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Commentaries

Experts' consensus on intraoperative radiotherapy for pancreatic cancer

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ABSTRACT

Pancreatic cancer (PC), one of the most lethal malignancies, accounts for 8%–10% of digestive system cancers, and the incidence is increasing. Surgery, chemotherapy, and radiotherapy have been the main treatment methods but are not very effective. However, only 20% of patients have the opportunity to undergo surgical operation. Approximately 30–40% of patients present with locally advanced, unresectable pancreatic cancer because of invasion of mesenteric vessels or adjacent organs.

The first patient with unresectable pancreatic cancer was treated with Intraoperative radiotherapy (IORT) in 1959 [1]. Since then, new surgical and radiotherapeutic techniques have been developed, clinical trials have provided new evidence, and intriguing long-term effects have emerged from global metadatabases. IORT has the advantages of more accurate target, better local control rate, less complications, longer survival time and better life quality. During the past decade, IORT has been applied in some hospitals in the world, but there is little agreement on technical details and standards. A guidelines of IORT in pancreatic cancer is therefore necessary and timely. To develop standardized criteria for the application of IORT in pancreatic cancer, the experts from China to discuss treatment methods and arrive at a consensus on the indications, contraindications, and preferred techniques of IORT in pancreatic cancer. This detailed and agreed technical description of IORT may have implications on training, assessment, quality control, and future research.

1. Introduction

Pancreatic cancer is the 14th most common cancer and the 7th leading cause of cancer death worldwide. The mortality and morbidity of pancreatic cancer rank both 4th among malignancies in the United States [2]. In 2017, pancreatic cancer was the 10th most common cancer and the 6th leading cause of cancer death in China. In Shanghai and other economically developed cities, morbidity ranks 7th in females and 6th in males. The incidence is trending to rapid growth [3]. It is estimated that the mortality will be the second among malignancies by 2030 [4].

Surgery remains as the first option for treatment. However, only 20% of patients have the opportunity to undergo surgical operation. Approximately 30–40% of patients present with locally advanced, unresectable pancreatic cancer because of invasion of mesenteric vessels or adjacent organs [5]. Effectiveness of traditional chemoradiation therapy (CRT) is still unsatisfactory, with 50% of patients suffering from tumor progression with pain or obstruction after CRT treatment. It is reported that R1 resection, proven by pathology, is 16–85% after standard radical surgery. The reason is pancreatic cancer infiltrates retroperitoneal connective tissues, peripancreatic nerve plexus and lymph nodes, increasing the difficulty of R0 resection. According to the European Consensus Report on pancreatic margins, most radical resections were, in fact, R1 resections [6]. The 2-year local recurrence after surgery is 67–86%. Higher rates of local control will be conducive to the improvement in prognosis and life quality.

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Radiotherapy is a main method of treatment for pancreatic cancer. However, because pancreas is a retroperitoneal organ and surrounded by normal tissues like liver and intestine, it is difficult to increase dose with external radiation alone and achieve satisfactory effectiveness. Intraoperative radiotherapy, or IORT, is applied either directly to unresectable locally advanced pancreatic cancer or the tumor bed after the tumor is removed [1,7–12].

In addition to exposing the tumor to a high dose of irradiation under direct visualization during the operation, IORT can decrease adverse effects since adjacent normal tissue structures can be displaced, thus improving patients' quality of life.

Local recurrence is significantly lower when IORT is used for treatment of the tumor bed after tumor removal. It has been reported that IORT after resection results in a median survival time of 19.1 months, 2-year survival rate of 42.1% and 2-year local control of 83.7%, which is better than historical controls [13]. Another study included 90 resectable pancreatic cancer patients, among whom 43 patients underwent IORT after resection with doses of 12.5–20Gy, and 47 patients only underwent surgery. There was no statistically significant difference on overall survival, disease free survival and procedure-related mortality between the two groups. However, the local recurrence rates of the two groups were 27% and 56%, respectively.

IORT is more widely used for locally advanced pancreatic cancer. It is reported that up to 75–95% patients achieve total pain relief with IORT. Massachusetts General Hospital reported a study of 194 locally advanced pancreatic cancer patients who underwent IORT. The median survival was 12 months and local control at 2 years was 41% [14]. Another study showed that 6-month and one-year survival rates in unresectable locally advanced pancreatic cancer patients with IORT was 100% and 57.1%, respectively, much better than patients treated with palliative therapy (42.9% and 0%). Furthermore, in this study, IORT provided substantial pain relief to patients [15]. Cancer Hospital, Chinese Academy of Medical Sciences, reported pain relief with IORT is as high as 94.9% in 247 locally advanced pancreatic cancer patients with a complete remission rate of 63.2%. The 1-year and 3-year survival rates in the group receiving IORT and CRT was 70% and 24%, respectively. Surgery related mortality and morbidity was 0.4% and 15.4%. These results prove IORT is an important method of treatment for locally advanced pancreatic cancer [16].

In summary, IORT is such an important method of treatment for pancreatic cancer that standardizing IORT is desirable.

2. Preoperative tumor assessment

The preoperative surgical evaluation of a pancreatic lesion aims to define the nature of the lesion (malignant or benign), stage the tumor, and to determine resectability or other non-surgical treatment options.

2.1. Surgical assessment

The first step is to adequately assess the pancreas and, in case a mass is present in the pancreas, to determine the extent of local, regional and distant spread and assess resectability [17]. Patients of pancreatic cancer are often elderly and may have significant comorbidities and malnutrition. Careful patient selection, appropriate preoperative evaluation (include anesthetic evaluation, anemia and malnutrition, cardiac and respiratory assessment) and optimization can greatly contribute to a favorable outcome after pancreatic resections [18].

2.2. Preoperative diagnosis, staging and defining resectability

For more accurate assessment of tumor stage and resectability, the surgeon would rely on radiological investigations including computed tomography (CT) scan, magnetic resonance cholangiopancreatography (MRCP), endoscopic ultrasonography (EUS) and positron emission tomography (PET) scanning [18]. CT is the modality of choice to preoperatively stage disease and to identify patients eligible for resection with curative intent [19]. The role of CT is to attempt to detect any contraindications to surgical resection. CT has been shown to have a high predictive value of unresectability (90%–100%) with a slightly lower predictive value of resectability (76%–90%) [20]. This is usually the result of CT's inability to detect tiny liver metastasis or minimal peritoneal spread. Typically, involvement of the celiac axis, hepatic artery, or SMA is a contraindication to surgical resection. Involvement of the portal vein or SMV is not a contraindication; nor does it preclude margin-negative resection, but it may alter the sequence of multimodal treatment. In addition to assessing the extent of adjacent vessel involvement and detecting possible nodal involvement, CT is the modality of choice to detect distant metastasis. In patients with pancreatic cancer, the liver is the most common organ involved with metastases. CT is excellent at detecting liver metastasis. However, there is still the limitation of CT: disease of some patients determined to be resectable by other criteria is sometimes found to be unresectable at surgery, and small liver and peritoneal implants are seen that are below the resolution of CT.

Careful correlation between preoperative CT findings and surgical results has better-defined CT criteria for resectability. The critical aspects that need be evaluated in a thorough radiographic assessment are the presence or absence of peritoneal or hepatic metastases; the potential involvement of the SMV and portal vein and the relationship of these vessels and their tributaries to the tumor; the relationship of the tumor to the SMA, celiac axis, hepatic artery, and gastroduodenal artery; and the presence of any aberrant vascular anatomy. Unequivocal radiographic findings contraindicating resection include distant metastases, major venous thrombosis of the portal vein or SMV extending for several centimeters, and tumor involve exceed $> 180^{\circ}$ of the circumference of the SMA, celiac axis or proximal hepatic artery.

2.3. Rationale for cytology or tissue biopsy

Pancreatic space occupied lesions include benign and malignant tumors, pseudocysts, mass-forming type pancreatitis, and so on [21]. Differentiating amongst these lesions by imaging alone is very difficult making tissue biopsy the gold standard of diagnosis. Without tissue biopsy, it is likely that overtreatment or undertreatment would occur, possibly causing medical disputes. While in any cancer of the body the first step is to histologically confirm the diagnosis, in pancreatic cancers, this may not always be possible. Obtaining a precise biopsy may be difficult owing to the location of the tumor [18]. The need for a preresection tissue diagnosis in patients with pancreatic cancer remains controversial. For patients who are being considered for resection with postoperative adjuvant treatment, tissue confirmation may not be necessary [18]. However, it is necessary to get cytology or tissue biopsy diagnosis before proceeding with treatment of unresectable pancreatic cancer [22–28] or when neoadjuvant treatment options are also considered in cases of borderline resectable pancreatic cancer.

2.4. Method of cytology or tissue biopsy

Paracentesis is the most widely used method of cytology biopsy for pancreatic space occupied lesions, including image guided puncture and endoscopic ultrasound guided puncture. Puncture needles are divided into two types: coarse and fine needle. Coarse needle biopsy involves the use of cutting biopsy and generally results in more tissue, which can be used for the histology diagnosis, classification, gradation and immuno-histochemical examination, resulting in improved accuracy of diagnosis. However, if tumors are located at uncinate process of pancreas, and have a diameter smaller than 2 cm or there are important vessels nearby, care must be taken if choosing coarse needle. Intraoperative fine needle biopsy for patients with IORT has these advantages: (1) simple method, without the need for any special equipment; (2) performed under direct visualization, resulting in more

accurate location, fewer injuries and lower postoperative complications; (3) higher sensitivity and specificity; (4) less time before surgery. Intraoperative fine needle biopsy is recommended for patients with IORT. Tissues gained from exfoliative cytology, laparotomy and laparoscopic surgery are also helpful for diagnosis.

3. Principles of surgery for IORT in pancreatic cancer

Multidisciplinary discussion and assessment is necessary before surgery [29]. Images help to clarify locations of the tumors, adjacent organs and vessels. It helps to make a full assessment of the feasibility of R0 resection. Typical Work Flow for making plan is shown in Table 1.

3.1. Routine preoperative preparation and informed consent for operation

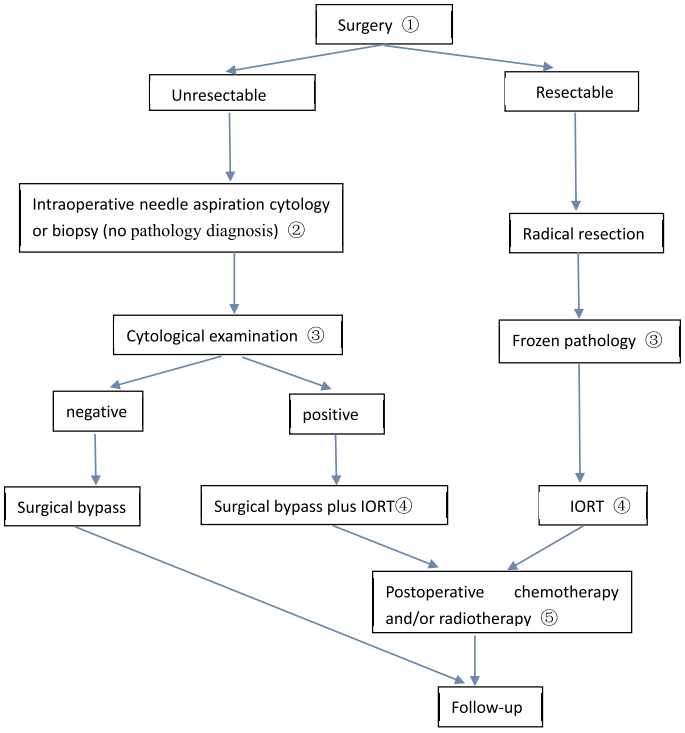
Standard preoperative preparation of the patient should be performed including obtaining informed consent for the surgical procedure and IORT.

3.2. Achieving R0 resection

Radical resection of primary tumors and clearance of local lymph nodes is key to optimal results. To achieve this goal, the following procedures and principles should be followed:

1) Disease-free principle: Avoid touching of tumors, and the blocking tumor-related vessels in advance of the surgical resection.
2) Resection scope: Pancreaticoduodenectomy involves the removal of 1/2–1/3 of distal stomach, duodenum, the bottom of common hepatic ducts, head of pancreas (distance between margin and tumor should be more than 3 cm), 15 cm of proximal jejunum, soft tissues in back of pancreas, local lymph nodes, nerve plexus and connective tissues. Distal pancreatectomy combined with splenectomy includes the removal of pancreatic body and tail (distance between margin and tumor should be more than 1 cm). Spleen should be cut at the beginning of splenic vessels.
3) Safe margins: Pancreaticoduodenectomy requires attention to margins of the pancreas, common hepatic ducts, stomach, duodenum,

Table 1
Work flow of IORT and MDT.



1.MDT members include: Surgeon, physician, radiation therapist, radiologist, pathologist, laboratory physician, interventional radiologist
2. The specific responsibility of each MDT member in IORT:
①Surgeon perform exploratory operation and evaluate the resectability of tumor in operation.
②Obtain pathological cytological evidence.
③Pathologist perform cytological and pathology examination in operation to confirm the diagnosis
④Surgeon and radiation therapist making plan of IORT.
⑤Physician and radiation therapist making plan of postoperative adjuvant therapy.

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retroperitoneal tissues and other soft tissues. The tumor clear margin should be a minimum of 1 mm [30]. Frozen pathological examination should be done for assurance of R0 resection. Distal pancreatectomy should take pancreatic and retroperitoneal margins into consideration.

4) Lymphadenectomy: Removal of more than 15 lymph nodes is necessary [31]. If less than 15 lymph nodes are removed, N-stage should be increased by one. For example, if lymph nodes are negative, N should be classified as PN1 rather than PN0.

3.3. Palliative surgery

Palliative surgery is performed for unresectable patients to relieve symptoms, especially digestive tract obstruction.

(1) Obstructive jaundice: biliary drainage operations, including anastomosis of the jejunum to common bile duct, hepatic duct or gall bladder, last longer and have better drainage than biliary stents. Biliary stents have the advantage of simpler process and fewer short-term complications, but have more long-term complications which are sometimes difficult to manage. Compared with biliary stents, biliary drainage operations have higher short-term risks and complications but fewer long-term complications and better results. It is therefore recommended that patients with long life expectancy undergo anastomosis of the jejunum to common bile duct or hepatic duct. If life expectancy is shorter than 3 months, biliary stents are recommended. If longer than 6 months, biliary drainage operations are recommended. If between 3 and 6 months, either method can be chosen [19].
(2) Digestive tract obstruction: gastrojejunostomy and jejunojejunostomy can effectively relieve digestive tract obstruction. Preventative gastrojejunostomy will, however, decrease nutrient absorption and this should be taken into consideration.
(3) For unresectable tumors, it is recommended to place clips to aid in post-operative radiotherapy delivery.

4. IORT

The work flow of IORT is shown in Table 1.

4.1. Indications for IORT

(1) Primary tumors that have the possibility of resection and whose stage is T3NxM0 or T4NxM0.
(2) Postoperative pathology indicates that margins have tumor residues to the naked eye (R2) or frozen pathology shows positive margins.
(3) Unresectable pancreatic cancer patients with tumor thickness less than 4.5 cm (the limit of contemporary IORT radiation equipment).
(4) Patients with moderate or severe pain and have had no effective pain relief by other treatments [33–35].

4.2. Contraindications of IORT

(1) Preoperative evaluation indicates metastasis.
(2) Patients in poor health who cannot undergo operations.
(3) Life expectancy is less than 3 months [33–35].

4.3. IORT target planning

(1) Radical resection:Target includes tumor bed, lymphatic drainage field and areas with a high-risk of recurrence [36]. Irradiation range includes right from bile duct margin to right kidney; left to medial of residual pancreas. The residual pancreas should be excluded. Irradiation range should be adjusted according to intraoperative conditions, such as exposing the tumor bed only [36].
(2) Palliative resection (R1 or R2 resection):Target includes residual tumors or 0.5–1 cm around lympatic drainage field, areas with high-risk of recurrence or providing an incremental dose to the residual area [37–39].
(3) Unresectable patients: Target includes tumor, 0.5–1 cm margin around the tumor and lympatic drainage field [37–39].

4.4. Radiotherapy dose

(1) Radical resection: Preventive dose of 15Gy to the tumor bed.
(2) Palliative resection: intraoperative dose of 15Gy and postoperative dose of 45–50Gy. For R1 resection or patients with expected long recovery times, the IORT dose to residual tumors should be increased to 20–25Gy with no postoperative irradiation.
(3) Unresectable tumors: When cavity organs are not in the irradiation field, the IORT dose should be 20–25Gy without postoperative irradation. When cavity organs are in the irradiation field, the IORT dose should be restricted to no more than 15Gy with a postoperative dose of 45–50Gy or CRT. (4) Metastasis: For patients with moderate or severe pain, the IORT dose should be 20–22Gy without cavity organs in the irradation field. Otherwise an IORT dose of 15Gy should be used. Chemotherapy should be followed by IORT [36–39].

4.5. IORT energy

(1) When the maximum diameter of tumor is less than 3 cm, 9 Mev is recommended.
(2) When the diameter of tumor is ≥ 3 cm, 12 Mev is recommended [36–39].

4.6. Complications and prevent alive measures

(1) Gastroparesis: can be a consequence of their radation of the gastrointestinal tract. It is important to avoid exposing duodenum and stomach. Treatments include decompression, nutrition support and drugs. Enteral nutrition with enough energy is the first option in nutrition support. Drugs like metoclopramide, domperidone, cisapride and erythroc in do not produce satisfactory results, while Chinese medicine often shows better effect [37].
(2) Digestive tract hemorrhage: can be a consequence of irradation of cavity organs. If cavity organs can not be avoided, the IORT dose should be decreased to 15Gy. Extended postoperative usage of gastric mucosa protectant and anti-acids are helpful in reducing the incidence of digestive tract hemorrhaging.
(3) Radiation myelopathy: the most serious and unusual complication. It can be characterized by paraplegia, hematorrhachis, autonomic dysfunction and limb paralysis.

5. Adjuvant therapy

Following the preoperative MDT and intraoperative treatments, postoperative MDT is necessary for planning adjuvant treatment.

5.1. External beam radiation therapy (EBRT)

5.1.1. Principle

(1) If the IORT dose does not reach a radical limit, postoperative radiotherapy or chemotherapy should be considered.
(2) If patients with unsatisfactory jaundice or postoperative biliary obstruction (jaundice or direct bilirubin increases), preoperative treatment of relieving jaundice should be implemented and digestive tract obstruction should be solved.
(3) Clinical trials to optimize adjuvant treatment are recommended.

5.1.2. Plan for radiotherapy

(1) Use a thin slice, enhanced CT examination of primary tumors and lymphatic drainage area.
(2) Determination of the Gross tumor volume (GTV) and pathologic lymph nodes (shortest diameter is more than 1 cm) should be made using both structural imaging (CT/MRI) and functional imaging (PET). Clinical target volume (CTV) includes region around GTV and high-risk lymphatic drainage area. Planning target volume (PTV) is 5–10 mm around CTV to allow for organ motion and patient set-up errors during fractionated radiotherapy. Organs at risk include liver, kidneys, stomach, small intestine and spinal cord. Dose delivered to the CTV is dependent on the residual tumor. Dose constraints are 40Gy for spinal cord, 30Gy for 50% of liver volume, 20Gy for 30% of bilateral kidneys volume.

5.1.3. Unresectable or locally advanced pancreatic cancer (with no metastasis)

(1) CT stimulation with three-dimensional conformal radiation therapy or intensity-modulated radiation therapy is preferred. If possible, image guided radiation therapy (IGRT) or stereotactic body radiation therapy (SBRT) is also recommended. For SBRT, there is not currently any standard of total and fractionated dose. Therefore, it is encouraged to participate in clinical trials.
(2) Volume is based on result of enhanced CT and MRI or intraoperative radiotherapy clips. Irradiation volume includes primary tumors and metastatic lymph nodes. Lymph nodes at high-risk can undergo preventive exposure.
(3) CRT or radiotherapy after induction chemotherapy is recommended.
(4) Chemotherapy regimens of CRT: monotherapy includes gemcitabine or fluorouracil drugs (continuous infusion 5-FU, capecitabine or S-1), multi-drug therapy includes gemcitabine or fluorouracil-based therapy.
(5) Radiotherapy regimens of CRT: 1.8–2.5Gy/fraction, total dose of 45–54Gy (If necessary, more than 54Gy) or 2.4Gy/fraction, total dose of 36Gy.

5.2. Chemotherapy

Over the past decade, there have been some major improvements in chemotherapy. Chemotherapy plays an important role in preoperative and postoperative adjuvant therapy for locally advanced pancreatic cancer, can improve the survival time. Although gemcitabine remains the key drug in the treatment of pancreatic cancer, traditional chemotherapy regimens based on gemcitabine and fluorouracil have limited effects in the treatment of advanced pancreatic cancer. Gemcitabine has become the standard regimen for advanced pancreatic cancer, but there is no standard second-line chemotherapy. There is little published data to support second-line treatment over optimal supportive treatment, most of which are phase II clinical trials. At the cost of side effects, the benefits of second-line chemotherapy are very limited. Future second-line chemotherapy will be evaluated not only in terms of efficacy or survival, but also in terms of clinical benefit. The combination chemotherapy (Gemcitabine plus albumin-bound paclitax, FOLFIRINOX) is emerging as a new paradigm for advanced pancreatic cancer patients with good performance status, and studies on molecular targeted therapies (erlotinib, nimotuzumab) have achieved some progress in recent years.

5.2.1. Neoadjuvant chemotherapy

Currently, neoadjuvant chemotherapy is mainly used for borderline and unresectable pancreatic cancer, when surgery is considered inefficient or impossible. For locally advanced unresectable pancreatic cancer patients with good performance, mono or multi-drug therapy can be implemented for down-staging. Preferred multi-drug therapy includes gemcitabine plus albumin-bound paclitaxel, or FOLFIRINOX.

(1) Gemcitabine plus albumin-bound paclitaxel: albumin-bound paclitaxel at 125 mg/m^2 and gemcitabine at 1000 mg/m^2 on days 1,8 and 15, every four weeks.
(2) FOLFIRINOX: infusion oxaliplatin at 85 mg/m^2, irinotecan at 180 mg/m^2, leucovorin at 400 mg/m^2, 5-FU at 400 mg/m^2 on day 1 and then continuous infusion 5-FU at 2400 mg/m^2 over 46 h, every 2 weeks.

5.2.2. Chemotherapy for resectable patients

Adjuvant chemotherapy recommends fluorouracil drugs (S-1,5-FU and leucovorin) or gemcitabine monotherapy. Patients with good performance should preferentially receive multi-drug therapy.

(1) S-1: 80–120 mg/day PO on days 1–28, every 6 weeks to six months.
(2) Gemcitabine: infusion gemcitabine at 1000 mg/m^2 on days 1,8 and 15, every 4 weeks to six months.
(3) 5-FU/LV: infusion 5-FU at 425 mg/m^2 and LV at 20 mg/m^2 on days 1–5, every 4 weeks to 6 months.
(4) Gemcitabine plus S-1 is recommended for patients with good performance.

5.2.3. Chemotherapy for unresectable patients

For unresectable locally advanced pancreatic cancer patients with IORT, chemotherapy should be followed by CRT (2–6 cycles).

(1) First-line chemotherapy
  1) Chemotherapy
    ① Gemcitabine plus albumin-bound paclitaxel, albumin-bound paclitaxel at 125 mg/m^2 and gemcitabine at 1000 mg/m^2, every 4 weeks.
    ② FOLFIRINOX: infusion oxaliplatin at 85 mg/m^2, irinotecan at 180 mg/m^2, leucovorin at 400 mg/m^2, 5-FU at 400 mg/m^2 on day 1 and then continuous infusion 5-FU at 2400 mg/m^2 over 46 h, every 2 weeks.
    ③ Gemcitabine: infusion at 1000 mg/m^2 weekly to 7 weeks and rest for 1 week, then continuous for 3 weeks and rest for 1 week, every four weeks.
    ④ Gemcitabine plus S-1: infusion gemcitabine at 1000 mg/m^2 on day 1 and day 8, taken orally twice of S-1 at 60–100 mg/day on day 1–28, every 3 weeks.
    ⑤ S-1: taking orally at 80–120 mg/day on day 1–28, every 6 weeks.
    ⑥ Gemcitabine plus capecitabine, gemcitabine plus cisplatin (especially for genetic tumors), fixed-dose-rate gemcitabine, docetaxel plus capecitabine (GTX), fluorouracil plus oxaliplatin.
  2) Chemotherapy plus molecule targeted therapy.
    ① Gemcitabine plus erlotinib: infusion gemcitabine at 1000 mg/m^2 on days 1,8,15,22,29,36 and rest for 1 week for first period; For second period infusion gemcitabine at 1000 mg/m^2 on days 1,8,15, every 4 weeks. Erlotinib PO 100 mg/day.
    ② Gemcitabine plus nimotuzumab: infusion gemcitabine at 1000 mg/m^2 over 30 min weekly (on days 1,8,15, every 3 weeks), infusion fixed-dose rate nimotuzumab at 400 mg weekly over 30 min.
(2) Second-line chemotherapy
  ① Gemcitabine is preferred for patients without prior gemcitabine-based therapy.
  ② For patients with prior gemcitabine-based therapy, second-line chemotherapy is fluororacil-based therapy, including S-1, capecitabine, 5-FU/LV/oxaliplatin, S-1/capecitabine or oxaliplatin.

For metastatic patients after operation, if time is more than 6 months before adjuvant therapy, alternative chemotherapy can substitute for primary chemotherapy.

③ Patients with pancreatic cancer who failed first-line therapy. Clinical trials is recommended. Bevacizumab plus erlotinib: bevacizumab 15 mg/kg as a 60–90 min infusion every 21 days (representing one treatment cycle) and erlotinib 150 mg by mouth daily. Docetaxel plus Capecitabine: Docetaxel: 30 mg/m^2, days 1 and 8 every 3 weeks. Capecitabine: Orally, 1600 mg/m^2/day given as (800 mg/m^2 bid), days 1 through 14 of 21-day cycle

5.3. Chinese herbal medicine

Chinese herbal medicine (CHM) is an important part of comprehensive treatment for pancreatic cancer. Compared with Western medicine, it emphasizes regulating rather than killing cancer cells. CHM is helpful to enhance the ability of anti-cancer drugs, reduce toxicity of radiotherapy and chemotherapy, improve symptoms and quality of life and prolong life-time [40]. Li et al. [41]studied the role of TCM in advanced pancreatic cancer by meta-analysis in 2015. The final analysis showed that treatment with CHM-containing regimens significantly improves1-year survival rate (95%CI = 1.49–2.31, $P < 0.00001$), objective response rate (95% CI = 1.26–1.59, $P < 0.00001$), disease control rate (95% CI = 1.12–1.39, $P < 0.000$) and quality of life (95% CI = 1.12–1.39, $P = 0.0002$) compared with the non-CHM-containing regimens. Therefore, CHM is an important adjunctive treatment for pancreatic cancer.

5.4. Targeted therapy

The advantage of targeted therapy in some tumors has been affirmed, but its effect in pancreatic cancer is still unsatisfactory. In the future, more efficient targeted drugs maybe found and can then be tested in clinical trials.

5.5. Other therapies

Arterial infusion chemotherapy can result in a high concentration of drugs in tumors (more than 10 times that of systemic chemotherapy). It kills a large number of cancer cells, inhibits the release of cancer cell factors, and achieves a satisfactory tumor inhibition effect. Other therapies such as CHM, particle implantation, or immunotherapy do not have large scale clinical studies to verify their efficacy or reliability.

Conflicts of interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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