

World Journal of *Gastroenterology*

World J Gastroenterol 2023 September 21; 29(35): 5094-5179



REVIEW

- 5094 Developments and challenges in neoadjuvant therapy for locally advanced pancreatic cancer
Zhou B, Zhang SR, Chen G, Chen P

ORIGINAL ARTICLE

Basic Study

- 5104 Regenerating gene 4 promotes chemoresistance of colorectal cancer by affecting lipid droplet synthesis and assembly
Zhang CY, Zhang R, Zhang L, Wang ZM, Sun HZ, Cui ZG, Zheng HC

Retrospective Cohort Study

- 5125 Clinical characteristics and outcome of autoimmune pancreatitis based on serum immunoglobulin G4 level: A single-center, retrospective cohort study
Zhou GZ, Zeng JQ, Wang L, Liu M, Meng K, Wang ZK, Zhang XL, Peng LH, Yan B, Pan F

Retrospective Study

- 5138 Machine learning-based decision tool for selecting patients with idiopathic acute pancreatitis for endosonography to exclude a biliary aetiology
Sirtl S, Żorniak M, Hohmann E, Beyer G, Dibos M, Wandel A, Phillip V, Ammer-Herrmenau C, Neesse A, Schulz C, Schirra J, Mayerle J, Mahajan UM

Clinical Trials Study

- 5154 Heparanase inhibition leads to improvement in patients with acute gastrointestinal injuries induced by sepsis
Chen TT, Lv JJ, Chen L, Li M, Liu LP

Observational Study

- 5166 Lowering the threshold of alanine aminotransferase for enhanced identification of significant hepatic injury in chronic hepatitis B patients
Yu HS, Jiang H, Li MK, Yang BL, Smayl A, Chen JN, Wu B, Yang YD

CORRECTION

- 5178 Correction to "Role of prebiotics, probiotics, and synbiotics in management of inflammatory bowel disease: Current perspectives"
Roy S, Dhaneshwar S

ABOUT COVER

Editorial Board Member of *World Journal of Gastroenterology*, Konstantinos Triantafyllou, MD, PhD, FEBGH, Full Professor, Hepatogastroenterology Unit, Second Department of Internal Medicine-Propaedeutic, Medical School, National and Kapodistrian University of Athens, "Attikon" University General Hospital, Athens 12462, Greece. ktriant@med.uoa.gr

AIMS AND SCOPE

The primary aim of *World Journal of Gastroenterology* (WJG, *World J Gastroenterol*) is to provide scholars and readers from various fields of gastroenterology and hepatology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online. WJG mainly publishes articles reporting research results and findings obtained in the field of gastroenterology and hepatology and covering a wide range of topics including gastroenterology, hepatology, gastrointestinal endoscopy, gastrointestinal surgery, gastrointestinal oncology, and pediatric gastroenterology.

INDEXING/ABSTRACTING

The WJG is now abstracted and indexed in Science Citation Index Expanded (SCIE, also known as SciSearch®), Current Contents/Clinical Medicine, Journal Citation Reports, Index Medicus, MEDLINE, PubMed, PubMed Central, Scopus, Reference Citation Analysis, China Science and Technology Journal Database, and Superstar Journals Database. The 2023 edition of Journal Citation Reports® cites the 2022 impact factor (IF) for WJG as 4.3; Quartile category: Q2. The WJG's CiteScore for 2021 is 8.3.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Yi-Xuan Cai*, Production Department Director: *Xiang Li*, Editorial Office Director: *Jia-Ru Fan*.

NAME OF JOURNAL

World Journal of Gastroenterology

ISSN

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

LAUNCH DATE

October 1, 1995

FREQUENCY

Weekly

EDITORS-IN-CHIEF

Andrzej S Tarnawski

EXECUTIVE ASSOCIATE EDITORS-IN-CHIEF

Xian-Jun Yu (Pancreatic Oncology), Jian-Gao Fan (Chronic Liver Disease), Hou-Bao Liu (Biliary Tract Disease), Naohisa Yoshida (Gastrointestinal Endoscopy)

EDITORIAL BOARD MEMBERS

<http://www.wjgnet.com/1007-9327/editorialboard.htm>

PUBLICATION DATE

September 21, 2023

COPYRIGHT

© 2023 Baishideng Publishing Group Inc

PUBLISHING PARTNER

Pancreatic Cancer Institute, Fudan University

Biliary Tract Disease Institute, Fudan University

INSTRUCTIONS TO AUTHORS

<https://www.wjgnet.com/bpg/gerinfo/204>

GUIDELINES FOR ETHICS DOCUMENTS

<https://www.wjgnet.com/bpg/GerInfo/287>

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH

<https://www.wjgnet.com/bpg/gerinfo/240>

PUBLICATION ETHICS

<https://www.wjgnet.com/bpg/GerInfo/288>

PUBLICATION MISCONDUCT

<https://www.wjgnet.com/bpg/gerinfo/208>

POLICY OF CO-AUTHORS

<WebSite><https://www.wjgnet.com/bpg/GerInfo/310></WebSite>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>

PUBLISHING PARTNER's OFFICIAL WEBSITE

<WebSite><https://www.shca.org.cn/></WebSite><NewLine/>

<WebSite><https://www.zs-hospital.sh.cn/></WebSite>





Developments and challenges in neoadjuvant therapy for locally advanced pancreatic cancer

Bo Zhou, Shi-Ran Zhang, Geng Chen, Ping Chen

Specialty type: Gastroenterology and hepatology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Nagaya M, Japan; Shalaby MN, Egypt

Received: June 10, 2023

Peer-review started: June 10, 2023

First decision: July 10, 2023

Revised: July 19, 2023

Accepted: August 31, 2023

Article in press: August 31, 2023

Published online: September 21, 2023



Bo Zhou, Shi-Ran Zhang, Geng Chen, Ping Chen, Department of Hepatobiliary Surgery, Daping Hospital, Army Medical University, Chongqing 400042, China

Corresponding author: Ping Chen, MD, PhD, Professor, Surgeon, Department of Hepatobiliary Surgery, Daping Hospital, Army Medical University, No. 10 Changjiang Branch Road, Yuzhong District, Chongqing 400042, China. chenpingsyd@126.com

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

©The Author(s) 2023. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: In recent years, neoadjuvant therapy (NAT) has emerged as a promising treatment option for many cancer types, including locally advanced pancreatic ductal adenocarcinoma, with the potential to improve patient outcomes. To analyze the role of NAT in the setting of locally advanced pancreatic ductal adenocarcinoma 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.

Citation: Zhou B, Zhang SR, Chen G, Chen P. Developments and challenges in neoadjuvant therapy for locally advanced pancreatic cancer. *World J Gastroenterol* 2023; 29(35): 5094-5103

URL: <https://www.wjgnet.com/1007-9327/full/v29/i35/5094.htm>

DOI: <https://dx.doi.org/10.3748/wjg.v29.i35.5094>

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 new cases (496000) each year[1-3]. Experts predict that PDAC will surpass breast cancer as the third leading cause of cancer-related deaths by 2025 in 28 European countries[4]. 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[5-7]. Unfortunately, approximately 60% of patients with LAPC present with metastatic disease and/or poor performance status, making them ineligible for surgery[8,9]. Despite improvements in diagnosis and treatment, clinical outcomes for these patients remain poor.

In 1992, Evans *et al*[10] 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[11,12]. 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[13]. The goal of this review was 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 2022 edition, the Chinese guidelines for the Neoadjuvant Therapy of Pancreatic Cancer 2021 edition, and the International Association of Pancreatology[5,14,15]. 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 [16]. Table 1 provides a summary of these criteria.

CHEMORADIOTHERAPY 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 of 15 mo[17,18]. Polychemotherapy treatment with combined leucovorin calcium (folinic acid), fluorouracil, irinotecan hydrochloride, and oxaliplatin (FOLFIRINOX) and GEM + nab-paclitaxel is recommended[19].

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[20]. Another study enrolled 485 patients with at least three cycles of first-line chemotherapy with FOLFIRINOX or GEM plus nanoparticle albumin-bound paclitaxel (GA) between 2010 and 2017 and revealed that according to the Response Evaluation Criteria in Solid Tumors 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 Response Evaluation Criteria in Solid Tumors-defined partial response and subsequent pancreatectomy than GA[21]. The different types of trials evaluating NAT for LAPC in recent years are summarized in Table 2[19,22-25].

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[26]. 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

Table 1 Definitions of locally advanced pancreatic cancer by different groups

Group	Definition	
	Arterial	Venous
NCCN [14]	Head/uncinate process: Solid tumor contact > 180° with the SMA or CA Body and tail Solid tumor contact of > 180° with the SMA or CA Solid tumor contact with the CA and aortic involvement	Unreconstructible SMV/PV due to tumor involvement or occlusion (can be due to tumor or bland thrombus)
IAP[15]	Tumor contact/invasion of 180 or more degree CHA Tumor contact/invasion showing tumor contact/invasion of the PHA and/or CA	Bilateral narrowing/occlusion, exceeding the inferior border of the duodenum
CMA[5]	Head Solid tumor contact of > 180° with the SMA or CA Body and tail Solid tumor contact of > 180° with the SMA or CA Solid tumor contact with the CA and aortic involvement	Unreconstructible SMV/PV due to tumor involvement or occlusion (can be due to tumor or bland thrombus). The tumor extensively involves the distal jejunal drainage branch of the superior mesenteric vein

CA: Celiac axis; CHA: Common hepatic artery; CMA: Chinese Medical Association; IAP: International Association of Pancreatology; NCCN: National Comprehensive Cancer Network; PHA: Proper hepatic artery; PV: Portal vein; SMA: Superior mesenteric artery; SMV: Superior mesenteric vein.

Table 2 Summary of trials evaluating neoadjuvant therapy for locally advanced pancreatic cancer

Ref.	Type of study	Years of accrual	No. of patients	Primary endpoint	Arms	Key findings
NCT03652428[19]	Phase 1; Phase 2	2019-2023	24	12 mo after registration or until death	Proton therapy with concurrent GEM + Nab-paclitaxel	Ongoing
NCT02578732[22]	Phase 2	2016-2024	28	Until progression, up to 5 yr	FOLFFOX	Ongoing
NCT04247165[23]	Phase 1; Phase 2	2020-2024	20	12 mo	Drug: GEM; Nab-paclitaxel; Nivolumab; Ipilimumab	Ongoing
NCT02873598[24]	Phase 1	2016-2021	15	Up to 5 yr	FOLFIRINOX or GEM/abraxane followed by SBRT	Not yet publicly available
NCT02704143[25]	Phase 2	2016-2020	63	3 yr	Combination of Cyberknife with S-1	Promising efficacy

FOLFFOX: Folinic acid, fluorouracil, and oxaliplatin; FOLFIRINOX: Folinic acid, fluorouracil, irinotecan hydrochloride, and oxaliplatin; GEM: Gemcitabine; S-1: Tegafur, gimeracil, and oteracil; SBRT: Stereotactic body radiation therapy.

placement. Geriatric assessment is recommended for patients who are aged 70 years and above[27]. 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[28].

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[29]. 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 eight cycles, followed by SBRT. The median overall survival and progression-free survival were reported as 26.4 mo (95% confidence

interval: 22.4-30.3) and 16.7 mo (95% confidence interval: 13.0-20.3), respectively[30]. While SBRT appears to have limited utility in the treatment of LAPC compared to conventional fractionated radiation, this study suggested 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[31] first proposed particle therapy for the treatment of tumors in 1946. After more than 70 years of development, particle therapy has become another well-established tumor treatment method after surgery, chemotherapy, traditional radiotherapy, and immunotherapy[32]. 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[33-35]. In addition, particle radiotherapy decreases the viability, proliferation, and migration of cancer cells[36-39]. 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[40,41]. 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[42,43].

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 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)[44-50].

Mesenchymal stem cells (MSCs) are present in some solid tumors, including PDAC, where they represent almost 100% of cells[51-54]. MSCs play a pivotal role in the development of PDAC. 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[51]. Numerous clinical studies are currently assessing MSC-based cell therapies[55,56].

Mucin 1 (MUC1) is overexpressed in approximately 90% of PDAC cells[57-60]. A study demonstrated that an antibody similar to the anti-MUC1 antibody GP1.4 could inhibit the proliferation and migration of cancer cells[61]. 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[62].

The overexpression of vascular endothelial growth factor mRNA is a common feature in most human tumors and is strongly associated with increased invasiveness, vascular density, metastasis, recurrence, and a poor prognosis[63]. The approval of bevacizumab, a mAb that targets vascular endothelial growth factor, has paved the way for the development of other inhibitors targeting this pathway[64,65].

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[66,67]. Elevated levels of AnxA6 have been documented during the progression of pancreatic cancer[48,68,69]. In a recent study, O'Sullivan *et al*[48] 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, which contributes significantly to cancer progression[70]. Demcizumab, a humanized anti-Delta-like ligand 4 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[71].

Radioimmunotherapy is emerging as a significant treatment option for patients with PDAC[72]. 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[73,74].

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[75,76]. 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[77,78].

Table 3 Monoclonal antibody-based therapies targeting non-immune cells for pancreatic ductal adenocarcinoma

Ref.	Type of study	Years of accrual	Target	mAb
NCT01521325[44]	Phase 1	2011-2013	Mesothelin	MORAb-009
Patel <i>et al</i> [45]	Preclinical study	2013	MUC-5AC	NPC-1C
NCT03376659[46]	Phase 1/Phase 2	2018-2023	VEGF	Bevacizumab
NCT00614653[47]	Phase 1	2008-2016	VEGF	Bevacizumab
O'Sullivan <i>et al</i> [48]	Preclinical study	2017	AnxA6	9E1
Smith <i>et al</i> [49]	Phase 1	2008-2011	DLL4	Demcizumab
NCT02722954[50]	Phase 1	2016-2017	DLL4	Demcizumab

AnxA6: Annexin A6; DLL4: Delta-like ligand 4; mAb: Monoclonal antibody; MUC: Mucin; VEGF: Vascular endothelial growth factor.

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[79,80].

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[80,81]. In addition, numerous receptor tyrosine kinases have been implicated in the development and progression of PDAC, including tropomyosin receptor kinase, epidermal growth factor receptor, insulin-like growth factor receptor, fibroblast growth factor receptor, vascular epidermal growth factor receptor, platelet-derived growth factor receptor, and others[79,82-84].

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, *p53*, and suppressor of mothers against decapentaplegic protein 4, are frequently mutated[80,82].

DNA repair factors

Studies have revealed that PDAC ranks as the third most common cancer associated with mutations in the BRCA1/2 gene and mismatch repair genes, following breast and ovarian cancers[85-87]. Novel combination therapies evaluating immune therapies and targeted agents are being tested for patients with PDAC linked to impaired DNA damage repair [88,89].

Epithelial-mesenchymal transition

Epithelial-mesenchymal transition is a critical process in which epithelial cells acquire mesenchymal features[90,91]. In the context of PDAC, epithelial-mesenchymal transition has been associated with tumor initiation, invasion, metastasis, and resistance to therapy[92].

Cancer stem cells

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[93]. 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.

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[94,95]. Multidetector computed 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[96]. 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[97]. Tumor markers are also commonly used as evaluation indicators, with carbohydrate antigen 19-9 being the only biomarker currently recommended by the National

Comprehensive Cancer Network guidelines for assessing NAT response. Other promising indicators being studied include circulating tumor cells, circulating tumor DNA, and microRNAs, among others[96].

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[98-100]. 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.

FOOTNOTES

Author contributions: Chen P contributed to the concept, design, and drafting of the article, and approved the final revision; Zhou B drafted the article; Zhang SR and Chen G revised the manuscript critically for intellectual content; all authors approved the version to be published.

Conflict-of-interest statement: All the authors report having no relevant conflicts of interest for this article.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <https://creativecommons.org/licenses/by-nc/4.0/>

Country/Territory of origin: China

ORCID number: Bo Zhou 0000-0001-8376-3182; Geng Chen 0000-0002-1642-7098; Ping Chen 0000-0001-6575-8582.

S-Editor: Yan JP

L-Editor: Filipodia

P-Editor: Cai YX

REFERENCES

- 1 Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin* 2021; **71**: 209-249 [PMID: 33538338 DOI: 10.3322/caac.21660]
- 2 Park W, Chawla A, O'Reilly EM. Pancreatic Cancer: A Review. *JAMA* 2021; **326**: 851-862 [PMID: 34547082 DOI: 10.1001/jama.2021.13027]
- 3 Wood LD, Canto MI, Jaffee EM, Simeone DM. Pancreatic Cancer: Pathogenesis, Screening, Diagnosis, and Treatment. *Gastroenterology* 2022; **163**: 386-402.e1 [PMID: 35398344 DOI: 10.1053/j.gastro.2022.03.056]
- 4 Ferlay J, Partensky C, Bray F. More deaths from pancreatic cancer than breast cancer in the EU by 2017. *Acta Oncol* 2016; **55**: 1158-1160 [PMID: 27551890 DOI: 10.1080/0284186X.2016.1197419]
- 5 Study Group of Pancreatic Surgery in China Society of Surgery of Chinese Medical Association; Pancreatic Disease Committee of China Research Hospital Association. [The guideline for neoadjuvant therapy of pancreatic cancer in China (2020 edition)]. *Zhonghua Wai Ke Za Zhi* 2020; **58**: 657-667 [PMID: 32878410 DOI: 10.3760/cma.j.cn112139-20200708-00549]
- 6 Ducreux M, Cuhna AS, Caramella C, Hollebecque A, Burtin P, Goéré D, Seufferlein T, Haustermans K, Van Laethem JL, Conroy T, Arnold D; ESMO Guidelines Committee. Cancer of the pancreas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2015; **26** Suppl 5: v56-v68 [PMID: 26314780 DOI: 10.1093/annonc/mdv295]
- 7 Neoptolemos JP, Kleeff J, Michl P, Costello E, Greenhalf W, Palmer DH. Therapeutic developments in pancreatic cancer: current and future perspectives. *Nat Rev Gastroenterol Hepatol* 2018; **15**: 333-348 [PMID: 29717230 DOI: 10.1038/s41575-018-0005-x]
- 8 Strobel O, Neoptolemos J, Jäger D, Büchler MW. Optimizing the outcomes of pancreatic cancer surgery. *Nat Rev Clin Oncol* 2019; **16**: 11-26 [PMID: 30341417 DOI: 10.1038/s41571-018-0112-1]
- 9 Mizrahi JD, Surana R, Valle JW, Shroff RT. Pancreatic cancer. *Lancet* 2020; **395**: 2008-2020 [PMID: 32593337 DOI: 10.1016/S0140-6736(20)30974-0]
- 10 Evans DB, Rich TA, Byrd DR, Cleary KR, Connelly JH, Levin B, Charnsangavej C, Fenoglio CJ, Ames FC. Preoperative chemoradiation and pancreaticoduodenectomy for adenocarcinoma of the pancreas. *Arch Surg* 1992; **127**: 1335-1339 [PMID: 1359851 DOI: 10.1093/ajcp/127.13.1335]

- 10.1001/archsurg.1992.01420110083017]
- 11 **Springfield C**, Ferrone CR, Katz MHG, Philip PA, Hong TS, Hackert T, Büchler MW, Neoptolemos J. Neoadjuvant therapy for pancreatic cancer. *Nat Rev Clin Oncol* 2023; **20**: 318-337 [PMID: 36932224 DOI: 10.1038/s41571-023-00746-1]
- 12 **Wang C**, Tan G, Zhang J, Fan B, Chen Y, Chen D, Yang L, Chen X, Duan Q, Maimaiti F, Du J, Lin Z, Gu J, Luo H. Neoadjuvant Therapy for Pancreatic Ductal Adenocarcinoma: Where Do We Go? *Front Oncol* 2022; **12**: 828223 [PMID: 35785193 DOI: 10.3389/fonc.2022.828223]
- 13 **Gemenetzi G**, Groot VP, Blair AB, Laheru DA, Zheng L, Narang AK, Fishman EK, Hruban RH, Yu J, Burkhart RA, Cameron JL, Weiss MJ, Wolfgang CL, He J. Survival in Locally Advanced Pancreatic Cancer After Neoadjuvant Therapy and Surgical Resection. *Ann Surg* 2019; **270**: 340-347 [PMID: 29596120 DOI: 10.1097/SLA.0000000000002753]
- 14 **Tempero MA**, Malafa MP, Al-Hawary M, Behrman SW, Benson AB, Cardin DB, Chiorean EG, Chung V, Czito B, Del Chiaro M, Dillhoff M, Donahue TR, Dotan E, Ferrone CR, Fountzilas C, Hardacre J, Hawkins WG, Klute K, Ko AH, Kunstman JW, LoConte N, Lowy AM, Moravek C, Nakakura EK, Narang AK, Obando J, Polanco PM, Reddy S, Reyngold M, Scaife C, Shen J, Vollmer C, Wolff RA, Wolpin BM, Lynn B, George GV. Pancreatic Adenocarcinoma, Version 2.2021, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw* 2021; **19**: 439-457 [PMID: 33845462 DOI: 10.6004/jncn.2021.0017]
- 15 **Isaji S**, Mizuno S, Windsor JA, Bassi C, Fernández-Del Castillo C, Hackert T, Hayasaka A, Katz MHG, Kim SW, Kishiwada M, Kitagawa H, Michalski CW, Wolfgang CL. International consensus on definition and criteria of borderline resectable pancreatic ductal adenocarcinoma 2017. *Pancreatol* 2018; **18**: 2-11 [PMID: 29191513 DOI: 10.1016/j.pan.2017.11.011]
- 16 **Kwon W**, Thomas A, Kluger MD. Irreversible electroporation of locally advanced pancreatic cancer. *Semin Oncol* 2021; **48**: 84-94 [PMID: 33648735 DOI: 10.1053/j.seminoncol.2021.02.004]
- 17 **Von Hoff DD**, Ervin T, Arena FP, Chiorean EG, Infante J, Moore M, Seay T, Tjuland SA, Ma WW, Saleh MN, Harris M, Reni M, Dowden S, Laheru D, Bahary N, Ramanathan RK, Tabernero J, Hidalgo M, Goldstein D, Van Cutsem E, Wei X, Iglesias J, Renschler MF. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. *N Engl J Med* 2013; **369**: 1691-1703 [PMID: 24131140 DOI: 10.1056/NEJMoa1304369]
- 18 **Mizusawa J**, Fukutomi A, Katayama H, Ishii H, Ioka T, Okusaka T, Ueno H, Ueno M, Ikeda M, Mizuno N, Ozaka M, Fukuda H, Furuse J; Hepatobiliary and Pancreatic Oncology Group of the Japan Clinical Oncology Group. Protocol digest of randomized phase II study of modified FOLFIRINOX versus gemcitabine plus nab-paclitaxel combination therapy for locally advanced pancreatic cancer: Japan clinical oncology group study (JCOG1407). *Pancreatol* 2018; **18**: 841-845 [PMID: 30075908 DOI: 10.1016/j.pan.2018.07.007]
- 19 **Department of Radiation Oncology**, University of Maryland, Baltimore. Phase I Nab-Paclitaxel Plus Gemcitabine With Proton Therapy for Locally Advanced Pancreatic Cancer (LAPC). [accessed 2023 Apr 25]. In: ClinicalTrials.gov [Internet]. Bethesda (MD): U.S. National Library of Medicine. Available from: <https://ClinicalTrials.gov/show/NCT03652428> ClinicalTrials.gov Identifier: NCT03652428
- 20 **McIntyre CA**, Cohen NA, Goldman DA, Gonen M, Sadot E, O'Reilly EM, Varghese AM, Yu KH, Balachandran VP, Soares KC, D'Angelica MI, Drebin JA, Kingham TP, Allen PJ, Wei AC, Jarnagin WR. Induction FOLFIRINOX for patients with locally unresectable pancreatic ductal adenocarcinoma. *J Surg Oncol* 2022; **125**: 425-436 [PMID: 34719035 DOI: 10.1002/jso.26735]
- 21 **Perri G**, Prakash L, Qiao W, Varadhachary GR, Wolff R, Fogelman D, Overman M, Pant S, Javle M, Koay EJ, Herman J, Kim M, Ikoma N, Tzeng CW, Lee JE, Katz MHG. Response and Survival Associated With First-line FOLFIRINOX vs Gemcitabine and nab-Paclitaxel Chemotherapy for Localized Pancreatic Ductal Adenocarcinoma. *JAMA Surg* 2020; **155**: 832-839 [PMID: 32667641 DOI: 10.1001/jamasurg.2020.2286]
- 22 **Brown University**. FOLFOX-A For Locally Advanced Pancreatic Cancer: A Phase II Brown University Oncology Research Group Trial. [accessed 2023 Apr 25]. In: ClinicalTrials.gov [Internet]. Bethesda (MD): U.S. National Library of Medicine. Available from: <https://ClinicalTrials.gov/show/NCT02578732> ClinicalTrials.gov Identifier: NCT02578732
- 23 **Chen I**. Nivolumab, Ipilimumab and Chemoradiation in Pancreatic Cancer. [accessed 2023 Apr 25]. In: ClinicalTrials.gov [Internet]. Bethesda (MD): U.S. National Library of Medicine. Available from: <https://ClinicalTrials.gov/show/NCT04247165> ClinicalTrials.gov Identifier: NCT04247165
- 24 **University of Colorado**, Denver. A Dose Escalation Trial of SBRT After Induction Chemotherapy for Locally Advanced Pancreatic Cancer. [accessed 2023 Apr 25]. In: ClinicalTrials.gov [Internet]. Bethesda (MD): U.S. National Library of Medicine. Available from: <https://ClinicalTrials.gov/show/NCT02873598> ClinicalTrials.gov Identifier: NCT02873598
- 25 **Zhu X**, Cao Y, Lu M, Zhao X, Jiang L, Ye Y, Ju X, Zhang H. Stereotactic body radiation therapy with sequential S-1 for patients with locally advanced pancreatic cancer and poor performance status: An open-label, single-arm, phase 2 trial. *Radiother Oncol* 2021; **162**: 178-184 [PMID: 34274393 DOI: 10.1016/j.radonc.2021.07.009]
- 26 **Stein SM**, James ES, Deng Y, Cong X, Kortmansky JS, Li J, Staugaard C, Indukala D, Boustani AM, Patel V, Cha CH, Salem RR, Chang B, Hochster HS, Lacy J. Final analysis of a phase II study of modified FOLFIRINOX in locally advanced and metastatic pancreatic cancer. *Br J Cancer* 2016; **114**: 737-743 [PMID: 27022826 DOI: 10.1038/bjc.2016.45]
- 27 **Tempero MA**, Malafa MP, Al-Hawary M, Asbun H, Bain A, Behrman SW, Benson AB 3rd, Binder E, Cardin DB, Cha C, Chiorean EG, Chung V, Czito B, Dillhoff M, Dotan E, Ferrone CR, Hardacre J, Hawkins WG, Herman J, Ko AH, Komanduri S, Koong A, LoConte N, Lowy AM, Moravek C, Nakakura EK, O'Reilly EM, Obando J, Reddy S, Scaife C, Thayer S, Weekes CD, Wolff RA, Wolpin BM, Burns J, Darlow S. Pancreatic Adenocarcinoma, Version 2.2017, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw* 2017; **15**: 1028-1061 [PMID: 28784865 DOI: 10.6004/jncn.2017.0131]
- 28 **Suker M**, Beumer BR, Sadot E, Marthey L, Faris JE, Mellon EA, El-Rayes BF, Wang-Gillam A, Lacy J, Hosein PJ, Moorcraft SY, Conroy T, Hohla F, Allen P, Taieb J, Hong TS, Shridhar R, Chau I, van Eijck CH, Koerkamp BG. FOLFIRINOX for locally advanced pancreatic cancer: a systematic review and patient-level meta-analysis. *Lancet Oncol* 2016; **17**: 801-810 [PMID: 27160474 DOI: 10.1016/S1470-2045(16)00172-8]
- 29 **Barros AG**, Pulido CF, Machado M, Brito MJ, Couto N, Sousa O, Melo SA, Mansinho H. Treatment optimization of locally advanced and metastatic pancreatic cancer (Review). *Int J Oncol* 2021; **59** [PMID: 34859257 DOI: 10.3892/ijo.2021.5290]
- 30 **Jung JH**, Song C, Jung IH, Ahn J, Kim B, Jung K, Lee JC, Kim J, Hwang JH. Induction FOLFIRINOX followed by stereotactic body radiation therapy in locally advanced pancreatic cancer. *Front Oncol* 2022; **12**: 1050070 [PMID: 36620548 DOI: 10.3389/fonc.2022.1050070]
- 31 **Wilson RR**. Radiological use of fast protons. *Radiology* 1946; **47**: 487-491 [PMID: 20274616 DOI: 10.1148/47.5.487]
- 32 **Missaglia A**, Bourkadi-Idrissi A, Casamichiela F, Mazzucconi D, Carminati M, Agosteo S, Fiorini C. Prompt-gamma fall-off estimation with C-ion irradiation at clinical energies, using a knife-edge slit camera: A Monte Carlo study. *Phys Med* 2023; **107**: 102554 [PMID: 36907030 DOI: 10.1016/j.ejmp.2023.102554]
- 33 **Broerse JJ**, Barendsen GW, van Kersen GR. Survival of cultured human cells after irradiation with fast neutrons of different energies in

hypoxic and oxygenated conditions. *Int J Radiat Biol Relat Stud Phys Chem Med* 1968; **13**: 559-572 [PMID: 5301983 DOI: 10.1080/09553006814550621]

- 34 **Charalampopoulou A**, Barcellini A, Frittitta GE, Fulgini G, Ivaldi GB, Magro G, Liotta M, Orlandi E, Pullia MG, Tabarelli de Fatis P, Facoetti A. In Vitro Effects of Photon Beam and Carbon Ion Radiotherapy on the Perineural Invasion of Two Cell Lines of Neurotropic Tumours. *Life (Basel)* 2023; **13** [PMID: 36983949 DOI: 10.3390/life13030794]
- 35 **Wozny AS**, Rodriguez-Lafrasse C. The 'stealth-bomber' paradigm for deciphering the tumour response to carbon-ion irradiation. *Br J Cancer* 2023; **128**: 1429-1438 [PMID: 36639527 DOI: 10.1038/s41416-022-02117-6]
- 36 **Kanai T**, Endo M, Minohara S, Miyahara N, Koyama-ito H, Tomura H, Matsufuji N, Futami Y, Fukumura A, Hiraoka T, Furusawa Y, Ando K, Suzuki M, Soga F, Kawachi K. Biophysical characteristics of HIMAC clinical irradiation system for heavy-ion radiation therapy. *Int J Radiat Oncol Biol Phys* 1999; **44**: 201-210 [PMID: 10219815 DOI: 10.1016/s0360-3016(98)00544-6]
- 37 **Reese AS**, Lu W, Regine WF. Utilization of intensity-modulated radiation therapy and image-guided radiation therapy in pancreatic cancer: is it beneficial? *Semin Radiat Oncol* 2014; **24**: 132-139 [PMID: 24635870 DOI: 10.1016/j.semradonc.2013.11.003]
- 38 **Bittner MI**, Grosu AL, Brunner TB. Comparison of toxicity after IMRT and 3D-conformal radiotherapy for patients with pancreatic cancer - a systematic review. *Radiother Oncol* 2015; **114**: 117-121 [PMID: 25497876 DOI: 10.1016/j.radonc.2014.11.043]
- 39 **Naumann M**, Czempel T, Löbner AJ, Pape K, Beyreuther E, Löck S, Drukewitz S, Hennig A, von Neubeck C, Klink B, Krause M, William D, Stange DE, Bütof R, Dietrich A. Combined Systemic Drug Treatment with Proton Therapy: Investigations on Patient-Derived Organoids. *Cancers (Basel)* 2022; **14** [PMID: 35954444 DOI: 10.3390/cancers14153781]
- 40 **Brahmer JR**, Tykodi SS, Chow LQ, Hwu WJ, Topalian SL, Hwu P, Drake CG, Camacho LH, Kauh J, Odunsi K, Pitot HC, Hamid O, Bhatia S, Martins R, Eaton K, Chen S, Salay TM, Alaparthi S, Grosso JF, Korman AJ, Parker SM, Agrawal S, Goldberg SM, Pardoll DM, Gupta A, Wigginton JM. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. *N Engl J Med* 2012; **366**: 2455-2465 [PMID: 22658128 DOI: 10.1056/NEJMoa1200694]
- 41 **Jiang Y**, Li Y, Zhu B. T-cell exhaustion in the tumor microenvironment. *Cell Death Dis* 2015; **6**: e1792 [PMID: 26086965 DOI: 10.1038/cddis.2015.162]
- 42 **Nevala-Plagemann C**, Hidalgo M, Garrido-Laguna I. From state-of-the-art treatments to novel therapies for advanced-stage pancreatic cancer. *Nat Rev Clin Oncol* 2020; **17**: 108-123 [PMID: 31705130 DOI: 10.1038/s41571-019-0281-6]
- 43 **Le DT**, Durham JN, Smith KN, Wang H, Bartlett BR, Aulakh LK, Lu S, Kemberling H, Wilt C, Luber BS, Wong F, Azad NS, Rucki AA, Laheru D, Donehower R, Zaheer A, Fisher GA, Crocenzi TS, Lee JJ, Greten TF, Duffy AG, Ciombor KK, Eyring AD, Lam BH, Joe A, Kang SP, Holdhoff M, Danilova L, Cope L, Meyer C, Zhou S, Goldberg RM, Armstrong DK, Bever KM, Fader AN, Taube J, Housseau F, Spetzler D, Xiao N, Pardoll DM, Papadopoulos N, Kinzler KW, Eshleman JR, Vogelstein B, Anders RA, Diaz LA Jr. Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. *Science* 2017; **357**: 409-413 [PMID: 28596308 DOI: 10.1126/science.aan6733]
- 44 **Morphotek**. A Single-Dose Pilot Study of Radiolabeled Amatuximab (MORAb-009) in Mesothelin Over Expressing Cancers. [accessed 2023 Apr 25]. In: ClinicalTrials.gov [Internet]. Bethesda (MD): U.S. National Library of Medicine. Available from: <https://ClinicalTrials.gov/show/NCT01521325> ClinicalTrials.gov Identifier: NCT01521325
- 45 **Patel SP**, Bristol A, Saric O, Wang XP, Dubeykovskiy A, Arlen PM, Morse MA. Anti-tumor activity of a novel monoclonal antibody, NPC-1C, optimized for recognition of tumor antigen MUC5AC variant in preclinical models. *Cancer Immunol Immunother* 2013; **62**: 1011-1019 [PMID: 23591984 DOI: 10.1007/s00262-013-1420-z]
- 46 **Georgetown University**. Durvalumab Plus CV301 With Maintenance Chemotherapy in Metastatic Colorectal or Pancreatic Adenocarcinoma. [accessed 2023 Apr 25]. In: ClinicalTrials.gov [Internet]. Bethesda (MD): U.S. National Library of Medicine. Available from: <https://ClinicalTrials.gov/show/NCT03376659> ClinicalTrials.gov Identifier: NCT03376659
- 47 **M.D. Anderson Cancer Center**. Bevacizumab, Erlotinib and Capecitabine for Advanced Pancreatic Cancer. [accessed 2023 Apr 25]. In: ClinicalTrials.gov [Internet]. Bethesda (MD): U.S. National Library of Medicine. Available from: <https://ClinicalTrials.gov/show/NCT00614653> ClinicalTrials.gov Identifier: NCT00614653
- 48 **O'Sullivan D**, Dowling P, Joyce H, McAuley E, McCann A, Henry M, McGovern B, Barham P, Kelleher FC, Murphy J, Kennedy S, Swan N, Moriarty M, Clynes M, Larkin A. A novel inhibitory anti-invasive MAb isolated using phenotypic screening highlights AnxA6 as a functionally relevant target protein in pancreatic cancer. *Br J Cancer* 2017; **117**: 1326-1335 [PMID: 28881357 DOI: 10.1038/bjc.2017.306]
- 49 **Smith DC**, Eisenberg PD, Manikhas G, Chugh R, Gubens MA, Staggs RJ, Kapoun AM, Xu L, Dupont J, Sikic B. A phase I dose escalation and expansion study of the anticancer stem cell agent demcizumab (anti-DLL4) in patients with previously treated solid tumors. *Clin Cancer Res* 2014; **20**: 6295-6303 [PMID: 25324140 DOI: 10.1158/1078-0432.CCR-14-1373]
- 50 **OncoMed Pharmaceuticals, Inc.** A Phase 1b Study of Demcizumab Plus Pembrolizumab in Locally Advanced or Metastatic Solid Tumors. [accessed 2023 Apr 25]. In: ClinicalTrials.gov [Internet]. Bethesda (MD): U.S. National Library of Medicine. Available from: <https://ClinicalTrials.gov/show/NCT02722954> ClinicalTrials.gov Identifier: NCT02722954
- 51 **51 Argani P**, Jacobuzio-Donahue C, Ryu B, Rosty C, Goggins M, Wilentz RE, Murugesan SR, Leach SD, Jaffee E, Yeo CJ, Cameron JL, Kern SE, Hruban RH. Mesothelin is overexpressed in the vast majority of ductal adenocarcinomas of the pancreas: identification of a new pancreatic cancer marker by serial analysis of gene expression (SAGE). *Clin Cancer Res* 2001; **7**: 3862-3868 [PMID: 11751476]
- 52 **Lan T**, Luo M, Wei X. Mesenchymal stem/stromal cells in cancer therapy. *J Hematol Oncol* 2021; **14**: 195 [PMID: 34789315 DOI: 10.1186/s13045-021-01208-w]
- 53 **Weng Z**, Zhang B, Wu C, Yu F, Han B, Li B, Li L. Therapeutic roles of mesenchymal stem cell-derived extracellular vesicles in cancer. *J Hematol Oncol* 2021; **14**: 136 [PMID: 34479611 DOI: 10.1186/s13045-021-01141-y]
- 54 **Timaner M**, Tsai KK, Shaked Y. The multifaceted role of mesenchymal stem cells in cancer. *Semin Cancer Biol* 2020; **60**: 225-237 [PMID: 31212021 DOI: 10.1016/j.semcancer.2019.06.003]
- 55 **Hassan R**, Cohen SJ, Phillips M, Pastan I, Sharon E, Kelly RJ, Schweizer C, Weil S, Laheru D. Phase I clinical trial of the chimeric anti-mesothelin monoclonal antibody MORAb-009 in patients with mesothelin-expressing cancers. *Clin Cancer Res* 2010; **16**: 6132-6138 [PMID: 21037025 DOI: 10.1158/1078-0432.CCR-10-2275]
- 56 **Fujisaka Y**, Kurata T, Tanaka K, Kudo T, Okamoto K, Tsurutani J, Kaneda H, Okamoto I, Namiki M, Kitamura C, Nakagawa K. Phase I study of amatuximab, a novel monoclonal antibody to mesothelin, in Japanese patients with advanced solid tumors. *Invest New Drugs* 2015; **33**: 380-388 [PMID: 25502863 DOI: 10.1007/s10637-014-0196-0]
- 57 **Qu CF**, Li Y, Song YJ, Rizvi SM, Raja C, Zhang D, Samra J, Smith R, Perkins AC, Apostolidis C, Allen BJ. MUC1 expression in primary and metastatic pancreatic cancer cells for in vitro treatment by (213)Bi-C595 radioimmunoconjugate. *Br J Cancer* 2004; **91**: 2086-2093 [PMID: 15599383 DOI: 10.1038/sj.bjc.6602232]

- 58 **Besmer DM**, Curry JM, Roy LD, Tinder TL, Sahraei M, Schettini J, Hwang SI, Lee YY, Gendler SJ, Mukherjee P. Pancreatic ductal adenocarcinoma mice lacking mucin 1 have a profound defect in tumor growth and metastasis. *Cancer Res* 2011; **71**: 4432-4442 [PMID: 21558393 DOI: 10.1158/0008-5472.CAN-10-4439]
- 59 **Striefler JK**, Riess H, Lohneis P, Bischoff S, Kurreck A, Modest DP, Bahra M, Oettle H, Sinn M, Bläker H, Denkert C, Stintzing S, Sinn BV, Pelzer U. Mucin-1 Protein Is a Prognostic Marker for Pancreatic Ductal Adenocarcinoma: Results From the CONKO-001 Study. *Front Oncol* 2021; **11**: 670396 [PMID: 34386419 DOI: 10.3389/fonc.2021.670396]
- 60 **Nagai K**, Adachi T, Harada H, Eguchi S, Sugiyama H, Miyazaki Y. Dendritic Cell-based Immunotherapy Pulsed With Wilms Tumor 1 Peptide and Mucin 1 as an Adjuvant Therapy for Pancreatic Ductal Adenocarcinoma After Curative Resection: A Phase I/IIa Clinical Trial. *Anticancer Res* 2020; **40**: 5765-5776 [PMID: 32988904 DOI: 10.21873/anticancer.14593]
- 61 **Hisatsune A**, Nakayama H, Kawasaki M, Horie I, Miyata T, Isohama Y, Kim KC, Katsuki H. Anti-MUC1 antibody inhibits EGF receptor signaling in cancer cells. *Biochem Biophys Res Commun* 2011; **405**: 377-381 [PMID: 21219855 DOI: 10.1016/j.bbrc.2011.01.029]
- 62 **Wu G**, Maharjan S, Kim D, Kim JN, Park BK, Koh H, Moon K, Lee Y, Kwon HJ. A Novel Monoclonal Antibody Targets Mucin1 and Attenuates Growth in Pancreatic Cancer Model. *Int J Mol Sci* 2018; **19** [PMID: 29987260 DOI: 10.3390/ijms19072004]
- 63 **Kelly PN**. The Cancer Immunotherapy Revolution. *Science* 2018; **359**: 1344-1345 [PMID: 29567702 DOI: 10.1126/science.359.6382.1344]
- 64 **Ferrara N**, Adamis AP. Ten years of anti-vascular endothelial growth factor therapy. *Nat Rev Drug Discov* 2016; **15**: 385-403 [PMID: 26775688 DOI: 10.1038/nrd.2015.17]
- 65 **Apte RS**, Chen DS, Ferrara N. VEGF in Signaling and Disease: Beyond Discovery and Development. *Cell* 2019; **176**: 1248-1264 [PMID: 30849371 DOI: 10.1016/j.cell.2019.01.021]
- 66 **Enrich C**, Rentero C, de Muga SV, Reverter M, Mulay V, Wood P, Koese M, Grewal T. Annexin A6-Linking Ca(2+) signaling with cholesterol transport. *Biochim Biophys Acta* 2011; **1813**: 935-947 [PMID: 20888375 DOI: 10.1016/j.bbamer.2010.09.015]
- 67 **Rentero C**, Blanco-Muñoz P, Meneses-Salas E, Grewal T, Enrich C. Annexins-Coordinators of Cholesterol Homeostasis in Endocytic Pathways. *Int J Mol Sci* 2018; **19** [PMID: 29757220 DOI: 10.3390/ijms19051444]
- 68 **Keklikoglou I**, Cianciaruso C, Güç E, Squadrino ML, Spring LM, Tazzyman S, Lambein L, Poissonnier A, Ferraro GB, Baer C, Cassará A, Guichard A, Iruela-Arispe ML, Lewis CE, Coussens LM, Bardia A, Jain RK, Pollard JW, De Palma M. Chemotherapy elicits pro-metastatic extracellular vesicles in breast cancer models. *Nat Cell Biol* 2019; **21**: 190-202 [PMID: 30598531 DOI: 10.1038/s41556-018-0256-3]
- 69 **Leca J**, Martinez S, Lac S, Nigri J, Secq V, Rubis M, Bressy C, Sergé A, Lavaut MN, Dusetti N, Loncle C, Roques J, Pietrasz D, Bousquet C, Garcia S, Granjeaud S, Ouassini M, Bachet JB, Brun C, Iovanna JL, Zimmermann P, Vasseur S, Tomasini R. Cancer-associated fibroblast-derived annexin A6+ extracellular vesicles support pancreatic cancer aggressiveness. *J Clin Invest* 2016; **126**: 4140-4156 [PMID: 27701147 DOI: 10.1172/JCI87734]
- 70 **Fasoulakis Z**, Koutras A, Ntounis T, Pergialiotis V, Chionis A, Katrachouras A, Palios VC, Symeonidis P, Valsamaki A, Syllaios A, Diakosavvas M, Angelou K, Samara AA, Pagkalos A, Theodora M, Schizas D, Kontomanolis EN. The Prognostic Role and Significance of Dll4 and Toll-like Receptors in Cancer Development. *Cancers (Basel)* 2022; **14** [PMID: 35406423 DOI: 10.3390/cancers14071649]
- 71 **Cubillo Gracian A**, Dean A, Muñoz A, Hidalgo M, Pazo-Cid R, Martin M, Macarulla Mercade T, Lipton L, Harris M, Manzano-Mozo JL, Maurel J, Guillen-Ponce C, Tebbutt N, Cooray P, Sohal D, Zalupski M, Kolevska T, Stagge R, Goldstein D. YOSEMITE: A 3 arm double-blind randomized phase 2 study of gemcitabine, paclitaxel protein-bound particles for injectable suspension, and placebo (GAP) vs gemcitabine, paclitaxel protein-bound particles for injectable suspension and either 1 or 2 truncated courses of demcizumab (GAD). *Ann Oncol* 2017; **28**: v211
- 72 **Sahlin M**, Bauden MP, Andersson R, Ansari D. Radioimmunotherapy--a potential novel tool for pancreatic cancer therapy? *Tumour Biol* 2015; **36**: 4053-4062 [PMID: 25926382 DOI: 10.1007/s13277-015-3479-y]
- 73 **Sugyo A**, Tsuji AB, Sudo H, Koizumi M, Ukai Y, Kurosawa G, Kurosawa Y, Saga T, Higashi T. Efficacy Evaluation of Combination Treatment Using Gemcitabine and Radioimmunotherapy with (90)Y-Labeled Fully Human Anti-CD147 Monoclonal Antibody 059-053 in a BxPC-3 Xenograft Mouse Model of Refractory Pancreatic Cancer. *Int J Mol Sci* 2018; **19** [PMID: 30274301 DOI: 10.3390/ijms19102979]
- 74 **Kasten BB**, Gangrade A, Kim H, Fan J, Ferrone S, Ferrone CR, Zinn KR, Buchsbaum DJ. (212)Pb-labeled B7-H3-targeting antibody for pancreatic cancer therapy in mouse models. *Nucl Med Biol* 2018; **58**: 67-73 [PMID: 29413459 DOI: 10.1016/j.nucmedbio.2017.12.004]
- 75 **Li E**, Huang X, Zhang G, Liang T. Combinational blockade of MET and PD-L1 improves pancreatic cancer immunotherapeutic efficacy. *J Exp Clin Cancer Res* 2021; **40**: 279 [PMID: 34479614 DOI: 10.1186/s13046-021-02055-w]
- 76 **Zhang X**, Huang X, Xu J, Li E, Lao M, Tang T, Zhang G, Guo C, Zhang X, Chen W, Yadav DK, Bai X, Liang T. NEK2 inhibition triggers anti-pancreatic cancer immunity by targeting PD-L1. *Nat Commun* 2021; **12**: 4536 [PMID: 34315872 DOI: 10.1038/s41467-021-24769-3]
- 77 **Huang X**, Zhang G, Tang TY, Gao X, Liang TB. Personalized pancreatic cancer therapy: from the perspective of mRNA vaccine. *Mil Med Res* 2022; **9**: 53 [PMID: 36224645 DOI: 10.1186/s40779-022-00416-w]
- 78 **Miao L**, Zhang Y, Huang L. mRNA vaccine for cancer immunotherapy. *Mol Cancer* 2021; **20**: 41 [PMID: 33632261 DOI: 10.1186/s12943-021-01335-5]
- 79 **Kang X**, Lin Z, Xu M, Pan J, Wang ZW. Deciphering role of FGFR signalling pathway in pancreatic cancer. *Cell Prolif* 2019; **52**: e12605 [PMID: 30945363 DOI: 10.1111/cpr.12605]
- 80 **Lai E**, Puzzoni M, Ziranu P, Pretta A, Impera V, Mariani S, Liscia N, Soro P, Musio F, Persano M, Donisi C, Tolu S, Balconi F, Pireddu A, Demurtas L, Pusceddu V, Camera S, Sclafani F, Scartozzi M. New therapeutic targets in pancreatic cancer. *Cancer Treat Rev* 2019; **81**: 101926 [PMID: 31739115 DOI: 10.1016/j.ctrv.2019.101926]
- 81 **Ebrahimi S**, Hosseini M, Shahidsales S, Maftouh M, Ferns GA, Ghayour-Mobarhan M, Hassani SM, Avan A. Targeting the Akt/PI3K Signaling Pathway as a Potential Therapeutic Strategy for the Treatment of Pancreatic Cancer. *Curr Med Chem* 2017; **24**: 1321-1331 [PMID: 28176634 DOI: 10.2174/0929867324666170206142658]
- 82 **Polireddy K**, Chen Q. Cancer of the Pancreas: Molecular Pathways and Current Advancement in Treatment. *J Cancer* 2016; **7**: 1497-1514 [PMID: 27471566 DOI: 10.7150/jca.14922]
- 83 **Drilon A**, Laetsch TW, Kummar S, DuBois SG, Lassen UN, Demetri GD, Nathanson M, Doebele RC, Farago AF, Pappo AS, Turpin B, Dowlati A, Brose MS, Mascarenhas L, Federman N, Berlin J, El-Deiry WS, Baik C, Deeken J, Boni V, Nagasubramanian R, Taylor M, Rudzinski ER, Meric-Bernstam F, Sohal DPS, Ma PC, Raza LE, Hechtman JF, Benayed R, Ladanyi M, Tuch BB, Ebata K, Cruickshank S, Ku NC, Cox MC, Hawkins DS, Hong DS, Hyman DM. Efficacy of Larotrectinib in TRK Fusion-Positive Cancers in Adults and Children. *N Engl J Med* 2018; **378**: 731-739 [PMID: 29466156 DOI: 10.1056/NEJMoa1714448]
- 84 **Miknyoczki SJ**, Lang D, Huang L, Klein-Szanto AJ, Dionne CA, Ruggeri BA. Neurotrophins and Trk receptors in human pancreatic ductal

- adenocarcinoma: expression patterns and effects on in vitro invasive behavior. *Int J Cancer* 1999; **81**: 417-427 [PMID: 10209957 DOI: 10.1002/(sici)1097-0215(19990505)81:3<417::aid-ijc16>3.0.co;2-6]
- 85 **Lal G**, Liu G, Schmock B, Kaurah P, Ozcelik H, Narod SA, Redston M, Gallinger S. Inherited predisposition to pancreatic adenocarcinoma: role of family history and germ-line p16, BRCA1, and BRCA2 mutations. *Cancer Res* 2000; **60**: 409-416 [PMID: 10667595]
- 86 **Iqbal J**, Ragone A, Lubinski J, Lynch HT, Moller P, Ghadirian P, Foulkes WD, Armel S, Eisen A, Neuhausen SL, Senter L, Singer CF, Ainsworth P, Kim-Sing C, Tung N, Friedman E, Llacuachqui M, Ping S, Narod SA; Hereditary Breast Cancer Study Group. The incidence of pancreatic cancer in BRCA1 and BRCA2 mutation carriers. *Br J Cancer* 2012; **107**: 2005-2009 [PMID: 23099806 DOI: 10.1038/bjc.2012.483]
- 87 **Macherla S**, Laks S, Naqash AR, Bulumulle A, Zervos E, Muzaffar M. Emerging Role of Immune Checkpoint Blockade in Pancreatic Cancer. *Int J Mol Sci* 2018; **19** [PMID: 30405053 DOI: 10.3390/ijms19113505]
- 88 **O'Reilly EM**, Lee JW, Zalupski M, Capanu M, Park J, Golan T, Tahover E, Lowery MA, Chou JF, Sahai V, Brenner R, Kindler HL, Yu KH, Zervoudakis A, Vemuri S, Stadler ZK, Do RKG, Dhani N, Chen AP, Kelsen DP. Randomized, Multicenter, Phase II Trial of Gemcitabine and Cisplatin With or Without Veliparib in Patients With Pancreas Adenocarcinoma and a Germline BRCA/PALB2 Mutation. *J Clin Oncol* 2020; **38**: 1378-1388 [PMID: 31976786 DOI: 10.1200/JCO.19.02931]
- 89 **Park W**, Chen J, Chou JF, Varghese AM, Yu KH, Wong W, Capanu M, Balachandran V, McIntyre CA, El Dika I, Khalil DN, Harding JJ, Ghalehsari N, McKinnell Z, Chalasani SB, Makarov V, Selenica P, Pei X, Lecomte N, Kelsen DP, Abou-Alfa GK, Robson ME, Zhang L, Berger MF, Schultz N, Chan TA, Powell SN, Reis-Filho JS, Iacobuzio-Donahue CA, Riaz N, O'Reilly EM. Genomic Methods Identify Homologous Recombination Deficiency in Pancreas Adenocarcinoma and Optimize Treatment Selection. *Clin Cancer Res* 2020; **26**: 3239-3247 [PMID: 32444418 DOI: 10.1158/1078-0432.CCR-20-0418]
- 90 **Pastushenko I**, Blanpain C. EMT Transition States during Tumor Progression and Metastasis. *Trends Cell Biol* 2019; **29**: 212-226 [PMID: 30594349 DOI: 10.1016/j.tcb.2018.12.001]
- 91 **Dongre A**, Weinberg RA. New insights into the mechanisms of epithelial-mesenchymal transition and implications for cancer. *Nat Rev Mol Cell Biol* 2019; **20**: 69-84 [PMID: 30459476 DOI: 10.1038/s41580-018-0080-4]
- 92 **van Mackelenbergh MG**, Strees CI, Spijker R, van Eijck CHJ, Wilmink JW, Bijlsma MF, van Laarhoven HWM. Clinical Trials Targeting the Stroma in Pancreatic Cancer: A Systematic Review and Meta-Analysis. *Cancers (Basel)* 2019; **11** [PMID: 31035512 DOI: 10.3390/cancers11050588]
- 93 **Hou YC**, Chao YJ, Hsieh MH, Tung HL, Wang HC, Shan YS. Low CD8⁺ T Cell Infiltration and High PD-L1 Expression Are Associated with Level of CD44⁺/CD133⁺ Cancer Stem Cells and Predict an Unfavorable Prognosis in Pancreatic Cancer. *Cancers (Basel)* 2019; **11** [PMID: 30991694 DOI: 10.3390/cancers11040541]
- 94 **Laura A**, Anna C, Cinquepalmi M, Giovanni M, Sole MM, Nava AK, Niccolò P, Giuseppe N, Stefano V, Paolo A, Francesco D, Giovanni R. Is Complete Pathologic Response in Pancreatic Cancer Overestimated? A Systematic Review of Prospective Studies. *J Gastrointest Surg* 2020; **24**: 2336-2348 [PMID: 32583324 DOI: 10.1007/s11605-020-04697-1]
- 95 **Gugenheim J**, Crovetto A, Petrucciani N. Neoadjuvant therapy for pancreatic cancer. *Updates Surg* 2022; **74**: 35-42 [PMID: 34628591 DOI: 10.1007/s13304-021-01186-1]
- 96 **Zhang Y**, Huang ZX, Song B. Role of imaging in evaluating the response after neoadjuvant treatment for pancreatic ductal adenocarcinoma. *World J Gastroenterol* 2021; **27**: 3037-3049 [PMID: 34168406 DOI: 10.3748/wjg.v27.i22.3037]
- 97 **Borhani AA**, Dewan R, Furlan A, Seiser N, Zureikat AH, Singhi AD, Boone B, Bahary N, Hogg ME, Lotze M, Zeh HJ III, Tublin ME. Assessment of Response to Neoadjuvant Therapy Using CT Texture Analysis in Patients With Resectable and Borderline Resectable Pancreatic Ductal Adenocarcinoma. *AJR Am J Roentgenol* 2020; **214**: 362-369 [PMID: 31799875 DOI: 10.2214/AJR.19.21152]
- 98 **ICGC/TCGA Pan-Cancer Analysis of Whole Genomes Consortium**. Pan-cancer analysis of whole genomes. *Nature* 2020; **578**: 82-93 [PMID: 32025007 DOI: 10.1038/s41586-020-1969-6]
- 99 **Peng L**, Bian XW, Li DK, Xu C, Wang GM, Xia QY, Xiong Q. Large-scale RNA-Seq Transcriptome Analysis of 4043 Cancers and 548 Normal Tissue Controls across 12 TCGA Cancer Types. *Sci Rep* 2015; **5**: 13413 [PMID: 26292924 DOI: 10.1038/srep13413]
- 100 **Traub B**, Link KH, Kornmann M. Curing pancreatic cancer. *Semin Cancer Biol* 2021; **76**: 232-246 [PMID: 34062264 DOI: 10.1016/j.semcancer.2021.05.030]



Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA

Telephone: +1-925-3991568

E-mail: bpgoffice@wjgnet.com

Help Desk: <https://www.f6publishing.com/helpdesk>

<https://www.wjgnet.com>

