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## Neoadjuvant therapy for resectable pancreatic cancer

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### Abstract

The use of neoadjuvant therapies has played a major role for borderline resectable and locally advanced pancreatic cancers (PCs). For this group of patients, preoperative chemotherapy or chemoradiation has increased the likelihood of surgery with negative resection margins and overall survival. On the other hand, for patients with resectable PC, the main rationale for neoadjuvant therapy is that the overall survival with current strategies is unsatisfactory. There is a consensus that we need new treatments to improve the overall survival and quality of life of patients with PC. However, without strong scientific evidence supporting the theoretical advantages of neoadjuvant therapies, these potential benefits might turn out not to be worth the risk of tumors progression while waiting for surgery. The focus of this paper is to provide the readers an overview of the most recent evidence on this subject.

**Key words:** Pancreatic adenocarcinoma; Neoadjuvant chemotherapy; Neoadjuvant chemoradiation therapy; Meta-analysis; Decision analysis; Borderline resectable; Locally advanced; Randomized controlled trial; Phase I trial; Phase II trial; Phase III trial

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**Core tip:** The use of neoadjuvant therapy for patients with resectable pancreatic cancer (PC) has been used by an increasing number of cancer centers around

the world. The main rationale of using neoadjuvant therapies in resectable PC is the hope that patients' likelihood of long-term overall survival will benefit from the chemo or chemoradiation therapy administered when their overall conditions allow them to tolerate the treatment. At this time, there is no phase III trial to support the use of neoadjuvant therapies in resectable PC. Without strong scientific evidence supporting the theoretical advantages of neoadjuvant therapies, these potential benefits might turn out not to be worth the risk of tumors progression while waiting for surgery.

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## INTRODUCTION

The most common form of pancreatic cancers (PCs) originates from the ductal cells of the exocrine gland<sup>[1,2]</sup>. In the United States, it represents the fourth leading cause of cancer-related deaths with 44000 new cases per year<sup>[2,3]</sup>. The prognosis of patients with PC remains poor with only 5%-10% of patients alive after five years<sup>[4]</sup>. Their outcome is significantly improved if they undergo surgery; however, even in this case, 5-year survival is only 25%-40%<sup>[1,4]</sup>. PC is a difficult tumor to cure as it behaves as a systemic disease even in its early stages. Although surgery remains the only potential cure, it is still inadequate for most of the patients who will develop recurrent disease within five years. The use of multimodality therapy (surgery, chemotherapy and radiation therapy) provides the best chance for long-term survival<sup>[5]</sup>, but the ideal sequence and duration of these treatments remain unknown due to the lack of scientific evidence.

Despite these limitations, there is a consensus that, because of the poor outcomes observed with old treatment modalities, new strategies are necessary<sup>[6]</sup>. Among them, the use of neoadjuvant chemotherapy has gained traction and, in recent years, an increasing number of oncologists and surgeons are recommending it<sup>[7,8]</sup>.

For borderline resectable and locally advanced PC, there is evidence that neoadjuvant therapy increases the probability of negative resection margins and the number of patients who can undergo surgery<sup>[8,9]</sup>. On the other hand, for resectable PC, neoadjuvant chemotherapy or chemoradiation remains debatable because of the conflicting data on its effectiveness, and because there is no phase III trial to support their use<sup>[10-12]</sup>. The focus of this publication is to provide an overview of the most recent evidence on this topic, appraise the potential benefits and disadvantages of neoadjuvant vs surgery first approach, and finally, to

review the ongoing phase III trials that might address some of the questions that are still unanswered.

## RESECTABILITY

Surgery remains the only potential cure for patients with PC. Determining if the disease is resectable or not at the time of diagnosis is crucial, but often subjective to the interpretation of preoperative imaging tests. Resectability is usually determined using a combination of imaging tests and laparoscopic assessment of the peritoneal cavity to rule out small hepatic or peritoneal metastases that might be missed even with high-quality contrast enhanced computerized tomography (CT scans) or magnetic resonance imaging (MRI) studies<sup>[2,13]</sup>. There are several definitions of tumor resectability that are summarized in Table 1<sup>[13-16]</sup>. All criteria currently used to identify patients with resectable disease are based on the degree of contact between the tumor and blood vessels adjacent to the pancreas in the absence of distant disease.

## TREATMENT STRATEGIES

Until recently, the most accepted treatment paradigm for resectable PC was surgery followed by postoperative systemic chemotherapy or chemoradiation. In recent years, the use of systemic pre-operative chemotherapy alone or in combination with radiation therapy has been offered to an increasing number of patients with the main intent of reducing the size of the tumor, increase the likelihood of negative resection margins, and test the effects of cytotoxic medications *in vivo*<sup>[9]</sup>. Most patients who are treated with neoadjuvant chemotherapy or chemoradiation receive oral or intravenous medications for the duration of three to six months before undergoing surgery<sup>[17]</sup>.

## ADVANTAGES AND DISADVANTAGES OF NEOADJUVANT THERAPY

Neoadjuvant therapy has several theoretical benefits but also drawbacks (Table 2). It is usually well tolerated, does not increase the perioperative morbidity, reduces the interval between diagnosis and the initiation of systemic treatment<sup>[17]</sup> and has the potential benefit of facilitating radical resections by lessening the size of the tumors before surgery. Despite these advantages, postponing surgery for neoadjuvant treatment might give enough time for the tumor to progress and become unresectable<sup>[17,18]</sup>.

## RECENT STUDIES

Table 3 summarizes details of the latest phase I and II trials reporting the outcomes of patients treated with neoadjuvant chemotherapy or chemoradiation for radiologically resectable PC. In all these studies, tumor

**Table 1 Operational definitions of resectability of pancreatic cancer**

| Classification of resectability of pancreatic cancer | Definition by AHPBA/SSO/SSAT   | Definition by MD Anderson Cancer Centre   |
|--|--|---|
| Resectable   | The tumor does not abut or encase any of the following vascular structures: the superior mesenteric vein or portal vein, superior mesenteric artery or common hepatic artery or celiac trunk   | The tumor abuts or encases the superior mesenteric vein or portal vein without occluding the lumen. Absence of abutment or encasement of the superior mesenteric artery, common hepatic artery or celiac trunk  |
| Borderline resectable                                | Abutment, encasement or occlusion of the superior mesenteric vein or portal vein. Abutment of the superior mesenteric artery. Abutment or short segment encasement of the common hepatic artery. Absence or abutment or encasement of the celiac trunk   | Tumor causing a short-segment occlusion of the superior mesenteric vein or portal vein. Presence of abutment of the superior mesenteric artery, abutment or encasement of a short segment of the common hepatic artery, absence of abutment or encasement of the celiac trunk |
| Locally advanced                                     | Tumor located in the proximity of the superior mesenteric vein or portal vein and the superior mesenteric vein or portal vein are unable to be resected and reconstructed. Tumor encasing the superior mesenteric artery, or long-segment encasement of the common hepatic artery, or abutment of the celiac trunk | Tumor located in the proximity of the superior mesenteric vein or portal vein that are not reconstructible. Presence of tumor encasement of the superior mesenteric artery, long-segment encasement of the common hepatic artery and encasement of the celiac trunk           |

AHPBA: Americas Hepato-Pancreato-Biliary Association; SSO: Society of Surgical Oncology; SSAT: Society for Surgery of the Alimentary Tract.

**Table 2 Summary of the benefits and drawbacks of neo-adjuvant and adjuvant therapies for the treatment of patients with resectable pancreatic cancer**

| Neo-adjuvant therapy  |   | Adjuvant therapy   |  |
|---|---|--|--|
| Advantages  | Disadvantages   | Advantages   | Disadvantages  |
| In comparison to the strategy of adjuvant chemotherapy or chemoradiation therapy where up to 50% of patients who undergo surgery cannot complete their therapy due to complications or decline of their function, neoadjuvant strategy has been shown to be well tolerated by the majority of patients and therefore a greater proportion receive systemic therapy<br>The use of neo-adjuvant therapy might sterilize the presence of small metastatic disease and reduce the size of the primary tumor. Downsizing the primary tumor might increase the likelihood of negative resection margins | Neoadjuvant therapy requires the placement of biliary stents to decompress the biliary obstruction prior to surgery of patients with jaundice. The placement of biliary stents before surgery increases the risk of infections in the perioperative period<br>Pre-operative therapy delays surgery and increases the risk of progression of the disease to the point of becoming unresectable | One of the advantages of surgery first approach is that patients have a short period of time between when they are diagnosed and when they undergo resections of their tumor. This might have some benefits on patients' and their families' anxiety<br>Since patients undergo surgery as soon as possible after their diagnosis, their risk of tumor progression is smaller than patients who wait a longer time before being operated on | About 20%-50% of patients will not be able to complete their postoperative therapy due to surgical complications or overall decline of their performance status<br>One of the risk of undergoing surgery first for pancreatic cancer is that, some patients will undergo a major operation without the benefit of being cured as they might already have micrometastases |
| Treating patients before surgery, gives physicians some time to identify the tumors with poor prognosis that do not respond to the therapy. The identification of those patients who are likely to experience early metastases is very important because prevents them to undergo unnecessary surgery<br>One of the advantages of using chemotherapy or chemoradiation therapy before surgery is that the blood supply to the pancreatic tumor is not compromised by the ligation of vessels. Therefore, chemotherapy agents can be delivered to the pancreatic tumor in higher concentrations    | The use of neoadjuvant therapies might increase the risk of perioperative morbidity and mortality due to the side effects of chemotherapy or chemoradiation   | Patients who undergo surgery first do not routinely need the placement of biliary stents to release their jaundice before undergoing resection   | Patients who undergo surgery first have a higher risk of positive resection margins  |

response was evaluated differently as some investigators reported radiographic or clinical response before surgical exploration and others the histopathological response observed in the surgical specimen.

Gillen *et al*<sup>[17]</sup> published the first systematic meta-analysis on the effects of preoperative therapy in PC.

The authors reviewed 515 studies, but only 111 trials were included with a total of 4394 patients. Among these studies, 15 were a phase I, 13 were a phase I / II , 28 were phase II , 14 were cohort studies, and 41 were case series. Most the studies were prospective (No. 78). Chemotherapy was used as neoadjuvant therapy in

**Table 3 Phase I and Phase II studies assessing the outcomes of patients with resectable pancreatic cancer treated with neoadjuvant therapies**

| Author (yr)/ journal/trial/ institution                                  | No. of patients | Clinical stage/ duration of neoadjuvant therapy | Study design  | Chemotherapy/ chemoradiation   | Radiological response  | Resection rate (%) | Negative resection margins (%) | Median overall survival (mo)   |
|--|-----------------|---|---|--|--|--------------------|--------------------------------|--|
| Hoffman (1998)/ <i>J Clin Oncol</i> /ECOG                                | 53              | Resectable PC/2.8 mo                            | Phase II, prospective study, November 1991 to September 1993                | 5-FU (1000 mg/m <sup>2</sup> per day + Mitomycin C (10 mg/m <sup>2</sup> ) + RT (50 Gy)                        | Partial response 8%; Stable disease 78%; Progression 16%                       | 45                 | 67                             | 15 with surgery; without surgery 8; 10.9 for the entire cohort               |
| Pisters (2002)/ <i>J Clin Oncol</i> /MD Anderson Cancer Centre           | 35              | Resectable PC/1.8 mo                            | Phase II, prospective study, timeframe not specified                        | Paclitaxel (60 mg/m <sup>2</sup> weekly, RT (30 Gy)  | Partial response 4%; Stable disease 23%; Progression 20%                       | 57                 | 68                             | 12 for the entire cohort; 19 with surgery; 10 without surgery                |
| Joensuu (2004)/ <i>Int J Radiat Oncol Biol Phys</i> /Helsinki University | 28              | Resectable PC/3.5 mo                            | Phase I - II prospective study, November 1999 to December 2001              | Gemcitabine (20 mg/m <sup>2</sup> vs 50 mg/m <sup>2</sup> vs 100 mg/m <sup>2</sup> ) twice a week + RT (50 Gy) | NA   | 71                 | NA                             | 13.6 for the entire cohort   |
| Talamonti (2006)/ <i>Ann Surg Oncol</i> /Northwestern University         | 20              | Resectable PC/3.8 mo                            | Phase II prospective, multi-institutional study, April 2002 to October 2003 | Gemcitabine (1000 mg/m <sup>2</sup> weekly) + RT (36 Gy)   | Partial response 15%; Stable disease 80%; Progression 5%                       | 85                 | 94                             | 26 mo with surgery   |
| Palmer (2007)/ <i>Ann Surg Oncol</i> /University of Birmingham           | 24              | Resectable PC/4 mo                              | Phase II, prospective study, November 1999 to May 2003                      | Gemcitabine (1000 mg/m <sup>2</sup> weekly)  | Partial Response 0%; Stable Disease 29%; Progression 4%; Unable to measure 4%  | 38                 | 75                             | 28.4 with surgery; 9.9 for the entire cohort                                 |
| Palmer (2007)/ <i>Ann Surg Oncol</i> /University of Birmingham           | 26              | Resectable PC/4 mo                              | Phase II, prospective study, November 1999 to May 2003                      | Gemcitabine (1000 mg/m <sup>2</sup> weekly) + Cisplatin (25 mg/m <sup>2</sup> )                                | Partial Response 0%; Stable Disease 66%; Progression 21%; Unable to measure 4% | 70                 | 75                             | 28.4 with surgery; 9.9 for the entire cohort                                 |
| Le Scodan (2009)/ <i>Ann Oncol</i> /SFRO-FFCD                            | 41              | Resectable PC/3 mo                              | Phase II, prospective study, January 1998 to March 2003                     | RT (50 Gy) + 5-FU (300 mg/m <sup>2</sup> daily) + Cisplatin (20 mg/m <sup>2</sup> )                            | Partial response 10%; Stable Disease 65%; Progression 25%                      | 63                 | 81                             | 11.7 with surgery; 9.4 for the entire cohort                                 |
| Heinrich (2008)/ <i>Ann Surg</i> /University Hospital of Zurich          | 28              | Resectable PC/2 mo                              | Phase II, prospective study, August 2001 to April 2007                      | Gemcitabine (1000 mg/m <sup>2</sup> twice weekly) + Cisplatin (50 mg/m <sup>2</sup> )                          | Partial response 4%; Stable Disease 61%; Progression 13%                       | 89                 | 80                             | 19.1 mo with surgery   |
| Evans (2008)/ <i>J Clin Oncol</i> /MD Anderson Cancer Centre             | 80              | Resectable PC/3 mo                              | Phase II, prospective study, July 1998 to October 2001                      | Gemcitabine (400 mg/m <sup>2</sup> weekly) + RT (30 Gy)  | NA   | 85                 | 82                             | 34 mo with surgery; 22.7 mo for the entire cohort; 7 mo without surgery      |
| Varadhachari (2008)/ <i>J Clin Oncol</i> /MD Anderson Cancer Centre      | 90              | Resectable PC/4.3 mo                            | Phase II, prospective study, October 2002 to February 2006                  | Gemcitabine (750 mg/m <sup>2</sup> weekly) + Cisplatin (30 mg/m <sup>2</sup> ) every 2 wk + RT (30 Gy)         | NA   | 58                 | 96                             | 31.0 mo with surgery; 17.4 mo for the entire cohort; 10.5 mo without surgery |
| Turrini (2009)/ <i>Oncology</i> /University Mediterranean                | 34              | Resectable PC/2.1 mo                            | Phase II, prospective study, May 2003 to July 2005                          | Docetaxel (30 mg/m <sup>2</sup> weekly) + RT (45 Gy)   | Partial response 9%; Stable disease 59%; Progression 32%                       | 68                 | 100                            | 32 mo with surgery; 15.5 mo for entire cohort; 11 mo without surgery         |

|  |   |                    |  |  |   |   |  |  |
|--|---|--------------------|--|--|---|---|--|--|
| Landry (2010)/ <i>J Surg Oncol/Emory University/Multicenter ECOG</i>       | 21  | Resectable PC/3 mo | Phase II, prospective two-arm study, October 2013 to June 2015   | Arm A: Gemcitabine (500 mg/m <sup>2</sup> ) weekly + RT (50 Gy) Arm B: Gemcitabine (175 mg/m <sup>2</sup> ) + Cisplatin (20 mg/m <sup>2</sup> ) + 5-FU (600 mg/m <sup>2</sup> ) + RT (50 Gy) | Arm A: Partial response 10%, Arm B: Partial response 18.2%              | NA  | NA   | Arm A: Entire cohort 19.4 mo. Arm B: entire cohort 13.4 mo. 26.3 mo with surgery |
| Wo (2014)/ <i>Radiother Oncol/Multicentric Shinoto (2013)/Cancer/Japan</i> | 10  | Resectable PC      | Phase I, prospective study   | Capecitabine (1650 mg/m <sup>2</sup> ) over 10 d + RT (30 Gy)  | NA  | 80  | NA   | NA   |
| O'Reilly (2014)/ <i>Ann Surg/Memorial Sloan Kettering Cancer Centre</i>    | 38  | Resectable PC      | Phase I, prospective study, April 2003 to December 2010  | Gemcitabine (1000 mg/m <sup>2</sup> ) + Oxaliplatin (80 mg/m <sup>2</sup> ) every 2 wk   | Partial response 3.8%; Stable disease 96.1%                             | 81  | 90   | 18.6 mo for entire cohort; NA for patients who underwent surgery                 |
| Golcher (2015)/ <i>Strahlenther Onkol/Germany</i>                          | 66 (33 patients allocated to surgery + 33 patients allocated to chemoradiation followed by surgery) | Resectable PC      | Phase II, prospective randomized trial with two arms: Primary surgery vs preoperative chemoradiation followed by surgery. June 2003 to December 2009 | Gemcitabine (300 mg/m <sup>2</sup> ) + Cisplatin (30 mg/m <sup>2</sup> ) + RT (50.4 Gy) (Preoperative for patients enrolled in Arm A)  | Partial response 10.5%; Stable disease 73.7%; Progression 7.9%; NA 7.9% | Preoperative chemoradiation: 69% Surgery first: 57% | Arm A (preoperative chemoradiation): 48. Arm B (surgery first): 51 | Arm A (preoperative chemoradiation): 18.9 mo. Arm B (surgery first): 25.0 mo     |
| Van Buren (2013)/ <i>Ann Surg Oncol/Multicenter/United States</i>          | 59  | Resectable PC      | Phase II, prospective study, February 2007 to February 2011  | Gemcitabine (1500 mg/m <sup>2</sup> ) ever 2 wk + Bevacizumab (10 mg/kg) + RT (30 Gy)  | Partial response 8.4%; Stable disease 73.7%; Progression 7.9%           | 74  | 88   | 19.7 mo with surgery; 16.8 mo for the entire cohort                              |

NA: Not available.

107 (96%) and radiotherapy in 104 (94%) with doses ranging from 24 to 63 Gy. In 13 trials, patients received intraoperative radiation therapy with doses between 10 and 30 Gy.

Six studies stated that the RECIST criteria were used to assess the preoperative radiological response to neoadjuvant therapy. The criteria used to evaluate tumor response were clearly stated in 44 studies, while in 61 studies the criteria used were not adequately reported. Pooled results of patients with resectable cancers at the time of diagnosis showed a complete response in 3.6%, partial response in 30.6%, progression in 20.9% and stable disease in 42.1%. Resections were performed in 73.6% (95%CI: 65.9%-80.6%) of patients. Perioperative morbidity occurred in 26.7% (95%CI: 20.7%-33.3%) and mortality in 3.9% (95%CI: 2.2%-6.0%) which were comparable to the outcomes

of patients undergoing surgery first. Negative resection margins (R0) were observed in 82.1% of patients (95%CI: 73.1%-89.6%) with a median survival of 23.3 mo (range 12-54). Analysis of trials with monotherapy vs poly-chemotherapy revealed higher rates of complete or partial response when multiple chemotherapy agents were used. Higher response rates, however, did not translate into higher resection rates.

One year later, Assifi *et al*<sup>[19]</sup>, published a second systematic review and meta-analysis of only phase II neoadjuvant therapy trials. Out of 397 studies published from 1993 to 2010, 14 trials were included with a total of 536 patients. All studies were prospective, with 12 out of 14 (86%) being a single arm. Patients who had resectable tumors were 402 (75% of the sample). Gemcitabine was used in 8 trials, while the remaining 6 used 5-FU. Radiotherapy was given in 12 of 14 studies

(85%) with doses ranging between 30 and 50.4 Gy. In patients with resectable disease at diagnosis, complete radiological response was observed in 0.8% (95%CI: 0.0%-2.6%), partial response in 9.5% (95%CI: 2.9%-19.4%), stable disease in 73.9% (95%CI: 63.2%-83.3%) and progression in 17.0% (95%CI: 11.9%-22.7%). After neoadjuvant therapy, the resection rate was 65.8% (95%CI: 55.4%-75.6%) and negative resection margins were observed in 85.1% (95%CI: 76.8%-91.9%). Median survival was 23.0 mo (range 11.7-34.0). The most significant finding of these two meta-analyses was that even if safe, neoadjuvant therapy did not seem to add any substantial survival advantage<sup>[18]</sup>.

Due to the heterogeneity of these studies, no conclusion can be drawn regarding the overall impact on survival and what are the most effective chemotherapy agents or the best combination of chemotherapy agents for resectable PC.

More recently, D'Angelo *et al*<sup>[20]</sup> completed another systematic review of randomized controlled trials on adjuvant and neoadjuvant therapies for resectable PC. Fifteen studies were included covering a period of 30 years (1985 to 2015). Their analysis suggested that despite all the best efforts, the question whether neoadjuvant therapy provides a better overall survival than adjuvant therapy remains unanswered.

## DECISION ANALYSES

VanHouten *et al*<sup>[21]</sup> used a decision analysis model to assess what is the best treatment strategy for resectable PC. A survival advantage of 7 mo was found in patients who underwent neoadjuvant therapy in comparison to surgery first (27.2 mo vs 19.9 mo).

Another Markov decision analysis by de Geus *et al*<sup>[22]</sup> supported the use of neoadjuvant chemotherapy that provided longer overall survival (32 mo vs 27 mo) and quality-adjusted life expectancy (25 mo vs 21 mo) in comparison to surgery followed by adjuvant chemotherapy. Sensitivity analysis of the model showed that if the probability of surgical resection after neoadjuvant therapy was lower than 57%, upfront surgery was the best treatment option.

Another group led by Sharma *et al*<sup>[23]</sup> compared the efficacy of neoadjuvant-based chemotherapy with adjuvant treatment with an intention-to-treat analysis using a two-arms Markov model. In the neoadjuvant group, patients were treated with an average of 3 mo of neoadjuvant therapy followed by surgery. After surgery, patients who received preoperative chemotherapy did not receive any adjuvant treatment. On the other hand, patients who underwent surgery first, underwent chemotherapy after they recovered from their operations. In this model, the median overall survival was longer for the neoadjuvant cohort (22 mo) in comparison to the adjuvant group (20 mo), and the cumulative quality-adjusted survival for patients who underwent the neoadjuvant strategy was

19.8 mo compared to 18.4 mo for patients who had adjuvant therapy. One-way sensitivity analysis showed that surgery first provided higher quality-adjusted survival rates if more than 44% of patients treated with neoadjuvant therapy experienced progression of their disease and failed to undergo surgical resection.

All these models provided evidence that neoadjuvant therapies have better overall survival and quality of life in comparison to surgery first, although the differences were clinically quite small.

## PERSISTENT CONTROVERSY

For borderline or locally advanced PC, the use of neoadjuvant therapy makes sense, and it is desirable for both patients and physicians. For patients' perspective, neoadjuvant treatments might decrease the tumor burden and give them the chance of becoming resectable. Similarly, for the surgeons' perspective, any reduction of the tumor size is welcomed as it facilitates the technical aspect of the resection around critical vascular structures such as the superior mesenteric-portal vein junction or superior mesenteric artery.

However, this is not the case for resectable PC. Neoadjuvant therapy does not facilitate surgery, as the tumor is resectable at the time of diagnosis. Preoperative therapy might increase the rate of negative margins; however, this needs to be proven in randomized controlled trials, as the current evidence is not sufficient. Furthermore, for patients' perspective, there is a considerable risk of missing out the only opportunity of being cured with surgery as the tumor might progress to become unresectable while neoadjuvant therapies are delivered.

Because the current evidence is inadequate, there are no unequivocal criteria able to assist health-care providers to select the strategy with the best long-term survival for resectable PC. Physicians are left to decide whether to use neoadjuvant therapy and whether to use of one or multiple pre-operative chemotherapeutic agents or chemoradiation is worth the risk of toxicities and the possibility of disease progression. In theory, neoadjuvant treatments would be unanimously recommended for patients at high risk of positive resection margins, as their surgery would not be curative. The selection of these patients is not easy. To overcome this concerns, Bao *et al*<sup>[24]</sup> developed a predictive module to maximize the probability of identifying patients with true resectable tumors by using commonly available preoperative imaging modalities. With this model, the authors could classify patients with low-risk and high-risk for non-curative resections and concluded that until better evidence is available, patients who are unlikely to have R0 margins should be treated with neoadjuvant therapy.

## FUTURE DIRECTIONS

D'Angelo *et al*<sup>[20]</sup> pointed out that the current literature is biased because the likelihood that radiologically

**Table 4** List of ongoing phase II and phase III trials comparing neoadjuvant therapies vs adjuvant strategies for resectable pancreatic adenocarcinoma

| Study                      | Design                         | No. of patients needed | Therapy   | Primary outcome                          |
|----------------------------|--------------------------------|------------------------|---|--|
| NEOPAC (NCT01314027)       | Phase III Enrollment 2009-2014 | 350                    | Neoadjuvant gemcitabineoxaliplatin + adjuvant gemcitabine vs Adjuvant gemcitabine   | Progression free survival                |
| NEOPAC (NCT01521702)       | Phase III Initiated in 2011    | 310                    | Preoperative FOLFIRINOX, followed by adjuvant gemcitabine after surgery vs adjuvant gemcitabine after resection                     | Five-year progression free survival      |
| NCT01900327                | Phase III                      | 410                    | Neoadjuvant gemcitabine-based chemoradiation therapy followed by adjuvant gemcitabine vs adjuvant gemcitabine                       | Three-year overall survival              |
| NCT01771146                | Phase II                       | 100                    | Neoadjuvant FOLFIRINOX  | Progression free survival                |
| NEONAX (NCT02047513)       | Randomized phase II            | 166                    | Neoadjuvant gemcitabine + nab-paclitaxel followed by adjuvant gemcitabine + nab-paclitaxel vs adjuvant gemcitabine + nab-paclitaxel | Disease-free survival at 18 mo           |
| NCT01150630                | Randomized phase II / III      | 370                    | Adjuvant PEXG vs adjuvant gemcitabine vs neoadjuvant PEXG - followed by surgery and then adjuvant PEXG                              | One year event-free survival             |
| ACOSOG-Z5041 (NCT00733746) | Phase II                       | 123                    | Neoadjuvant gemcitabine + erlotinib (completed; results pending)  | Two-year overall survival                |
| NCT00727441                | Phase II                       | 87                     | Neoadjuvant GVAX +/- IV or oral cyclophosphamide followed by adjuvant gemcitabine + CRT   | Safety, feasibility, and immune response |
| NCT02178709                | Phase II                       | 48                     | Neoadjuvant FOLFIRINOX  | Pathologic complete response             |
| GEMCAD1003 (NCT01389440)   | Phase II                       | 24                     | Neoadjuvant gemcitabine + erlotinib   | R0 resection rate                        |
| NCT02562716                | Phase II Enrollment 2015-2019  | 112                    | Neoadjuvant and adjuvant mFOLFIRINOX vs neoadjuvant and adjuvant Nab-paclitaxel and gemcitabine                                     | Overall survival                         |
| NCT02243007                | Randomized phase II            | 112                    | Neoadjuvant FOLFIRINOX vs gemcitabine + nab-paclitaxel  | 18-mo overall survival                   |
| NCT02030860                | Pilot                          | 15                     | Neoadjuvant gemcitabine + nab-paclitaxel ± paricalcitol   | Number of adverse events                 |
| NCT02305186                | Randomized phase I b/ II       | 56                     | Neoadjuvant capecitabine-based CRT ± pembrolizumab (MK-3745)  | Safety and immune response               |

CRT: Chemoradiation therapy; GVAX: Granulocyte-macrophage colony-stimulating factor gene-transfected tumor cell vaccine; PEXG: Cisplatin, epirubicin, capecitabine, gemcitabine; R0: Margin-negative surgical resection.

resectable PCs is indeed unresectable at the time of surgery is only about 40%<sup>[25]</sup>. Therefore, the only way to find out if there is any benefit from neoadjuvant therapy is to complete an intention to treat randomized controlled trial where one arm entails surgery followed by adjuvant therapy (current standard of care) and the second arm involves neoadjuvant therapy followed by surgery followed by adjuvant therapy (experimental group).

Recent chemotherapy regimens, such as FOLFI RINOX [folinic acid (leucovorin)/5-FU/Irinotecan/Oxaliplatin], have already demonstrated promising results in a small group of patients with borderline resectable tumors<sup>[26,27]</sup>. Given these findings, several ongoing prospective studies are examining the role of FOLFIRINOX in a neoadjuvant setting for resectable disease (Table 4). Other studies include NEOPAC, NEONAX, NCT01660711, and NCT02172976. NEOPAC (Adjuvant vs Neoadjuvant Plus Adjuvant Chemotherapy in Resectable Pancreatic Cancer) will compare neoadjuvant gemcitabine and oxaliplatin plus adjuvant gemcitabine vs adjuvant gemcitabine alone. NEONAX, (Neoadjuvant Plus Adjuvant or Only Adjuvant Nab-Paclitaxel Plus Gemcitabine for Resectable Pancreatic Cancer) will assess the effects of neoadjuvant plus

adjuvant Nab-Paclitaxel plus gemcitabine vs adjuvant only Nab-Paclitaxel plus gemcitabine. Other ongoing trials are a single-arm nonrandomized trial evaluating preoperative and postoperative FOLFIRINOX in patients with resectable disease (NCT01660711) and the multi-center German randomized trial investigating adjuvant gemcitabine compared with neoadjuvant and adjuvant FOLFIRINOX (NCT02172976).

## CONCLUSION

Based on the current literature, there is still insufficient evidence to fully support the use of neoadjuvant therapy for all patients with radiologically resectable PC. Randomized controlled trials are urgently needed to address many of the questions that are still unanswered. Until then, clinicians need to weigh the pros and cons of the two treatment strategies and guide their patients. Ideally, patients should be educated on the advantages, and detrimental effects associated with each of the two possible therapies and their preferences should be elicited. Since each patient is unique, proposing neoadjuvant therapy with one-size-fits-all approach should be discouraged, and patients should become active participants and share with their

physicians the responsibility of selecting the treatment strategy that fits best with their goals and values.

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