

Conversion surgery with gemcitabine plus nab-paclitaxel for locally advanced unresectable pancreatic cancer: A case report

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Abstract. The standard treatment for locally advanced unresectable (UR-LA) pancreatic ductal adenocarcinoma (PDAC) is chemo-radiotherapy. Surgery following chemo-radiotherapy (conversion surgery), has been considered a useful strategy and has been used for UR-LA PDAC. The current study presents the case of a 43-year-old woman who complained of back pain. A radiological examination revealed a pancreatic tumor in contact with >270 degrees of the superior mesenteric artery (SMA) perimeter, with invasion extending from the superior mesenteric vein (SMV) to the portal vein (PV). An endoscopic ultrasonography-guided fine needle aspiration biopsy revealed adenocarcinoma as the pathological diagnosis and the patient was diagnosed with UR-LA PDAC. Following 12 courses of combined gemcitabine plus nab-paclitaxel (GnP) for 9 months, the extent of tumor invasion to the SMA and SMV was improved and the level of cancer antigen (CA) 19-9 decreased. A pancreatoduodenectomy with PV resection and reconstruction using a left renal vein graft were performed. Pathological examination revealed that the operative outcome was R0 (no residual tumor) resection and the patient was alive 19 months after the initial treatment (9 months post surgery), however, there was local tumor recurrence. Between March 2015 and February 2016 a total of 10 cases of UR-LA PDAC were

encountered at the Department of General Surgery, Chiba University Hospital (Chiba, Japan), in which GnP therapy was performed. Including the present case, 6 of the 11 cases (55%) underwent conversion surgery with curative resection. Kaplan-Meier analysis revealed that patients treated with conversion surgery presented significantly longer overall survival (OS) than those treated with no conversion surgery (median OS, 22.5 vs. 11 months; $P=0.047$, Wilcoxon test). The minimum reduction of CA19-9 was 67%. In conclusion, conversion surgery following GnP therapy is a desirable option for UR-LA PDAC. A significant reduction in the CA19-9 levels may be useful in determining the timing of changeover from medicine to surgery in patients with UR-LA PDAC in whom conversion surgery is being considered.

Introduction

More than 50% of all cases of pancreatic ductal adenocarcinoma (PDAC) are initially considered unresectable (UR) (1), and the standard treatment for locally advanced unresectable (UR-LA) PDAC is chemo-radiotherapy (2). Even if an effective regimen, such as combination therapy with gemcitabine and nab-paclitaxel (GnP), is administered, the median overall survival (OS) is only 8.5 months (3). Recent case reports and retrospective studies of chemo-radiotherapy prior to surgery, i.e., conversion surgery, for UR PDAC have been published (4,5), and the significance of conversion surgery is now being evaluated. This report describes a case of successful conversion surgery after GnP therapy for UR-LA PDAC.

Case report

A 43-year-old woman was referred to the Department of General Surgery, Chiba University Hospital (Chiba, Japan) from a local hospital with the complaint of back pain. Initial laboratory findings showed a high level of cancer antigen 19-9 (CA 19-9), at 205.7 U/ml. Abdominal computed tomography (CT) revealed a hypovascular tumor measuring 24 mm in the head of the pancreas. The tumor was in contact with more than 270 degrees of the superior mesenteric artery (SMA) perimeter, with invasion extending from the superior mesenteric vein (SMV) to the portal vein (PV) (the longitudinal axis was 30 mm) (Fig. 1A and B). Endoscopic ultrasonography (EUS)

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Abbreviations: BR, borderline resectable; CA19-9, cancer antigen 19-9; CT, computed tomography; EUS, endoscopic ultrasonography; GnP, gemcitabine plus nab-paclitaxel; MST, median survival time; OS, overall survival; PET, positron emission tomography; PDAC, pancreatic ductal adenocarcinoma; PV, portal vein; SMA, superior mesenteric artery; SMV, superior mesenteric vein; UR-LA, locally advanced unresectable

Key words: conversion surgery, gemcitabine plus nab-paclitaxel, locally advanced unresectable pancreatic cancer, cancer antigen 19-9

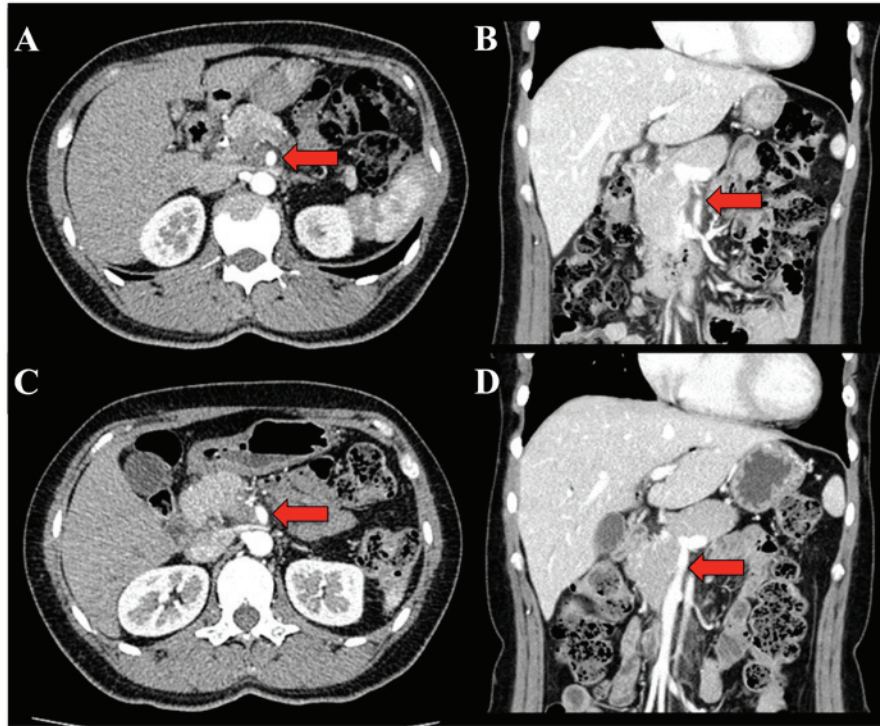


Figure 1. CT prior to and post GnP therapy. (A) A CT on the patient's initial visit revealed a hypovascular tumor measuring 24 mm in the head of the pancreas. The tumor was in contact with >270 degrees of the SMA perimeter (red arrow). (B) The tumor invaded from the SMV to the PV. The longitudinal axis was 30 mm (red arrow). Following GnP therapy, (C) the tumor size decreased to 20 mm and the contact with the SMA decreased to 90 degrees (red arrow) and (D) the longitudinal tumor axis invading from the SMV to the PV decreased to 15 mm (red arrow). CT, computed tomography; SMV, superior mesenteric vein; PV, portal vein; SMA, superior mesenteric artery; GnP, gemcitabine plus nab-paclitaxel.

indicated that the tumor was in contact with >180 degrees of the SMA perimeter, and the histological finding of fine needle aspiration biopsy was adenocarcinoma. Both positron emission tomography (PET) and ethoxybenzyl-magnetic resonance imaging (MRI) showed no evidence of distant metastasis.

On the basis of these clinical findings, the patient was diagnosed with UR-LA PDAC, and subsequently treated with a combined chemotherapy regimen of gemcitabine (GEM, 1,000 mg/m²) and nab-paclitaxel (125 mg/m²), aimed at conversion surgery. This combination chemotherapy was intravenously administered on days 1 and 8 and repeated every 3 weeks. After 12 courses of combination chemotherapy for 9 months, CT and EUS imaging demonstrated an effective response to chemotherapy. The tumor size decreased to 20 mm and the contact with the SMA was reduced to 90 degrees (Fig. 1C). The length of tumor invasion to the SMV decreased from 30 to 15 mm in the longitudinal axis (Fig. 1D). EUS examination also showed that the extent of tumor invasion to the SMA and SMV had decreased. Preoperative stage was T4N2M0 stage III according to the 8th edition of the UICC (International Union Against Cancer)-TNM classification (6). Furthermore, the level of CA 19-9 decreased from 205.7 to 67.5 U/ml (Fig. 2). The radiological efficacy of chemotherapy was stable disease (SD) on the Response Evaluation Criteria in Solid Tumors (RECIST) (7). After discussion with the patient and her family, conversion surgery was planned.

Pancreaticoduodenectomy with portal vein resection and reconstruction using a left renal vein graft were performed (8) (Fig. 3A and B). The margins of the bile duct and stump of the pancreas were negative for cancer on intraoperative

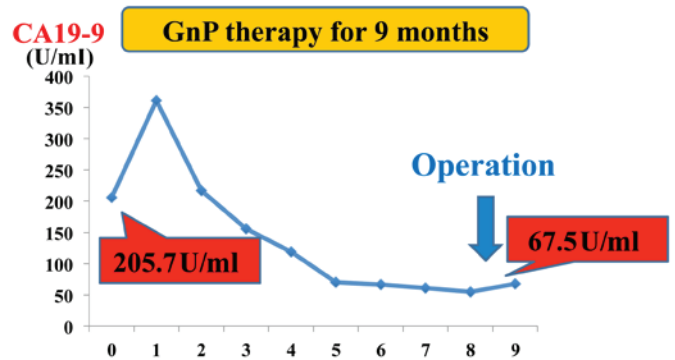


Figure 2. The transition of serum CA 19-9 level during GnP therapy. GnP, gemcitabine plus nab-paclitaxel; CA, cancer antigen.

pathological diagnosis of a frozen section. Microscopic pathological examination showed R0 (no residual tumor) resection, and 10-50% of the tumor cells were replaced with fibrosis (Evans' criteria IIa) (9). Based on the pathological findings (moderately differentiated tubular adenocarcinoma, pT2 (24 mm), pN2 (4/32), pM0), the tumor was defined as stage III (Fig. 3C). After surgery, the patient showed bleeding from the ligated inferior pancreaticoduodenal artery due to a pancreatic fistula (grade C) (10). Embolization with coiling and reoperation (remnant pancreatectomy) were performed to stop bleeding. The patient made a satisfactory recovery and was discharged on postoperative day 53. The patient is alive at 19 months after initial treatment (9 months after surgery), but with local tumor recurrence.

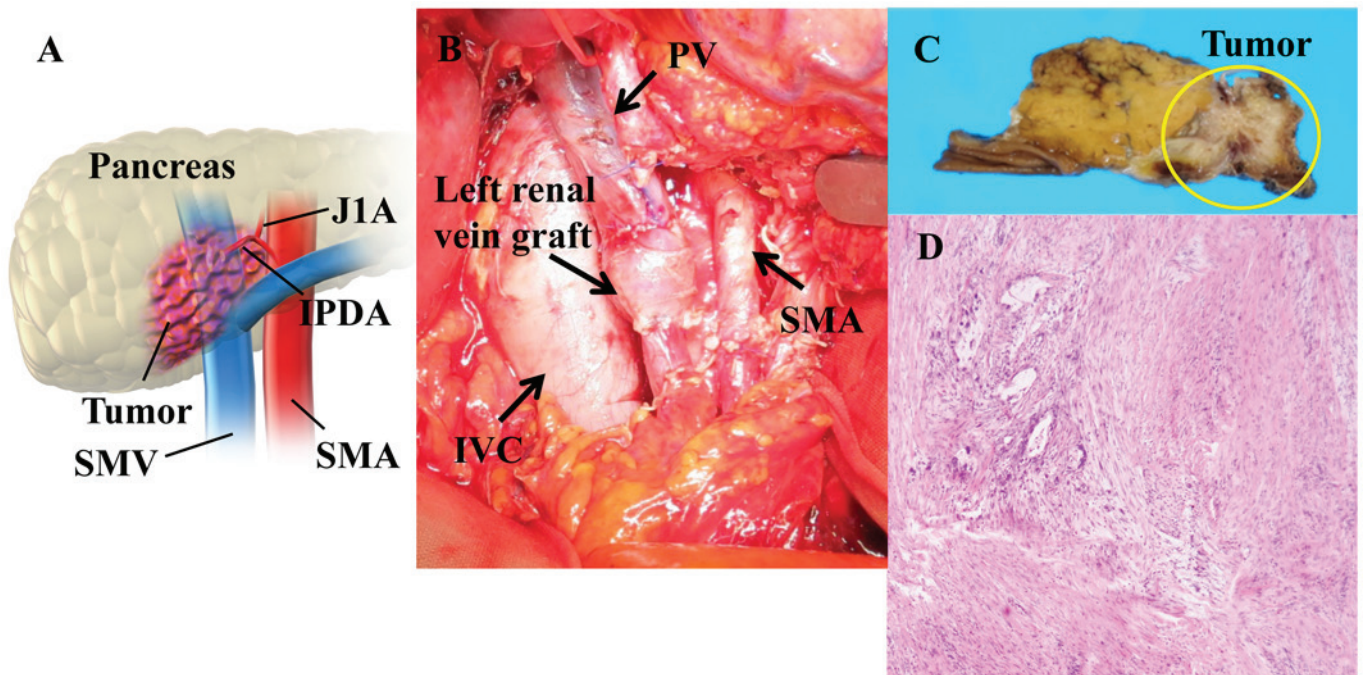


Figure 3. Pancreatoduodenectomy with portal vein resection and reconstruction using a left renal vein graft. (A) The schema of operative findings. (B) Intraoperative image. Pathological findings. (C) Macroscopic findings. (D) Microscopic findings of the surgical specimen with hematoxylin/eosin staining revealed a change to 10-50% fibrous tissue with grade IIa per Evans' criteria following chemotherapy. Magnification, x40. PV, portal vein; SMA, superior mesenteric artery; SMV, superior mesenteric vein; IVC, IVC; inferior vena cava; IPDA, inferior pancreaticoduodenal artery; J1A, first jejunal artery.

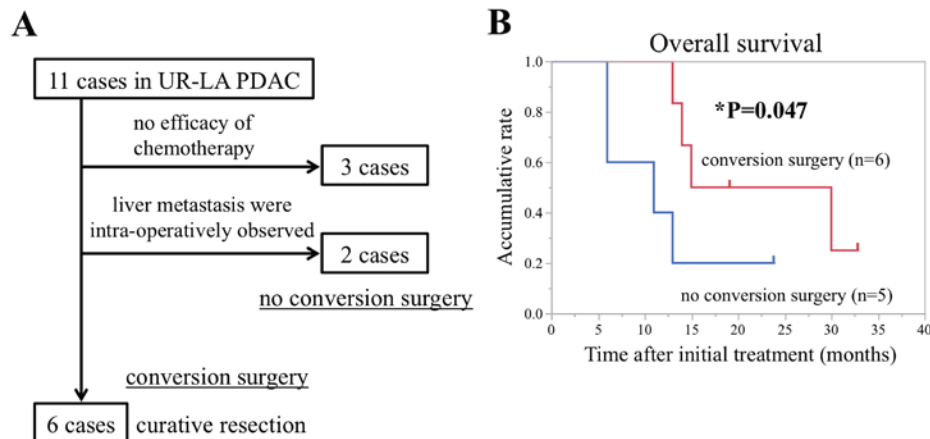


Figure 4. (A) Flow chart of patient selection for conversion surgery following gemcitabine plus nab-paclitaxel therapy in UR-LA PDAC. (B) The Kaplan-Meier survival curve revealed a favorable prognosis in conversion surgery group compared with the no conversion surgery group. *P=0.047, Wilcoxon test. UR-LA PDAC, locally advanced unresectable pancreatic ductal adenocarcinoma.

Discussion

Chemotherapy for PDAC has advanced since gemcitabine was introduced (11). The MPACT trial demonstrated the effectiveness of GnP therapy for UR PDAC (3). Ueno *et al* reported that GnP therapy (response rate: 69.2%) shows better efficacy compared to gemcitabine or gemcitabine plus S-1 therapy (response rate: 30%) for patients with UR PDAC (12,13). To utilize these chemotherapies before surgery, it is possible to exclude the cases showing aggressive growth or having distant metastasis afterward. The selection of patients with a good response to chemotherapy is important for successful conversion surgery in UR PDAC. Satoi *et al* demonstrated that the median OS of patients with UR PDAC treated with

conversion surgery after gemcitabine or S-1 therapy was significantly improved compared to that with chemotherapy alone (39.7 vs. 20.8 months, respectively; $P<0.001$) (14). Furthermore, Ielpo *et al* reported that OS of patients treated with conversion surgery with GnP therapy for resectable or borderline resectable (BR) PDAC was significantly improved compared to that with chemotherapy alone (21 vs. 12.5 months, respectively; $P<0.0002$) (15). Taken together, these results suggest that GnP therapy is one of the most useful options for the treatment of UR-LA PDAC and is expected to improve prognosis when followed by conversion surgery.

Recent cases of conversion surgery with GnP therapy for UR-LA PDAC have been reported. Satoi *et al* demonstrated that the median OS of patients with UR-LA PDAC treated with

Table I. Preoperative characteristics of locally advanced unresectable pancreatic ductal adenocarcinoma patients preparing for conversion surgery with GnP therapy.

No.	Age/ gender	Location	Factors determining unresectability	Period of Tx (months)	CA19-9 (before Tx) (U/ml)	CA19-9 (after Tx) (U/ml)	Reduction rate of CA19-9 (%)	RECIST
1	61/M	Head	Contact with SMA 360°	5	0.8	0.1	87.5	PR
2	56/F	Head	Contact with CHA with extension to hepatic artery bifurcation	3.9	150.4	35.2	76.6	PR
3	45/M	Body	Contact with CEA	2.4	2909	884	69.6	SD
4	71/M	Body	Contact with SMA and CEA	1.4	165.7	35.4	78.0	SD
5	77/M	Head	Contact with SMA >270°	3.8	726.0	51.3	92.8	PR
Present case	43/M	Head	Contact with SMA >270°	9	205.7	67.5	67.1	SD

CEA, celiac artery; CHA, common hepatic artery; F, female; M, male; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumor; SD, stable disease; Tx, chemotherapy.

Table II. Clinical characteristics and outcomes of locally advanced unresectable pancreatic ductal adenocarcinoma in patients who underwent conversion surgery following gemcitabine plus nab-paclitaxel therapy.

No.	Operation method	Curability	Evans' criteria	OS from initial treatment (months)	Survival
1	PD	R0	IIa	14	No
2	PD-CAR, PVR	R0	I	33	Yes
3	DP-CAR, PVR	R0	IIa	30	No
4	DP-CAR	R0	IIa	15	No
5	PD, PVR	R1	IIa	16	No
Present case	PD, PVR	R0	IIa	19	Yes

DP-CAR, distal pancreatectomy with en block celiac axis resection; OS, overall survival; PD, pancreaticoduodenectomy; PVR, portal vein resection; PD-CAR, pancreaticoduodenectomy with en block common hepatic artery resection.

conversion surgery after GnP therapy was 13.3 months in a retrospective study (5). FOLFIRINOX (5-fluorouracil/leucovorin combined with irinotecan and oxaliplatin) is another effective chemotherapeutic regimen to UR PDAC (16). Suker *et al* demonstrated that the median OS of patients with UR-LA PDAC treated with conversion surgery after FOLFIRINOX therapy was 24.2 months in a systematic review (17). Based on the efficacy of chemotherapy, the use of conversion surgery for UR-LA PDAC will likely increase. However, it is important to determine whether the soft tissue around major vessels such as the SMA is truly involved with tumor invasion. Therefore, it is difficult to make a decision to convert treatment from chemotherapy to surgery solely on the basis of radiological examination. A retrospective cohort study reported that a >50% decrease in pretreatment CA 19-9 levels after chemotherapy resulted in improved OS, compared to that with a ≤50% decrease (28.0 vs. 11.1 months; $P < 0.0001$) (18). Thus, the CA 19-9 level should be taken into account in the evaluation of chemotherapy efficacy.

We performed GnP therapy in 10 consecutive cases of UR-LA PDAC between March 2015 and February 2016 in the Department of General Surgery, Chiba University Hospital.

Although there is still no definite surgical indication for conversion surgery during multidisciplinary treatment in patients with initially UR PDAC, the following points were considered; i) tumor shrinkage from UR to resectable or BR PDAC on radiological examinations, ii) serum CA 19-9 level is clearly decreased, and iii) good performance status. Adding the present case to these 10 cases, 3 of the 11 cases (27%) were not converted to resection because chemotherapy was ineffective, while 6 of 11 cases (55%) excluding 2 cases which intra-operatively showed liver metastases in successfully underwent conversion surgery with curative resection (Fig. 4A). In this retrospective cohort study, the Kaplan-Meier analysis showed that patients treated with conversion surgery presented significantly longer overall survival (OS) than those treated with no conversion surgery (the median OS: 22.5 vs. 11 months, $P = 0.047$, Wilcoxon test; Fig. 4B). The average duration of chemotherapy before conversion surgery was 4.3 months and the minimum reduction rate of CA 19-9 was 67% among 6 curative resection cases (Table I). The rate of R0 resection was 83% (Table II). Based on these clinical data, a significant decrease in CA 19-9 levels might be useful in determining the time of changeover from

medicine to surgery in patients with UR-LA PDAC in whom conversion surgery is being considered.

In conclusions, we described a case of successful conversion surgery with gemcitabine plus nab-paclitaxel for UR-LA PDAC. GnP therapy decreased the level of CA 19-9, enabling surgical resection. Conversion surgery after GnP therapy is a useful treatment option for UR-LA PDAC. Further evidence and prospective cohort studies are required to establish the optimal strategy for treatment of UR-LA PDAC.

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Availability of data and materials

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

Authors' contributions

RO gathered the patient's data and wrote the manuscript. ST treated the patient with preoperative and adjuvant chemotherapy. ST, TY, and MM performed the surgery. TM and MO were responsible for the pathological diagnosis of the case. ST, TY, HY, KF, TT, SaK, DS, NS, ShK, HN, MM and MO discussed and analyzed the data with RO and assisted in writing the manuscript. All authors approved the final manuscript.

Ethics approval and consent to participate

The Ethics Committees of Chiba University approved the content of this manuscript (approval no. 2732) and written informed consent was obtained from each patient prior to surgery.

Patient consent for publication

Written informed consent was obtained from the patient for the publication of this case report and any accompanying images.

Competing interests

The authors declare that they have no competing interests.

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