Review Article

Management of pancreatic cancer in China: the Tianjin Medical University Cancer Institute and Hospital experience

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Abstract: Pancreatic cancer is one of the most aggressive malignancies with a dismal prognosis. The incidence and mortality of pancreatic cancer in China has been increasing dramatically during the past several decades. With the development of surgery, chemotherapy drugs and radiotherapy technologies, the prognosis of pancreatic cancer has changed greatly in recent years in China, especially in our cancer center, Tianjin Medical University Cancer Institute and Hospital. First, we will make a precise pre-surgery diagnosis in our center involves computerized tomography (CT) images, circulating tumor cell (CTC) measure and KRAS sequence. Second, according to the pre-surgery diagnosis, we will perform the *en bloc* resection and standard lymphadenectomy for pancreatic cancer patient. Third, multidisciplinary team (MDT) is a feature in our cancer center that choose the best therapy for different stage patients with individualized treatment. Finally, clinical trial is important characteristic in our cancer center because the new drug and target drug can be used to treat pancreatic cancer in time. This article reviews the development of pancreatic cancer diagnosis and therapy, highlights the hallmarks of management in our cancer center and discusses the future necessary efforts to improve the quality of life and prognosis for Chinese patients.

Keywords: Pancreatic cancer; Tianjin Medical University Cancer Institute and Hospital; management

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Introduction

Pancreatic ductal adenocarcinoma (PDAC) is one of the most aggressive malignancies which is the fourth leading cancer death in USA, with a 5-year overall survival rate of only 7.7% and a median survival time of less than 6 months (1). The incidence and mortality of pancreatic cancer in China has been increasing dramatically during the past several decades. Among the most common cancers considered in the trend analyses for men, incidence rate of pancreatic cancer increased dramatically from 2000 to 2011. An upward trend in age-standardized mortality rates was observed for pancreatic cancer in men (2).

For localized pancreatic cancer (15–20%) patients, surgical resection is the only potentially curative therapy and the 5-year survival rate is about 20%. For the 80% to 85% patients who have locally advanced or metastatic disease, the median survival rate is about 6 months (3). Assessment the localization, size, local vessels and lymph nodes metastasis of tumor are the key to determine the resectability. And importantly, surgeon's expertise and patient's overall status are the major factors influencing prognosis. With safety improved on pancreatic surgery in the past years, surgeons still focused on the role of more extensive surgery for improving long-term survival. However, whether surgeon should perform extended lymphadenectomy for patients

or not is controversial. The data shows that the extended lymphadenectomy during pancreaticoduodenectomy did not benefit overall survival and may increase morbidity (4). So, in our pancreatic cancer center, standard lymphadenectomy during pancreaticoduodenectomy continues to be the choice for pancreatic cancer patients.

To improve the prognosis, early diagnosis and treatment is crucial for management of pancreatic cancer. Combined with our basic experiments data [circulating tumor cell (CTC), BRAC1 and WT1 sequencing], the rate of early diagnosis for pancreatic cancer improved greatly. According to the condition of patients, neoadjuvant therapy and chemotherapy are applied to improve the survival in our cancer center. Immunotherapy and targeted therapy are potential methods to achieve better and more durable clinical responses.

Currently, multidisciplinary team (MDT) dominates the treatment for pancreatic cancer, although surgery and other therapies have rapidly development. As we perform the highest number of pancreatic cancer surgeries in Tianjin and the 5-year survival rate has reached 7% for operable patients, we will introduce the overall management mode of pancreatic cancer in our cancer center, Tianjin Medical University Cancer Institute and Hospital, and share our experiences of clinical exploration during the last decade in this review.

Diagnosis

Imaging techniques have been used in the finding and diagnosis of pancreatic cancer. We will introduce computerized tomography (CT) scan and Endoscopic ultrasound in pre-surgery diagnosis. CT scan for upper abdomen with arterial and venous phase enhancement is the preferred examine method and can assess local and regional disease extent. Thin slice cuts of CT allow for better visualization of essential vasculature including the celiac trunk, superior mesenteric artery, and portal vein that determine the resectability of the pancreatic cancer. Endoscopic ultrasound is also important for diagnosis and management of pancreatic cancer. It not only can measure the depth and wide of the tumor, but also can guide a fine needle biopsy to obtain tissue diagnosis (5).

CTCs are the cells that fall off from solid tumor lesions and circulate into the peripheral blood, and they can be detected by the CellSearch system and used as promising biomarker to evaluate chemotherapeutic efficacy in prostate cancer, breast cancer and colorectal cancer (6-8). Recent study shows that CTCs have the diagnostic value in PDAC. Total CTC number had 75.8% sensitivity and 68.7% specificity at a cutoff value of 2 CTC cells/3.2 mL. This report is the first to demonstrate that CTC number is useful in PDAC diagnosis. It concluded that both CTC subtype and total CTC number may act as potential biomarkers for PDAC (9). In our pancreatic cancer center, we also detect CTCs in PDAC patients for diagnosis and evaluation the distal metastasis. We use the negative enrichment combined with immunofluorescence and *in situ* chromosomal hybridization (NE-iFISH) to detect CTCs in PDAC patients. The NE-iFISH system can measure aneuploidy in CTCs from PDAC patients and dynamically monitored CTCs during the process of chemotherapy in PDAC patients. We also explored the sensitivity and specificity of the combination of carbohydrate antigen 19-9 (CA19-9) and CTCs determined by the NE-iFISH system in the early diagnosis of pancreatic cancer (10). Our data showed that the NE-iFISH system exhibited a dramatically high detection rate of CTCs in PDAC patients (90%). The diagnostic rate of PDAC reached 97.5% when combining CTCs ≥2 and CA19-9 >37 μmol/L.

BRAC1 and *BRCA2* are two tumor suppressor genes which can repair DNA sequence. Somatic mutations and germline genetic variants on *BRCA1/BRCA2* have been found associated with the tumorigenesis of pancreatic cancer. It reported that three tag missense variants on *BRCA1/BRCA2* in 603 sporadic pancreatic cancer patients in a Chinese population. The data discovered a germline missense variant on *BRAC1* associated with dismal prognosis of PDAC patients with locally advanced stage (11). In our center, we also measure the mutation of *BRCA1/BRCA2* genes by sequencing from peripheral blood of PDAC patients. If the patients with *BRCA1/BRCA2* or other DNA repair mutations, we will choose gemcitabine + cisplatin as chemotherapy according to the NCCN Guideline for Pancreatic Adenocarcinoma, Version 2.2017 (12). These works may contribute to the precision management of this disease.

The Wilms' tumor 1 (*WT1*) gene is act as a tumor suppressor gene expressed in the etiology of Wilms' tumor (13). It has been reported 75% of PDAC cells express *WT1* gene and protein (14). And recent reports have showed that *WT1*-targeted cancer vaccines have an obviously antitumor effect combined with chemotherapy for PDAC patients (15). Therefore, we will sequence the *WT1*

gene to find and confirm the mutation. After analysis the sequence data, we want to set the criteria to help diagnosis and instruct chemotherapy and immunotherapy.

In a word, in our cancer center, to make a precise diagnosis for pancreatic cancer we will make a regular CT scan and combined with CA19-9, CTCs measure, *BRCA1/2* and *WT1* sequence.

Precise surgical mode: en bloc resection and standard lymphadenectomy

Radical resection is the only potentially curative therapy for pancreatic cancer patients. For PDAC patients, it is important to give a precise tumor-node-metastasis (TNM) staging pre-surgical resection according the CT and ultrasound. Therefore, during the surgical operation, we will make an *en bloc* resection for tumor and perform the standard lymphadenectomy. The meta-analysis comparing standard lymphadenectomy with extended lymphadenectomy for pancreatic cancer showed that the extended procedure did not benefit overall survival, and may even cause a trend towards increased morbidity (16). So, in our cancer center, standard pancreaticoduodenectomy is the choice for pancreatic cancer.

In our center, for early stage pancreatic cancers and benign and low-malignancy tumors, laparoscopic operation is the best choice for patients. The meta-analysis showed that laparoscopic pancreatectomy resulted in less loss of blood and time during operation, and lower rates of overall complications and infections compared with open pancreatectomy (17). Another choice is application of robotic surgery, because of the advantages including the rate of R0 resections, greater lymph node yield, shorter hospitalization and faster recovery. Robotic pancreatectomy is not a common procedure in China due to cost.

Current and future therapies for pancreatic cancer

Adjuvant therapy

Recurrent disease can be seen in up to 70% of the resected patients (18). Adjuvant chemotherapy is recommended in all resected cancers including T1N0 disease. In our center, the current standard adjuvant treatment is the gemcitabine (1,000 mg/m^2 on days 1, and 8, of each 21-day cycle) for six cycles. We will examine the CT scan and CA19-9 value to evaluate the abdominal situation of patients every two-cycle.

Borderline resectable cancer and locally advanced pancreatic cancer (LAPC)

There is no uniform treatment for borderline resectable pancreatic in the world. Using the rationale neoadjuvant therapy for borderline resectable pancreatic cancer can achieve a negative surgical margin. It reported that pancreatic cancer patients receiving neoadjuvant FOLFIRINOX have a significant increase in median overall survival compared with patients who were treated with surgery but not neoadjuvant therapy (P=0.008) (19). Other centers use neoadjuvant FOLFIRINOX (leucovorin, fluorouracil, irinotecan, and oxaliplatin) to treat borderline resectable pancreatic cancer and get an R0 rate of approximately 90% (20,21). Prof. Von Hoff reported that combined with Nab-paclitaxel (albumin-bound paclitaxel particles) and the standard gemcitabine treatment regimen significantly improved overall survival, progression-free survival, and response rate with metastatic pancreatic cancer (22). In our cancer center, firstly, we will conduct the FOLFIRINOX or the combination of gemcitabine and nab-paclitaxel chemotherapy for borderline resectable patients according overall status and cost situation, and then repeat the CT scan to reevaluate the tumor by RECIST criteria.

LAPC is recognized inoperable due to primary tumor encasement the celiac axis or the superior mesenteric artery. In our center, LAPC patients get FOLFIRINOX or gemcitabine and nab-paclitaxel chemotherapy to eradicate micro-metastatic disease and downstage the primary tumor (5).

Advanced and metastasis pancreatic cancer

Gemcitabine has been the standard treatment for unresectable pancreatic cancer patients for a couple of decades. Gemcitabine with a low response rates (only 5–10%) and short survival (less than 6 months) due to drug resistance. Attempts were made to combine with gemcitabine and other chemical-drugs and target-drugs but there was no improve in overall survival of pancreatic cancer patients over the past years.

In 2010, there is a breakthrough in the treatment of metastatic pancreatic cancer when FOLFIRINOX versus gemcitabine chemotherapy get a doubling of median overall survival (11.1 *vs.* 6.8 months, HR 0.57, P<0.0001) and response rate significantly improved (31.6 *vs.* 9.4%, P=0.0001) (19). Results of the Metastatic Pancreatic Adenocarcinoma Clinical Trial (MPACT) were showed an obviously improvement in OS with the combination of

gemcitabine plus nab-paclitaxel over gemcitabine alone (8.5 *vs.* 6.7, HR 0.72, P=0.000015) and PFS (5.5 *vs.* 3.7, HR 0.69, P=0.000024) and RR (23% *vs.* 7%) (22). The toxicity profile of nab-paclitaxel was better than FOLFIRINOX chemotherapy.

There is another novel oral fluoropyrimidine derivative, S-1, used for treating gastric, pancreatic, lung, head, neck and breast carcinomas. It consists of three pharmacological agents (at a molar ratio of 1:0.4:1)—tegafur (FT), 5-chloro-2,4-dihydroxypyridine (CDHP), and Oxonic acid (Oxo) (23). The S-1 has been used to treat pancreatic cancer since the early 2000s in Japan (24). The randomized phase III GEST (Gemcitabine and TS-1 Trial) study for locally advanced or metastatic pancreatic cancer investigated the superiority of gemcitabine plus S-1 (GS) and the non-inferiority of S-1 alone versus gemcitabine alone on OS (25). Recently, GS achieved better health-related quality of life (HRQOL) than gemcitabine alone, resulting a good balance between overall survival and HRQOL benefits (26).

So, in our cancer center, the choice of FOLFIRINOX, gemcitabine and nab-paclitaxel or GS determined by the patient's functional status, general condition, comorbidities and economic condition, etc.

Current and future biomarkers for pancreatic adenocarcinoma

Diagnostic biomarkers

Up to now, there is no ideal biomarker for early diagnosis of PDAC. The following part reviews the present and future diagnostic biomarkers for pancreatic cancer.

CA19-9 and carcinoembryonic antigen (CEA)

CA19-9 is the most used biomarker for PDAC diagnosis and the only biomarker permitted by the FDA (27,28). Nevertheless, the sensitivity and specificity of CA19-9 are only 75.5% and 77.6% for the diagnosis of PDAC (29). In other disease, for example, liver cirrhosis, acute cholangitis, pancreatitis, obstructive jaundice and digestive tumor, CA19-9 is also elevated. Important, CA19-9 does not secret in patients with Lewis-null blood type.

CEA is also limited for early detection and diagnosis PDAC. The sensitivity and specificity of CEA is only 39.5%/81.3% (29). Recently, Liu *et al.* reported that serum of CEA(+)/CA125(+)/CA19-9 ≥1,000 U/mL is associated with poor surgical outcome and can be applied to choose proper patients for pancreatectomy (30).

Genetic and epigenetic markers

KRAS is an oncogene and the mutation rate is more than 90% in pancreatic cancer (31). A recently research show that combination KRAS mutation analysis with the cytological analysis of an EUS-FNA specimen can obviously improve the sensitivity from 80.6% to 88.7%, compared to EUS-FNA alone, with a specificity of 92% (32). According to the surprisingly result, we also examine the KRAS mutation by sequence from peripheral blood of PDAC patients in our center.

There are other genes including *TP53*, *SMAD4*, and *CDKN2A* (cyclin dependent kinase inhibitor 2A) also mutated in PDAC (33). Thus, additional studies are needed to investigate the potential role of *TP53*, *SMAD4*, and *CDKN2A* mutation as a diagnostic biomarker.

MicroRNAs (miRNAs)

miRNAs are a group of small non-coding RNAs consisting of 18–25 nucleotides that regulates post-transcriptional modifications of multiple genes (34). Nowadays, using miRNA as a potential biomarker for pancreatic cancer has increased. miRNAs have been investigated in pancreatic tumor tissue, blood samples, pancreatic juice, stool, and urine (35). Among these, miR-21, miR-155, miR-196a, and miR-210 were shown to be upregulated in pancreatic tissue (36), serum samples (37), fecal specimen (38) and pancreatic juice (39) of PDAC patients. Future studies need to assess the benefit of miRNAs as early detection marker. There are other non-coding RNAs [including long non-coding RNAs (lncRNAs) and small ncRNAs] might play a potential function as a detection marker for PDAC (28).

In our cancer center, we not only detect the value of CA19-9 and CEA for detection and diagnosis, but also measure the level of KRAS and other miRNAs for clinical trial.

Conclusions

In conclusion, Tianjin Medical University Cancer Institute and Hospital performs standard, distinctive management based on clinical guidelines, research studies and the context in China. It can be summarized in following parts. First, pre-surgery diagnosis in our center involves CT images, CTC measure and KRAS sequence to increase accuracy. Second, we will perform the *en bloc* resection and standard lymphadenectomy for pancreatic cancer patient. Third, MDT is a feature in our cancer center that choose the best therapy for different stage patients. Finally, clinical trial is important characteristic in our cancer center because the

new drug and target drug can be used to treat pancreatic cancer in time. In a word, our therapy experience always considers patient survival and quality of life and is consistent with international therapy standards.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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