Conversion Therapy of Unresectable Pancreatic Cancer: A Retrospective Study of the Real World

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Research Article

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Abstract

Objective: A retrospective study of the real world was conducted to analyze whether patients with unresectable pancreatic cancer (URPC) can benefit from conversion therapy, and to screen out pancreatic cancer patients who are suitable for conversion therapy.

Patients and Methods: Inquired about patients with URPC who visited Zhejiang Provincial People's Hospital from January 2015 to April 2021. We selected 25 patients with URPC who underwent conversion therapy, and 19 patients with locally advanced pancreatic cancer (LAPC) who directly underwent surgery to conducted a retrospective analysis.

Results: The median overall survival (OS) of 25 patients with URPC who received conversion therapy was 28 months (95%CI: 15.46-40.54 months), and the median progression-free survival (PFS) was 12 months (95%CI: 9.26-14.74 months). The curative resection (R0) rate was 84% (22/25).

Conclusions: Conversion therapy improves the R0 rate of patients with URPC, and prolongs OS and PFS.

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is one of the most highly malignant solid malignancies with the fourth fatality rate among all cancer types in the United States(1). It is estimated that pancreatic cancer will become the second leading cause of cancer-related deaths by 2030 in the United States(2). Pancreatic cancer is the cancer with the highest mortality rate in China, the 5-year relative survival rate (7.2%) is lower than that of the United States (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). 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 LAPC(8). Schneitler et al. reported that 2 patients with liver metastasis of pancreatic cancer achieved complete remission after receiving FOLFIRINOX regimen chemotherapy, achieved R0 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 the efficacy and safety of URPC patients who have undergone conversion therapy, and explore new treatment options for patients with inoperable pancreatic cancer.

Patients And Methods

Patients

44 patients with URPC who were admitted to Zhejiang Provincial People's Hospital from January 1, 2015 to April 1, 2021 were retrospectively analyzed. Clinical staging of patients according to the American Joint Committee on Cancer (AJCC) guidelines(10). 25 patients with URPC underwent surgical resection after conversion therapy, and 19 patients with LAPC chose surgery at initial diagnosis. The definition of URPC excludes metastatic disease, but also refers to tumors that invades superior mesenteric artery (SMA), portal vein (PV), celiac artery (CA) and common hepatic artery or their main branches(11). Here, URPC included LAPC.

Treatment regimens and the response evaluation

The conversion treatment plan was mainly based on the first-line chemotherapy regimen such as FOLFIRINOX[oxaliplatin 85 mg/m2, irinotecan 180 mg/m2, 5-fluorouracil 400 mg/m2, 5-fluorouracil 2400 mg/m2, every 2 weeks], GS[gemcitabine 1,000 mg/m2 on days 1 and 8, S-1 60 mg twice daily on days 1-14, every 3 weeks], AG[albumin-bound paclitaxel 125 mg/m2 on days 1, 8, 15, gemcitabine 1,000 mg/m2 on days 1 and 8,15, every 4 weeks], AS[albumin-bound paclitaxel 125mg/m2 on days 1 and 8, S-1 60 mg twice daily on days 1-14, every 3 weeks](12-15). Clinicians adjusted the chemotherapy cycle and chemotherapy dose according to the patient's Eastern Cooperative Oncology Group (ECOG) score and individual differences. A part of patients with URPC had an ECOG score of 0-1 after conversion therapy, and the efficacy was evaluated as clinical remission or stable disease. These patients were treated with surgery. Some patients with URPC received surgical treatment at the first visit due to their ECOG score of 0-1 and strong desire for surgery.

Tumor responses were evaluated according to new response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1)(16). Computed Tomography (CT), Magnetic Resonance Imaging (MRI) and Positron Emission Tomography (PET) were used to evaluate the curative effect of patients every 3 or 4 cycles of chemotherapy. 44 patients with URPC were divided into conversion therapy group (n=25) and surgical treatment group (n=19), analyzed the differences in prognosis of the two groups. Subgroup analysis was performed on 25 patients with URPC who had undergone conversion therapy to explore the factors affecting the prognosis of conversion therapy.

Statistical analysis

OS was defined as the time from the start of chemotherapy or surgery to death or the last follow-up. For the conversion therapy group, progression-free survival (PFS) referred to the time from the start of chemotherapy to the first progression of the disease. For the surgery group, 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. Continuous variables are expressed in terms of mean with standard deviation and were compared using the independent Student's *t* test. All

statistical analyses were performed using the SPSS version 25 (IBM, Chicago, IL, USA). A *p* value <0.05 (two-sided) was defined as statistically significant.

Results

Patient demographics

We reviewed the clinical data of 44 patients with URPC, of which 25 cancer patients received conversion therapy, and the remaining 19 patients chose direct surgery (Figure 1). Of the 25 patients who received conversion therapy, 11 patients are still alive, 10 patients died, and 4 patients were lost to follow-up. Of the 19 patients who underwent surgical treatment, 4 patients are still alive, 9 patients died, and 5 patients were lost to follow-up.

Efficacy of treatment and Survival analysis

25 patients with URPC received conversion therapy, mOS was 28 months (95%CI: 15.46-40.54 months), median progression-free survival (mPFS) was 12 months (95%CI: 9.26-14.74 months), R0 rate was 84% and the disease control rate (DCR) was 92%. The 6-month survival rate was 100%, the 1-year survival rate was 84%, and the 2-year survival rate was 20%. 19 patients with LAPC received direct surgical treatment, mOS was 16.5 months (95%CI:5.48-27.53 months), mPFS was 8 months (95%CI:5.41-10.59 months) and R0 rate was 73.68% (Table 1). The Kaplan-Meier survival curve showed that the OS and PFS of 25 patients with URPC who underwent conversion therapy were significantly different from those of 19 patients with LAPC who underwent surgery first (p<0.05) (Figure 2).

Our subjects included 9 patients with metastatic pancreatic cancer (mPC) with mOS of 29 months and mPFS of 12 months. The mOS and mPFS of 16 patients with LAPC were 23 months and 15 months respectively. The Kaplan-Meier survival curve showed that the survival time of patients with metastatic pancreatic cancer after conversion therapy is not necessarily shorter than that of patients with locally advanced pancreatic cancer (Figure 4). The R0 rate of patients with LAPC is greater than that of patients with mPC (87.50% vs.77.78%).

The mOS of the 6 patients who chose FOLFIRINOX as the conversion treatment regimen was 14 months, and the mPFS was 7.5 months. The mOS of 14 patients who took gemcitabine as the basis of the conversion treatment plan was 23 months, and the mean PFS was 12 months. The OS and PFS of the gemcitabine-based chemotherapy regimen were slightly longer than those of the FOLFIRINOX regimen, but there is no significant statistical difference (p>0.05) (Table 2).

We found that the OS and PFS of patients with pancreatic cancer whose preoperative serum carbohydrate antigen 19-9(CA19-9) level observably decreased from baseline or remained in the normal range were prolonged after conversion therapy (OS: 22.00 months vs. 13.09 months, p=0.008, PFS: 11.46 months vs. 8.41 months, p=0.033). The mean OS of patients with lymph node metastasis less than or equal to 2 was longer than that of patients with lymph node metastasis more than 2(OS: 20.47 months

vs. 13.00 months, *p*=0.044). There were no significant differences in the effects of age, gender, T staging, and distant metastasis on the OS and PFS of conversion therapy.

Discussion

25 patients received surgical treatment after conversion therapy and achieved a R0 rate of 84%, of which the R0 rate of patients with LAPC was 87.50%. The R0 rate of patients with surgery first was 73.68%. The R0 rate in the patients with unresectable pancreatic cancer was improved to some extent by conversion therapy. Studies have reported that appropriate chemotherapy can increase the possibility of surgical resection of initial unresectable pancreatic cancer, which is beneficial to prognosis and long-term survival(17-19).

Currently, the main treatment for URPC is chemotherapy combined with or without radiotherapy. For patients with unresectable LAPC receiving chemotherapy and radiotherapy, the mOS was 11-15 months, and the mPFS was 10.4-12 months(20, 21). For patients with mPC, with the application of FOLFIRINOX and gemcitabine plus albumin paclitaxel, the mOS was extended to 5 -11.1 months, and the mPFS was extended to 3.7-5.5 months(13, 22, 23). The prognosis and long-term survival of pancreatic cancer are still unsatisfactory. The subjects of this study were 25 patients with URPC who had no chance of surgical resection. The mOS was 28 months and the mPFS was 12 months. The survival time after conversion therapy is significantly longer than that of pancreatic cancer patients after traditional palliative care. After conversion therapy, the median OS and PFS of patients with mPC were not significantly different from those of patients with LAPC. We found that conversion therapy can significantly improve the OS and PFS of patients with mPC.

Whether surgical resection is an option for patients with LAPC has been discussed for a long time(24, 25). In 2004, a multicenter randomized controlled study in Japan showed that the effect of surgery for LAPC was better than that of radiotherapy and chemotherapy(26). Surgery is also being tried for advanced pancreatic cancer. 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)(27). With the advancement of surgical technology and the improvement of chemotherapy regimens, surgery has gradually become a treatment option for patients with URPC. 19 patients with LAPC chose to receive surgery first, achieving an R0 rate of 73.68%, with mOS of 16.5 months and mPFS of 8 months. 25 patients with URPC underwent surgical resection after conversion therapy, and 9 of them had distant metastases. The Kaplan-Meier survival curve showed that conversion therapy prolonged the OS and PFS of patients with URPC compared with surgical treatment. One patient with liver metastases of pancreatic cancer achieved R1 resection, with an OS of 29 months and a PFS of 5 months. One patient with bone metastasis of pancreatic cancer 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(28, 29).

The preoperative CA19-9 level is an independent factor that affects the OS and PFS achieved by conversion therapy. The number of lymph node metastases is an independent factor that affects the OS. It has been reported in the literature that low preoperative CA19-9 levels and fewer lymph node metastases are associated with a good prognosis after conversion therapy(19, 30). We found that age, gender, T stage, and distant metastasis are not independent prognostic factors for conversion therapy.

This study has several limitations. First, this is a single-center retrospective study, the small sample size limits the credibility of the conclusions drawn. Second, the 25 patients involved in this study who received conversion therapy were not all assessed as resectable before surgery, and most of the patients' condition was relieved or remained stable. Third, there are 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(18, 19, 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.

Declarations

Funding

This study has no financial support.

Conflicts of interest

The authors declare that they have no conflict of interest.

Data sharing statement

No additional data are available.

Code availability

Not applicable.

Authors' contributions

The authors acknowledge Liu Yang, Zhe-ling Chen and Peng-fei Zhu for their assistance with the preparation of the manuscript. Liu Yang and Zhe-ling Chen contributed to the conception of the study. Peng-fei Zhu helped to collected the data.

Ethics approval

The study was based on the principles outlined in the Declaration of Helsinki. The protocol was approved by the ethics committee of the Zhejiang Provincial People's Hospital (2017KY007).

Consent to participate

All patients expressed their informed understanding of this study and agreed to participate in this study, and obtained their informed consent.

Consent for publication

All patients agree to publish their data in this paper. All authors read and approved the final manuscript.

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Tables

Table1. Clinical efficacy of conversion therapy and surgery

	Conversion therapy(n=25)	Surgery(n=19)
mOS	28months	16.5months
mPFS	12months	8months
R0 resection rate	84% (21/25)	73.68% (14/19)
DCR	92% (23/25)	

mOS: median overall survival, mPFS: median progression-free survival, DCR: disease control rate.

Table2. Characteristics of 25 patients

	n	*p*（OS）	*p*（PFS）
Gender			
Male	15（60%）		
Female	10（40%）	0.285	0.056
Age (years)			
≤60	11（44%）		
＞60	14（56%）	0.0854	0.337
Depth of tumor invasion(T)			
T3	10（40%）		
T4	15（60%）	0.935	0.718
Number of Lymph node metastasis			
0～2	17（68%）		
＞2	8（32%）	0.044*	0.568
Distant metastasis			
M1	9（36%）		
M0	16（64%）	0.677	0.279
Preoperative CA199 level（U/ml）			
Normal or decreased（900	14（56%）		
decreased（900	11（44%）	0.008*	0.033*
Conversion therapy regimen			
FOLFIRINOX	6（24%）		
Based on gemcitabine	14（56%）	0.314	0.963
Others	5（20%）		

* statistically significance (p <0.05).

Figures

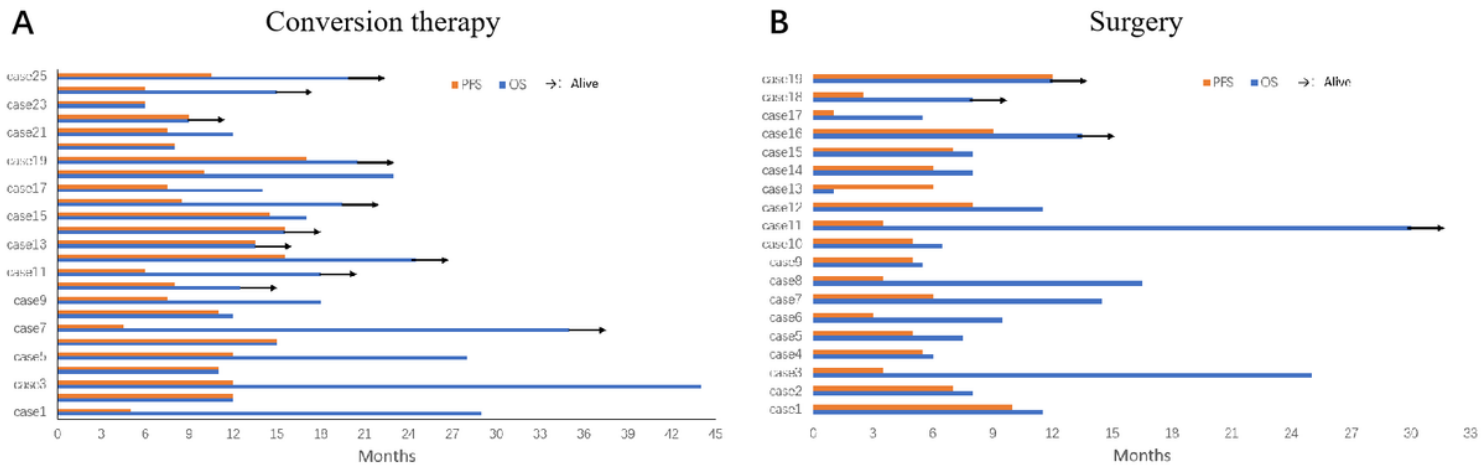

Figure 1

Survival status of 44 patients with unresectable pancreatic cancer. A. Survival status of 25 patients with unresectable pancreatic cancer after receiving conversion therapy. B. Survival status of 19 patients with unresectable pancreatic cancer after undergoing surgery. OS: overall survival, PFS: progression-free survival.

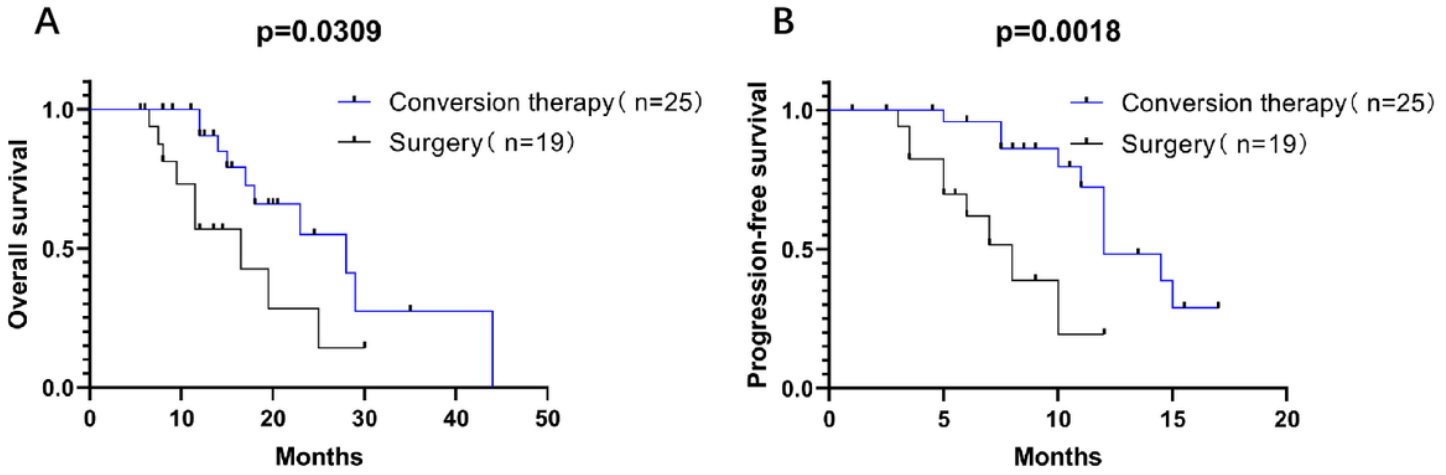

Figure 2

Kaplan–Meier curves of the OS (A) and DFS (B) of patients with conversion therapy and surgery. Patients who received conversion therapy had significantly longer median OS and PFS than those who underwent surgery (OS: 28 months vs. 16.5 months p=0.0309, PFS: 12 months vs. 8 months p=0.0018). OS: overall survival, PFS: progression free survival.

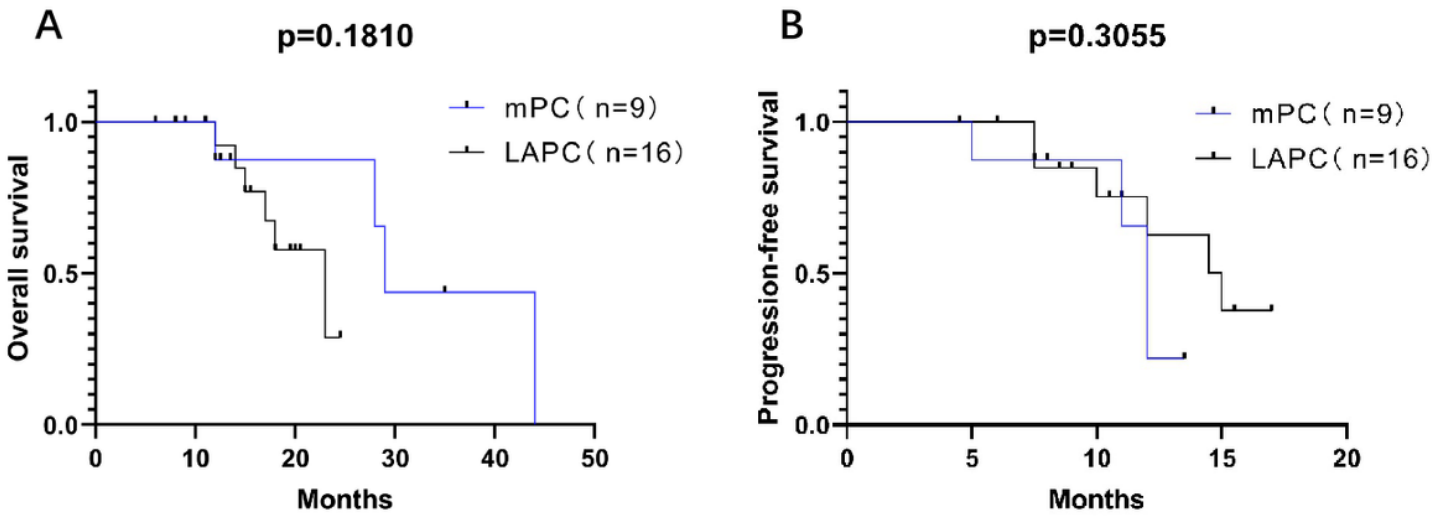

Figure 3

Kaplan–Meier curves of OS(A) and PFS(B) after conversion therapy in patients with mPC and patients with LAPC. After conversion therapy, the median OS and PFS of patients with mPC were not significantly different from those of patients with LAPC (OS: 29 months vs. 23 months p=0.1810, PFS: 12 months vs. 15 months p=0.3055). OS: overall survival, PFS: progression free survival. mPC: metastatic pancreatic cancer, LAPC: locally advanced pancreatic cancer.