

## Original Research Article

# Comparison of efficacy and safety of three different drugs combined with radiotherapy in the treatment of patients with advanced pancreatic cancer

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### Abstract

**Purpose:** To investigate the clinical efficacy and safety of three different drugs combined with radiotherapy, viz, apatinib mesylate combined radiotherapy (group A), gemcitabine combined oxaliplatin (group B), and Huachansu capsules combined radiotherapy (group C) in advanced pancreatic cancer patients.

**Methods:** A total of 174 patients with advanced pancreatic cancer treated in Yantai Qishan Hospital, Yantai, China from June 2015 to December 2016 were randomly and evenly divided into groups A, B, and C. The incidence of adverse reactions during treatment, immune reaction, efficacy, quality of life, and survival were compared among the three groups after four courses of treatment.

**Results:** Compared with groups B and C, the incidence of nausea and vomiting was higher in group A ( $p < 0.05$ ), but the incidence of other adverse events was not significantly different ( $p > 0.05$ ). Group A showed higher response rate and disease control rate, higher CD4+, CD4+/CD8+ levels and QOL scores, as well as lower CD8+ level in peripheral blood after treatment than groups B and C ( $p < 0.05$ ). Group A also exhibited longer median OS and median PFS, and higher 2-year survival than groups B and C ( $p < 0.05$ ).

**Conclusion:** Among the three different drug treatments combined with radiotherapy, apatinib mesylate combined radiotherapy enhanced efficacy and quality of life, and lengthen the survival time of advanced pancreatic cancer patients. However, additional clinical trials are required to validate these findings.

**Keywords:** Pancreatic cancer, Radiotherapy, Chemotherapy, Apatinib mesylate, Gemcitabine, Oxaliplatin, Huachansu capsules

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## INTRODUCTION

Pancreatic cancer is one of the most common malignant tumors of the digestive system. With the increasing pressure of social life, the change

of living habits and the influence of environmental changes, the incidence of pancreatic cancer is gradually increasing [1]. The clinical symptoms of pancreatic cancer are mostly upper abdomen fullness, lower back pain,

weight loss and fatigue, which are not characteristic [2,3]. After patients are diagnosed, most of the cancer cells have metastasized to distant places, and about 80% of patients are in advanced stage [4].

Surgical resection is the only curable therapy for pancreatic carcinoma. However, radical surgery is difficult to achieve good results. The mortality of patients with advanced pancreatic cancer is high, and the 5-year survival is < 5 % [5,6]. Therefore, new treatment options are urgently needed to prolong the survival and improve the quality of life of patients with advanced pancreatic cancer.

## METHODS

### General information

Following a research strategy adopted for this study (Figure 1), 174 advanced pancreatic carcinoma patients receiving treatment in Yantai Qishan Hospital, Yantai, China from June 2015 to December 2016 were enrolled in the study. The ethics committee of Yantai Qishan Hospital approved this study (approval no. 201401156B), which followed the guidelines of Declaration of Helsinki [7]. All patients/subjects and family members agreed and signed a consent form. The enrolled participants were randomly assigned to groups A, B and C, with 58 patients per group. Group A included 34 male and 24 female patients (age from 34 to 75 years; mean age,  $53.36 \pm 10.81$  years), while Group B had 32 male and 26 female patients (age range, 35 to 71 years; mean,  $52.66 \pm 10.95$  years). Group C comprised of 35 male and 23 female patients (age range 32 to 74 years; mean,  $52.02 \pm 12.84$  years old).

### Inclusion criteria

1) Aged from 18 to 75 years; 2) histopathological and cytological examination confirmed the diagnosis of pancreatic cancer; 3) Patient's clinical staging was III-IV phrase based on the pancreatic cancer staging criteria of the eighth edition of AJCC; 4) The physical condition was good, and the performance status (PS) score was 0 - 2 points.

### Exclusion criteria

1) Expected survival time < 3 months; 2) Patients allergic to apatinib mesylate, gemcitabine, oxaliplatin or Huachansu capsules; 3) Patients were complicated with severe organic diseases or other malignant tumors; 4) Patients with radical surgery for pancreatic cancer; 5). Patients

used chemotherapy, surgical treatment, or biological anti-tumor treatment in the past.

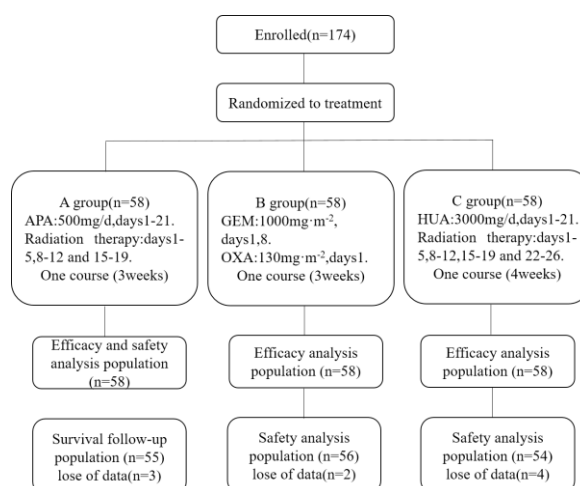


Figure 1: Research strategy

### Treatments

#### Radiotherapy

Patients were given oral contrast agent 1h before localization to better show the position of stomach and intestine. Patients lay on the flat bed of the CT machine with heads in his hands. All patients were instructed to breathe gently while a qualified radiologist performed an enhanced CT scan of the abdomen. The scanning layer thickness is 5mm. The target area and endangered organs were delineated based on CT images. Gross tumor volume (GTV) was the tumor visible on imaging, and the GTV extended 0.5cm outward as the clinical target volume (CTV). Considering the position deviation caused by the movement of the organ, the CTV was expanded by 0.5cm in the front and back and left and right directions, and the head and foot direction was expanded by 1.0cm as the plan target volume (PTV). Delineated vital organs and limited safe doses were confirmed. Using three-dimensional adapted radiotherapy technology, the prescribed dose was selected as 95 % PTV 50.4-59.0, 4 Gy / 1.8 Gy / 28-33F, 5 times a week. Dose-volume histograms were used to evaluate and optimize radiotherapy plans.

Patients in group A were given apatinib mesylate (APA, Jiangsu Hengrui Medicine, China), orally daily, 500mg; combined with radiotherapy, once a day, 5 days per week, treated on days 1-5, stopped for 2 days. Three week was taken as a course of treatment. Patients in group B were given gemcitabine (GEM, Eli Lilly, USA), 1000 mg/m<sup>2</sup>, intravenous infusion for 30 min, treated on days 1, 8; combined with oxaliplatin (OXA,

Jiangsu Hengrui Medicine, China), 130 mg/m<sup>2</sup>, treated on day 1, with 3 weeks as a course.

Patients in group C were given Huachansu capsules (HUA, Shaanxi Dongtai Pharmaceutical, China) combined with radiotherapy, with oral administration, treated on day 1 to day 21, then stopped for 7 days, with three weeks for a course.

All three groups were treated for four courses until the tumor progressed or the treatment became intolerable.

## Evaluation of parameters/indicators

### Incidence of adverse events

Immune function, efficacy, quality of life score, median overall survival (OS), median progression-free survival (PFS), and 2-year survival were compared after four courses of treatment. Toxicity evaluation was conducted according to adverse event evaluation criteria. Adverse reactions mainly included gastrointestinal reactions (nausea, vomiting, and so on) and hematological events.

### Immune function

A sample of 3 ml blood was drawn from the peripheral veins of patients after fasting before and after treatment. Flow cytometry (BD FACSVerser, USA) was used to determine the distribution of CD3+, CD4+, and CD8+, and CD4+ / CD8+ ratio was calculated.

### Efficacy

RECIST 1.1 criteria for solid tumors was used to evaluate the efficacy, including complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD). Response rate (RR) = CR + PR. Disease control rate (DCR) = CR + PR + SD.

### Quality of life

The QLQ-C30 measurement scale was applied. The questionnaire consisted of 5 sub-scale, which focused on the patient's physical, cognitive, emotional and social functions. Each dimension is scored on a scale of 0-100, with higher scores indicating higher quality of life. The three groups were followed up by telephone and outpatient services to investigate their progression-free survival (PFS) and overall survival (OS). The enrollment time was taken as the start time of follow-up, and the end events

were loss of follow-up, death of patients, or end of follow-up.

## Statistical analysis

Using SPSS 24.0 software, data are expressed as mean ± standard deviation (SD). If the data satisfied the normal distribution, single-factor ANOVA was used for multi-group comparison; if not, non-parametric test was used for inter-group analysis. Count data are recorded in percentages. Chi-square test was applied for comparison between the two groups. We made use of Kaplan-Meier method for survival analysis, calculated median PFS, median OS, and survival rate, and performed log-rank test.  $P < 0.05$  was considered statistically significant. GraphPad Prism 7.0 software was used for graphical analysis.

## RESULTS

### General profile of patients

174 participants were enrolled, randomly divided into three groups, and treated in varying ways. There is no statistically significance in age, gender composition ratio, PS score and disease stage of the three groups ( $p > 0.05$ ), and they were comparable. Patients were followed up for survival states. There were 3, 2 and 4 lost cases in groups A, B, and C.

### Incidence of adverse reactions

Neither treatment discontinuation-related serious adverse events nor treatment-related deaths happened. The main adverse reactions that occurred primarily were nausea and vomiting, liver and kidney function injury, bone marrow suppression, hematological adverse events, and so on. Compared with groups B and C, the incidence of leukopenia was higher in group A.

### Immune function of patients before and after treatment

Before treatment, CD3+, CD4+, CD8+ levels in peripheral blood and CD4+ / CD8+ ratio in 3 groups showed no statistical significance ( $p > 0.05$ ). After treatment, the CD3+, CD4+, and CD4+ / CD8+ of group A elevated, whereas CD8+ diminished compared to groups B and C ( $p < 0.05$ ). Verse to group B, the CD4+ and CD4+ / CD8+ decreased in group C ( $p < 0.05$ ).

### Quality of life

Before treatment, the quality-of-life scores was not statistically significant in groups ( $p > 0.05$ ).

**Table 1:** General clinical data of study subjects (mean  $\pm$  SD)

Classification	A group (n=58)	B group (n=58)	C group (n=58)
Age (years)	53.36 $\pm$ 10.81	52.66 $\pm$ 10.95	52.02 $\pm$ 12.84
Gender n (%)			
Male	34(58.62)	32(55.17)	35(60.34)
Female	24(41.38)	26(44.83)	23(39.66)
PS scores n (%)			
0	37(63.79)	40(68.97)	38(65.52)
1	18(31.04)	16(27.58)	19(32.76)
2	3(5.17)	2(3.45)	1(1.72)
Disease staging n (%)			
Local progression	14(24.14)	17(29.31)	16(27.59)
Advanced stage	44(75.86)	41(70.69)	42(72.41)

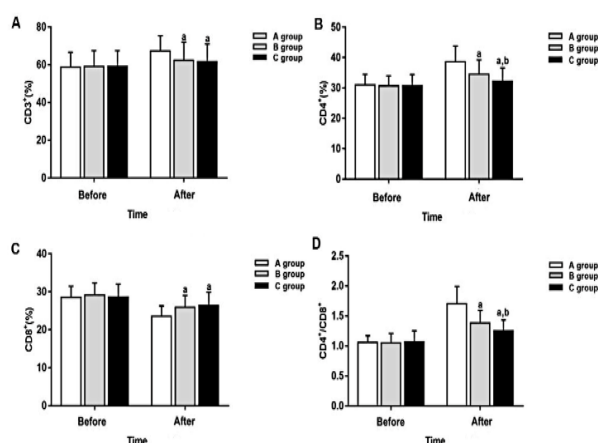
PS scores = performance status scores

**Table 2:** Comparison of the incidence of adverse reactions amongst the three groups of patients (mean  $\pm$  SD)

Adverse reaction	A group (n=58)	B group (n=58)	C group (n=58)
Nausea, vomiting	9(15.52)	10(17.24)	7(12.07)
Rash	4(6.90)	8(13.79)	5(8.62)
Liver and kidney function injury	15(25.86)	11(18.96)	9(15.52)
Peripheral nerve injury	5(8.62)	7(12.07)	6(10.34)
Bone marrow suppression	8(13.79)	9(15.52)	11(18.96)
Leukopenia	19(32.76)	7(12.07) <sup>a</sup>	9(15.52) <sup>a</sup>
Thrombocytopenia	5(8.62)	7(12.07)	8(13.79)
Anemia	9(15.52)	3(5.17)	7(12.07)

**Table 3:** Comparison of immune function of patients before and after treatment (mean  $\pm$  SD)

Indicator	A group (n=58)		B group (n=58)		C group (n=58)	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
CD3 <sup>+</sup> (%)	58.73 $\pm$ 7.86	67.23 $\pm$ 8.18	59.17 $\pm$ 8.33	62.34 $\pm$ 9.75 <sup>a</sup>	59.22 $\pm$ 8.26	61.73 $\pm$ 9.36 <sup>a</sup>
CD4 <sup>+</sup> (%)	31.02 $\pm$ 3.46	38.62 $\pm$ 5.16	30.69 $\pm$ 3.28	34.51 $\pm$ 4.78 <sup>a</sup>	30.72 $\pm$ 3.69	32.24 $\pm$ 4.32 <sup>a,b</sup>
CD8 <sup>+</sup> (%)	28.52 $\pm$ 2.97	23.56 $\pm$ 2.74	29.19 $\pm$ 3.15	25.89 $\pm$ 3.17 <sup>a</sup>	28.63 $\pm$ 3.41	26.38 $\pm$ 3.54 <sup>a</sup>
CD4 <sup>+</sup> /CD8 <sup>+</sup>	1.06 $\pm$ 0.11	1.70 $\pm$ 0.29	1.05 $\pm$ 0.16	1.38 $\pm$ 0.21 <sup>a</sup>	1.07 $\pm$ 0.18	1.25 $\pm$ 0.18 <sup>a,b</sup>

<sup>a</sup> $P < 0.05$ : compared with group A after treatment; <sup>b</sup> $p < 0.05$ : compared with group B after treatment**Figure 2:** Comparison of the immune function of patients before and after treatment. Flow cytometry was used to determine the levels of T lymphocyte subsets CD3<sup>+</sup> (A), CD4<sup>+</sup> (B), CD8<sup>+</sup> (C) and CD4<sup>+</sup>/CD8<sup>+</sup> ratio (D) in the peripheral blood of the three groups of patients before and after treatment. <sup>a</sup> $P < 0.05$ : compared with group A after treatment, <sup>b</sup> $p < 0.05$ : compared with group B after treatment

Subsequent to treatment, in terms of quality of life, the scores of groups B and C were lower than those of group A ( $p < 0.05$ ), not different between them two ( $p > 0.05$ ).

### Short-term efficacy and survival follow-up

After 4 cycles of treatment, the efficacy of the three groups were 68.97, 31.04 and 29.31 %. Compared with groups B and C, the response efficacy of the A group was higher ( $P < 0.05$ ). The disease control percents of the three groups were 82.76, 70.69 and 53.45 %. Group A held higher disease control rate than group B ( $p > 0.05$ ) and group C ( $p < 0.05$ ). In comparison to group B, group C owned lower disease control rate, with statistical significance ( $p < 0.05$ ). Compared with groups B and C, the median PFS, median OS and two-year survival of group A were higher, and the median PFS of group B was higher than that of group C ( $p < 0.05$ ) (Table 5, Table 6 and Figure 4).

**Table 4:** Comparison of quality-of-life scores of patients before and after treatment

Index	A group (n=58)		B group (n=58)		C group (n=58)	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
PF	74.79±15.75	85.25±13.29	74.19±15.61	78.23±12.69 <sup>a</sup>	75.24±14.68	77.78±13.44 <sup>a</sup>
RF	53.15±9.49	60.92±10.57	54.74±9.06	55.85±9.96 <sup>a</sup>	53.27±9.12	56.13±10.46 <sup>a</sup>
CF	64.47±12.61	72.83±11.51	63.83±12.55	66.25±10.62 <sup>a</sup>	63.97±11.69	65.38±11.32 <sup>a</sup>
EF	61.59±13.99	60.36±9.11	60.78±13.45	55.29±11.77 <sup>a</sup>	61.35±14.01	55.41±12.56 <sup>a</sup>
SF	60.36±9.11	63.84±9.54	56.04±10.86	58.15±9.11 <sup>a</sup>	55.73±11.43	57.46±8.98 <sup>a</sup>

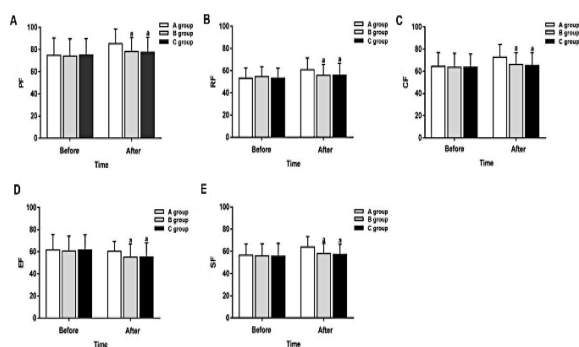
**Table 5:** Comparison of clinical efficacy of the three groups of patients

Index	A group (n=58)	B group (n=58)	C group (n=58)
CR	6(10.35)	4(6.90)	1(1.72)
PR	34(58.62)	14(24.14)	16(27.59)
SD	8(13.79)	23(39.65)	14(24.14)
PD	10(17.24)	17(29.31)	27(46.55)
RR(%)	68.97	31.04 <sup>a</sup>	29.31 <sup>a</sup>
DCR(%)	82.76	70.69	53.45 <sup>a,b</sup>

<sup>b</sup>*P* < 0.05: compared with group B. CR: complete remission, PR: partial remission, SD: stable disease, PD: progressive disease, RR: response rate, DCR: disease control rate. RR=CR+PR, DCR=CR+PR+CD. <sup>a</sup>*P* < 0.05, compared with group A.

**Table 6:** Comparison of survival rates of the three groups

Indicator	Group A (n=58)	Group B (n=58)	Group C (n=58)
PFS (95% CI) /months	5.70(5.40-6.60)	4.77(4.54-5.46) <sup>a</sup>	4.85(4.71-5.29) <sup>a,b</sup>
OS (95% CI) /months	11.52(11.07-12.93)	9.62(9.25-10.75) <sup>a</sup>	8.61(8.23-9.77) <sup>a</sup>
Two-year survival (%)	29.09	14.28 <sup>a</sup>	12.73 <sup>a</sup>

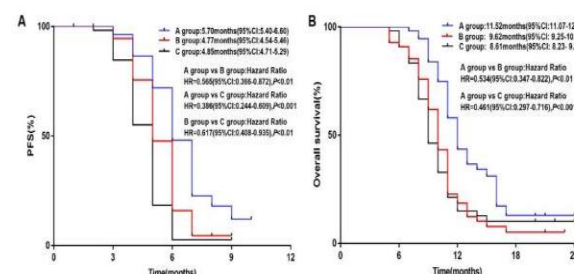


**Figure 3:** Comparison of quality of life scores of patients before and after treatment. The QLQ-C30 was used to evaluate the quality of life of the three groups of patients before and after treatment. <sup>a</sup>*P* < 0.05, compared with group A after treatment, <sup>b</sup>*p* < 0.05, compared with group B after treatment. PF: physical function (A); RF: role function (B); CF: cognitive function (C); EF: emotional function (D); SF: social function (E)

## DISCUSSION

95 % of pancreatic cancer refers to an epithelial malignant tumor occurring in the pancreatic exocrine region with a high degree of malignancy [8]. In the early stage of this disease, some

patients likely experience symptoms such as jaundice, pain, and weight loss. Some patients with pancreatic cancer may not have these symptoms [9, 10]. Pancreatic cancer originating from the head of the pancreas is close to the common bile duct.



**Figure 4:** Survival curves of the three groups of patients. Kaplan-Meier was used to estimate the overall survival (OS) (A) and progression-free survival (PFS) (B) of the three groups of patients

For early pancreatic cancer, the tumor compresses the duct and cause jaundice. However, pancreatic cancer originating from the body of the pancreas or the tail of the pancreas compresses the bile ducts only when the cancer cells spread throughout the pancreas. Thus,

about 80 % of patients diagnosed with pancreatic cancer are in advanced stage.

The incidence of pancreatic carcinoma increases with years, and the trend of younger patients is obvious. Risk factors include smoking, drinking, poor eating habits, and genetics [11]. Epidemiological investigation confirmed that pancreatic cancer develops rapidly and has a very poor prognosis. The 5-year survival of advanced pancreatic carcinoma patients is as low as about 5 %. The cancer cell can spread to the nerves around the pancreas, or the tumor can press on surrounding organs. In advanced stage, patients have unbearable physical pain. When the tumor compresses the stomach, it is likely to cause gastrointestinal reactions such as nausea and vomiting after eating [12]. In view of the significant decline in the quality of life of patients with advanced pancreatic cancer, it is of great significance to solve this issue and prolong the survival period. Radical surgery for pancreatic cancer patients is the only approach to cure patients. When patients with advanced pancreatic cancer are diagnosed, the cancer cells infiltrate and develop complex anatomical relationships with surrounding organs. At this time, radical mastectomy has no arresting clinical effect [13]. For advanced patients, chemotherapy and radiotherapy are still the leading treatments, but cancer cells are highly resistant to traditional chemotherapy drugs and radiotherapy.

Gemcitabine is a difluorocytosine nucleoside monohydrochloride, which primarily functions in the synthesis of DNA. The active product after phosphorylation is a potential ribonucleotide reductase inhibitor, which exhausts the raw material deoxynucleotides needed in DNA synthesis and leads to DNA synthesis disorder in cells [14]. Gemcitabine can also be inserted into the deoxycytidine site in the DNA chain that is being replicated, adding a base that acts as an effective inhibitor of DNA polymerase, interrupting the synthesis of DNA strands and thus inhibiting tumor cell proliferation. It has good efficacy in the treatment of pancreatic cancer and is listed as a first-line drug for pancreatic cancer by FDA. As gemcitabine began to be used in clinical practice, clinicians found that the efficacy of gemcitabine alone was not high.

In order to improve the effective rate of treatment, chemotherapy combined treatment strategies, including paclitaxel, tegafur, gemmeracil, oteracil potassium capsule, are mostly used in clinical treatment at present. Treatment like gemcitabine combined paclitaxel has problems such as expensive treatment costs, while treatments like gemcitabine

combined tegafur, gimeracil, and oteracil potassium capsules have obvious gastrointestinal reactions and poor compliance of out-of-hospital patients. Oxaliplatin is the third-generation platinum anticancer drug marketed after cisplatin and carboplatin. Like other platinum drugs, oxaliplatin also targets DNA. It produces hydrated derivatives in the body which can be cross-linked with the DNA chain, thereby blocking its replication and transcription. Clinical studies have confirmed that oxaliplatin performs a curative influence on diverse tumor cells, and has a crucial impact on tumors of the digestive system [15]. Gemcitabine and oxaliplatin act on DNA, and the combination of the two boosts the ability to repress cancer cell proliferation, thereby prolonging survival time [16].

Radiotherapy is a pervasive method for treating patients with advanced pancreatic cancer and its radiation directly or indirectly damage cellular DNA [17], and lengthen the survival time of patients. Pancreas has a special physiological and anatomic location deep in the abdominal cavity. Around the pancreas are important organs such as the stomach, kidneys, and liver. While killing cancer cells, normal cells will also be damaged by radiotherapy. The difficulty of radiotherapy lies in the control of the dose. Pancreatic cancer cells have low sensitivity to radiation, while the surrounding normal cells have bad tolerance to radiation. Hence, high doses kill normal cells, while low doses do not kill abnormally proliferating pancreatic cancer cells [18]. Radiotherapy alone is not effectual in advanced patients. Therefore, radiotherapy combined with chemotherapy drugs can be considered as the treatment of advanced pancreatic cancer.

The microenvironment of pancreatic cancer includes substantial fibroblasts, capillaries and inflammatory cells [19]. Cancer cells secrete a diversity of growth factors such as VEGF, which foster the proliferation of fibroblasts, angiogenesis, and recruit inflammatory cell infiltration. Microenvironment also stimulates the proliferation of cancer cells in a feedback manner and enhance the invasion ability. New angiogenesis can promote the growth and metastasis of cancer cells and is one of the signs of malignant tumors. Patients with advanced pancreatic cancer usually have distant metastasis by the time they are diagnosed. Cancer cells-secreted vascular endothelial growth factor is pro-angiogenic. VEGF binds to its corresponding receptor, activates downstream pathways, and ultimately contributes to angiogenesis in the microenvironment.

Apatinib mesylate is a small molecule VEGF receptor 2 (VEGFR-2) tyrosine kinase inhibitor widely used in clinical practice. It competitively binds to the tyrosine ATP site of VEGFR-2 and blocks VEGF-related pathways, thereby inhibiting angiogenesis. However, the efficacy of apatinib mesylate alone is not high, which may be related to multiple pathways of angiogenesis. Therefore, apatinib mesylate combined with radiotherapy can be used to improve the inhibitory effect.

This study was to investigate the efficacy and safety of three treatment modalities for advanced pancreatic carcinoma patients. The effective rate and disease control rate in group A were higher than those in groups B and C, suggesting that apatinib mesylate combined with radiotherapy had better effects, possibly because radiotherapy enhanced the ability of apatinib mesylate to inhibit angiogenesis. The immune function exerts key functions in the emergence and progress of malignant tumors.

Subsequent to treatment, peripheral blood CD3+, CD4+, CD4+/CD8+, and QOL scores in group A were higher, and CD8+ was lower than that in groups B and C, indicating that group A had more improvement in immune function. Group A had longer median OS and median PFS, and higher 2-year survival than groups B and C. In terms of safety, the three groups of patients had adverse reactions, mainly including nausea and vomiting, liver and kidney injury, bone marrow suppression, and hematological adverse events. Compared with groups B and C, the incidence of nausea and vomiting was higher in group A ( $p < 0.05$ ), than those of other adverse events but the difference was not significant.

## CONCLUSION

The use of the combination of apatinib mesylate and radiotherapy in treating advanced pancreatic carcinoma patients enhances curative effect and quality of life, and prolongs patient survival, probably due to improvement in the levels of T cell subsets. Nevertheless, the disadvantage is that it causes mild hematological toxicity.

## DECLARATIONS

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None provided.

### Funding

None provided.

## Ethical approval

This study was approved by the Ethics Committee of Yantai Qishan Hospital (approval no. 201401156B).

## Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

## Conflict of Interest

No conflict of interest associated with this work.

## Contribution of Authors

We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. Yan Zhang and Chenggang Sun conceived and designed the study, and drafted the manuscript. Yan Zhang, Haifeng Liu, Ying Wang, Chenggang Sun collected, analyzed and interpreted the experimental data. Haifeng Liu, Ying Wang revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

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