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In advanced pancreatic cancer: The value and significance of interventional therapy

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ABSTRACT

Pancreatic cancer is famous as "the king of cancer" due to its high degree of malignancy, rapid course of disease development, and poor prognosis. Relevant epidemiological studies have indicated that with improvement in people's standard of living, the morbidity and mortality of pancreatic cancer has increased. At the same time, the disease shows an obvious upward trend worldwide. Pancreatic cancer has become a major public health problem that seriously affects the life and health of people. The present review focuses on the recent advances in interventional therapy such as transcatheter arterial infusion, radiofrequency ablation, microwave ablation, and irreversible electroporation of pancreatic cancer.

1. The background

Since pancreatic cancer is usually asymptomatic in the early stage, it is discovered most frequently in the advanced stage. To date, the doctors have been unable to achieve specific and effective treatments. Therefore, the prognosis of the disease becomes poorer with time. Pancreatic cancer is considered one of the most highly malignant tumors of the digestive system around the world. The United Kingdom and the United States ranked fifth[1] and fourth,[2] respectively in the mortality rate associated with pancreatic cancer. With the achievements in intensive basic research regarding pancreatic cancer, the development of examination techniques, and the progress of clinical research on interventional therapy and surgery, the prognosis of pancreatic cancer has improved. However, according to the data from National Cancer Center, the 5-year survival rate of pancreatic cancer in China is only 7.2%.[3] Due to its high mortality rate and low survival rate, pancreatic cancer has become a major public health problem that threatens the safety of people's lives. This paper reviews the progress in interventional therapy for pancreatic cancer in recent years.

2. Staging definitions of pancreatic cancer

The advanced pancreatic cancer referred to in this paper is unresectable pancreatic ductal cell carcinoma that has undergone local and/or distant metastasis.[4,5] The latest details regarding TNM staging, which is frequently used by doctors in clinical work, are shown in Table 1. Bailey's[6] basic study including 456 samples of pancreatic cancer that underwent genome analysis and protein detection revealed four pancreatic cancer subtypes, namely squamous, pancreatic progenitor, immunogenic, and aberrantly differentiated endocrine exocrine. Not only genetic factors, but also the environment plays a dominant role in the development of pancreatic cancer. Although the pathogenesis of pancreatic cancer is unknown, previous studies have shown that smoking, obesity, chronic pancreatitis, and a history of diabetes are important independent risk factors for pancreatic cancer.[7]

3. Interventional therapy

Interventional therapy is a type of diagnostic and therapeutic procedure that is invasive or surgical and requires the expertise of a specially trained radiologist. It is more invasive than diagnostic imaging but less invasive than major surgery. It often includes transcatheter arterial infusion (TAI), radiofrequency ablation (RFA), microwave ablation (MWA), and irreversible electroporation (IRE).

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Table 1
Staging definitions of pancreatic cancer according to the eighth edition of American Joint Committee on Cancer (AJCC) staging system [4,5].

The AJCC (eighth edition) staging definitions for pancreatic cancer					
Details		Stage	T	N	M
T1	Maximum tumor diameter ≤2 cm	0	Tis	N0	M0
T2	Maximum tumor diameter >2 cm and ≤4 cm	IA	T1	N0	M0
T3	Maximum tumor diameter >4 cm	IB	T2	N0	M0
T4	Involvement of celiac axis or superior mesenteric artery (unresectable tumor)	IIA	T3	N0	M0
N0	No regional lymph node metastasis	IIB	T1~3	N0	M0
N1	Metastasis in 1–3 regional lymph nodes	III	T4	Any N	M0
N2	Metastasis in ≥4 regional lymph nodes		Any T	N2	M0
M0	No distant metastasis	IV	Any T	Any N	M1
M1	Distant metastasis				

3.1. Transcatheter arterial infusion

TAI involves the use of artery catheter or microcatheter inserted into the main pancreatic blood supply artery. Due to the anatomical characteristics of the pancreas, the abdominal cavity and the superior mesenteric artery can cover the entire pancreas. Avital's[8] study of 895 cases of pancreatic cancer showed that dry intraperitoneal perfusion was the most frequently used method, accounting for 51.1% of the cases. Among 115 patients from Qiu's[9] research, disease control was achieved in 72 (62.6%) patients and the median progression-free survival and median overall survival (mOS) were 56 days and 147 days, respectively. Takamori et al.[10] administered 5-fluorouracil TAI and intraoperative radiotherapy to patients with advanced pancreatic cancer. The mOS of the included patients was 36.5 months and the 5-year overall survival rate was 30.5%. TAI also has a therapeutic effect on metastatic foci.[11] Some authors have evaluated the clinical significance of adjuvant surgical resection after TAI. Doi's[12] research suggested that the duration of TAI ranged from 45 to 83 months in half of the patients and the likelihood of long-term survival might be increased if TAI was used in combination with resection.

3.2. I-125 seed implantation

I-125 seed implantation involves the use of endoscopy, computed tomography (CT), magnetic resonance imaging (MRI), or ultrasound to confirm the number of I-125 particles and the target areas under Treatment Planning System. Subsequently, I-125 particles are implanted into the pancreatic cancer and the metastatic lesion tissue, resulting in necrosis of the tumor cells. A study by Du et al.[13] showed few differences in pain remission between different treatment methods such as stent intervention alone and I-125 seed implantation in addition to stent intervention. A significant difference in the mean survival time was observed between different implantation methods (13.7 ± 3.4 months vs. 8.4 ± 3.8 months, $t = 3.73$, $P < 0.01$). However, no statistically significant difference was observed in the long-term survival between the groups. These findings indicate that stent intervention combined with I-125 seed implantation is an effective treatment to relieve the clinical symptoms and to prolong the survival time in advanced pancreatic cancer. This result is consistent with the result from a study by Lu et al.,[14] wherein I-125 seed implantation under the guidance of CT greatly reduced the cancer pain of patients, shortened the operation time, and improved patients' tolerance. The author believes that evaluation of the long-term efficacy of I-125 seed implantation requires further large-scale controlled studies. Although I-125 seed implantation is an effective and relatively safe solution to treat pancreatic cancer, it can also result in serious complications. Lv et al.[15] retrospectively analyzed the clinical data regarding I-125 seed implantation in 78 patients with advanced pancreatic cancer. They found that the incidence of complication was 23.08% (18/78) including nine cases of pancreatitis (11.54%), five cases of infection (6.41%), two cases of seed migration (2.56%), one case of intestinal perforation, and one case of intestinal obstruction (1.28%). Generally, the pancreas is surrounding by abundant blood vessels and many organs. Surgeons should improve the preoperative preparation to reduce unnecessary injuries.

3.3. Radiofrequency ablation

RFA involves the removal of pathological tissue by application of heat generated from electrodes delivering an alternating electrical current under the guidance of CT, ultrasound, or other radiological technologies. Unresectable pancreatic cancer often leads to malignant bile duct obstruction. Therefore, RFA combined with ballistics implantation is considered the standard treatment. However, excessive heating of the bile duct by the current RFA system can lead to serious complications. Recently, more number of new devices and RFA systems with special advanced functions have been developed. In Laleman's[16] study, a new radiofrequency catheter ablation device was used for advanced pancreatic tumors with obstructive jaundice. The results showed that at 90 and 180 days after the intervention, biliary patency of 80% and 69%, respectively was observed in patients who were still alive. The median overall stent patency duration was 110 days (range: 16–374) and the median survival time was 227 days (range: 16–374). Thus, intraductal RFA with a new device in patients with unresectable pancreatic cancer was observed to be feasible and safe with acceptable biliary patency. Another prospective multicenter study by Lee et al.[17] showed that the cumulative duration of stent patency and survival were 236 and 383 days, respectively and three patients (two with mild pancreatitis and one with cholangitis) showed adverse complications.

Microbubbles generated during ablation can interfere with the visibility of lesions undergoing ablation during and after the surgery. Minami et al.[18] suggested that ultrasound-ultrasound fusion imaging could allow the observation of tumor images in real time. These images allowed the evaluation of the ablative margin three-dimensionally during and after the surgery, ensuring improved completion of ablation and reduced recurrence. Some authors employed ^{18}F-FDOPA positron emission tomography (PET)/CT-guided radiofrequency ablation to solve this problem. Cazzato et al.[19] achieved a 100% ablation success rate and there was no recurrence of in situ lesions during the follow-up.

3.4. Microwave ablation

MWA uses high heat to cause necrosis of the tumor tissue. The primary difference between MWA and RFA is the principle of heat generation. MWA uses microwaves to drive the body's polar molecules to generate high heat. A study by Vogl et al.[20] showed promising results regarding feasibility and safety of percutaneous approach after short-term follow-up with no major complications and minor complication of severe local pain related to MWA in only two patients. Compared to RFA, MWA has several advantages such as more rapid warming and wider ablation range. However, it still needs further improvements in terms of controllability and safety. Many researchers have suggested[21,22] that the safety of MWA needs to be considered, which may be related to the lack of standards, small sample size, and lack of long-term follow-up among other factors. Notably, the risk of postoperative bleeding and needle tumor implantation is relatively high.

However, in doctors' daily clinical work, comprehensive therapy is valuable in extending the survival time and improving the quality of life in most of the cases. Comprehensive treatment including surgery, chemotherapy, radiotherapy, and interventional therapy (TAI, RFA, and MWA) can improve the prognosis and the survival rate. Ouyang et al. showed that patients treated with three or more approaches (including surgery, chemotherapy, radiotherapy, interventional therapy, and physical therapy) had a longer median survival time than patients treated with two approaches and those treated with a single approach (8.6 vs. 5.2

vs. 4.6 months, P < 0.001).[23] Thus, using a single method of interventional treatment to cure pancreatic cancer has several disadvantages and comprehensive treatment is a better way to achieve the desired effect. Hence, while selecting treatment methods, doctors should select the most effective therapy suitable for the patients.

3.5. Irreversible electroporation: a novel treatment approach

IRE has recently been used as an ablative treatment in advanced pancreatic cancer. Electroporation is a common phenomenon that occurs on the cell membrane when the cells are exposed to high-intensity electric pulses. In 2013, Venkat et al. proposed the Miami protocol[24] for pancreatic cancer, a new treatment approach involving IRE. According to their research, the overall survival was 14.5 months (95% confidence interval: 10.4–18.6) from the date of IRE. Phase I/II clinical studies have shown that electrochemical treatment is effective for liver metastatic cancer and it is especially suitable for tumors located next to blood vessels.[25,26] The outcomes of IRE in advanced pancreatic cancer have been meaningful, but they are limited by the retrospective nature of the data. However, in the study by Christopher et al.,[27] no evident survival benefits of IRE were observed in patients with pancreatic cancer. Moreover, IRE was related with several severe complications. Six patients had severe complications and one patient died after 50 days. An essential period of chemotherapy[24,28–30] may be needed to select patients who are more suitable for IRE.

4. Methods for evaluating the effect of interventional therapy

Pancreatic tumor cells in most patients cannot be killed completely after one interventional therapy. Therefore, these patients need to undergo multiple treatments. It is very important to evaluate the postoperative efficacy, especially for planning further treatment. All cases must be reviewed by a multidisciplinary tumor board including interventional radiologists, medical oncologists, radiation oncologists, and surgeons to determine the quality of treatment. Subsequently, interventional oncologists should finish the preoperative work. All patients should be instructed to undergo laboratory inspection and CT/MRI examinations, which are frequently used imaging detection methods. After the interventional therapy, patients should undergo the same examinations at regular intervals.

Carbohydrate antigen (CA) 19–9 is one of the most widely used tumor markers in the laboratory examination of pancreatic cancer. It is commonly used to help diagnose pancreatic cancer or to evaluate its therapeutic effect. A recent study by Engle et al.[31] found that the expression of CA 19–9 in mice leads to rapid severe pancreatitis with overactivation of epidermal growth factor receptor signaling. Moreover, fluorodeoxyglucose (FDG) PET/CT has been widely used in the diagnosis of tumors, often using FDG as a developer. Asagi et al.[32] reported that FDG-PET/CT sensitivity was 42% in 108 patients with pancreatic cancer, which was superior to contrast-enhanced CT (35%).

The current mainstream view in clinical research is to use CA 19–9 or CT and other radiological technologies according to the modified Response Evaluation Criteria In Solid Tumors[33] to evaluate the treatment effect by comparing the data at different time points before and after the interventional therapy.

5. Conclusion

Pancreatic cancer is a digestive tract tumor with extremely high degree of malignancy, rapid progression, and poor prognosis. Interventional therapy is useful in the treatment of advanced pancreatic cancer, especially in prolonging patients' survival time and improving the quality of life. Although the progress of current research is slow, an effective therapy will be discovered in the future.

Declaration of competing interest

We declare that we have no financial and personal relationships with other people or organizations that can inappropriately influence our work, there is no professional or other personal interest of any nature or kind in any product, service and/or company that could be construed as influencing the position presented in, or the review of, the manuscript entitled.

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