



# Transcatheter arterial infusion for pancreatic cancer: a 10-year National Cancer Center experience in 115 patients and literature review

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## Abstract

**Purpose** To evaluate the efficacy and safety of transcatheter arterial infusion (TAI) for the treatment of pancreatic cancer in patients ineligible for or refractory to systemic chemotherapy.

**Materials and methods** The medical records of 115 consecutive patients (mean age, 58.9 years; 71 males) with documented pancreatic cancer ineligible for or refractory to systemic chemotherapy and underwent TAI between February 2007 and January 2017 were reviewed.

**Results** A total of 224 TAI sessions [mean, 1.9 (range 1–8)] were performed. Technical success rate was 100%. Disease control (i.e., complete response, partial response, and stable disease) was achieved in 72 (62.6%) patients. The median progression-free survival and median overall survival were 56 days and 147 days, respectively. Subgroup analysis revealed that disease control, progression-free survival, and overall survival were significantly improved in patients with an Eastern Cooperative Oncology Group score of  $\leq 1$  compared with those in patients with an Eastern Cooperative Oncology Group score of 2 (all  $p < 0.001$ ) and in patients who received  $> 1$  sessions of TAI compared with that in patients who received only 1 session of TAI ( $p = 0.012$ ,  $< 0.001$ , and  $= 0.002$ , respectively). A major complication in the form of cerebral infarction occurred in 1 (0.9%) patient 1 day after the procedure. This patient was treated with conservative therapy and recovered without permanent adverse sequelae. No other major complications were observed.

**Conclusions** TAI may be effective and safe for the treatment of pancreatic cancer.

**Keywords** Infusion · Intra-Arterial · Pancreatic neoplasms · Chemotherapy

## Key take home message

1. Transcatheter arterial infusion may be effective and safe for the treatment of pancreatic cancer in patients ineligible for or refractory to systemic chemotherapy.
2. Pancreatic cancer patients with a more favorable Eastern Cooperative Oncology Group score may be associated

with better treatment outcomes after transcatheter arterial infusion.

## Introduction

Pancreatic cancer is one of the most lethal forms of malignancy and is expected to become the second leading cause of cancer-related death by the year 2030 [1, 2]. At the time of diagnosis, only approximately 15% of patients have resectable disease, and the remaining 85% have either locally advanced or metastatic disease [3]. Liver is the most common site of metastasis and accounts for approximately 80% of metastatic disease [4]. The 5-year overall survival (OS) rate is  $< 5\%$  for patients with locally advanced and metastatic disease [5].

Systemic chemotherapy has been recommended as the first line for the treatment of advanced pancreatic cancer [6].

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However, systemic chemotherapy can only be recommended for selected patients based on age, comorbidities, and performance status due to chemotoxicity. In addition, the outcome remains dismal after systemic chemotherapy, with a median OS of approximately 5–11 months for advanced pancreatic cancer [7]. Nonetheless, alternative treatment options are very limited for patients who were ineligible for or refractory to systemic chemotherapy.

Transcatheter arterial infusion (TAI) involves catheter-based localized delivery of chemotherapeutics [8]. TAI has the potential to be more efficacious and tolerable compared with systemic chemotherapy due to higher local drug concentration and reduced systemic concentration [9–11]. Therefore, TAI represents an attractive option for patients with pancreatic cancer ineligible for or refractory to systemic chemotherapy as it may delay local tumor progression. In addition, it may also be effective for liver metastasis since hepatic arterial infusion is often performed during TAI [12, 13]. The purpose of this study was to evaluate the efficacy and safety of TAI for the treatment of pancreatic cancer.

## Materials and methods

### Study design

This retrospective study was approved by our institutional review board, and the requirement to obtain written informed consent was waived. The departmental electronic database was searched to identify eligible patients for inclusion in this study. All consecutive patients with documented pancreatic cancer (i.e., adenocarcinoma) who underwent TAI at our institution between February 2007 and January 2017 were included in this study. The institutional indications for TAI for pancreatic cancer were as follows: (i) unresectable or inoperable pancreatic cancer (i.e., locally advanced, metastatic, and recurrent pancreatic cancer) and (ii) ineligible for or refractory to systemic chemotherapy. The institutional contraindications for TAI were as follows: (i) active infection, (ii) total bilirubin > 3 mg/dl, (iii) Eastern Cooperative Oncology Group (ECOG) score > 2, (iv) serum creatinine > 2 mg/dl, (v) international normalized ratio > 2, and (vi) pregnancy. Technical success was defined as successful injection of chemotherapeutics in the targeted vessel. Tumor response was evaluated according to the Response Evaluation Criteria in Solid Tumors on computed tomography (CT) or magnetic resonance imaging (MRI) based on consensus of 2 investigators [14]. Disease control was defined as complete response (CR), partial response (PR), or stable disease (SD). Progression-free survival (PFS) was defined as the time from index TAI until disease progression or death by any cause. OS was defined as the interval between

index TAI and death from any cause. Complications were classified according to the classification system proposed by the Society of Interventional Radiology Standards of Practice Committee [15].

### Patient population

A total of 115 patients (mean age,  $58.9 \pm 11.1$  years; range 37–79) with pancreatic cancer were included in the study. The demographics and clinical characteristics of the patients are presented in Table 1. In approximately half (49.6%) of the patients, the tumor was located in the head of the pancreas. Most of the patients had metastatic disease (62.6%) or locally advanced disease (27.0%). Twelve (10.4%) patients had recurrent cancer after curative surgical resection. Only 4 (3.5%) patients previously underwent systemic chemotherapy. Seven (6.1%) patients previously underwent percutaneous transhepatic biliary stenting (5.2%) and drainage (0.9%) due to malignant obstructive jaundice. With the exception of 1 (0.9%) patient who received radiation therapy, none of the patients underwent any treatment for pancreatic cancer after TAI.

**Table 1** Demographics and clinical characteristics of the patients

	Patients ( <i>n</i> = 115)
Age (years)	58.9 ± 11.1
Sex	
Male	71 (61.7)
Female	44 (38.3)
Tumor location	
Head	57 (49.6)
Body and tail	53 (46.1)
Both	5 (4.3)
TNM stage	
II	12 (10.4)
III	31 (27.0)
IV	72 (62.6)
Previous treatment	
Curative surgical resection	12 (10.4)
Systemic chemotherapy	4 (3.5)
Radiotherapy	4 (3.5)
Brachytherapy	1 (0.9)
ECOG score	
0	2 (1.7)
1	77 (67.0)
2	36 (31.3)

Plus-minus data = mean ± standard deviation; number in parentheses = percentage of patients

TNM tumor/node/metastasis, ECOG Eastern Cooperative Oncology Group

## TAI procedure

All procedures were performed under local anesthesia via the femoral approach. Chemotherapeutics were infused via a 5-Fr Rösch hepatic or Cobra 2 catheter (Radiofocus; Terumo, Tokyo, Japan) into the common hepatic or gastroduodenal artery (two-thirds dose) followed by the superior mesenteric artery (one-third dose) in patients with tumors in the head of the pancreas and into the splenic or celiac artery (two-thirds dose) followed by the superior mesenteric artery (one-third dose) in patients with tumors in the body and tail of the pancreas. After April 2013, chemotherapeutics were alternatively infused via a 2.5- to 2.7-Fr microcatheter [MiraFlex (Cook, Bloomington, IN) or Progreat (Terumo)] into the anterior superior pancreaticoduodenal artery (one-third dose) followed by the posterior superior pancreaticoduodenal artery (one-third dose) and the inferior pancreaticoduodenal artery (one-third dose) in patients with tumors in the head of the pancreas and into the dorsal pancreatic artery (one-third dose) followed by the great pancreatic artery (one-third dose) and the caudal pancreatic artery (one-third dose) in patients with tumors in the body and tail of the pancreas. A single-drug regimen [gemcitabine (1000 mg/m<sup>2</sup>)] or a two-drug regimen [gemcitabine (1000 mg/m<sup>2</sup>) with lobaplatin (50 mg/m<sup>2</sup>) or cisplatin (75 mg/m<sup>2</sup>)] was used according to the operator's preference. Chemotherapeutics were diluted to 20–30 mL with saline and injected over 15 min.

## Follow-up

All patients were discharged within a 2–3 days after TAI and were re-evaluated with CT and/or MRI 4–6 weeks after TAI. Additional sessions of TAI were only considered for patients who achieved disease control.

## Statistical analysis

Continuous variables were compared using Student's *t* test. Categorical variables were compared using the Chi-square or Fisher's exact test. Time-to-event distributions were estimated using the Kaplan–Meier method and compared using the Log-Rank test. A two-sided *p* value of < 0.05 was considered indicative of a statistically significant difference. Statistical analyses were performed using SPSS software (version 22.0; SPSS, Chicago, IL, USA).

## Results

### Procedure details

A total of 224 TAI sessions [mean, 1.9 (range 1–8)] were performed for the 115 patients. Technical success was

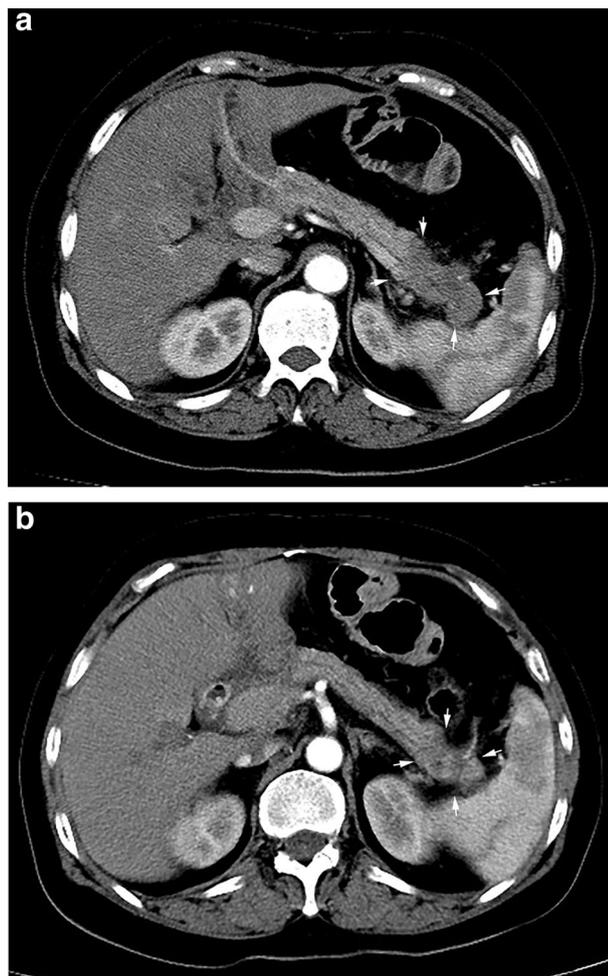
achieved in all (100%) patients. Chemotherapeutics were infused through a 5-Fr catheter in 100 (87.0%) patients and through a microcatheter in 15 (13.0%) patients. Thirty-one (27.0%) patients received a single-drug regimen, and 84 (73.0%) received a two-drug regimen. Sixty-two (54.0%) patients received only 1 session of TAI. Thirty-two (27.8%) patients who achieved disease control did not receive an additional session of TAI due to extrapancreatic tumor progression. Thirteen (11.3%) patients with disease progression received an additional session of TAI with a 5-fluorouracil-based regimen [5-fluorouracil (500 mg/m<sup>2</sup>) with or without lobaplatin (50 mg/m<sup>2</sup>) or cisplatin (75 mg/m<sup>2</sup>)].

## Tumor response

Tumor response was noted in patients as follows: CR in 0 (0%) patients, PR in 6 (5.2%), SD in 66 (57.4%), and progressive disease (PD) in 43 (37.4%) patients. Disease control was achieved in 72 (62.6%) patients (Fig. 1). Subgroup analysis of disease control is presented in Table 2. Disease control did not significantly differ between patients with locally advanced disease and patients with metastatic disease (*p* = 0.074) as well as between patients with tumors in the head of the pancreas and patients with tumors in the body and tail of the pancreas (*p* = 0.926). Disease control did not significantly differ between patients who used a microcatheter and patients who used a 5-Fr catheter (*p* = 0.407) or between patients who received a single-drug regimen and patients who received a two-drug regimen (*p* = 0.286). However, disease control was significantly different between patients with an ECOG score of ≤ 1 and patients with an ECOG score of 2 (*p* < 0.001) as well as between patients who received only 1 session of TAI and patients who received > 1 session of TAI (*p* = 0.012).

## Survival

As of May 2018, only 1 (0.9%) patient was alive. The median PFS was 56 days [interquartile range (IQR), 32–98 days; Fig. 2]. The median OS was 147 days (IQR, 96–223 days; Fig. 3). The 3-, 6- and 12-month survival rates were 75.7, 37.1, and 4.4%, respectively. Subgroup analyses of PFS and OS are presented in Table 3. The median PFS and median OS were not significantly different between patients with locally advanced disease and patients with metastatic disease (*p* = 0.131 and *p* = 0.228, respectively) or between patients with tumors in the head of the pancreas and patients with tumors in the body and tail of the pancreas (*p* = 0.717 and *p* = 0.882, respectively). The median PFS and median OS were also not significantly different between patients who used a microcatheter and patients who used a 5-Fr catheter (*p* = 0.789 and *p* = 0.768, respectively) or between patients who received a single-drug regimen and patients



**Fig. 1** A 43-year-old female with pancreatic cancer (TNM stage IV; ECOG score, 1) who underwent TAI. **a** CT image reveals a maximum tumor diameter of 4.9×2.7 cm before TAI (arrow). **b** CT image reveals a maximum tumor diameter of 3.3×1.8 cm 4 weeks after 1 session of TAI (arrow)

who received a two-drug regimen ( $p=0.221$  and  $p=0.349$ , respectively). However, the median PFS and median OS were significantly different between patients with an ECOG score of  $\leq 1$  and patients with an ECOG score of 2 ( $p < 0.001$  and  $p < 0.001$ , respectively) as well as between patients who received only 1 session of TAI and patients who received  $> 1$  sessions of TAI ( $p < 0.001$  and  $p = 0.002$ , respectively).

### Complications

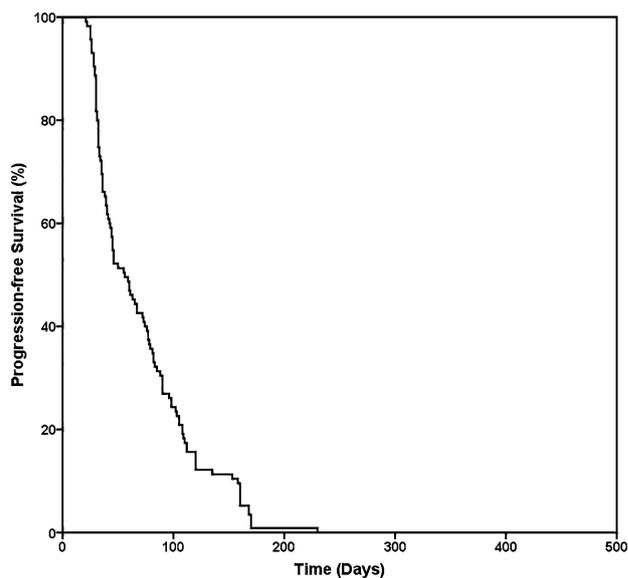
Minor complications occurred in 61 (53.0%) patients, including transient abdominal pain in 35 (30.4%), nausea with or without vomiting in 25 (21.7%), and fever in 10 (8.7%) patients immediately after the procedure, and fatigue in 2 (1.7%) and thrombocytopenia in 1 (0.9%) patient within 1 month after the procedure. A major

**Table 2** Subgroup analysis of disease control

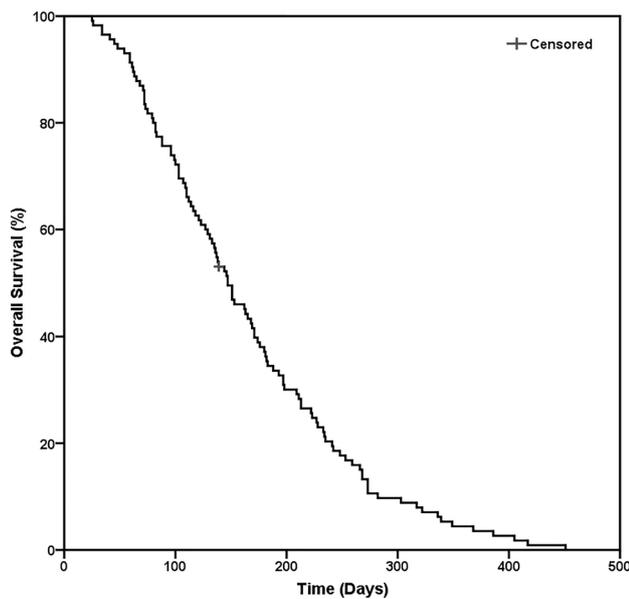
	Disease control	Progressive disease	p value
TNM stage ( $n = 103$ )			0.074
III	24 (23.3)	7 (6.8)	
IV	41 (39.8)	31 (30.1)	
Tumor location ( $n = 110$ )			0.926
Head of pancreas	35 (31.8)	22 (20.0)	
body and tail of pancreas	33 (30.0)	20 (18.2)	
ECOG score ( $n = 115$ )			$< 0.001$
$\leq 1$	63 (54.8)	16 (13.9)	
$= 2$	9 (7.8)	27 (23.5)	
Catheter type ( $n = 115$ )			0.407
5-Fr catheter	61 (53.0)	39 (33.9)	
Microcatheter	11 (9.6)	4 (3.5)	
Drug regimen ( $n = 115$ )			0.286
Single-drug	22 (19.1)	9 (7.8)	
Two-drug	50 (43.5)	34 (29.6)	
TAI sessions ( $n = 115$ )			0.012
1	32 (27.8)	30 (26.1)	
$> 1$	40 (34.8)	13 (11.3)	

Number in parentheses = percentage of patients

TNM tumor/node/metastasis, ECOG Eastern Cooperative Oncology Group, TAI transcatheter arterial infusion



**Fig. 2** Kaplan–Meier curve of PFS



**Fig. 3** Kaplan–Meier curve of OS

complication in the form of cerebral infarction occurred in 1 (0.9%) patient 1 day after the procedure. This patient underwent conservative treatment and recovered without permanent adverse sequelae. No other complications were observed.

## Discussion

The authors reviewed the literature (MEDLINE/PubMed) for studies published in the past 10 years that included > 10 pancreatic cancer patients who underwent TAI monotherapy and identified 3 studies [16–18]. The results of these studies are summarized in Table 4. The authors also identified a meta-analytic study comparing TAI and systematic chemotherapy for pancreatic cancer published in 2012 [10]. All 6 included studies were randomized controlled trials published between 1998 and 2008, with a sample size ranging from 7 to 70 (mean, 25 ± 9) patients [19–24]. The results showed that patients who received TAI had better tumor response (CR + PR, 62% vs. 29%) and fewer complications (49% vs. 71%) than patients who received systemic chemotherapy. In addition, the results also showed that the median OS with TAI was longer (5–21 months vs. 2.7–14 months) and 1-year survival rate was higher (28.6–41.2% vs. 0–12.9%) than with systematic chemotherapy. It should be noted, however, that the patients included in these studies represent a different population to our current study as our patients were ineligible for or refractory to systemic chemotherapy.

In the present study, disease control was achieved in 62.6% of patients with pancreatic cancer treated with TAI. Although the interval between TAI and response assessment was relatively short and there may therefore not be enough time for the tumor to respond before assessment, our disease

**Table 3** Subgroup analysis of PFS and OS

	Median PFS (days)	<i>p</i> value	Median OS (days)	<i>p</i> value
TNM Stage ( <i>n</i> = 103)		0.131		0.228
III	78 (40–109)		180 (110–235)	
IV	45 (32–90)		135 (88–213)	
Tumor location ( <i>n</i> = 110)		0.717		0.882
Head of pancreas	45 (32–88)		151 (96–233)	
Body and tail of pancreas	59 (32–98)		137 (96–213)	
ECOG score ( <i>n</i> = 115)		<0.001		<0.001
≤ 1	82 (45–112)		188 (139–253)	
= 2	32 (29–39)		72 (59–100)	
Catheter type ( <i>n</i> = 115)		0.789		0.768
5-Fr catheter	46 (32–96)		147 (88–213)	
Microcatheter	60 (43–110)		139 (103–241)	
Drug regimen ( <i>n</i> = 115)		0.221		0.349
Single-drug	67 (36–112)		188 (107–242)	
Two-drug	46 (32–90)		137 (82–198)	
TAI sessions ( <i>n</i> = 115)		<0.001		0.002
1	40 (30–76)		121 (75–171)	
> 1	82 (41–120)		183 (123–266)	

Number in parentheses = interquartile range

PFS progression-free survival, OS overall survival, TNM tumor/node/metastasis; ECOG Eastern Cooperative Oncology Group, TAI transcatheter arterial infusion

**Table 4** A review of the literature

First author	Study design	Publication year	Geographical region	Sample size	Age (year)	Male sex	Tumor location		TNM stage			ECOG score
							Head	Body and tail	III	IV	≤1	
Hong et al. [16]	RCT	2012	China	24/24	61 ± –	15 (63)	6 (25)	15 (63)	10 (42)	14 (58)	–	–
Chen et al. [17]	Case series	2014	China	32	61 ± –	20 (63)	7 (22)	7 (22)	–	–	–	32 (100)
Liu et al. [18]	Case series	2016	China	354	62 ± –	230 (65)	172 (49)	198 (56)	–	–	–	–
Current study	Case series	2018	China	115	59 ± 11	71 (62)	57 (50)	53 (46)	31 (27)	72 (63)	79 (69)	36 (31)
TAI sessions	Microcatheter usage	Drug regimen	Technical success	Disease control		Complication		Median PFS (days)	Median OS (days)			
				Single-drug	Two-drug	Minor	Major					
1	> 1											
–	–	0 (0)	24 (100)	18 (75)	10 (46)	2 (8)	–	360				
–	–	0 (0)	32 (100)	21 (66)	23 (78)	7 (22)	–	300				
274 (77)	80 (23)	0 (0)	354 (100)	–	–	–	–	210				
44 (38)	71 (62)	31 (27)	115 (100)	72 (63)	61 (53)	1 (1)	56	147				

Plus-minus data = mean ± standard deviation; number in parentheses = percentage of patients

TNM tumor/node/metastasis, ECOG Eastern Cooperative Oncology Group, RCT randomized controlled trial, TAI transcatheter arterial infusion, SIR Society of Interventional Radiology, PFS progression-free survival, OS overall survival

control rate remains similar to those reported in previous studies (66–75%) [16–18]. However, the median PFS in our current study was only 56 days even though the median OS was 147 days. This finding indicates that disease control was not maintained until death in the majority of patients. The median OS in our current study is lower compared with those reported in previous studies (210–360 days) [16–18]. This could be attributed to the exclusive inclusion of patients who were ineligible for or refractory to systemic chemotherapy and a high proportion (31%) of patients with an ECOG score of 2 in our current study. All patients in our current study were ineligible for or refractory to systemic chemotherapy and that 89.6% had locally advanced or metastatic disease. In addition, our subgroup analysis demonstrated that patients who received > 1 sessions of TAI and patients with an ECOG score of ≤ 1 had significantly improved treatment outcomes. Although our subgroup analysis may be biased due to the fact that majority of patients who received > 1 session of TAI achieved disease control, it should be noted that a small portion of patients with disease progression who received > 1 session of TAI was also included in the analysis. These findings suggest that TAI was effective, particularly in patients with better performance status.

The majority of complications in the present study were minor and associated with the use of chemotherapeutics, including abdominal pain, nausea with or without vomiting, fever, fatigue, and thrombocytopenia. The minor complication rate in our current study is within the range of those reported in previous studies (53% vs. 46–78%) [16, 17]. However, major complication rate is lower compared with those reported in previous studies (1% vs. 8–22%) [16, 17]. Hematological complications, which were only observed in 1 (1%) patient in our current study, were much more common (1% vs. 33–46%) and more often severe (0% vs. 0–4%) in previous studies [16, 17]. Although some late complications were likely missed in our current study, as patients were typically discharged within a few days after TAI, these differences were likely due to differences in drug regimens. In the study of Hong et al. [16], patients received 1000 mg/m<sup>2</sup> gemcitabine on the day when TAI was performed and 600 mg/m<sup>2</sup> 5-fluorouracil thereafter for 5 days. Comparatively, our patients only received 1000 mg/m<sup>2</sup> gemcitabine with or without 50 mg/m<sup>2</sup> lobaplatin or 75 mg/m<sup>2</sup> cisplatin on the day TAI was performed.

Percutaneous irreversible electroporation (IRE) has recently been introduced and has demonstrated promising results for pancreatic cancer in preliminary studies [25, 26]. However, the procedure is not widely available and very expensive. Furthermore, the safety of percutaneous IRE for pancreatic cancer remains under investigation. Scheffer et al. [26] recently reported the outcomes of percutaneous IRE for pancreatic cancer in a prospective cohort of 25 patients. In their study, 23 complications occurred, including 11 major

events, such as pancreatitis, biliary obstruction, cholangitis and biloma, gastrointestinal bleeding, and superior mesenteric artery stenosis.

The present study has several important limitations. First, this was a retrospective study and was therefore prone to selection bias. Second, the absence of a control group limits evaluation of the true efficacy of TAI for pancreatic cancer. Third, a microcatheter was used only in a few patients; however, subgroup analyses demonstrated that microcatheter usage was not associated with better treatment outcomes. Fourth, several different drug regimens were used; however, subgroup analyses demonstrated that the drug regimen was not associated with improved treatment outcomes. Finally, patients were discharged within a few days after TAI and re-evaluated 4–6 weeks later; therefore, complication that occurred between this period of time could be missed.

In conclusion, TAI may be effective and safe for the treatment of pancreatic cancer in patients ineligible for or refractory to systemic chemotherapy. In addition, patients with a better ECOG score appear to be associated with better treatment outcomes. Further prospective studies are required to validate the findings of our current study.

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## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

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