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REVIEW

Role of neoadjuvant therapy for nonmetastatic pancreatic cancer: Current evidence and future perspectives

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Abstract

Pancreatic adenocarcinoma (PDAC) is one of the most common and lethal human cancers worldwide. Surgery followed by adjuvant chemotherapy offers the best chance of a long-term survival for patients with PDAC, although only approximately 20% of the patients have resectable tumors when diagnosed. Neoadjuvant chemotherapy (NACT) is recommended for borderline resectable pancreatic cancer. Several studies have investigated the role of NACT in treating resectable tumors based on the recent advances in PDAC biology, as NACT provides the potential benefit of selecting patients with favorable tumor biology and controls potential micro-metastases in high-risk patients with resectable PDAC. In such challenging cases, new potential tools, such as ct-DNA and molecular targeted therapy, are emerging as novel therapeutic options that may improve old paradigms. This review aims to summarize the current evidence regarding the role of NACT in treating non-metastatic pancreatic cancer while focusing on future perspectives in light of recent evidence.

Key Words: Pancreatic cancer; Pancreatic duct adenocarcinoma; Neoadjuvant chemotherapy; Borderline resectable; Locally advanced pancreatic cancer

Core Tip: Pancreatic adenocarcinoma (PDAC) is one of the most common and lethal human cancers worldwide; yet patients diagnosed with it still have a poor prognosis. Multimodal therapy is one of the most promising treatment options that increase the overall survival. Neoadjuvant chemotherapy (NACT) is recommended for treating borderline resectable PDAC. While recent studies have tried to explore the role of NACT in treating resectable and locally advanced PDAC, novel therapeutic modalities, such as ct-DNA and molecular targeted therapy, may guide both treatment and monitoring during the disease course to improve prognosis.

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INTRODUCTION

Pancreatic duct adenocarcinoma (PDAC) is the fourth most common cause of cancer-related deaths worldwide, with a continuously increasing incidence that will likely bring it to the second place in the upcoming decades[1]. The standard treatment of PDAC has always been surgical resection, which in combination with medical chemotherapy (CT) results in the best survival outcomes[2]. Actual real-world data shows a 5-year overall survival (OS) rate of approximately 20% in patients who have undergone resection (rising from less than 5% in 2011), while it is less than 1% in patients who have not (as it was 10 years ago)[3]. However, less than 15% of the patients have resectable tumors when diagnosed, whereas approximately 60% are diagnosed with metastatic tumors and/or have a poor performance status that precludes them from undergoing surgery[4,5]. Furthermore, international multicenter studies based on nationwide registries across Europe and the United States showed that a high percentage of patients with early PDAC were not required for surgical resection, with consequently high variations in the overall resection rates, from 13.2% to 68.7%[6]. Patient age and institutional volumes of pancreatic resections were associated with stage-adjusted resection rates and, more importantly, with postoperative morbidity, mortality, and long-term survival[7-10].

Large cohort studies have reported that approximately 20% of patients who underwent resection experience recurrence within 6 mo and 40% experience recurrence within the postoperative first year, even in cases of margin-free (R0) resection[11]. Such evidence suggests the different biological nature of PDAC, which is now regarded as a systemic disease, from the nature of its early stages. Therefore, surgery cannot allow a total tumor clearance, as a multimodal treatment approach is required. Surgical-related morbidity and mortality may even lead to a delay in the initiation of adjuvant therapy in time in up to one-third of the patients[12].

Based on the anatomical criteria (mainly the extension of the tumor to major locoregional vessels), non-metastatic PDAC was divided in 2006 by the National Comprehensive Cancer Network (NCCN) into resectable (R-PDAC), borderline resectable (BR-PDAC), and non-resectable (UR-PDAC)[13]. A deeper knowledge of the biological and clinical evolution of PDAC has led to a review of its definition, which also includes biological and clinical criteria[14]. Current guidelines recommend an upfront surgery for R-PDAC and neoadjuvant chemotherapy (NACT) for BR-PDAC, combined with modified 5-fluorouracil, leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX) and Gemcitabine + Capecitabine as preferred regimens[15]. NACT is not recommended for UR-PDAC and metastatic PDAC (M-PDAC); however, the latest chemotherapy protocols have shown encouraging results. This allows a higher proportion of patients with locally advanced (LA) and metastatic tumors to gain an opportunity to undergo surgery, with conversion surgery rates ranging from 0% to 40% for LA and from 4% to 9% for M- PDAC[16-18].

Including PDAC in the indications of NACT has gained a great interest. Theoretically, NACT can treat occult non-detected micrometastases in the early stages of macroscopically resectable tumors in a timely manner and can also reduce the size or stage of the tumor, thus ensuring a better surgical control and higher R0 rates. Moreover, it can help in selecting the patients that best fit for surgical resection, exempting non-responders from an unnecessary procedure of ineluctable poor oncological outcomes and relatively high morbidity rates. Finally, it may provide a multimodal treatment option for all patients, owing to its early administration in patients with a better performance status, without any postoperative dropout caused by surgery-related complications. NACT also improves the extent of local tumor control; however, to date, only one randomized prospective trial has failed to show a significant improvement in OS[19].

This review aims to show the actual evidence supporting the wide use of NACT in treating PDAC, while focusing on the possible challenges and future perspectives.

ROLE OF NACT IN TREATING RESECTABLE TUMORS

The recommended treatment for R-PDAC is an upfront surgery followed by adjuvant chemotherapy (AC). The benefits of AC regarding the survival outcomes have been demonstrated in several trials. Particularly, the first milestones were represented by the ESPAC1 and ESPAC3 trials that showed an improved OS after AC with 5-fluorouracil combined with leucovorin and gemcitabine, respectively[20, 21]. The Prodige randomized controlled trial revealed surprising outcomes when FOLFIRINOX were used as the AC regimen when compared to the outcomes of the previous standard of care based on gemcitabine (median OS of 53.5 *vs* 35.5 mo, respectively; $P = 0.001$)[22]. Moreover, well-differentiated tumors, young age, lower-staged tumors, large-volume institutions, and complete treatment were associated with a better OS, while early relapse was a negative prognostic factor.

Several trials have investigated the role of NACT in treating R-PDAC (Table 1). As early as in 2006, the first single-arm phase II trial investigating the safety of NACT (gemcitabine plus radiation) in treating R-PDAC was published by Talamonti *et al*[23]. Similarly, Heinrich *et al*[24] published a phase II single-arm trial enrolling 28 patients receiving NACT. It showed an 89%-resectability after the administration of gemcitabine plus cisplatin regimen that has an acceptable tolerability. However, many double-arm randomized controlled trials (RCT) comparing NACT and upfront surgery failed to reach any significant conclusions. Finally, the Dutch PREOPANC trial recently reported significant long-term outcomes after comparing neoadjuvant radio-chemotherapy (gemcitabine plus radiotherapy) with upfront surgery. The study enrolled 246 patients with R-PDAC of a diameter of more than 2 cm or BR-PDAC. After a median follow-up of 59 mo, the median OS was 15.7 mo in the radio-chemotherapy group *vs* 14.3 mo in the upfront surgery group, with a 5-year OS of 20.5% and 6.5%, respectively ($P = 0.025$)[25]. However, this study had some important drawbacks. First, the enrolled patients underwent a monoregimen AC, which was the standard approach in Netherlands when PREOPANC was initiated; however, it has now been replaced with combination chemotherapy, which is superior. Furthermore, the use of chemo-radiation in either adjuvant or neoadjuvant settings is not supported by other randomized studies[21,26]. Indeed, the recent A021501 phase II trial reported better results for neoadjuvant FOLFIRINOX than the results of chemoradiation in treating BR-PDAC according to both R0 resection rate (57% *vs* 33%, respectively) and 18-month OS (66.7% *vs* 47.3%, respectively)[27]. Similarly, the ESPAC-5F study showed inferior results for chemo-radiotherapy when compared to the results of FOLFIRINOX and gemcitabine combined with capecitabine[28]. Therefore, chemoradiation in the neoadjuvant setting could be more harmful than CT alone; thus, it should not be recommended. Finally, the PREOPANC study enrolled patients with both BR-PDAC and R-PDAC. The results were confounding as they were superior in the subgroup of BR-PDAC, while the hazard ratio (HR) for R-PDAC was not statistically significant: 0.79 [95% confidence interval (CI): 0.54-1.16, $P = 0.23$].

Perri *et al*[29] conducted a retrospective study with a propensity-score matching that focused on 485 patients with R-PDAC. He compared the preoperative use of FOLFIRINOX *vs* gemcitabine combined with NAB-paclitaxel (GA). The FOLFIRINOX cohort had higher rates of radiologic partial response (19% *vs* 6%; $P < 0.01$), as well as higher resection rates (29% *vs* 18%; $P = 0.02$), and patients who underwent R0 resection had significantly better median OS (55 *vs* 17 mo; $P < 0.001$). However, few months later the SWOG-S1505 phase II trial showed similar median OS durations for FOLFIRINOX and GA (23.2 *vs* 23.6 mo, respectively), with survival results similar to those reported for upfront surgery [30].

Regarding the postoperative outcomes of patients with resected tumors who received NACT, a large study on 3748 patients has showed no differences in postoperative complications and mortality, despite the high number of vascular resections in the NACT cohort[31]. Furthermore, the multivariable analysis showed a low likelihood of pancreatic fistula after receiving NACT (OR 0.67, $P < 0.001$). Similar results were published by Cools *et al*[31], even for older patients, with higher rates of major complications after undergoing upfront surgery than the rates after receiving NACT (38% *vs* 24%; $P = 0.06$) and a higher Comprehensive Complication Index (20.9 *vs* 20; $P = 0.03$, respectively).

In conclusion, the use of NACT in treating R-PDAC remains inconclusive despite the encouraging results. The aforementioned theoretical benefits have been applied to other gastrointestinal malignancies, such as esophageal cancer. However, some drawbacks of the wide use of NACT persist, such as the possible delay of surgical resection, possibly due to the complications of CT, or the progression of the disease due to nonresponding to treatment. A negative association of patients' malnutrition with NACT and its outcomes has also been proposed. However, previous studies have showed that, despite the worsening status of nutritional laboratory markers and the poor prognostic nutrition index after receiving NACT, the incidence of postoperative complications, length of hospital stay, and time to postoperative adjuvant therapy initiation is not significantly affected when compared to the incidence of complications after upfront surgery[32]. Finally, a positive biopsy is required to initiate NACT; however, it is not always easy to obtain due to the low cellularity of PDAC and its retroperitoneal anatomical position (close to major vessels)

We are looking forward to the results of several ongoing trials evaluating the role of different NACT regimens such as NEPAFOX and NorPACT-1 and investigating FOLFIRINOX *vs* upfront surgery or NEOPAC focusing on gemcitabine plus oxaliplatin *vs* upfront surgery, as they may lead to significant clinical implications.

Table 1 Trials investigating the role of neoadjuvant chemotherapy for resectable pancreatic adenocarcinoma

Ref.	Study type	Treatment	No. of patients	Resection rate (%)	Median OS (mo)
Talamonti *et al*[23], 2006	Single arm, phase II	Gem + RT	22	85	26[1]
Evans *et al*[113], 2008	Single arm, phase II	Gem + RT	86	74	22
Heinrich *et al*[24], 2008	Single arm, phase II	Gem or Cis	28	89	27
Varadhachary *et al*[114], 2008	Single arm, phase II	Gem/Cis	90	58	19
O'Reilly *et al*[115], 2014	Single arm, phase II	GemOx	38	71	27
Golcher *et al*[116], 2015	Randomized, double arm, phase II	Gem/Cis + RT *vs* upfront surgery	66	19 *vs* 23	17.4 *vs* 14.4 (P = 0.96)
Okano *et al*[117], 2017	Single arm, phase II	S1 + RT	33	96[2]	NA
Motoi *et al*[118], 2019	Randomized, double arm, phase II/III	GemS1 *vs* upfront surgery	364	NA	37
Versteijne *et al*[25], 2022	Randomized, double arm, phase III	Gem + RT *vs* upfront surgery	246	NA	15.7 *vs* 14.3[2]

[1]Calculated only in resected patients.
[2]Cumulative results for both resectable- and borderline resectable- pancreatic adenocarcinoma.
Gem: Gemcitabine; Ox: Oxaliplatin; Cis: Cisplatin; RT: Radiotherapy; OS: Overall survival; NA: Not available.

ROLE OF NACT IN TREATING BORDERLINE-RESECTABLE TUMORS

BR-PDAC was defined by the International Association of Pancreatology based on anatomical, biological, and clinical criteria[13]. From an anatomical point of view, BR-PDAC is defined as a lesion with a high risk for margin-positive resection (R1, R2) due to its proximity to the main vessels. In particular, BR-PDAC is considered in the following cases: any contact of ≥ 180° with the portal vein or superior mesenteric vein (SMV), any contact with the inferior vein cava, and/or any contact of < 180° with a major artery. It should be noted that unlike the definitions based on the NCCN guidelines, this definition does not include the extension to any jejunal branches of the SMV, mainly because of the wide anatomical variability[14]. From a biological point of view, the definition of BR-PDAC includes high levels of cancer antigen 19.9 (CA 19.9 > 500 U/mL), as well as positive lymph nodes on a PET-computed tomography scan, because of the high risk of early metastatic progression[33,34]. Indeed, a recent study by Hata *et al*[33] showed that both serum and peritoneal levels of CA 19.9 are independent prognostic factors of OS. The clinical definition of BR-PDAC is based on the performance status of the patient; an Eastern Cooperative Oncology Group (ECOG) score of more than two was shown to be associated with a high risk of distant metastases (up to 30%)[35]. Biological and clinical criteria also apply when R0 surgery is considered technically achievable.

Current guidelines have a consensus on the effectiveness of NACT as the first-line therapeutic strategy for BR-PDAC. High quality evidence including the results of the recent four-arm randomized phase II trial ESPAC-5F28 supports these recommendations. Patients with BR-PDAC were randomized to receive upfront surgery *vs* NACT (with two different arms, FOLFIRINOX or GA) *vs* chemoradiotherapy, followed by surgery and AC. There were no differences in the R0/R1 resection rate, which was the primary endpoint (44% *vs* 41% after NACT, P = 0.668), or in the number of patients able to undergo adjuvant therapy. However, the 1-year OS was significantly improved after receiving NACT (77% *vs* 42%, respectively; HR = 0.28; P < 0.001), with the FOLFIRINOX arm showing the best results (1-year OS 84% *vs* 79% after GA and 64% after chemoradiotherapy) at the cost of a higher, but manageable, toxicity. Regarding the best NACT regimen, initially, both gemcitabine and capecitabine were chosen because of their application in the metastatic setting. Indeed, gemcitabine has shown a great success in the treatment of PDAC, which was actually considered chemo-resistant prior to its introduction[36,37]. Later on, the good results of FOLFIRINOX and GA in the metastatic and adjuvant settings encouraged their use in combination with the existing NACT regimens. This promoted very encouraging oncological outcomes[22,38]. Recently, Macedo *et al*[39] showed a comparable effectiveness of FOLFIRINOX and GA in a retrospective study comprising 274 consecutive patients. They reported no differences regarding both median OS (37.3 *vs* 31.9 mo) and R0 resection rate (82.8% *vs* 81.8%). Both FOLFIRINOX and GA are the regimens of choice for NACT in treating BR-PDAC when patient conditions are acceptable. Moreover, the multidisciplinary team agrees with these findings.

The additional value of radiotherapy in the neoadjuvant setting of BR-PDAC remains a matter of debate. The largest number of RCTs, such as the aforementioned ESPAC-1 trial, failed to prove its

superiority regarding survival outcomes, which led the European guidelines to not recommend its use [40]. Simultaneously, neoadjuvant chemoradiotherapy is still commonly used in the United States[14]. Indeed, new radiotherapy modalities, such as intraoperative radiotherapy following NACT, have been introduced. A study by Chapman *et al*[41] showed a rather good tolerability; however, compared to NACT followed by surgery alone (26.6 *vs* 35.1 mo; $P > 0.05$), there was no significant advantage in survival outcomes as well as the additional cost of an increased hospital stay (4 *vs* 3.5 d). Newer techniques to minimize the dose directed at the radiosensitive tissues in the abdomen, including stereotactic body radiation therapy and intensity-modulated radiation therapy, are increasingly used in neoadjuvant settings for patients with BR/LA-PDAC[41]. However, there is still limited evidence regarding the supposed advantage of receiving NACT alone.

Traditionally, for non-metastatic tumors, NACT aims to shrink the tumor to facilitate R0 surgery. However, for BR-PDAC, several studies showed improved outcomes after receiving NACT, even in the case of radiologically stable tumors[42,43]. This may be attributed to an additional selective role of NACT, in which it helps in selecting the best candidates for surgery as biologically aggressive tumors progress despite treatment[44]. This biological selection plays an important role in improving the outcomes of pancreatectomies with arterial resections. In the past, many reports have shown poor outcomes of arterial resections [borderline resectable tumors with arterial invasion (BR-A)], supporting the stance that the risks largely outweigh the benefits[45,46]. However, in the era of modern NACT regimens for treating BR-PDAC, an increasing number of studies have shown better outcomes of surgical resections than those of medical therapy alone. The most recent series by Loos *et al*[47] showed encouraging results of 385 consecutive patients undergoing pancreatectomies with associated arterial resection or periadventitial dissection, with a median OS of 20.1 mo, while the five-year OS was 12.5%. The reported in-hospital mortality rate was 8.8%; however, it significantly decreased to 4.8% ($P = 0.005$), showing a learning curve of 15 procedures for pancreatic surgeons with sufficient preexisting experience. In contrast, a recent meta-analysis showed an increased risk of mortality and complications compared to those of standard non-arterial resections (HR 4.09, $P < 0.001$). Therefore, the real risks and benefits of NACT followed by surgery for treating BR-PDAC with arterial involvement remain unclear; thus, well-planned clinical trials should be carried to evaluate its efficacy.

CONVERSION SURGERY AND CHEMOTHERAPY FOR TREATING UNRESECTABLE NON-METASTATIC TUMORS

UR-PDAC is divided into UR-M (metastatic) when there are distant metastases, and UR-LA (locally advanced) when there is a venous involvement nontechnically amenable to reconstruction or a contact of ≥ 180° with the superior mesenteric artery (SMA) or celiac artery or an arterial involvement of the first jejunal branch of the SMA[13,14]. In these cases, even if arterial resection is technically feasible, it has a poor prognosis due to the high rate of local recurrence and systemic progression[48,49]. Patients with UR-LA are candidates for medical therapy, which is classically considered as a palliative solution. However, as early as in 2010, a systematic review reported encouraging outcomes in patients initially classified as having an unresectable tumor and then underwent conversion surgery after CT[50]. Although the regimens were based only on 5-florouracil or gemcitabine, the median OS after conversion surgery was 20 mo, which is comparable to the median OS after upfront surgery which was 23 mo. Many studies followed the first encouraging series, including different CT regimens with or without a radiation therapy, and all reported encouraging results of conversion surgery. However, all studies revealed a high heterogeneity regarding not only the CT protocols, but also the definition of BR-PDAC and UR-PDAC. Data from a meta-analysis including 653 patients with locally advanced PDAC from 21 observational studies showed a median resection rate after FOLFIRINOX-based CT of 26%, with a high variability in median OS, ranging from 10.0 to 32.7 mo, as well as a high heterogeneity among the studies ($I^2 = 61\%$), with different definitions of "locally advanced" PDAC. Recently, a retrospective study enrolling 279 consecutive patients receiving FOLFIRINOX for defined UR-LA-PDAC reported interesting results in a definite setting[51]. After at least four cycles of CT, a partial response (PR) was observed in 34.1% of the patients, and stable disease (SD) in 51.4% of the patients. Fifty patients underwent surgical exploration and 47 (16.8%) underwent curative-intent surgery. The median survival after conversion surgery was 56 mo compared to that of those who did not undergo resection which was only 21 mo ($P < 0.001$). After multivariate analysis, curative-intent surgery was the most important prognostic factor (HR 0.260; $P < 0.001$). Similarly, the Heidelberg group reported a higher resection rate after treatment with FOLFIRINOX than it was after treatment with GA or other regimens (61% *vs* 46% *vs* 52%, respectively; $P = 0.026$) from a retrospective analysis of 575 consecutive patients who underwent conversion surgery after CT[52]. Median OS was higher when conversion surgery was feasible (15.3 *vs* 8.5 mo, $P < 0.0001$), independent from the CT regimen (16.0 mo after FOLFIRINOX *vs* 16.5 mo after gemcitabine and 14.5 mo for others; $P = 0.085$). In a multivariable analysis, a FOLFIRINOX-based regimen was independently associated with better survival outcomes. Importantly, both these studies only included UR-PDAC and not borderline-resectable tumors. Regarding the role of the CT regimen used, a study from Johns Hopkins University reported that 28% of the patients with UR-LA-PDAC

underwent surgical exploration after CT, with a total of 20% of the patients being able to undergo a curative-intent surgery[53]. Of these patients, 60% received a FOLFIRINOX regimen and 19% received gemcitabine. Therefore, the CT regimen could significantly influence the outcomes of UR-LA-PDAC. However, it must be noted that patients who did not undergo resection had a lower ECOG-performance status, higher CA 19-9 Levels, and larger tumors on cross-sectional imaging.

All published studies had many shortcomings, such as having a retrospective study design and the absence of an intention-to-treat (ITT) analysis. Recently, the Verona group published an interesting prospective study with an ITT analysis of NACT followed by a conversion surgery. A cohort of 680 patients was analyzed, including 29.3% with BR-PDAC and 60.7% with UR-LA-PDAC. After clinical, radiological, and biochemical evaluations, 23.9% of the patients underwent surgical exploration, with an overall rate of subsequent resections of 15.1%, accounting for 24.1% of BR-PDAC and 9% of UR-LA-PDAC cases. The independent predictors of resection were age, BR-PDAC, chemotherapy completion, radiologic response, and biochemical response. The median OS for the entire cohort was 12.8 mo with completion of chemotherapy, complementary radiation therapy, and resection, which were found to be associated with improved survival outcomes. Interestingly, in the subgroup analysis, the median OS of patients with UR-LA-PDAC undergoing conversion surgery was 41.8 mo, and no pretreatment and posttreatment factors were associated with survival after pancreatectomy[54].

Post-CT prediction of resectability remains a major challenge that is difficult to standardize since it largely depends on the experiences, skills, and preferences of surgeons, oncologists, and radiologists. A recent multicenter study showed an interinstitutional agreement below 50% when dealing with both resectability evaluation and treatment allocation in BR-PDAC and UR-LA-PDAC[55]. A clear radiological post-CT response is difficult to detect on conventional contrast-enhanced computed tomography scan, with a low correlation between radiological findings and subsequent surgical resection rates[56,57]. Dholakia *et al*[57] reported a series of 50 consecutive LA patients receiving NACT followed by surgery in 58% of cases, although the tumor volume and degree of tumor vessel involvement were not significantly reduced after receiving NACT. Therefore, many authors have suggested that every patient undergoing CT for BR-PDAC or UR-LA-PDAC should undergo surgical exploration, and much debate remains about this argument. Rangelova *et al*[58] suggested a routine surgical exploration in every case of non-progressed LA tumor, regardless of the level of CA 19-9 and the type and dose of the CT regimen. Similarly, the Heidelberg group recommends surgical exploration in every case of SD or PR and suitable performance status, while patients with progressive or worsened clinical conditions must continue systemic treatment[59]. Moreover, the same authors suggested the usefulness of an artery-first approach during surgical exploration to rule out eventual unresectability [60]. In the case of curative-intent resection, more radical surgical procedures, such as systematic mesopancreas dissection and the TRIANGLE approach, have been proposed to achieve higher rates of R0 resections; however, more evidence is needed to support such surgical strategies[61,62]. Finally, some conversion surgeries have been reported to have a high risk for early recurrence (up to 30% within the first 6 mo.) However, the risk factors for early recurrence remain unclear[63].

The multidisciplinary decision process after receiving NACT should consider radiological findings, as well as clinical and biological factors. A strong effort should be made to standardize evaluation and management in this setting, as well as to identify prognostic factors for adequate response and early recurrence. Similarly, larger prospective studies on ITT have aimed to establish objective selection criteria for conversion surgery.

Finally, another interesting argument is the possibility of undergoing conversion surgery after CT for patients with oligo-metastatic UR-M-PDAC. Many authors have proposed the feasibility of such an approach, with improved outcomes when compared to the outcomes of CT alone; however, risk factors and appropriate indications remain unclear[64,65]. A recent study by the Verona Pancreas Institute showed very interesting results of 52 consecutive UR-M-PDAC patients who initially only had liver metastases and underwent conversion surgery[66]. FOLFIRINOX was the most commonly used chemotherapy regimen (63.5%). The median OS of the initial diagnosis was 37.2 mo, while the disease-free survival (DFS) of pancreatectomy was 16.5 mo. Multivariate analysis revealed that vascular resection, operative time, prognostic nutrition index, and neutrophil-to-lymphocyte ratio were associated with OS. A phase III trial comparing the simultaneous resection of the primary tumor and liver metastases after conversion chemotherapy *vs* standard CT in liver-only UR-M-PDAC is currently carried and will likely provide more insights (NCT03398291)[67].

FUTURE PERSPECTIVES

Role of circulating DNA in treating non-metastatic pancreatic cancer

The preoperative determination of resectability is an unresolved issue since the most common sites of metastases are the liver or peritoneum, where sub-centimeter implants may be difficult to detect radiographically[68]. Previous studies have shown that even laparoscopic exploration can miss up to 30% of occult metastases[69]. Similarly, an elevated CA 19-9 Level is a predictor of occult metastases; however, this can also be impaired by a relatively high rate (47%) of false negative results[70]. Several

studies have investigated the possible role of circulating tumor DNA (ct-DNA). Indeed, ct-DNA is a promising new tool for the assessment of many gastrointestinal tumors, despite not being routinely used[71,72]. Patients with R-PDAC have lower levels of ct-DNA, as well as a lower number of genetic mutations in ct-DNA than the levels in patients with UR-PDAC[73,74]. ct-DNA is a reliable and easy-to-use tool for detecting tumoral mutations, such as mutations in the *KRAS* gene, which can be mutated in up to 90% of PDAC patients[75]. *KRAS* mutations are more common in patients with distant metastases than in patients with non-metastatic PDAC (58.9% *vs* 18.2%, respectively)[76], with the association with worse survival outcomes independent of the tumor[77-80]. Furthermore, since ct-DNA has shown higher concordance with metastatic lesions than with primitive tumors, the detection of such mutations may theoretically indicate the presence of occult metastases[73]. However, further studies are required to confirm this hypothesis.

A negative preoperative ct-DNA liquid test was reported to be associated with a low rate of early recurrence (4.6% within 6 mo)[75]. Similarly, non-detectable preoperative ct-DNA was associated with a higher rate of R0 resection with negative lymph nodes than the rate for patients with positive results (80% *vs* 38%)[81]. Furthermore, negative results of preoperative ct-DNA were associated with a better DFS even for patients undergoing R0 resection, suggesting a prognostic role independent of the subsequent surgery[82].

The combination of radiological staging with ct-DNA analysis may optimize the prognostic stratification of non-metastatic tumors, resulting in an additional tool that may aid in deciding whether to undergo surgery, which has high rates of morbidity, or to administer medical therapy[83,84].

Molecular targeted therapy

Genetic mutations are currently considered important, not only for diagnostic and prognostic purposes, but also as targets for molecular targeted therapy in many gastrointestinal cancers[85-87]. Both next-generation sequencing and ct-DNA may be useful tools for identifying such genetic alterations in a non-invasive manner.

To date, three kinds of targets have been investigated for PDAC: oncogenes, tumor suppressors, and caretaker genes[88]. *KRAS* is commonly involved in PDAC carcinogenesis, and its upregulation is considered a potential target of PDAC therapy. Thus, irreversible tyrosine kinase inhibitors may be considered a viable strategy; however, the first studies investigating the possible benefit of cetuximab did not show positive results (median OS 6.3 *vs* 5.9 mo, P = 0.23)[89]. Subsequently, newer epidermal growth factor receptor (EGFR) inhibitors have been tested: Nimotuzumab in combination with gemcitabine improved the OS of patients with both UR-LA-PDAC or UR-M-PDAC in a phase II trial (median OS 8.6 *vs* 6.0 mo, P = 0.03), with better outcomes in the KRAS wild-type subgroup (median OS 11.6 *vs* 5.6 mo, P = 0.03)[90]. In contrast, the EGFR inhibitor, vandetanib, has not shown any efficacy, while a clinical trial investigating the efficacy of afatinib is currently carried (NCT02451553)[91]. There are likely resistance mechanisms in PDAC cells that circumvent EGFR inhibition. Indeed, the additional inhibition of *C-RAF*, together with *KRAS*, led to complete tumor regression in murine PDAC models and human patient-derived xenografts[92]. Further trials are now investigating the possibility of inactivating both oncogenes and downstream crosstalk pathways.

Another frequent mutation in PDAC affects the *CDKN2A* gene, with an estimated frequency of approximately 60%, affecting the tumor suppression pathway that involves the proteins CD4/6 and p53 [93,94]. Ribociclib and palbociclib are newly developed drugs acting on CDK4/6. They have shown encouraging results in many preclinical models of PDAC, as well as for other solid cancers, with promising ongoing clinical trials (NCT02501902)[95-100]. Similarly, the SMAD4/TGF-β pathway can be mutated in 40% of PDAC93 cases. The TGF-β inhibitor, galunisertib, showed encouraging results in both preclinical investigations and phase I/II trials in combination with gemcitabine (estimated HR = 0.796) [101-103]. Moreover, *BRCA* is a well-known caretaker gene whose mutations are involved in many human solid tumors, including PDAC, with a frequency of approximately 6%-7%[104-106]. Newly developed PARP inhibitors have shown significant efficacy in treating other *BRCA* mutant solid tumors [107]. Olaparib was recently tested in a prospective phase III trial (the POLO trial, Pancreas Cancer Olaparib, NCT02184195) to evaluate its efficacy in patients with BRCA-mutant metastatic PDAC[108]. The PFS was increased in the olaparib group (7.4 *vs* 3.8 months, HR = 0.53, P = 0.004), at the cost of higher rates of adverse effects. The median OS did not significantly improve, although the trial is ongoing. In light of these encouraging results, further well-designed trials involving PARP inhibitors in BRCA-mutated PDAC are required.

Finally, chimeric antigen receptor T cells (CAR-T) are another therapeutic option for oncologic immunotherapy based on the reprogramming of autologous T cells from patients against tumoral antigens[109]. CAR-T has already been proven to be effective in treating blood tumors, with some drugs already approved by the FDA[110]. Subsequently, CAR-T cells were engineered and tested against possible targets in PDAC models. A phase II trial is testing CAR-T therapy against the mutant KRAS G12D that had previously shown a reduced response to other immunotherapies (NCT01174121)[111]. Furthermore, HER2/ERBB2 is considered a potential target in this setting, even if it is expressed less frequently (NCT01935843)[112].

Despite being promising, these strategies have not yet produced any significant clinical benefit and have not yet been investigated in the neoadjuvant setting. However, for traditional CT, the regimens were taken from the adjuvant and systemic protocols, suggesting possible future developments in molecular-targeted NACT. This tool may be added to existing protocols for nonmetastatic PDAC in cases of non-responsiveness to other regimens, as well as to obtain an improved response. Therefore, further studies are warranted.

CONCLUSION

Despite the encouraging results of the most recent NACT regimens for treating BR-PDAC, the current evidence supporting their use for R-PDAC remains inconclusive. We are looking forward to the results from several ongoing trials evaluating the role of different NACT regimens such as NEPAFOX and NorPACT-1 and investigating FOLFIRINOX *vs* upfront surgery or NEOPAC focusing on gemcitabine plus oxaliplatin *vs* upfront surgery, as they may have important clinical implications.

In the subset of BR-PDAC with arterial involvement, the benefits of NACT followed by surgery remain unclear; thus, well-planned clinical trials should be carried out to evaluate its efficacy.

Regarding UR-LA-PDAC, a strong effort should be made to standardize evaluation and management, as well as to identify prognostic factors for adequate response and early recurrence. Larger prospective studies on ITT aimed to establish objective selection criteria for conversion surgery. The multidisciplinary decision process after receiving NACT should consider radiological findings, as well as clinical and biological factors. Similarly, encouraging results suggest that also patients with oligo-metastatic UR-M-PDAC should undergo conversion surgery after CT. However, risk factors and appropriate indications remain unclear. Although the road towards protocol standardization remains lengthy and tedious, it is necessary to ensure treatment success and improve overall clinical outcomes.

FOOTNOTES

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