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REVIEW ARTICLE

Neoadjuvant therapy for pancreatic cancer

Jean Gugenheim[1,2] · **Anna Crovetto**[3] · **Niccolo Petrucciani**[3]

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Abstract
Multimodal treatment including surgery and chemotherapy is considered the gold standard treatment of pancreatic cancer by most guidelines. Neoadjuvant therapy (NAT) has been seen as a possible treatment option for resectable, borderline resectable and locally advanced PaC. The aim of this paper is to offer a state-of-the-art review on neoadjuvant treatments in the setting of pancreatic ductal adenocarcinoma. A systematic literature search was performed using PubMed, Cochrane, Web of Science and Embase databases, in order to identify relevant studies published up to and including July 2021 that reported and analyzed the role of neoadjuvant therapy in the setting of pancreatic carcinoma. Most authors are concordant on the strong role of neoadjuvant therapy in the setting of borderline resectable pancreatic cancers. Recent randomized trials demonstrated improvement of R0 rate and survival after NAT in this setting. Patients with locally advanced cancers may become resectable after NAT, with better results than those obtained with palliative therapies. Even in the setting of resectable cancers, NAT is being evaluated by ongoing randomized trials. Chemotherapy regimens in the setting of NAT and response to NAT are discussed. NAT has an important role in the multimodal treatment of patients with borderline resectable pancreatic cancer. It has a role in patients with locally advanced tumors as it can allow surgical resection in a relevant proportion of patients. For resectable pancreatic cancers, the role of NAT is under evaluation by several randomized trials.

Keywords Pancreatic cancer · Neoadjuvant therapy · Surgery · Chemotherapy · Pancreas

Introduction

Ductal adenocarcinoma of the pancreas (PaC) is one of the most aggressive types of cancer, with an overall 5-year survival around 9%. More than 57,000 new cases are expected in 2020 in the United States, causing more than 47,000 estimated deaths [1]. Its incidence has risen in the last years, and by 2030 PaC is expected to represent one of the leading causes of cancer-related deaths [2, 3]. The only curative option for PaC is surgical resection, but only a minority of patients can be considered eligible for surgery, as the disease is frequently locally advanced or metastatic at the time of diagnosis [4]. Even after a successful surgical resection, prognosis is poor. As a matter of fact, in patients undergoing surgery alone the 2-year survival rate is between 30 and 42%, mostly due to the highly frequent recurrences [5]. These results have led to the introduction of multimodal treatments as gold standard in the main international guidelines [6–8]. Adjuvant chemotherapy has been established as an effective strategy to lengthen the disease-free and overall survival of patients with resectable disease by several clinical trials such as ESPAC-1 [9], ESPAC-3 [10], PRODIGE-24 [11]. However, a significant group of patients is not able to go through any adjuvant treatment: as a matter of fact, it has been reported that 40–53% of patients do not receive postoperative antineoplastic treatments. This is mostly due to disease progression, surgical complications and poor performance status [12]. Therefore, taking into consideration the importance of a multimodal approach in PaC and the difficulties in completing the whole treatment plan, neoadjuvant therapy has been seen as a possible treatment option for resectable, borderline resectable and locally advanced PaC. The recent outbreak of the COVID-19

✉ Jean Gugenheim
gugenheim.j@chu-nice.fr

1 Université Côte d'Azur, Nice, France

2 Division of Digestive Surgery and Liver Transplantation, Archet 2 Hospital, University Hospital of Nice, 151 Route de Saint-Antoine, 06200 Nice, France

3 Faculty of Medicine and Psychology, Department of Medical and Surgical Sciences and Translational Medicine, Sant'Andrea Hospital, Sapienza University of Rome, Rome, Italy

pandemic has further increased the complexity of balancing the risks and benefits of undergoing preoperative chemotherapy or upfront surgery [13].

The aim of this paper is to offer a state-of-the-art review on neoadjuvant treatments in the setting of pancreatic ductal adenocarcinoma.

Methods

A systematic literature search was performed by two authors (AC, NP) using PubMed, Cochrane, Web of Science and Embase databases, in order to identify relevant studies published up to and including July 2021 that reported and analyzed the role of neoadjuvant therapy in the setting of pancreatic carcinoma. The search was conducted using the following search algorithm: [(pancreas OR pancreatic AND adenocarcinoma OR carcinoma OR cancer AND neoadjuvant OR preoperative). The research was restricted to English language articles dealing with human patients. The "related articles" function was used to broaden the search, and all abstracts, studies and citations scanned were reviewed. Relevant papers were selected following the PRISMA statement for systematic reviews and meta-analysis [14]. The risk of bias was evaluated using the Cochrane tool and studies at high risk of bias were excluded. The flowchart of the included studies is shown in Fig. 1.

Potential benefits of neoadjuvant therapy

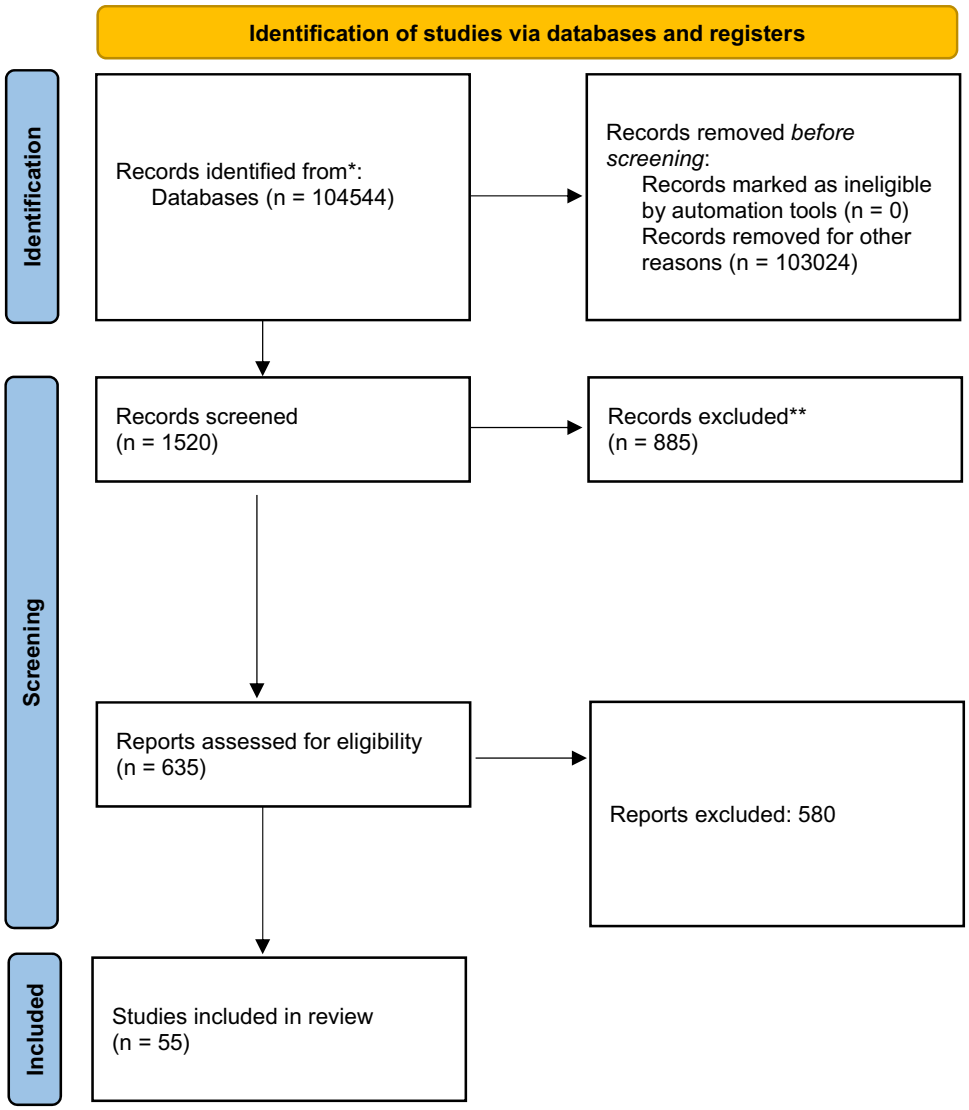
As highlighted by a survey performed by E-AHPBA and EORTC in 2019 [15], the reasons behind preoperative treatment in resectable and non-resectable PaC are different. It might be useful to define preoperative therapy in RPC as "neoadjuvant", as it has the objective of reducing recurrence and R1 resections in an already resectable tumor. On the other hand, preoperative treatment in case of unresectable tumors aims to increase resection rates, and therefore it has been referred in the mentioned paper as "conversion" or "downsizing" therapy. Such differentiation might be of use when it comes to comparing results in the borderline resectable group. Preoperative chemotherapy is gaining more and more consensus as it allows some patients with locally advanced (LAPC) or borderline resectable (BRPC) pancreatic cancer to access effective surgical treatment [6, 16, 17]. The benefits of neoadjuvant therapy have been studied and are starting to gain relevance even in resectable pancreatic cancer (RPC) [18], as it might help increase the number of patients who receive systemic treatment and increase the rate of margin-negative resections. Furthermore, is has been reported that neoadjuvant therapy can select the patients with progressive disease, that therefore might not benefit from surgery. It is also believed that the administration of antineopalstic agents before surgery might be more effective (as free-radicals generation is greater in a well oxygenated environment), associated with less systemic toxicity and protective of intraperitoneal tumor seeding at time of surgery. Furthermore, neoadjuvant treatment may be able to treat micrometastasis that may be present at the time of diagnosis [19]. As a matter of fact, neoadjuvant therapy was associated with a lower rate of both local, lymphnodal and liver recurrences in two retrospective studies [20, 21]. Moreover, chemotherapy followed by surgical resection has been studied in the treatment of oligometastatic pancreatic cancer with resectable liver metastases in strictly selected patients; although strong evidence about the potential benefits of this strategy is still lacking [17, 22].

Pancreatic surgery remains extremely challenging, with high complication rates, therefore the increase in preoperative therapy administration raised some doubts around the safety of pancreatic resections after neoadjuvant treatments. However, even though increased blood loss and surgical time might occur, overall post-surgical morbidity is not affected [23]. Studies even show a decrease in postoperative pancreatic fistula (POPF) when compared to upfront surgery, although associated with an higher rate of delayed gastric emptying [24, 25]. Nevertheless, among the patients who develop a postoperative complication, those who underwent NAT were associated with increased postoperative burden, measured through the Modified Accordion Severity Grading System and average complication burden (ACB) [26].

How to evaluate the response to NAT

Preoperative assessment of NAT response is crucial especially in patients with locally advanced and borderline resectable disease, to effectively select patients for surgery. However, a correct disease assessment after NAT is challenging and the best diagnostic option to evaluate patients after neoadjuvant treatment is still not clear. As a matter of fact, even though CT still remains the most commonly used imaging tool to be used to assess disease progression after neoadjuvant therapy, its accuracy in predicting surgical resectability is debated. Ferrone et al. [24] suggested that CT scan is no longer appropriate in assessing resectability after FOLFIRINOX. This result can be explained by the inability of CT to distinguish between fibrosis and neoplasia. 18F-glucose Positron emission tomography has been found to be more accurate of both CT scan and MRI, however, high-quality evidence is still lacking [26, 27].

The best way to evaluate disease response to neoadjuvant therapy is pathological: nevertheless, pathologic response can only be assessed after surgical resection. Complete pathologic response is rare (around 4%) and often overestimated [28], but associated with significant improvement in surgical outcomes (43 months vs 24 and



*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).

**If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

Fig. 1 PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only. From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. https://doi.org/10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/

23 months in case of near-complete pathologic response and incomplete response, respectively; $P < 0.0001$) [29, 30].

CA19-9 is a serum marker often used in clinical setting for diagnosis and follow-up of pancreatic cancer, and it has been studied as a useful tool to evaluate the response to preoperative treatments [31]. Tsai et al. [32] suggested that the normalization of CA19-9 has a stronger prognostic value than breadth of the reduction.

Treatment regimens

Regarding the types of regiments to use, current literature is not clear. Combination therapies, especially FOLFIRINOX

[12], seem to be the most effective as adjuvant treatments, and have shown the most promising results as neoadjuvant therapies in resectable and borderline resectable pancreatic tumors compared to monotherapies [33, 34]. The PACT-15 [5] trial showed an increased overall survival after perioperative PEXG over adjuvant gemcitabine or adjuvant PEXG + gemcitabine for RPC, with an ITT 5-year overall survival of 49% (13% in patients receiving only gemcitabine; 24% in patients receiving a combination of PEXG and gemcitabine). The early results from a recent randomized trial (SWOG S1505) confronting neoadjuvant mFOLFIRINOX versus Gemcitabine/Nab-paclitaxel for perioperative treatment in RPC were published: although the comparative results between the two regimens are yet to be published, this trial showed promising outcomes after preoperative chemotherapy, with a 33% rate of complete or near-complete pathological response; however, it highlighted the challenges of administering complete perioperative therapy [35]. Currently there are no clear guidelines on which neoadjuvant systemic protocol is better to increment resection rates and survival in patients with LAPC. The use of FOLFIRINOX in the setting of metastatic pancreatic cancer has been associated with an increased survival over gemcitabine, at the expense of higher toxicities, deemed, therefore, more appropriate for young and fit patients [36]. However, recent results from the multicenter retrospective RESPECT study found similar oncological outcomes and resection rates between patients > 70-years old and patients < 70-years old who underwent treatment with FOLFIRINOX for BRPC or LAPC: this could possibly expand the pool of patients who might benefit from FOLFIRINOX [37].

Even though radiotherapy might help control local disease recurrence, the role of radiotherapy in the preoperative treatment of RPC is still not clear, as, to our knowledge, there are no studies comparing neoadjuvant chemotherapy to radiotherapy or chemoradiotherapy for the treatment of RPC or BRPC. However, Stessin et al. reported the results of their retrospective study using the SEER Registry, that show how neoadjuvant radiotherapy ± chemotherapy may increase overall survival compared to adjuvant radiotherapy and no radiotherapy [38]. Considering the results of LAP07 trial, no significant difference was found in terms of OS between chemotherapy and chemoradiotherapy in LAPC [39]; therefore chemotherapy alone is still considered as the upfront treatment in LAPC over chemoradiotherapeutic regimens. Recently, Stereotactic Body Radiation Therapy (SBRT) use has been implemented: its advantage compared to standard radiotherapy is the possibility of administering a higher radiation dose selectively on the tumor, sparing surrounding tissues. Given its ability to increase radical surgical resection, SBRT has been inserted in the NCCN guidelines as a feasible option in the setting of LAPC, although more strong evidence is needed. [6, 40].

Neoadjuvant therapy in resectable pancreatic cancer

The NCCN Guidelines still recommend upfront surgery as the first therapeutic choice in most resectable pancreatic cancer cases, limiting NAT only to extremely selected, high-risk patients. However, neoadjuvant treatment is being studied as a therapeutic option to improve the patients' outcomes and to increase resection rate. To our knowledge the only published multicenter randomized controlled trial comparing neoadjuvant chemoradiotherapy to upfront surgery in RPC and BRPC is the 2020 PREOPANC trial [41]; it did not show a significant OS and DFS benefit in the subgroup of patients with resectable disease at time of diagnosis undergoing neoadjuvant chemoradiotherapy (NAT 14.6 months vs immediate surgery 15.6 months; $P = 0.830$). However, the overall results, comprehensive of both RPC and BRPC, showed a significant increase in DFS and R0 resections after neoadjuvant therapy (DFS: NAT 8.1 months vs immediate surgery 7.7 months; $P = 0.032$; R0 rate: NAT 71% vs immediate surgery 40%; $P < 0.001$); no significant OS difference was found. Of those who received neoadjuvant chemotherapy 17.6% did not undergo surgery: the most common reason for surgery exclusion was disease progression (81.25%). These results are in line with previous single center randomized trials, two of which were terminated early because of poor accrual [42, 43]. However, there are several limitations to this trial, especially regarding the regiments used: as highlighted before, multi-drug regimens have shown to be the most effective in pancreatic cancer, while in the PREOPANC trial gemcitabine-based monotherapies where used. The study protocol for PREOPANC-2 trial has been recently published, comparing neoadjuvant FOLFIRINOX to neoadjuvant gemcitabine and adjuvant gemcitabine [44].

Data supporting neoadjuvant therapy in RPC still needs to be implemented. However, there are some difficulties in gaining high quality information on this topic. As a matter of fact, there are difficulties in recruiting patients for randomized trials, as they often refuse chemoradiotherapy over the possibility of immediate surgery. Moreover, retrospective studies are often biased: Versteijne et al. [45], indeed, highlight a major selection bias, typical of retrospective studies regarding neoadjuvant therapy. In fact, it is often not clear how many patients with resectable disease at time of diagnosis undergoing neoadjuvant therapy are excluded from surgery because of disease progression or poor PS, as most of the studies report survival after resection rather than by intention-to-treat. This datum, however, is of outmost importance, as one of the major advantages attributed to neoadjuvant therapy in RPC is the possibility to select patients who can gain an advantage from surgery by identifying undetected metastases and the patient's physiologic reserve. As a matter of fact, a retrospective analysis

performed at the MD Anderson Cancer Center shows that around 25% of patients have progressive disease at restaging after neoadjuvant therapy and therefore are deemed not resectable [46].

Recently, as cited earlier, Ahmad et al. published the early results of the SWOG S1505 trial [35]: the authors highlighted the fact that the adherence to strict definitions of resectable disease is challenging, and this inaccuracy may lead to a high rate of ineligibility (30%) in clinical trials.

More randomized control trials are needed to fully understand the implications of neoadjuvant therapy in the setting of RPC. The ongoing PANACHE01 multicenter trial is studying the role of neoadjuvant FOLFIRINOX in RPC [47].

Neoadjuvant therapy in borderline resectable pancreatic cancer

BRPC is complex clinical entity, as oftentimes the resectability criteria may vary between centers, but can be defined as a tumor at high risk of incomplete surgical resection (R1 or R2) if treated with immediate surgery [48]. The 2020 NCCN guidelines recommend neoadjuvant treatment as the first therapy for borderline pancreatic cancer and do no longer recommend upfront surgery, even if deemed feasible. The European Society of Medical Oncology (ESMO) only recommends preoperative treatment in case of BRPC, suggesting that patients with BRPC are not good candidates for upfront surgery and, indeed, can benefit from medical neoadjuvant treatment [7]. The PREOPANC trial showed significant results favoring NAT in BRPC. As a matter of fact, in the borderline resectable group, OS, DFS and R0 resection rate were significantly increased after NAT (OS: NAT 17.6 months vs immediate surgery 13.2 months; $P=0.029$; DFS: NAT 6.3 months vs immediate surgery 6.2 months; $P=0.013$; R0 rate: NAT 79% vs immediate surgery 13%; $P<0.001$). Previous trials results were comparable, showing high resection R0 resection rates in BRPC [49, 50]: 93% of R0 resection rate was achieved in the ALLIANCE A021101 single-arm trial. The same trial showed a high rate of vascular resections (80%). However, no differences in surgical morbidity were found between NAT and upfront surgery even after complex vascular reconstructions [51]. As achieving an R0 resection represents the most important prognostic factor for PaC [52], the fact that neoadjuvant therapy seems to be able to reduce positive-margin resections is of outmost importance. Versteijne et al. [45] confirmed in a 2018 meta-analysis the increase in R0 resections in both RPC and BRPC after NAT (RPC: NAT 85.5% vs immediate surgery 71.4%; BRPC: NAT 88.6% vs immediate surgery 63.9%). The fact that the R0 rate for BRPC is higher than the one of resectable tumors is not entirely clear, but it could be explained by the inhomogeneity in the preoperative assessment of surgical resectability between centers. The ongoing PRODIGE 44 trial, due to end in 2026, aims to assess the role of neoadjuvant FOLFIRINOX associated with capecitabine based chemoradiotherapy [53].

Conversion therapy in locally advanced pancreatic cancer

LAPC has historically been considered not deemed for surgical resection given the generally aggressive tumor biology and extreme difficulty achieving a complete resection. In this context the possible therapeutic options are either palliative chemotherapy with best supporting care or chemotherapy and/or radiation with the intent of subsequent surgical resection. Less than 40% of LAPC patients who undergo neoadjuvant treatment eventually become resectable [54]; however, the possibility of surgical resection gives survival advantage over palliative care in selected patients as reported by Gurusamy et al. in a 2014 meta-analysis of two randomized trials [55]. NCCN guidelines recommend surgical treatment after NAT in patients with LAPC with a good performance status (defined as ECOG 0–1) and no signs of disease progression. As high-quality evidence supporting surgical resection after NAT over systemic therapy in LAPC is still scarce, in the clinical setting it is fundamental to carefully select the patients to refer to surgery.

Conclusions

NAT has an important role in the multimodal treatment of patients with borderline resectable pancreatic cancer. It has a role in patients with locally advanced tumors as it can allow surgical resection in a relevant proportion of patients. For resectable pancreatic cancers, the role of NAT is under evaluation by several randomized trials.

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Declarations

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