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Editorial Commentary Open Access

Pancreatic Ductal Adenocarcinoma: Basic and Clinical Challenges for Better Prognosis

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Pancreatic cancer, one of the most lethal types of tumors, is the fourth and fifth leading cause of cancer-related death in the USA and Japan, respectively [1]. Pancreatic Ductal Adenocarcinoma (PDAC)—a major histological subtype, comprising 90% of all pancreatic cancer—displays local invasion and distant metastasis during early disease stages. This aggressiveness leads to an extremely poor prognosis with an overall survival rate of only 5% [1]. Surgery offers the only chance for a cure for PDAC; however, 80% of PDAC patients are considered to be inoperable at diagnosis. No curative treatment is available for advanced stages of the disease. Adjuvant chemotherapies or chemoradiotherapies with 5-FU, gemcitabine, cisplatin, interferon alfa2b, or erlotinib have successfully reduced tumors or prolonged prognosis, but the beneficial effects of these treatments are limited [2-6].

Even after surgery, the five-year survival rates for PDAC remain low, ranging from 15–20%, with most patients dying due to metastatic disease or local recurrence [7]. Thus, the development of early diagnostic methods and new therapeutic approaches for PDAC is a high priority. Serum levels of CA19-9 and CEA are the best known PDAC tumor markers, but they are not useful for early diagnosis. Recently, high levels of microRNAs—including miR-1290 [8], miR-192 [9], miR-99a, miR-155, miR-16, miR-185, miR191, miR-196a, miR-20a, miR-200a, miR-200b, miR-210, miR-21, miR-210, miR-221, miR-24, and miR-27a-3p [10]—have been detected in the serum of PDAC patients and these miRNAs are expected to become novel tumor markers for early stages of PDAC.

Improving the prognosis of PDAC will require approaches of both basic and clinical research. For this special issue about PDAC, I have selected two basic research papers and three clinical papers that cover a broad range of topics related to developing new and more effective PDAC treatment methods.

Recent studies have shown that Cancer Stem Cells (CSCs) have self-renewal ability, undergoing multilineage differentiation that is critically important in cancer cell proliferation, invasion, metastasis, and recurrence [11]. Nestin is a class VI intermediate filament protein that is expressed in a variety of stem/progenitor cells, including pancreatic exocrine progenitor cells [12]. Furthermore, nestin is a CSC markers for glioblastoma [13], malignant melanoma [14], and PDAC [15]. Nestin expression is increased in pancreatic intraepithelial lesions according to grade [16], and nestin inhibition decreases PDAC migration and metastasis [17]. These findings suggest that nestin plays important roles in PDAC carcinogenesis and progression, and that it is a candidate therapeutic target for PDAC treatment. Matsuda's review paper focuses on the regulatory mechanisms of nestin, and the correlation between nestin and CSCs in PDAC.

A major cause of the poor prognosis of PDAC is the frequent metastasis of PDAC cells to the liver, lungs, and other organs. Thus, the development of anticancer drugs to inhibit remote metastasis is important for PDAC treatment. Many studies have evaluated tumor proliferation and metastasis using orthotopic implantation of human PDAC cells in immunodeficiency mice. It is possible to monitor tumor size and metastatic status in real time without animal sacrifice using *in vivo* imaging systems, including ultrasound, positron tomography (PET), CT, MRI, and fluorescent and bioluminescent imaging. However, it is technically difficult to accurately and non-invasively detect intraperitoneal tumors. Dr. Yoshimura established luciferase-transfected PANC-1 cells, and successfully performed *in vivo* bioluminescence imaging in orthotopic, intravenous injection, and intraperitoneal implantation models of NOG mice with severe immunodeficiency, including T and B cell dysfunction, macrophage and complement depression, and defectiveness of natural killer and dendritic cells [18]. This model is expected to be an effective method for analyzing the mechanisms of metastasis and for developing anti-metastatic drugs for PDAC.

Even among patients who receive curative resection for PDAC, a high percentage experiences remote metastasis, which can lead to poor prognosis. In search of a novel therapeutic reagent for PDAC, Dr. Kang et al. studied the mushroom species *Phellinus linteus* (PL). PL and extracts from PL are reportedly effective anti-cancer agents for various malignant tumors, including hepatocellular carcinoma, melanoma, lung cancer, lymphomas, colon cancer, and prostate cancers [19,20]. In their review paper, Dr. Kang et al. summarize the underlying mechanisms of the anti-cancer effects of PL and its extracts. Furthermore, they retrospectively investigated the effects of commercially available PL polysaccharides (Aclang) in PDAC patients after surgical resection; adjuvant chemotherapy combined with gemcitabine or 5-FU and Aclang resulted in statistically longer disease-free survival times compared with in the non-Aclang-treated group. Although this study was based on only a small number of patients, PL and its extracts are expected to be a promising novel adjuvant therapy for PDAC when used in combination with other anti-PDAC drugs.

While adjuvant therapy can improve survival, the effectiveness remains limited. Neoadjuvant therapy has several advantages, including the possibility for early treatment of occult micrometastatic disease such that therapy is delivered to an undisturbed and well-vascularized tumor, as well as the ability to assess drug activity *in vivo* during surgery [21]. In some cases, neoadjuvant therapy reduces tumor size or metastatic foci, downstaging tumors and thus enabling less radical operation. In resectable pancreatic cancer, neoadjuvant chemotherapy with gemcitabine and cisplatin is associated with a high resection rate and a favorable survival rate [22]. Dr. Matsushita et al.

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administered neoadjuvant chemotherapy with gemcitabine and S-1 (NeoGS) in resectable and borderline resectable PDAC patients. This study included only a small number of patients, but NeoGS therapy showed favorable results with a 27% partial response, and high R0 resection and low lymph node metastasis rates.

In resectable PDAC patients, laparoscopic pancreatectomy is one applicable technique. Laparoscopic surgery has the benefit of improved visualization, but also the disadvantage of a limited sense of touch. Laparoscopic surgery is less invasive, making it particularly useful in PDAC patients of advanced age or with complicated diseases. Dr. Nakamura and his colleagues have performed laparoscopic pancreatectomies in 148 patients, including 25 PDAC cases [23,24]. In this review, the authors describe their laparoscopic surgery techniques for PDAC, and focus on the oncologic outcomes and long-term outcomes of laparoscopic surgery for PDAC patients.

Overall, this special issue covers a broad range of PDAC-related topics, including CSC markers for PDAC, a newly established metastatic mouse model, an anti-PDAC reagent from a mushroom species, novel neoadjuvant chemotherapy, and laparoscopic pancreatectomy. The new information from each of these avenues of investigation greatly contributes to the progress of basic and clinical research towards improving the treatment and prognosis of patients with PDAC.

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