Original Article on Pancreas Cancer

Conversion surgery in patients with pancreatic cancer and peritoneal metastasis

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Background: Pancreatic ductal adenocarcinoma (PDAC) is among the most lethal malignancies globally. We have previously explored the clinical efficacy of intraperitoneal (IP) paclitaxel therapy for patients with PDAC and peritoneal metastasis, which demonstrated favourable response and disease control rates. However, the real implications of conversion surgery after IP therapy remain unclear.

Methods: We conducted two multicenter clinical trials of IP therapy with paclitaxel in patients with PDAC and peritoneal metastasis. We focused on patients who underwent conversion surgery and investigated the long-term outcomes, particularly, initial recurrence patterns and long-term survival.

Results: Seventy-nine patients with PDAC and peritoneal metastasis were treated, and 33 (41.8%) patients received SP (intravenous IP paclitaxel with S-1) and 46 (58.3%) were administered GAP (intravenous gemcitabine + nab-paclitaxel combined with IP paclitaxel) combination therapy. Of the 79 patients, 16 (20.3%) underwent conversion surgery. The median time to surgery was 9.0 (range, 4.1–13.0) months after the initiation of chemotherapy. Finally, 13 (81.3%) patients underwent R0 resection. Evans grade was IIA in nine patients, IIB in four patients, III in two patients, and IV in one patient. The median overall survival time in patients who underwent conversion surgery was 32.5 (range, 13.5–66.9) months. Twelve (75.0%) patients were found to have experienced recurrence after conversion surgery. Especially, peritoneal recurrence was observed in 50% of patients as the initial recurrence pattern. The median recurrence-free survival time was 9.2 (range, 5.1–32.8) months, and three patients have survived without recurrence to date.

Conclusions: Our IP therapy displays promising clinical efficacy with acceptable tolerability in patients with PDAC and peritoneal metastasis. Although we could observe some super-responders in the cohort, further improvements in IP therapy are warranted.

Keywords: Conversion surgery; pancreatic cancer; peritoneal metastasis; intraperitoneal therapy (IP therapy)

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Introduction

Pancreatic ductal adenocarcinoma (PDAC) is one of the most lethal malignancies worldwide. The median survival time (MST) of patients with distant metastasis is estimated to be less than 12 months (1). In particular, the presence of peritoneal metastasis can cause the development of massive ascites and intestinal obstruction, leading to malnutrition and poor performance status, which could deprive patients of the opportunity to receive chemotherapy (2,3). Peritoneal metastasis is generally treated with systemic chemotherapy in the same manner as other distant metastases. However, intraperitoneal (IP) chemotherapy appears advantageous for treating peritoneal dissemination because of the high drug concentration that is achievable in the peritoneal cavity, which is in direct contact with tumour nodules, compared with the effects of systemic chemotherapy (4-9).

To treat this dismal disease, we previously explored the clinical efficacy of IP paclitaxel therapy in patients with PDAC and peritoneal metastasis, demonstrating favourable response and disease control rates. In our studies, the MST and 1-year overall survival rate were 14.5–16.3 months and 61–62%, respectively, with conversion surgery performed in 17.4–24.2% of the enrolled patients (10). Concerning overall survival, the patients who underwent conversion surgery survived significantly longer than those who did not.

However, the real implications of conversion surgery after IP therapy in patients with PDAC and peritoneal metastasis are still unclear because of the lack of clinical experience in this therapy. Therefore, we focused on patients who underwent conversion surgery and investigated long-term outcomes including initial recurrence patterns and long-term survival. We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/jgo-20-243).

Methods

Enrolled patients

We conducted two multicenter clinical trials of IP therapy with paclitaxel in patients with PDAC and peritoneal metastasis. In the first trial, intravenous (IV) and IP paclitaxel with S-1 (SP) were tested as combination therapy (10), and IV gemcitabine + nab-paclitaxel combined with IP paclitaxel (GAP) was subsequently evaluated in the second trial (11).

The eligibility criteria in both trials were briefly as follows: histologically or cytologically proven PDAC; peritoneal metastasis in patients with otherwise resectable cancer, or the presence of cancer cells in patients with unresectable locally advanced cancer; no prior receipt of chemotherapy, or chemotherapy started within 2 months; Eastern Cooperative Oncology Group performance status of 0 or 1; adequate bone marrow, liver, and renal function; and age ≥20 years and <80 years (10,11).

The exclusion criteria were as follows: presence of distant metastasis excluding the ovaries; contraindication for S-1, gemcitabine, nab-paclitaxel, or paclitaxel; massive ascites; bleeding in the alimentary tract with repetitive blood transfusion; other active concomitant malignancies; and invasion of more than half of the alimentary tract by the primary tumour or peritoneal deposits. These studies were conducted in accordance with the Declaration of Helsinki (as revised in 2013), and the study protocol was approved by the institutional review board of the affiliated hospital (UMIN000009446) (UMIN000018878) and informed consent was taken from all individual participants.

Treatment

If peritoneal dissemination or positive peritoneal cytology was detected during staging laparoscopy or open laparotomy, a peritoneal access port was implanted in the lower abdomen. In the former SP trial, S-1 was orally administered twice daily at a dose of 80 mg/m^2/d for 14 consecutive days, followed by 7 days of rest. Paclitaxel was administered intravenously at a dose of 50 mg/m^2 and intraperitoneally at 20 mg/m^2 on days 1 and 8. Whereas in the latter GAP trial, IV nab-paclitaxel combined with gemcitabine was administered combined with IP paclitaxel on days 1, 8, and 15, followed by 1 week of rest. The

Table 1 Patient characteristics at diagnosis

Characteristics	Value
Age, years	69 (47.0–79)
Sex, male/female	40 (50.6)/39 (49.4)
BMI, kg/m^2	20.3 (13.3–30.5)
Performance status, 0/1	55 (69.6)/24 (30.4)
Tumor location, head/body and tail	22 (27.8)/57 (72.2)
Tumor size, mm	37 (18–105)
Resectability, R/BR/UR	12 (15.2)/25 (31.6)/42 (53.2)
Ascites, –/+	34 (43.0)/45 (57.0)
Peritoneal dissemination, –/+	28 (35.4)/51 (64.6)
Peritoneal (washing) cytology, –/+	1 (1.3)/78 (98.7)
Albumin, g/dL	3.7 (2.5–4.8)
CA19-9 level, U/mL	539 (0.9–38,000)
CA125 level, U/mL	43.9 (9–385.4)
Biliary drainage, –/+	65 (82.3)/14 (17.7)
Duration of protocol therapy, months	7.1 (0–22.6)
Regimen, SP/GAP	33 (41.8)/46 (58.3)

Data are presented as the median (range) or n (%). BMI, body mass index; CA19-9, carbohydrate antigen 19-9; CA125, carbohydrate antigen 125; R, resectable; BR, borderline resectable; UR, unresectable; SP, S-1 + paclitaxel; GAP, gemcitabine + nab-paclitaxel + paclitaxel.

treatment course was repeated until unacceptable toxicity, disease progression, or surgery. The criteria for surgical resection (defined as conversion surgery) were as follows: Eastern Cooperative Oncology Group performance status of 0 or 1; marked tumour shrinkage; decreased or normalisation of tumour marker levels; washing cytology via peritoneal access port turned negative (twice in a row); and disappearance of peritoneal deposits on staging laparoscopy. The decision to proceed to conversion surgery was based on an interval exceeding 8 months between the initial treatment and surgical resection (12).

Statistical analysis

All statistical analyses were performed using JMP Pro version 14.2.0 (SAS Institute, Cary, NC, USA). Continuous variables were expressed as the median (range). Overall survival was defined as the time from treatment introduction to all-cause death. Recurrence-free survival was defined as the time from conversion surgery to diagnosis of recurrence.

Results

Patient recruitment

A total of 79 patients with pancreatic cancer and peritoneal metastasis were treated in our two studies that used IP therapy with paclitaxel. Among them, 33 (41.8%) patients received SP (IV and IP paclitaxel with S-1) and 46 (58.3%) underwent GAP (IV gemcitabine + nab-paclitaxel combined with IP paclitaxel) combination therapy.

Patient characteristics

Patient characteristics of 79 cases are shown in *Table 1*. The tumour was located at the pancreatic head in 22 (27.8%) patients and at the pancreatic body/tail in 57 (72.2%) patients, and the median tumour diameter was 37 (range, 18–105) mm. Primary tumours were categorised as resectable in 12 (15.2%) patients, borderline resectable in 25 (31.6%) patients, and unresectable and locally advanced in 42 (53.2%) patients (13), based on the National Comprehensive Cancer Network (NCCN) guidelines. Malignant ascites was observed in 45 (57.0%) patients upon laparoscopy or laparotomy, and peritoneal dissemination was confirmed in 51 (64.6%) patients. The median treatment duration was 7.1 (range, 0–22.6) months (*Table 1*).

Conversion surgery

Of the 79 patients, 16 (20.3%) patients underwent conversion surgery, and their clinical characteristics are shown in *Table 2*. The tumour location in 13 (81.3%) patients was the pancreatic body and tail. Eleven (68.8%) patients had peritoneal dissemination at diagnosis, and five patients had positive peritoneal washing cytology plus unresectable locally advanced cancer preoperatively. The median time to surgery was 9.0 (range, 4.1–13.0) months after the initiation of chemotherapy. Finally, 13 (81.3%) patients underwent R0 resection. Evans grade was IIA in nine patients, IIB in four patients, III in two patients, and IV in one patient.

Survival outcomes

The median overall survival time of the patients who

Table 2 Clinical characteristics of patients who underwent conversion surgery

No.	Age	Sex	Location	Tumor size (mm)*	Tumor resectability	P	Regimen	RECIST best	CA19-9, IU/L*	Time to surgery (months)	Operative procedure	R	Evans grade	Recurrence		OS (months)	Alive or dead
														Site	RFS (months)		
1	60	F	Pbt	35→20	UR	–	SP	PR	131→17	8.8	DP-CAR	R0	IIA	L	7.3	27.8	Dead
2	69	M	Pbt	43→22	UR	+	SP	PR	977→69	8.4	DP	R0	IIA	H	5.1	26.1	Dead
3	75	M	Pbt	44→13	UR	+	SP	PR	598→56	10.5	DP	R1	IIA	L	8.3	24.0	Dead
4	50	F	Pbt	25→13	UR	+	SP	PR	418→12	11.9	DP-CAR	R0	IIB	P	8.6	36.9	Dead
5	74	F	Ph	41→12	UR	–	SP	PR	1,778→13	13.0	TP + PV	R0	IIB	P	12.6	26.9	Dead
6	73	M	Pbt	22→20	PR	+	SP	SD	106→70	10.0	DP	R1	IIA	P	32.8	66.9	Alive
7	73	F	Ph	34→17	UR	–	SP	PR	175→18	8.3	PD	R0	IIA	P	7.1	22.3	Dead
8	67	M	Pbt	26→26	PR	+	SP	PR	26→24	8.5	DP	R0	IIA	P	19.0	49.3	Dead
9	74	F	Pbt	46→18	UR	–	GAP	PR	232→14	9.3	PD + PVR	R0	IIB	Unknown	NA	13.5	Dead
10	67	F	Pbt	25→10	R	+	GAP	PR	837→48	9.2	DP	R0	IIA	P	12.3	39.3	Dead
11	75	M	Pbt	38→25	BR	+	GAP	PR	1,127→43	4.7	DP-CAR	R0	IIA	L	7.9	15.1	Dead
12	73	F	Pbt	41→40	UR	–	GAP	SD	59→47	12.2	PD + PVR	R1	IIA	None	NA	34.6	Alive
13	77	M	Pbt	30→30	R	+	GAP	SD	246→23	4.1	DP	R0	IIB	P	9.7	32.5	Dead
14	54	F	Pbt	25→0	BR	+	GAP	CR	167→12	7.9	DP	R0	IV	None	NA	27.5	Alive
15	74	M	Ph	52→10	UR	+	GAP	PR	162→37	9.7	PD + PVR	R0	III	None	NA	25.7	Alive
16	77	F	Pbt	46→23	R	+	GAP	PR	703→17	6.7	DP	R0	III	P	12.4	24.5	Alive

*, change from before treatment to before surgery. M, male; F, female; Pbt, pancreatic body and tail; Ph, pancreatic head; UR, unresectable; R, resectable; BR, borderline resectable; P, peritoneal dissemination at diagnosis; SP, S-1 + paclitaxel; GAP, gemcitabine + nab-paclitaxel + paclitaxel; PR, partial response; CR, complete response; SD, stable disease; CA19-9, carbohydrate antigen 19-9; PD, pancreatoduodenectomy; PVR, portal vein resection; DP, distal pancreatectomy; DP-CAR, distal pancreatectomy with celiac artery resection; TP, total pancreatectomy; RFS, recurrence free survival; L, locoregional; H, liver; OS, overall survival; NA, not available.

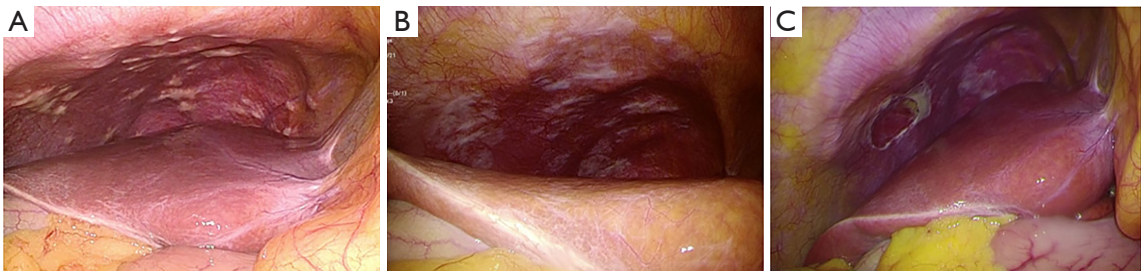

Figure 1 Intra-abdominal findings on diagnostic laparoscopy. (A) Multiple peritoneal deposits were observed in the right subphrenic space before treatment introduction. (B) Withdrawal of peritoneal deposits was confirmed at second diagnostic laparoscopy, and pathological examination showed no evidence of malignancy. (C) Intra-abdominal findings at the time of conversion surgery.

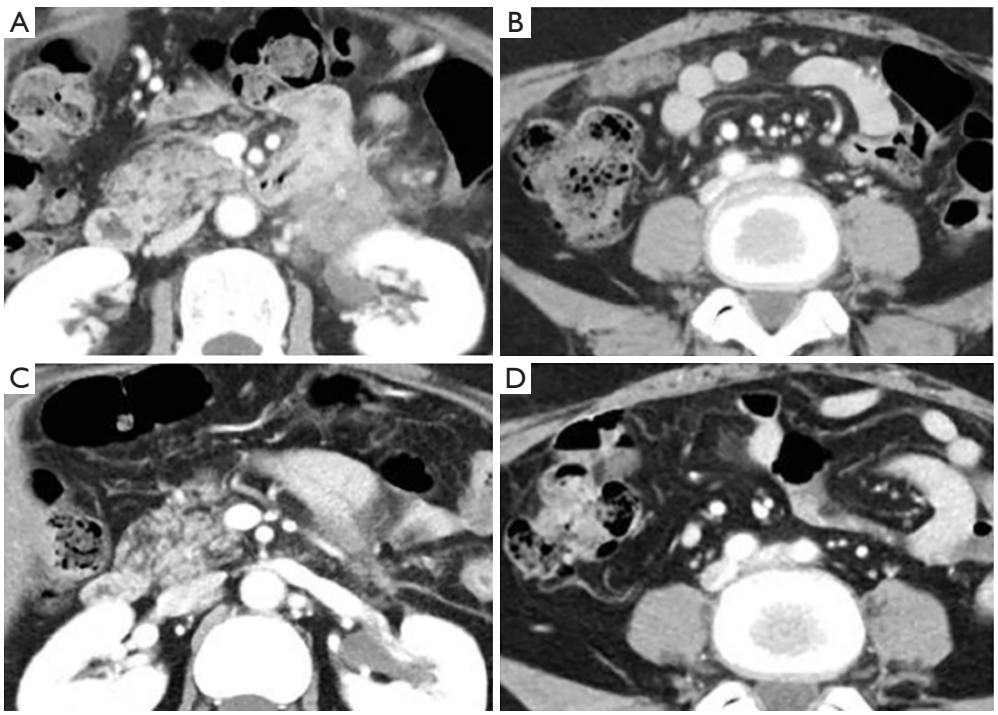

Figure 2 Computed tomography findings during treatment. (A) The tumour located in pancreatic tail was observed before treatment introduction. (B) The peritoneal deposits were also found in peritoneal cavity. (C) The tumour shrinkage following treatment was confirmed. (D) The disappearance of peritoneal deposits was observed.

underwent conversion surgery was 32.5 (range, 13.5–66.9) months. After conversion surgery, a total of 12 (75.0%) patients experienced recurrence. Especially, peritoneal recurrence was observed in 50% of patients as the initial recurrence pattern. The median recurrence-free survival time was 9.2 (range, 5.1–32.8) months, and three patients have survived without recurrence thus far.

Among the patients, case no. 14 was successfully cured. GAP therapy was introduced in this 54-year old female patient because she was diagnosed as having PDAC with peritoneal metastasis. During her 8-month treatment, the disappearance of peritoneal deposits was confirmed pathologically (*Figures 1-3*). Finally, she underwent distal pancreatectomy as conversion surgery, and surprisingly, the

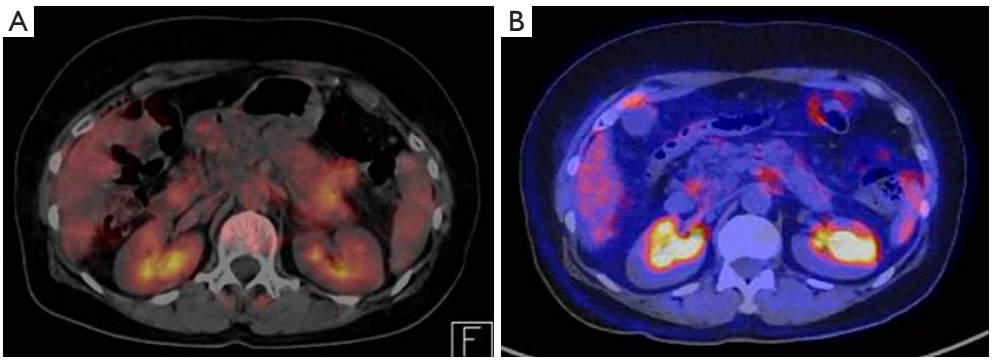

Figure 3 Positron emission tomography findings during treatment. (A) Standardized uptake value on the pancreatic tail was observed before treatment introduction. (B) There was no uptake in the area.

final pathological finding showed Evans grade IV.

Discussion

IP chemotherapy enables peritoneal deposits to be exposed to high concentrations of drugs without increasing the blood concentration, which is considered to be advantageous (14). Further, the effective duration after IP administration is determined by the molecular characteristics of the drugs; in that sense, paclitaxel is suitable for use (4). In the area of gastroenterological malignancies, IV/IP paclitaxel + S-1 therapy in gastric cancer and peritoneal metastasis was evaluated in a phase I/II study (6,14), and the phase III PHOENIX-GC trial was conducted to compare this regimen with standard therapy (15). We also reported the promising clinical efficacy and acceptable tolerability of IP paclitaxel therapy in PDAC and peritoneal metastasis patients (10,11).

In general, most patients with PDAC and peritoneal metastasis exhibit massive ascites and a subsequent poor performance status, leading to fewer opportunities to receive chemotherapy (3). Surprisingly, a previous report observed considerably poor survival following weekly paclitaxel in patients with PDAC and malignant ascites (16). More recently, the MST in patients with PDAC and peritoneal dissemination was reported to be only 7 months, and that in patients with locally advanced disease with positive peritoneal washing cytology was 6 months (17). Our previous report also revealed MSTs of 8 months in patients with PDAC and peritoneal metastasis and 13 months in patients with locally advanced disease and positive peritoneal washing cytology (3). Considering that patients with peritoneal metastasis generally have an extremely poor prognosis, the results of our studies are encouraging.

Recently, multidisciplinary treatment combining chemo- or chemoradiotherapy and subsequent surgery has been widely accepted and regarded as a promising strategy. Generally, the rate of conversion surgery after induction therapy in locally advanced PDAC ranged from 1.3–36%, and the MST after resection has been reported to reach 18.2–41.8 months (18-25). Also, Suker *et al.* conducted a systematic review that showed the ratio of conversion surgery was 28%, however; the long-term survival outcomes remain unconfirmed (26).

In metastatic disease, the rate of conversion surgery is even lower. Inherently, few studies regarding this disease have been reported, in which the conversion ratio ranged from 2–4.5% (27,28). That is, the conversion ratio of the intention-to-treat population remained below 5%. Notably, there has been no report focused on peritoneal metastasis. In our study, the combination therapy enabled 17.4–24.2% patients to be eligible for conversion surgery, a considerable achievement given the generally poor outcomes of patients with PDAC and peritoneal metastasis. Although our therapy had a marked impact, most patients who underwent conversion surgery unfortunately recurred. However, we observed some super-responders in the cohort, and thus further improvement of IP therapy is warranted.

In conclusion, our IP therapy displayed promising clinical efficacy with acceptable tolerability in patients with PDAC and peritoneal metastasis. However, these studies were conducted as a phase I/II study with a single-arm design. Therefore, we have launched a phase III study to compare survival outcomes between this IP therapy and

standard chemotherapy.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/jgo-20-243). The focused issue was sponsored by the Peritoneal Surface Oncology Group International (PSOGI). The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. These studies were conducted in accordance with the Declaration of Helsinki (as revised in 2013), and the study protocol was approved by the institutional review board of the affiliated hospital (UMIN000009446) (UMIN000018878) and informed consent was taken from all individual participants.

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