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**Developments and challenges in neoadjuvant therapy for locally advanced pancreatic cancer**

Zhou B *et al.* Neoadjuvant therapy for locally advanced pancreatic cancer

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## **Abstract**

Pancreatic ductal adenocarcinoma (PDAC) remains a significant public health challenge and is currently the fourth leading cause of cancer-related mortality in developed countries. Despite advances in cancer treatment, the 5-year survival rate for patients with PDAC remains less than 5%. In recent years, neoadjuvant therapy (NAT) has emerged as a promising treatment option for many cancer types, including locally advanced PDAC, with the potential to improve patient outcomes. To analyze the role of NAT in the setting of locally advanced PDAC over the past decade, a systematic literature search was conducted using PubMed and Web of Science. The results suggest that NAT may reduce the local mass size, promote tumor downstaging, and increase the likelihood of resection. These findings are supported by the latest evidence-based medical literature and the clinical experience of our center. Despite the potential benefits of NAT, there are still challenges that need to be addressed. One such challenge is the lack of consensus on the optimal timing and duration of NAT. Improved criteria for patient selection are needed to further identify PDAC patients likely to respond to NAT. In conclusion, NAT has emerged as a promising treatment option for locally advanced PDAC. However, further research is needed to optimize its use and to better understand the role of NAT in the management of this challenging disease. With continued advances in cancer treatment, there is hope of improving the outcomes of patients with PDAC in the future.

**Key Words:** Neoadjuvant therapy; Pancreatic ductal adenocarcinoma; Locally advanced pancreatic cancer; Chemoradiotherapy; Immunotherapy; Vaccine therapy

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**Core Tip:** In recent years, neoadjuvant therapy (NAT) has emerged as a promising treatment option for many cancer types, including locally advanced PDAC, with the

potential to improve patient outcomes. To analyze the role of NAT in the setting of locally advanced PDAC over the past decade, a systematic literature search was conducted using PubMed and Web of Science. Despite the potential benefits of NAT, there are still challenges that need to be addressed. Additionally, there is a need for better patient selection criteria to identify those who are most likely to benefit from this approach.

## **INTRODUCTION**

Pancreatic ductal adenocarcinoma (PDAC) is a malignancy with a poor prognosis, and it is currently the seventh leading cause of cancer-related death worldwide. The number of deaths from PDAC (466000) is almost equal to the number of cases (496000) each year<sup>[1-3]</sup>. Experts predict that PDAC will surpass breast cancer as the third leading cause of cancer-related death by 2025 in 28 European countries<sup>[4]</sup>. The 5-year survival rate for patients with PDAC is less than 5%, and locally advanced pancreatic cancer (LAPC) accounts for one-third of all pancreatic cancer cases<sup>[5-7]</sup>. Unfortunately, approximately 60% of patients with LAPC present with metastatic disease and/or poor performance status, making them ineligible for surgery<sup>[8,9]</sup>. Despite improvements in diagnosis and treatment, clinical outcomes for these patients remain poor.

In 1992, Evans *et al*<sup>[10]</sup> first proposed the use of neoadjuvant therapy (NAT) for PDAC, and found that patients treated with NAT had superior outcomes compared to those treated with postsurgical adjuvant therapy<sup>[11,12]</sup>. NAT is administered before surgery to reduce tumor mass, promote tumor downstaging, or eliminate early metastatic cells, thereby improving prognosis. In the last decade, the strategy of NAT followed by conversion surgery has been increasingly employed in the treatment of LAPC<sup>[13]</sup>. The goal of this review is to summarize and discuss research exploring the use of NAT for LAPC.

## **DEFINITIONS OF LAPC**

Pancreatic cancer is typically classified based on its resectability on preoperative imaging, according to guidelines such as the National Comprehensive Cancer Network (NCCN) 2022 edition, the Chinese guidelines for the Neoadjuvant Therapy of Pancreatic Cancer 2021 edition, and the International Association of Pancreatology<sup>[5,14,15]</sup>. LAPC is generally defined as local tumor growth with major involvement (> 180° circumferential) or true invasion of the superior mesenteric artery, celiac axis, or hepatic artery and/or involvement of the portal vein/superior mesenteric vein that prevents reconstruction<sup>[16]</sup>. Table 1 provides a summary of these criteria.

### **CHEMORADIOOTHERAPY FOR LAPC**

LAPC, previously thought to be an incurable disease stage and an indication for palliative treatment, is now strongly considered a potentially curable disease. Gemcitabine (GEM)-based chemoradiotherapy is the standard treatment for LAPC, with a reported median survival of 24.2 mo and progression-free survival (PFS) of 15 mo<sup>[17,18]</sup>. Polychemotherapy treatment with combined leucovorin calcium (folinic acid), fluorouracil, irinotecan hydrochloride, and oxaliplatin (FOLFIRINOX) and GEM + nab-paclitaxel is recommended<sup>[19]</sup>.

In a database query of patients who received induction FOLFIRINOX for LAPC between 2010 and 2016, nearly 20% responded sufficiently to undergo resection, which improved overall survival compared to that of patients who did not undergo resection<sup>[20]</sup>. Another study enrolled 485 patients with at least three cycles of first-line chemotherapy with FOLFIRINOX or gemcitabine plus nanoparticle albumin-bound paclitaxel (GA) between 2010 and 2017 and revealed that according to the Response Evaluation Criteria in Solid Tumors (RECIST), a partial response was more common among patients treated with FOLFIRINOX [27 of 140 patients (19%)] than among those treated with GA [8 of 140 patients (6%);  $P = 0.001$ ]. In this cohort of patients, FOLFIRINOX was associated with higher rates of RECIST-defined partial response and subsequent pancreatectomy than GA<sup>[21]</sup>. The different types of trials evaluating NAT for LAPC in recent years are summarized in Table 2<sup>[19,22-25]</sup>.

Before the administration of chemotherapy, patients diagnosed with LAPC should undergo a thorough preliminary assessment of their performance status based on the Eastern Cooperative Oncology Group (ECOG) score<sup>[26]</sup>. In addition, it is imperative to evaluate nutritional status, symptom burden, and active comorbidities (with appropriate adjustments made for treatment as warranted) and to assess biliary tract patency while considering the need for diversion or stent placement. Geriatric assessment is recommended for patients who are aged 70 years and above<sup>[27]</sup>. For those patients exhibiting a good performance status (ECOG score between 0-1) along with good nutritional health, first-line chemotherapy is advised, similar to the approach for patients diagnosed with metastatic liver cancer. In contrast, for patients with higher ECOG scores, a GEM-based regimen is preferred due to its lower toxicity profile<sup>[28]</sup>.

The use of stereotactic body radiation therapy (SBRT) with adjuvant chemotherapy in the treatment of LAPC has been a subject of interest among oncologists. While conventional fractionated radiation has been the standard approach, studies have explored the potential of SBRT in downstaging LAPC<sup>[29]</sup>. One recent study examined the efficacy of sequential SBRT following FOLFIRINOX chemotherapy in patients with stable but unresectable LAPC. The study authors reviewed medical records from 50 patients who were treated with induction FOLFIRINOX for a median of 8 cycles, followed by SBRT. The median overall survival (OS) and PFS were reported as 26.4 mo [95% confidence interval (CI): 22.4-30.3] and 16.7 mo (95%CI: 13.0-20.3), respectively<sup>[30]</sup>. While SBRT appears to have limited utility in the treatment of LAPC compared to conventional fractionated radiation, this study suggests that it may have a role in certain cases. A multidisciplinary approach should be considered when determining optimal treatment strategies for patients with LAPC who are not surgical candidates.

In addition to SBRT, Robert R. Wilson first proposed particle therapy for the treatment of tumors in 1946<sup>[31]</sup>. After more than 70 years of development, particle therapy (PT) has become another well-established tumor treatment method after surgery, chemotherapy, traditional radiotherapy and immunotherapy<sup>[32]</sup>. Currently, particle radiotherapy, which includes proton and heavy ion radiotherapy, has been

successfully applied to the treatment of cancer. C-ion and proton radiotherapy are the most commonly used types of particle radiotherapy in clinical practice and have higher accuracy and better cell killing effects, especially in high hypoxia areas and radiation-resistant cell cycle phases. In addition, particle radiotherapy decreases the viability, proliferation and migration of cancer cells<sup>[33-39]</sup>. Therefore, particle therapy is used to treat deeply penetrating and radiation-resistant tumors, especially pancreatic cancers.

### **IMMUNOTHERAPY FOR LAPC**

Currently, the use of immunotherapy for LAPC is supported by limited data. A recent immune checkpoint inhibitor trial investigating anti-PD-L1 therapy in patients with LAPC failed to demonstrate efficacy due to the poor immunogenicity and immunosuppressive tumor microenvironment of pancreatic cancer<sup>[40,41]</sup>. However, a minority of patients have genetic mutations that may be targeted with specific interventions. Ongoing clinical trials targeting these mutations have led to discoveries<sup>[42,43]</sup>.

Monoclonal antibodies (mAbs) have been an integral tool in cancer treatment for several decades. They possess the ability to directly kill cells through antibody-dependent cytotoxicity and other pathways and to regulate <sup>1</sup>the immune microenvironment by blocking corresponding signaling pathways, reversing immunosuppression, and enhancing the activity of antitumor effector cells. Moreover, mAbs can even be utilized for the delivery of various therapeutic reagents (Table 3)<sup>[44-50]</sup>.

Mesenchymal stem cells (MSCs) are present in some solid tumors, including PDAC, where they represent almost 100% of cells<sup>[50-52]</sup>. MSCs play a pivotal role in the development of PDAC, and <sup>15</sup>by attenuating MSC recruitment into tumors and inhibiting their tumor-supportive activities, therapeutic outcomes for cancer patients can be improved when MSCs are combined with other anticancer drugs, such as immunotherapy<sup>[50]</sup>. Numerous clinical studies are currently assessing MSC-based cell therapies<sup>[53,54]</sup>.



Mucin 1 (MUC1) is overexpressed in approximately 90% of PDAC cells<sup>[55-58]</sup>. A study<sup>1</sup> demonstrated that an antibody similar to the anti-MUC1 antibody GP1.4 could inhibit the proliferation and migration of cancer cells<sup>[59]</sup>. Additionally, Muc1-c, an isoform of MUC1 with the ability to cross membranes and inhibit tumor growth, could be used as a carrier for cytotoxins in the future<sup>[60]</sup>.

The overexpression of vascular endothelial growth factor (VEGF) mRNA is a common feature in most human tumors and is strongly associated with increased invasiveness, vascular density, metastasis, recurrence, and a poor prognosis<sup>[61]</sup>. The approval of bevacizumab, a mAb that targets VEGF, has paved the way for the development of other inhibitors targeting this pathway<sup>[62,63]</sup>.

Annexin A6 (AnxA6) is the largest member of the conserved annexin family of proteins and is known for its modular domain organization and interactions with a variety of proteins and lipids<sup>[64,65]</sup>. Elevated levels of AnxA6 have been documented during the progression of pancreatic cancer<sup>[48,66,67]</sup>. In a recent study, O'Sullivan *et al.*<sup>[48]</sup><sup>1</sup> isolated a novel anti-AnxA6 antibody, 9E1, and demonstrated its ability to reduce the invasion capacity of pancreatic cancer cells.

The Notch signaling pathway plays a vital role in the development of embryonic and tissue homeostasis, and it has been implicated in various malignancies. One of the key ligands in mammals is Delta-like ligand 4 (Dll4), which contributes significantly to cancer progression<sup>[68]</sup>. Demcizumab, a humanized anti-Dll4 antibody, has shown potential for reversing chemotherapy resistance when used in combination with paclitaxel and GEM. However, a recent study showed that while the combination was safe, it did not improve efficacy<sup>[69]</sup>.

Radioimmunotherapy is emerging as a significant treatment option for patients with PDAC<sup>[70]</sup>. Recent studies have identified CD147 and B7-H3 as potential targets for radioimmunotherapy and have demonstrated the highly promising therapeutic effects of such treatments for PDAC<sup>[71,72]</sup>.

## **NOVEL THERAPIES FOR LAPC**



### *Vaccine therapy for LAPC*

Owing to the intertumoral and intratumoral heterogeneity of pancreatic cancer, immunotherapy, targeted therapy, and other promising treatments have been extensively tested in preclinical studies and clinical trials. However, almost all strategies have shown little significant advantage over conventional chemotherapy against pancreatic cancer, and this issue is often compounded by prevalent therapeutic resistance<sup>[73,74]</sup>. Cancer vaccines have emerged as a promising therapeutic approach for pancreatic cancer because of their multiple targets, small nonspecific effects, wide therapeutic windows, low toxicity, and induction of lasting immune memory. In particular, mRNA-based vaccines possess numerous advantages over conventional vaccines in terms of factors including efficiency, safety, increased developmental potential, and low production costs. They have facilitated significant technological and conceptual progress in personalized and precise treatment. Hence, they represent a potential choice for novel therapies for pancreatic cancer<sup>[75,76]</sup>.

### *Cancer gene and signaling pathway therapy for LAPC*

Recent evidence has revealed that numerous genes and signaling pathways play critical roles in the pathogenesis and progression of PDAC and thus could be potential valuable therapeutic targets<sup>[77,78]</sup>.

### *Molecular pathways*

Activating mutations of KRAS and the phosphoinositide 3 kinase/AKT/mammalian target of rapamycin (PI3K/AKT/mTOR) signaling pathway are frequently observed in PDAC and are associated with a poor prognosis<sup>[78-80]</sup>. In addition, numerous receptor tyrosine kinases have been implicated in the development and progression of PDAC, including tropomyosin receptor kinase, epidermal growth factor receptor (EGFR), insulin-like growth factor receptor, fibroblast growth factor receptor, vascular EGFR, platelet-derived growth factor receptor, and others<sup>[77,80-82]</sup>.

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### *Tumor suppressor genes*

Tumor suppressor genes play a vital role in regulating cell growth by preventing severe metastasis; in tumors, these genes can be altered *via* mutation or chromosomal rearrangement. In PDAC, several tumor suppressor genes, including cyclin-dependent kinase inhibitor p16 (Ink4A), p53, and suppressor of mothers against decapentaplegic protein 4, are frequently mutated<sup>[19,80]</sup>.

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### *DNA repair factors*

Studies have revealed that PDAC ranks as the third most common cancer associated with mutations in the BRCA1 and BRCA2 genes and mismatch repair genes, following breast and ovarian cancers<sup>[83-85]</sup>. Novel combination therapies evaluating immune therapies and targeted agents are being tested for patients with PDAC linked to impaired DNA damage repair<sup>[86,87]</sup>.

### *Epithelial-mesenchymal transition*

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Epithelial-mesenchymal transition (EMT) is a critical process in which epithelial cells acquire mesenchymal features<sup>[88,89]</sup>. In the context of PDAC, EMT has been associated with tumor initiation, invasion, metastasis, and resistance to therapy<sup>[90]</sup>.

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### *Cancer stem cells*

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Cancer stem cells (CSCs) play a critical role in tumor initiation, progression, and therapeutic resistance. In PDAC, CSCs express cell surface markers such as CD24, CD44, CD133, epithelial-specific antigen, c-Met, C-X-C motif chemokine receptor 4, and aldehyde dehydrogenase<sup>[91]</sup>. CSCs have been shown to protect tumor cells from the cytotoxic effects of chemotherapy drugs and are associated with advanced tumor recurrence. However, the mechanisms underlying CSC-mediated drug resistance remain unclear.

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## **EVALUATION OF TREATMENT RESPONSE AFTER NAT**

Evaluation of treatment response and prediction of resectability after NAT remains a challenge for patients with LAPC. Pathological assessment of response after surgical resection remains the gold standard, but this approach is limited by its invasiveness<sup>[92,93]</sup>. Multidetector computerized tomography is the most commonly used imaging modality to evaluate the response of LAPC after NAT. Its advantages over other techniques include higher spatial resolution and multiplanar reconstruction capabilities<sup>[94]</sup>. Other imaging modalities, such as endoscopic ultrasound, diffusion-weighted imaging, positron emission tomography, and perfusion computerized tomography, show significant potential to become powerful tools for assessing tumor resectability and predicting survival after NAT<sup>[95]</sup>. Tumor markers are also commonly used as evaluation indicators, with carbohydrate antigen 19-9 being the only biomarker currently recommended by the NCCN guidelines for assessing NAT response. Other promising indicators being studied include circulating tumor cells, circulating tumor DNA, and microRNA, among others<sup>[94]</sup>.

## **CONCLUSION**

LAPC remains a challenging disease, despite significant progress made in its treatment over the past decade. Notably, immunotherapy has shown remarkable improvements in the management of LAPC. Across all fields of pancreatic cancer research, substantial advancements have been achieved. Basic research has significantly improved the understanding of this disease. Moreover, the advent of advanced DNA and RNA sequencing technologies has enabled The Cancer Genome Atlas consortium to study both the whole genome and transcriptomes of human tumors, thereby facilitating the identification of driver mutations and transcriptional programs implicated in carcinogenesis. These efforts are poised to accelerate the application of precision medicine strategies<sup>[96-99]</sup>. Administration of NAT for the treatment of LAPC can provide important benefits, although more in-depth studies are needed. Therefore, a multidisciplinary team comprising surgeons, oncologists, radiation oncologists, and radiologists is essential for the optimal treatment of LAPC. The most urgent issues to

address include identifying patients who are most suitable for NAT and evaluating treatment effects in a timely and accurate manner to achieve more precise and effective treatments for patients with LAPC.

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