 months for normalization of CA 19-9 vs 26 months) [104]. Although CA 19-9 is not used in decision-making for surgical resection following neoadjuvant therapy, quantitative changes in CA 19-9 may be useful in re-evaluation of patients especially in the absence of a radiographic response. Other biomarkers are being explored in this setting, but in the meantime patients who have been reimaged and are without disease progression, should be routinely explored after neoadjuvant therapy as imaging may not accurately reflect a biological/pathological response.

## Current neoadjuvant trials

As the optimal neoadjuvant regimen is not yet known, multiple clinical trials are currently evaluating several treatment strategies.

Neoadjuvant chemotherapy using FOLFIRINOX has been adopted by the Alliance for Clinical Trials in Oncology in a multicenter single-arm pilot study (Alliance A021101) for patients with borderline resectable disease. In this study, patients receive FOLFIRINOX followed by chemoradiation standard fractionation (50.4 Gy with concurrent capecitabine) followed by surgery and adjuvant gemcitabine. This trial is the first multicenter trial specifically evaluating neoadjuvant FOLFIRINOX in pancreatic cancer. The primary aims of this study include accrual rate, treatment-related toxicities, rate of treatment delay >4 weeks, and completion rate of preoperative and operative therapy. Secondary end points include R0/R1 resection rates, radiographic and histological response, time to locoregional and distant recurrence, and OS. We anticipate results in 2020 [29].

The ongoing NEOPA trial (NCT01900327) is the first study to investigate the impact of the neoadjuvant approach on survival of patients with resectable pancreatic cancer. In this prospectively randomized Phase III trial, patients receive neoadjuvant chemoradiation followed by curative surgery versus primary surgery followed by adjuvant therapy. The primary end point of this study is 3-year OS. Once this study completes accrual of 410 patients, R0 and R1 rates, surgical resectability rate, local and distant disease-free and global survival, and first site of tumor recurrence will also be compared for both approaches [105,106].

The pending NEOPANC trial (NCT01372735) is a single-arm prospective Phase I/II study investigating neoadjuvant short-course intensity-modulated radiation therapy (5 Gy × 5) prior to surgery and intraoperative radiation therapy (15 Gy) followed by adjuvant chemotherapy for patients with resectable pancreatic cancer [107].

We also await the results of recently completed trials evaluating neoadjuvant gemcitabine-based regimens including:

- NEOPAC study (NCT01521702), a multicenter prospective randomized Phase III trial, comparing neoadjuvant gemcitabine and oxaliplatin followed by surgery and adjuvant gemcitabine versus initial surgical resection followed by adjuvant gemcitabine in patients with biopsy-proven resectable pancreatic head adenocarcinoma. This study compares progression-free survival rates for both approaches [108]. There is no radiation included in this trial;
- GAIN-1 trial, Gemcitabine With Abraxane and Other Investigational Therapies in Neoadjuvant Treatment of Pancreatic Adenocarcinoma (NCT01470417) [109], with primary end points including pathologic downstaging and margin status, radiographic response and biochemical response in patients with locally advanced and borderline resectable pancreatic cancer;
- Regional Chemotherapy in Locally Advanced Pancreatic Cancer: RECLAP trial (NCT01294358) which explores intra-arterial gemcitabine delivered to the tumor through an indwelling subcutaneous port. End points of this study include toxicity, disease-free survival and OS, and conversion

## EXECUTIVE SUMMARY

### Background

- Surgical resection is considered the only potentially curative treatment modality in pancreatic cancer.
- Neoadjuvant therapy has the potential to increase the number of patients eligible for curative resection and increase the R0 resection rate.

### Limitations of available data

- A number of publications include patients with resectable, borderline resectable and locally advanced unresectable tumors rendering the results difficult to interpret.
- Interpretation of data from early studies is limited by use of older chemotherapy regimens, monochemotherapy or radiation alone in addition to small sample size.

### Preoperative staging & surgical resectability

- The ability to accurately stage patients is essential for the development and evaluation of stage-specific therapies to maximize outcome and quality of life for all patients.
- Historically, the lack of a standard definition of surgical resectability has confounded surgical outcome data.
- Standardization of definitions of resectability has recently been incorporated into staging systems for pancreatic cancer.
- Many trials incorporate patients with borderline and unresectable tumors, making data difficult to interpret.

### Resectable disease

- Conflicting data exist regarding the benefit of neoadjuvant therapy in patients with initially resectable pancreatic tumors.

### Borderline resectable disease

- Patients with borderline resectable tumors are most likely to benefit from downstaging using the neoadjuvant approach.
- The use of neoadjuvant chemoradiation is associated with higher response and R0 resection rates compared with the surgery first approach in this subset of patients.
- Studies are investigating alternative methods of radiation delivery offering enhanced biologically effective tumor doses and relative normal tissue sparing.
- Patients with initial borderline resectable disease who undergo R0 resection have similar outcomes to those who are diagnosed with initially resectable disease.
- Distant failures continue to limit survival in patients who receive neoadjuvant chemoradiation.
- Studies have demonstrated feasibility and efficacy of high-dose systemic chemotherapy followed by chemoradiation in an attempt to improve upon the distant failure rate although longer follow-up is needed.
- Aggressive systemic treatment regimens have been used in the neoadjuvant setting resulting in similar resection and R0 resection rates despite the omission of radiation.

### Unresectable disease

- A small population of locally advanced unresectable pancreatic cancer patients is downstaged following preoperative therapy.
- Radiographic downstaging may not be adequate to determine which patients may benefit from neoadjuvant therapy.
- Development of treatment response indicators will be important in tailoring prospective validation studies and patient selection for subsequent surgical exploration.

### Radiologic assessment of response to neoadjuvant therapy

- There are inconsistent data surrounding the correlation of radiological and pathological response following neoadjuvant therapy.

## EXECUTIVE SUMMARY (CONT.)

**Radiologic assessment of response to neoadjuvant therapy (cont.)**

- The optimal method of response evaluation following neoadjuvant therapy is yet to be determined and will likely incorporate biomarker, and perhaps functional imaging.

**Current neoadjuvant trials**

- Many trials continue to evaluate the potential benefit of neoadjuvant therapy in pancreatic cancer using different chemotherapy and radiation approaches.
- We should continue to enroll eligible patients in clinical trials to gain further insight into the benefit of this approach.

from unresectable to potentially resectable tumors [110].

Other ongoing trials that continue to examine the efficacy of various neoadjuvant strategies include:

- Neoadjuvant GTX with chemoradiation for pancreatic cancer (stage II/III; NCT01065870) [111];
- Combination chemotherapy (gemcitabine, docetaxel and capecitabine), intensity-modulated radiation therapy and surgery in treating patients with localized pancreatic cancer that can be removed by surgery (NCT00609336) [112];
- Neoadjuvant FOLFIRINOX followed by capecitabine and limited field radiation for localized pancreatic head adenocarcinoma (NCT01677988) [113];
- Vaccine therapy with or without cyclophosphamide in treating patients undergoing chemotherapy and radiation therapy for stage I or stage II pancreatic cancer that can be removed by surgery (NCT00727441) [114].

## Conclusion

Resectable pancreatic cancer represents approximately 15–20% of patients and surgical resection alone is inadequate. The neoadjuvant approach holds promise to increase the number of patients that can undergo curative resection with negative margins, which is the most important factor influencing survival, especially in patients with borderline resectable disease. Neoadjuvant trials for patients with nonmetastatic pancreatic cancer patients are ongoing and patients should be encouraged to enroll in clinical trials. In addition, improvements in staging techniques and standardization of imaging criteria to evaluate resectability at initial diagnosis and after neoadjuvant therapy will continue to be important in defining operability and determining which subset of patients are likely to benefit from an attempt at curative surgery. As we attempt to identify subsets of patients who may benefit from aggressive therapies including neoadjuvant approaches, translational science and biomarker studies should be incorporated into prospective validation studies.

## Future perspective

As we continue to study and better understand the biology of pancreatic cancer and genomic subtypes, we will be able to develop more effective chemotherapy and targeted agents that may be incorporated into neoadjuvant treatment strategies. By incorporating these new therapies into neoadjuvant strategies for patients with nonmetastatic pancreatic cancer, we will be better able to assess efficacy *in vivo* and correlate with pathologic response. Early data will use resection and R0 resection rates as a surrogate for efficacy, but long-term follow-up will demonstrate whether treating patients with aggressive neoadjuvant regimens translates into a survival advantage. We also await results of larger randomized trials to help determine the optimal setting for use of neoadjuvant therapies. In addition, use of newer radiation technologies and delivery methods may help to optimize local response rates leading to more curative resections and improved survival.

### Financial & competing interests disclosure

*The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.*

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