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Conversion therapy, palliative chemotherapy and surgery, which of these is the best treatment for locally advanced and advanced pancreatic cancer?

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A retrospective study was conducted to analyze which translational therapy, palliative chemotherapy and surgery is the best treatment for locally advanced and advanced pancreatic cancer, and to screen out the dominant population for the best treatment. A total of 83 patients with pancreatic cancer, including locally advanced and advanced pancreatic cancer, who had lost the opportunity for radical surgery and were admitted to Zhejiang Provincial People's Hospital between January 2015 and July 2021 were collected. A total of 39 patients received palliative chemotherapy, 25 patients received conversion therapy and 19 patients tried surgery at the first visit. We conducted survival follow-up and prognostic evaluation of 83 patients. The median overall survival (mOS) and median progression-free survival (mPFS) of 25 pancreatic cancer patients who received conversion therapy were longer than those of pancreatic cancer patients who received palliative chemotherapy (mOS: 16 months vs. 9 months, $P = 0.001$; mPFS: 11 months vs. 7.5 months, $P = 0.038$) and surgery (mOS: 16 months vs. 9 months, $P = 0.018$; mPFS: 11 months vs. 5.5 months, $P < 0.001$). Multivariate and Kaplan–Meier analysis showed that age, distant metastasis, and the degree of CA199 declined after chemotherapy were independent factors affecting overall survival (OS) of pancreatic cancer patients who received conversion therapy. Conversion therapy can improve OS and progression-free survival in patients with locally advanced or advanced pancreatic cancer to a certain extent. Some patients with advanced pancreatic cancer have surprising results after receiving conversion therapy.

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Introduction

Pancreatic ductal adenocarcinoma is one of the most highly malignant solid malignancies with the fourth fatality rate among all cancer types in the USA [1]. It is estimated that pancreatic cancer will become the second leading cause of cancer-related deaths by 2030 in the USA [2]. Pancreatic cancer is cancer with the highest mortality rate in China, the 5-year relative survival rate (7.2%) is lower than that of the USA (8.5%) [3,4].

Surgery is the only way to cure pancreatic cancer, only 10–20% of patients with pancreatic cancer have the opportunity of surgical resection, unresectable pancreatic cancer (URPC) patients accounted for the majority of newly diagnosed patients [5]. URPC includes locally advanced and advanced pancreatic cancer The prognosis of URPC is poor, the median overall survival (mOS) without special treatment is 3–11 months [6,7]. Palliative treatment is mainly used to improve quality of life for patients with pancreatic cancer who do not have the opportunity of surgical treatment initially. In recent years, with the development of chemotherapy, conversion therapy has been paid more and more attention. Clinicians have found that some patients with URPC have achieved a tumor-lowering phase during chemotherapy, which gives them the opportunity to have their tumors surgically removed.

Suker *et al*. found that FOLFIRINOX as a first-line chemotherapy regimen can achieve the R0 rate of 22.5% and the mOS can be prolonged to 13.7–24.2 months in patients with locally advanced pancreatic cancer [8]. Schneitler *et al*. reported that 2 patients with liver metastasis of pancreatic cancer achieved complete remission after receiving FOLFIRINOX regimen chemotherapy, achieved R0 resection of the primary tumor, and obtained overall survival of 22 and 26 months, respectively [9]. Conversion therapy has brought hope to patients with URPC, but it is still in the immature stage. Therefore, we conducted a retrospective study to analyze which of translational therapy, palliative chemotherapy and surgery is the best treatment for patients with URPC.

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Patients and methods

Patients

We retrospectively analyzed 83 patients with locally advanced or advanced pancreatic cancer who were admitted to Zhejiang Provincial People's Hospital from January 2015 to July 2021. Of these, 25 patients received conversion therapy, 39 patients received palliative chemotherapy and the remaining 19 patients received surgery. We performed clinical staging of patients according to the American Joint Committee on Cancer guidelines.

All procedures are carried out in accordance with the ethical standards of the Committee on Human Experimentation (institutional and national) and the Declaration of Helsinki. The study was approved by the Ethics Committee of Zhejiang Provincial People's Hospital.

Treatment regimens and the response evaluation

The chemotherapy regimen were mainly on the basis of the first-line chemotherapy regimen such as FOLFIRINOX[oxaliplatin 85 mg/m^2, irinotecan 180 mg/m^2, 5-fluorouracil 400 mg/m^2, 5-fluorouracil 2400 mg/m^2, every 2 weeks], GS[gemcitabine 1,000 mg/m^2 on days 1 and 8, S-1 60 mg twice daily on days 1–14, every 3 weeks], AG[albumin-bound paclitaxel 125 mg/m^2 on days 1, 8, 15; gemcitabine 1,000 mg/m^2 on days 1 and 8,15, every 4 weeks], AS[albumin-bound paclitaxel 125 mg/m^2 on days 1 and 8, S-1 60 mg twice daily on days 1–14, every 3 weeks] [10–13]. Clinicians adjusted the chemotherapy cycle and chemotherapy dose according to the patient's Eastern Cooperative Oncology Group (ECOG) score and individual differences.

Tumor responses were evaluated according to new response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1) [14]. Computed tomography (CT), magnetic resonance imaging (MRI) and PET were used to evaluate the curative effect of patients every three or four cycles of chemotherapy.

None of the 19 patients who underwent direct surgical treatment developed distant metastasis and were assessed as locally advanced before surgery. It was difficult for these patients to undergo radical surgical resection, but the patients have strong desire for surgery, then the primary lesion was surgically removed under the premise of obtaining the informed consent of the patients.

Surgical intervention and indications for conversion therapy: Some patients with locally advanced or advanced pancreatic cancer responded well to chemotherapy, and the tumor lesions had shrunk, making the original unresectable or marginally resectable tumors regained the opportunity of R0 resection again. Even in some patients with distant metastases, the metastatic lesions may have a chance of resection.

Statistical analysis

OS was defined as the time from the start of chemotherapy or surgery to death or the last follow-up. For the patients who received conversion therapy or palliative chemotherapy, PFS referred to the time from the start of chemotherapy to the first progression of the disease. For the patients who received surgery, PFS referred to the time from surgery to the first progression of the disease. OS and PFS were calculated using the Kaplan–Meier method, and the survival was compared using the log-rank test. Univariate Cox proportional hazard models were used to identify independent significant factors associated with the survival time of conversion therapy. Relative risks were expressed as hazard ratios (HR) and 95% confidence intervals (CI). In univariate analysis, the variables with P value <0.05 entered into the multivariate model.

Results

Patient demographics

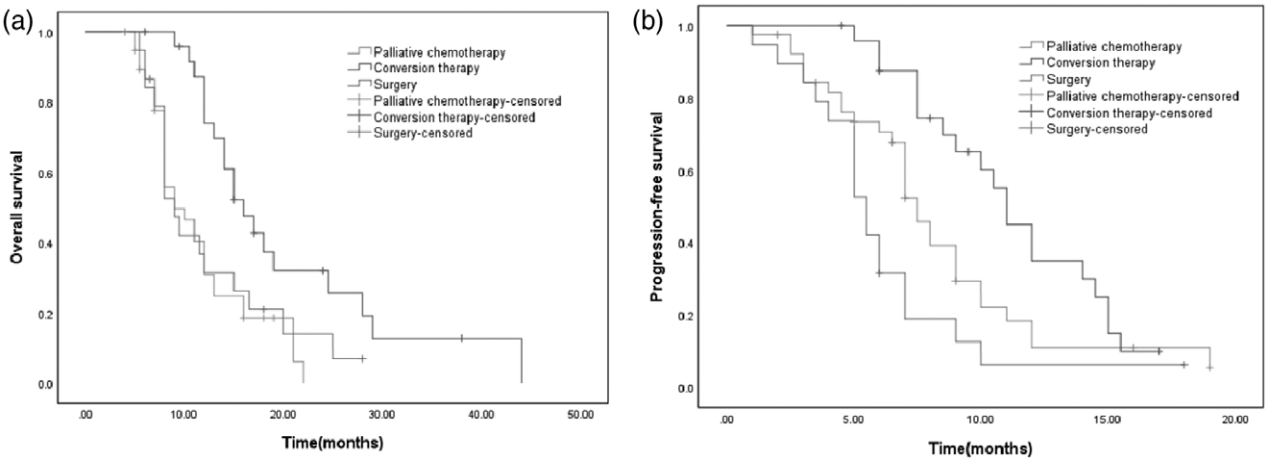
The demographic data of all patients who received palliative chemotherapy, patients who received conversion therapy and patients who received surgery are listed

Table 1 Clinical characteristics of 83 patients

	Conversion therapy $n = 25$ (%)	Palliative chemotherapy $n = 39$ (%)	Surgery $n = 19$ (%)
Sex			
Men	15 (60)	29 (74.4)	12 (63.2)
Women	10 (40)	10 (25.6)	7 (36.8)
Age (years)			
<60	12 (48)	12 (30.8)	7 (36.8)
≥60	13 (52)	27 (69.2)	12 (63.2)
Initial CA19-9(U/mL)			
<37	5 (20)	5 (12.8)	5 (26.3)
≥37	20 (80)	34 (87.2)	14 (73.7)
Preoperative CA19-9(U/mL)			
<37	11 (44)		
≥37	14 (56)		
ΔCA19-9(U/mL)			
<37	14 (56)		
≥37	11 (44)		
Depth of tumor invasion(T)			
T3	8 (32)	10 (25.6)	5 (26.3)
T4	17 (68)	29 (74.4)	14 (73.7)
Lymph node metastasis			
No	14 (56)	20 (51.3)	13 (68.4)
Yes	11 (44)	19 (48.7)	6 (31.6)
Distant metastasis			
No	16 (64)	22 (56.4)	19 (100)
Yes	9 (36)	17 (43.6)	0 (0)
Preoperative chemotherapy regimen			
FOLFIRINOX	9 (36)	14 (35.9)	
G/S/A	16 (64)	25 (64.1)	
Preoperative assessment			
PR	13 (52)		
SD	12 (48)		
Preoperative ECOG score			
0-1	12 (48)		15 (78.9)
≥2	13 (52)		4 (21.1)
Postoperative chemotherapy regimen			
FOLFIRINOX	11 (44)		
G/S/A	14 (56)		

ΔCA199, The difference between preoperative CA199 and initial CA199; ECOG, Eastern Cooperative Oncology Group; G/S/A, gemcitabine; PR, partial remission; S-1, albumin paclitaxel; SD, stable disease.

Fig. 1



Survival analysis of patients with locally advanced or advanced pancreatic cancer. (a) Patients who received conversion therapy survived longer than those who received palliative care and surgery ($P = 0.001$; $P = 0.018$). (b) Patients who received conversion therapy had longer progression-free survival than those who received palliative care and surgery ($P = 0.038$; $P < 0.001$).

Table 2 Univariate and multivariate analyses of independent factors of OS of conversion therapy

	Univariate analysis		Multivariable analysis	
Parameters	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Sex (men)	1.417(0.539–3.667)	0.486		
Age (<60years)	5.238(1.662–16.509)	0.005	16.370(1.549–173.015)	0.020
Initial CA19-9(<37 U/mL)	4.664(1.038–20.959)	0.045	3.768(0.593–23.947)	0.160
Preoperative CA19–9(<37 U/mL)	5.486(1.659–18.141)	0.005	0.665(0.102–4.320)	0.669
ΔCA19-9(<0 U/mL)1	4.596(1.463–14.440)	0.009	8.007(1.293–49.596)	0.025
T Staging(T3)	1.612(0.565–4.603)	0.372		
Distant metastases(N0)	0.163(0.036–0.747)	0.020	0.175(0.033–0.927)	0.040
lymphnode metastasis (no)	2.344(0.921–5.969)	0.074		
Preoperative chemotherapy regimen (FOLFIRINOX)	0.886(0.306–2.569)	0.824		
Preoperative assessment (PR)	1.855(0.720–4.776)	0.200		
Preoperative ECOG score (0–1)	4.388(1.433–13.436)	0.010	0.248(0.024–2.526)	0.239
Postoperative chemotherapy regimen (FOLFIRINOX)	1.413(0.522–3.821)	0.496		

ΔCA199, The difference between preoperative CA199 and initial CA199; ECOG, Eastern Cooperative Oncology Group; PR, partial remission.

in Table 1. Of the 39 patients who received palliative chemotherapy, 22 were locally advanced pancreatic cancer patients and 17 were advanced pancreatic cancer patients. Of the 25 patients who received conversion therapy, 16 were locally advanced pancreatic cancer patients and 9 were advanced pancreatic cancer patients. The 19 patients who underwent direct surgery were all patients with locally advanced pancreatic cancer. The R0 resection rate of patients who received conversion therapy (21/25=84%) was higher than that of patients who received direct surgical resection (14/19=73.7%).

Efficacy of treatment and survival analysis

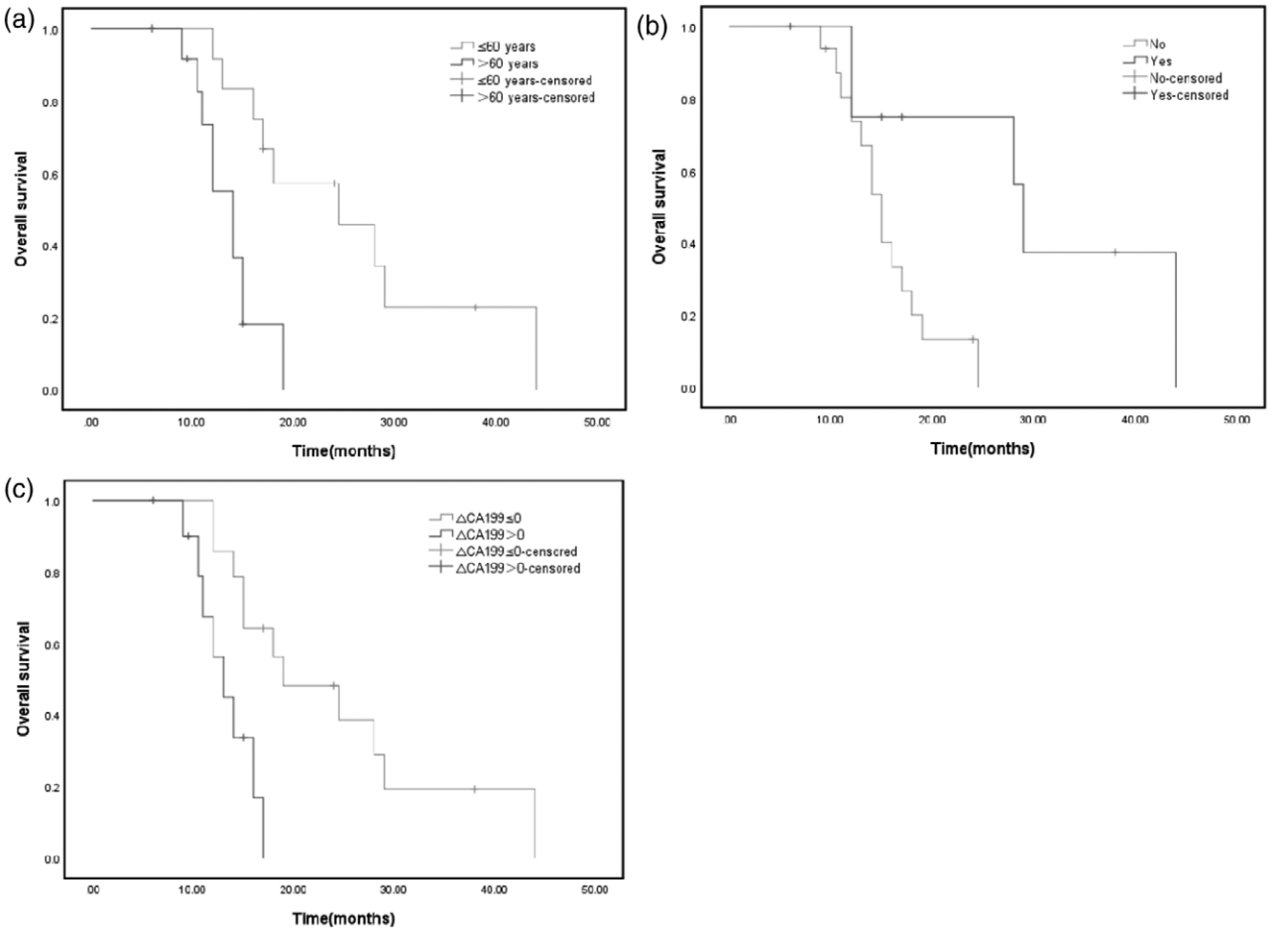
The mOS of the 39 patients who received palliative chemotherapy was 9 months, and their mPFS was 7.5 months. The mOS of the 25 patients who received conversion therapy was 16 months, and their mPFS was 11 months. The mOS of the 19 patients who received surgery was 9 months, and their mPFS was 5.5 months. Kaplan–Meier analysis showed that the mOS and mPFS of pancreatic cancer patients who received conversion therapy were longer than those of pancreatic cancer patients who received palliative care ($P = 0.001$; $P = 0.038$) and surgery ($P = 0.018$; $P < 0.001$) (Fig. 1). The 1-year, 2-year and 3-year survival rates of patients who received conversion therapy were 80, 24 and 8%, respectively.

Univariate and multivariate Cox proportional hazards models showed that age, distant metastasis and the degree of CA199 declined after chemotherapy were independent significant factors of OS of pancreatic cancer patients who received conversion therapy (Table 2). Kaplan–Meier analysis showed that patients who were younger than 60 years old, with distant metastasis, and decreased CA199 after chemotherapy were more likely to respond to conversion therapy (Fig. 2).

Discussion

A total of 25 patients with locally advanced or advanced pancreatic cancer achieved a mOS of 16 months and a mPFS of 11 months after receiving conversion therapy.

Fig. 2



Independent significant factors of long-term survival in conversion therapy. (a) The age of patients <60 years lived longer than that of patients ≥60 years ($P = 0.002$). (b) Patients with distant metastasis responded better to conversion therapy than patients without distant metastasis ($P = 0.008$). (c) The survival time of patients with CA199 decreased before surgery was longer than that of patients without CA199 decreased or even increased ($P = 0.004$). ΔCA199: The difference between preoperative CA199 and initial CA199.

Compared with palliative chemotherapy and surgery, conversion therapy prolonged the survival time and progression-free survival (PFS) time of patients with locally advanced or advanced pancreatic cancer.

For pancreatic cancer that was clinically evaluated as unresectable at the initial diagnosis, the National Comprehensive Cancer Network (NCCN) guidelines recommended systemic comprehensive treatment on the basis of radiotherapy and chemotherapy [15]. For patients with locally advanced pancreatic cancer, the mOS for those receiving chemoradiotherapy was 11–15 months, and the mPFS was 10.4–12 months [16,17]. For patients with metastatic pancreatic cancer, with the introduction of the FOLFIRINOX regimen and gemcitabine combined with albumin paclitaxel regimen, the mOS was extended to 5–11.1 months, and the mPFS was extended to 3.7–5.5 months [11,18,19]. In general, the prognosis and long-term survival of pancreatic cancer are still unsatisfactory. Conversion therapy is a new treatment that has emerged in recent years, providing patients with the opportunity to undergo radical surgical resection. In a phase II clinical trial, 49 patients with locally advanced pancreatic cancer received FOLFIRINOX combined with Losartan as a chemotherapy regimen before conversion surgery [20]. Approximately 42 (86%) patients underwent surgical exploration, with a final conversion rate of 69% and an R0 rate of 61%. The mOS of the entire cohort was 31 months, and the mPFS of patients who underwent surgical resection was 36 months. The conclusion of our study that conversion therapy prolongs the OS and PFS of patients compared with palliative care is consistent with previous reports in the literature [21,22].

Whether patients with locally advanced pancreatic cancer can choose surgical resection has been discussed for a long time [23,24]. In 2004, a multicenter randomized controlled study in Japan showed that surgery for locally

advanced pancreatic cancer was superior to chemoradiotherapy [25]. Advanced pancreatic cancer is also constantly being tried for surgical treatment. Shrikhande *et al*. reported that the median survival time of patients with liver metastases from pancreatic cancer after R0/R1 resection was longer than without surgical resection (11.4 months vs. 5.9 months, $P = 0.0384$) [26]. With the advancement of surgical technology and the improvement of chemotherapy regimens, surgery has gradually become a treatment option for patients with URPC. A total of 19 patients with locally advanced pancreatic cancer chose to receive surgery first, achieving an R0 rate of 73.68%, with a mOS of 16.5 months and a mPFS of 8 months. A total of 25 patients with URPC underwent surgical resection after conversion therapy, 9 of them are patients with metastatic pancreatic cancer. The Kaplan–Meier survival curve showed that conversion therapy prolonged the OS and PFS of patients with URPC compared with surgical treatment. The R0 resection rate of patients who received conversion therapy (84%) was also higher than that of patients who received direct surgical resection (73.7%). One patient with liver metastases of pancreatic cancer who received conversion therapy achieved R1 resection, with an OS of 29 months and a PFS of 5 months. One patient with bone metastasis of pancreatic cancer who received conversion therapy only underwent resection of the primary lesion, with an OS of 35 months and a PFS of 4.5 months. Radical surgery for patients with metastatic pancreatic cancer may benefit the long-term survival of patients even if R0 resection cannot be achieved [27,28].

We also found that patients who were younger than 60 years old, with distant metastasis, and CA199 decreased after chemotherapy responded well to conversion therapy.

This study has several limitations. First, it was a single-center retrospective study, the small sample size limits the credibility of the conclusions drawn. Second, there were individual differences in the response of patients to treatment. Fourth, there may be selection bias.

Conclusion

Conversion therapy may become an important role in the treatment of URPC in the future. Conversion therapy is currently not widely used clinically. Conversion therapy has the potential to benefit long-term survival and prognosis in URPC from limited clinical studies [21,29,30]. Screening out patients with URPC suitable for conversion therapy is the key. The purpose of conversion therapy is not necessarily to transform unresectable tumors into resectable tumors. Even if R0 resection is not achieved, it can extend the survival time of the patients and improve the prognosis.

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M.W. was responsible for writing the manuscript. L.Y. and Z.C. contributed to the conception of the study. P.Z. helped collect the data. All authors read and approved the final manuscript.

In this study, the informed consent of all subjects was obtained. The study was approved by the Ethics Committee of Zhejiang Provincial People's Hospital.

Conflicts of interest

There are no conflicts of interest.

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