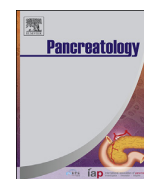




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Improved prognosis of pancreatic cancer patients with peritoneal metastasis

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ABSTRACT

Background: Peritoneal metastasis is one of the most important poor prognostic factors in advanced pancreatic cancer (PC). Whether the prognosis of PC with peritoneal metastasis has improved with the advent of gemcitabine plus nab-paclitaxel (GnP) and modified FOLFIRINOX (mFFX) is uncertain. The aim of this study was to evaluate the improvements in treatment outcomes of PC with peritoneal metastasis.

Methods: We retrospectively investigated consecutive PC patients with peritoneal metastasis treated with chemotherapy at our institution between 2010 and 2019. We compared the clinical characteristics and survival outcomes according to the period of diagnosis (group A, 2010–2014; group B, 2015–2019) and chemotherapy regimen. We also examined the prognostic factors for overall survival (OS).

Results: Among 180 patients included (GnP 88; mFFX 14; other regimens 78), distant metastasis was confined to the peritoneum in 89 patients. Although group B had a worse performance status compared to group A, median OS was significantly longer in group B. GnP and mFFX showed a significantly higher objective response rate and disease control rate in addition to longer progression free survival and OS compared to other regimens. The administration of GnP or mFFX, performance status, and neutrophil to lymphocyte ratio ≥ 5 were identified as independent prognostic factors for OS. Furthermore, the amount of ascites and extent of peritoneal metastasis were significantly associated with OS in patients with distant metastasis confined to the peritoneum.

Conclusions: The prognosis of PC with peritoneal metastasis has significantly improved over time with the advent of GnP and mFFX.

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Introduction

Pancreatic cancer (PC) is the fourth leading cause of cancer-related death in Japan with a dismal prognosis [1]. Surgical resection with negative margins is the only chance for long-term survival, however the majority of patients are diagnosed at an advanced stage [2]. Peritoneal metastasis, defined as the presence of cancer cells that have spread or metastasized to the peritoneal cavity, has been considered as one of the most important poor

prognostic factors in metastatic PC [3]. Peritoneal metastasis often leads to severe complications such as intestinal obstruction, massive ascites, and malnutrition, resulting in reduced performance status (PS) and impaired quality of life [4]. Consequently, patients with peritoneal metastasis are usually underrepresented in most clinical trials and the efficacy of chemotherapy in these patients has not been well established. Furthermore, it has been reported that the prognosis of PC patients with peritoneal metastasis has not improved over time despite the advances in chemotherapy for metastatic PC [4,5].

Gemcitabine monotherapy has long been the standard first-line chemotherapy for metastatic PC [6]. Many randomized clinical trials have been conducted to develop a more effective regimen than gemcitabine alone. Gemcitabine plus erlotinib demonstrated a significant improvement in prognosis compared to gemcitabine alone, however the median survival difference between the two regimens was only two weeks [7]. Recently, FOLFIRINOX (FFX) and

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Abbreviations

PC	pancreatic cancer
PS	performance status
mFFX	modified FOLFIRINOX
GnP	gemcitabine plus nab-paclitaxel
CT	computed tomography
PET	positron emission tomography
ECOG	Eastern Cooperative Oncology Group
BMI	body mass index
CEA	carcinoembryonic antigen
CA19-9	carbohydrate antigen 19-9
mGPS	modified Glasgow prognostic score
CRP	C-reactive protein
NLR	neutrophil to lymphocyte ratio
OS	overall survival
PFS	progression free survival
HR	hazard ratio
CI	confidence interval

gemcitabine plus nab-paclitaxel (GnP) have been shown to significantly improve the prognosis of metastatic PC patients with a good PS and are considered as first-line treatment [8,9]. However, it still remains uncertain whether these two regimens have similar

beneficial effects on PC patients presenting with peritoneal metastasis.

Therefore, we conducted this retrospective study to evaluate the improvements in treatment outcomes and examine the prognostic factors for advanced PC patients with peritoneal metastasis.

Patients and methods*Patients*

Consecutive patients diagnosed with metastatic or recurrent PC who received first-line chemotherapy at our institution between January 2010 and December 2019 were identified from our prospectively maintained database. Recurrent PC patients who had received neoadjuvant therapy were excluded from this study because we intended to evaluate the efficacy of first-line chemotherapy in chemotherapy-naïve PC patients. Each patient underwent a computed tomography (CT) for tumor staging. Magnetic resonance imaging and/or positron emission tomography (PET)/CT were also performed at the discretion of the physician. Although the diagnosis of peritoneal metastasis was confirmed by the presence of peritoneal nodules detected on CT or PET/CT in most of the patients, peritoneal metastasis was also confirmed by laparoscopy or laparotomy in cases with negative findings on CT in some of the patients. Since modified FFX (mFFX) and GnP became commercially available in December 2013 and December 2014, respectively, in Japan, we divided the study population into two groups: group A,

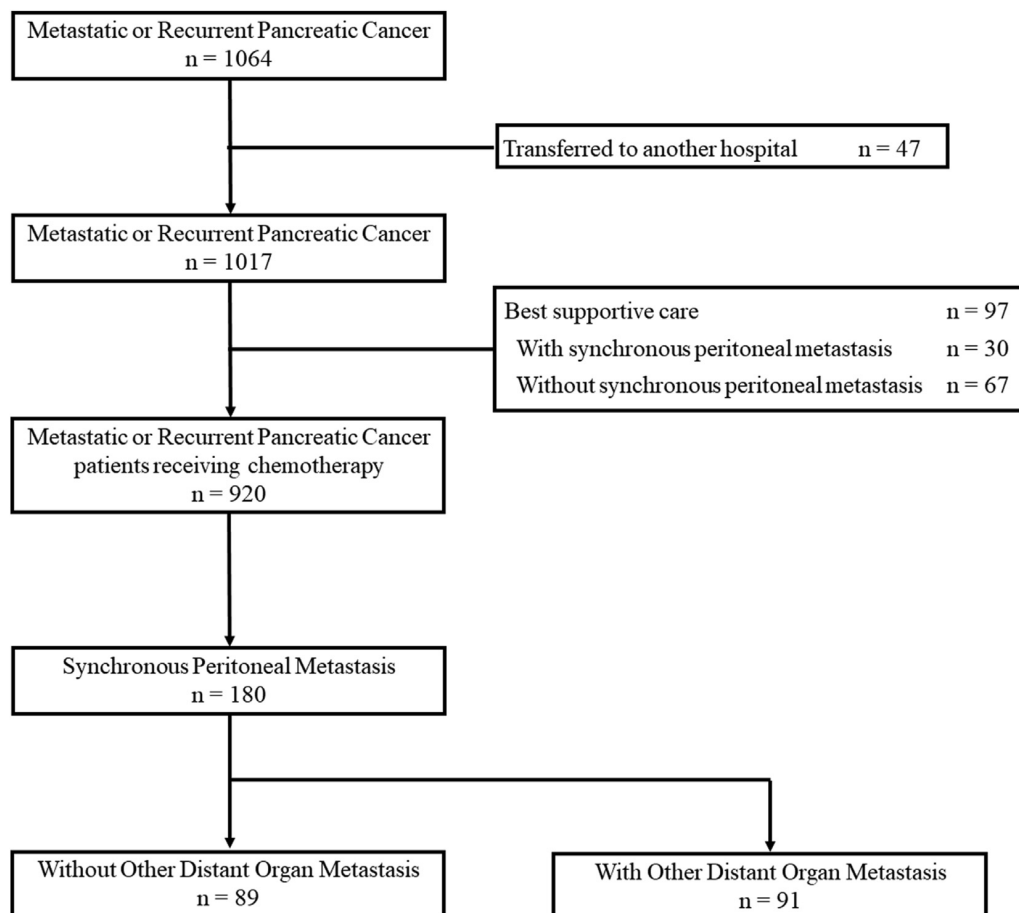


Fig. 1. Patients flowchart.

Table 1

Patient characteristics according to the period of diagnosis.

	n = 180	Period of diagnosis		P value
		Group A (n = 60)	Group B (n = 120)	
Age, years	67 (37–88)	68 (37–80)	67 (39–88)	0.490
Sex, Male	88 (49%)	32 (53%)	56 (47%)	0.432
BMI, kg/m ²	20.6 (15.0–30.5)	20.7 (17.6–28.5)	20.6 (15.0–30.5)	0.419
Disease status				1.000
Metastatic	152 (84%)	51 (85%)	101 (84%)	
Recurrent	28 (16%)	9 (15%)	19 (16%)	
Tumor location [n = 152]				0.251
Head	25 (16%)	11 (22%)	14 (14%)	
Body or tail	127 (84%)	40 (78%)	87 (86%)	
ECOG PS				0.021
0	119 (66%)	47 (78%)	72 (60%)	
1	56 (31%)	11 (18%)	45 (38%)	
2	5 (3%)	2 (3%)	3 (3%)	
Amount of ascites ^a				0.262
None or Small	131 (73%)	41 (68%)	90 (75%)	
Moderate	39 (22%)	17 (28%)	22 (18%)	
Massive	10 (6%)	2 (3%)	8 (7%)	
Extent of peritoneal metastasis ^b				0.528
P1	91 (51%)	28 (47%)	63 (53%)	
P2/P3	89 (49%)	32 (53%)	57 (48%)	
Metastatic sites other than the peritoneum				
Liver	68 (38%)	22 (37%)	46 (38%)	0.872
Lung	15 (8%)	3 (5%)	12 (10%)	0.392
Distant lymph node	37 (21%)	15 (25%)	22 (18%)	0.330
mGPS				0.548
0	116 (64%)	41 (68%)	75 (63%)	
1	32 (18%)	8 (13%)	24 (20%)	
2	32 (18%)	11 (18%)	21 (18%)	
NLR [n = 176]	3.2 (1.0–46.5)	3.0 (1.1–23.0)	3.2 (1.0–46.5)	0.601
CEA, ng/mL	6.4 (0.7–16984.4)	7.7 (0.8–1306.1)	5.8 (0.7–16984.4)	0.909
CA19-9, IU/mL	1411 (2–50000)	1013 (2–50000)	2122 (2–50000)	0.801
Regimen of chemotherapy				< 0.001
GnP	88 (49%)	0	88 (73%)	
mFFX	14 (8%)	2 (3%)	12 (10%)	
Gemcitabine plus S-1	3 (2%)	3 (5%)	0	
Gemcitabine plus erlotinib	1 (1%)	1 (2%)	0	
Gemcitabine monotherapy	63 (35%)	44 (73%)	19 (16%)	
S-1 monotherapy	5 (3%)	4 (7%)	1 (1%)	
Investigational new drug	6 (3%)	6 (10%)	0	

Continuous variables are expressed as median (range) and categorical variables are expressed as absolute numbers (proportions).

BMI, body mass index; ECOG PS, Eastern Cooperative Oncology Group performance status; mGPS, modified Glasgow prognostic score; NLR, neutrophil to lymphocyte ratio; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; GnP, gemcitabine plus nab-paclitaxel; mFFX, modified FOLFIRINOX.

^a Evaluated by computed tomography: none, ascites undetected by CT; small, ascites localized in only one area such as the pelvic cavity; moderate, ascites neither small nor massive; and massive, ascites extending throughout the abdominal cavity.^b Evaluated by computed tomography or positron emission tomography: P1, metastatic nodule(s) limited to one area of the peritoneum; P2, multiple scattered metastatic nodules within the peritoneal cavity; P3, numerous metastatic nodules throughout the peritoneal cavity.

patients who started chemotherapy between 2010 and 2014; and group B, patients who started chemotherapy between 2015 and 2019. This study was conducted in accordance with the Declaration of Helsinki and was approved by the ethics committee of our institution (Institutional Review Board number: 2020-1279). All patients provided informed consent for chemotherapy.

Treatment

Before mFFX and GnP became commercially available in our institution, most of the patients received gemcitabine monotherapy (gemcitabine, 1000 mg/m², on days 1, 8, and 15, every 4 weeks) or S-1 monotherapy (S-1, 40 mg, 50 mg, 60 mg on the basis of body surface area, orally administered twice daily for 4 weeks followed by 2 weeks rest), while the other patients received gemcitabine plus erlotinib (n = 1), gemcitabine plus S-1 (n = 3), or investigational new drugs (n = 6).

After mFFX and GnP became commercially available in our institution, we basically administered either of the following

regimens considering the patients' age, Eastern Cooperative Oncology Group (ECOG) PS and comorbidities: (1) GnP (gemcitabine, 1000 mg/m², nab-paclitaxel, 125 mg/m², on days 1, 8, and 15 every 4 weeks), (2) mFFX (oxaliplatin 85 mg/m², leucovorin, 400 mg/m², irinotecan, 150 mg/m², infusional 5-FU, 2400 mg/m², every 2 weeks), (3) gemcitabine monotherapy or (4) S-1 monotherapy. Treatment delay and dose reduction were performed based on toxicity and physician/patient discretion, and treatment was continued until disease progression, intolerable toxicity, or patient refusal. Radiologic tumor response was assessed according to Response Evaluation Criteria in Solid Tumors version 1.1. Treatment-related adverse events were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0.

Data collections and outcome measurements

We retrieved data on pretreatment clinical characteristics including age, sex, body mass index (BMI), primary tumor location,

Table 2

Patient characteristics and treatment efficacy according to the chemotherapy regimen.

	GnP or mFFX (n = 102)	Other regimens (n = 78)	P value
Age, years	66 (39–83)	70 (37–88)	< 0.001
Sex, Male	47 (46%)	41 (53%)	0.452
BMI, kg/m ²	21.0 (15.0–30.5)	20.6 (15.1–28.5)	0.573
Disease status			0.061
Metastatic	91 (89%)	61 (78%)	
Recurrent	11 (11%)	17 (22%)	
Tumor location [n = 152]			0.383
Head	13 (14%)	12 (20%)	
Body or tail	78 (86%)	49 (80%)	
ECOG PS			0.108
0	61 (60%)	58 (74%)	
1	38 (37%)	18 (23%)	
2	3 (3%)	2 (3%)	
Amount of ascites ^a			0.435
None or Small	78 (76%)	53 (68%)	
Moderate	19 (19%)	20 (26%)	
Massive	5 (5%)	5 (6%)	
Extent of peritoneal metastasis ^b			1.000
P1	52 (51%)	39 (50%)	
P2/P3	50 (49%)	39 (50%)	
Metastatic sites other than the peritoneum			
Liver	41 (40%)	27 (35%)	0.535
Lung	10 (10%)	5 (6%)	0.588
Distant lymph node	21 (21%)	16 (21%)	1.000
mGPS			0.119
0	60 (59%)	56 (72%)	
1	23 (23%)	9 (12%)	
2	19 (19%)	13 (17%)	
NLR [n = 176]	3.4 (1.0–46.5)	3.0 (1.0–23.0)	0.098
CEA, ng/mL	6.0 (0.7–16984.4)	6.6 (0.8–1306.1)	0.990
CA19-9, IU/mL	2122 (2–50000)	1091 (2–50000)	0.866
Best tumor response			< 0.001
Complete response	0	0	
Partial response	29 (28%)	4 (5%)	
Stable disease	45 (44%)	33 (42%)	
Progressive disease	27 (26%)	33 (42%)	
Not evaluable	1 (1%)	8 (10%)	
Objective response rate	28%	5%	< 0.001
Disease control rate	73%	47%	< 0.001

Continuous variables are expressed as median (range) and categorical variables are expressed as absolute numbers (proportions).

BMI, body mass index; ECOG PS, Eastern Cooperative Oncology Group performance status; mGPS, modified Glasgow prognostic score; NLR, neutrophil to lymphocyte ratio; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; GnP, gemcitabine plus nab-paclitaxel; mFFX, modified FOLFIRINOX.

^a Evaluated by computed tomography: none, ascites undetected by CT; small, ascites localized in only one area such as the pelvic cavity; moderate, ascites neither small nor massive; and massive, ascites extending throughout the abdominal cavity.^b Evaluated by computed tomography or positron emission tomography: P1, metastatic nodule(s) limited to one area of the peritoneum; P2, multiple scattered metastatic nodules within the peritoneal cavity; P3, numerous metastatic nodules throughout the peritoneal cavity.

metastatic site, ECOG PS, amount of ascites, extent of peritoneal metastasis, laboratory data, and serum tumor markers (carcinoembryonic antigen [CEA] and carbohydrate antigen 19-9 [CA 19-9]). The amount of ascites was evaluated by CT and was categorized according to the Japanese Classification of Gastric Carcinoma [10]: none, ascites undetected by CT; small, ascites localized in only one area such as the pelvic cavity; moderate, ascites neither small nor massive; and massive, ascites extending throughout the abdominal cavity. The extent of peritoneal metastasis was evaluated by CT or PET/CT and was classified using criteria modified from the Japanese Classification of Gastric Carcinoma [10]: P1, metastatic nodule(s) limited to one area of the peritoneum; P2, multiple scattered metastatic nodules within the peritoneal cavity; and P3, numerous metastatic nodules throughout the peritoneal cavity. Since the difference between P2 and P3 is ambiguous, we combined the category into P2/P3 with reference to a previous study [11]. Modified Glasgow prognostic score (mGPS) [12] was calculated as follows: C-reactive protein (CRP) $\leq$ 1 mg/dL, 0 point; CRP > 1 mg/dL and albumin $\geq$ 3.5 g/dL, 1 point; CRP > 1 mg/dL and albumin < 3.5 g/dL, 2 points. Neutrophil to lymphocyte ratio (NLR) was calculated by dividing neutrophil count by lymphocyte count [13]. Overall

survival (OS) was defined as the time from treatment initiation until death from any cause or the last follow up. Progression free survival (PFS) was defined as the time from treatment initiation until disease progression, death from any cause, or the last follow up. The follow-up data was confirmed until December 31, 2020.

First, we compared the clinical and treatment characteristics according to the period of diagnosis (group A vs. group B). Second, we compared PFS and OS according to the chemotherapy regimen (GnP or mFFX vs. other regimens). Finally, we examined the prognostic factors for OS in PC patients with peritoneal metastasis.

Statistical analysis

Continuous variables are presented as median (range), and were compared using Mann-Whitney *U* test or Kruskal-Wallis test as appropriate. Categorical variables are described as absolute numbers (proportions), and were analyzed using χ^2 test or Fisher's exact test as appropriate. PFS and OS were estimated using the Kaplan-Meier method and the Kaplan-Meier curves were compared by the log-rank test. Multivariate analysis was conducted using the cox proportional hazards model to identify prognostic

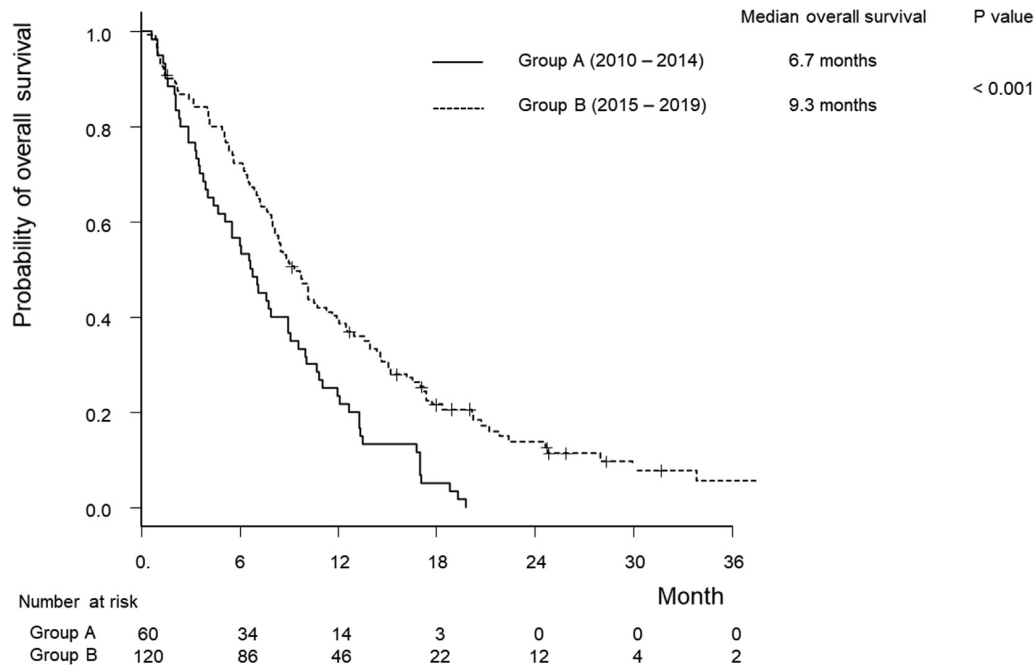


Fig. 2. Kaplan-Meier curves of overall survival according to the period of diagnosis.

factors for OS. Statistical tests were two-sided and a P value < 0.05 was considered statistically significant. Statistical analysis was carried out using the EZR software version 1.40 [14].

Results

Patient characteristics

A total of 1064 consecutive patients were diagnosed as metastatic or recurrent PC at our institution between January 2010 and December 2019. Forty-seven patients were transferred to another hospital and 97 patients received best supportive care, and the remaining 920 patients received palliative chemotherapy at our institution. Among them, 180 patients (20%) were diagnosed with synchronous peritoneal metastasis and were included in this study; the peritoneum was the only site of metastasis in 89 patients, whereas the remaining 91 patients presented with distant organ metastasis other than the peritoneum (Fig. 1). Of the 180 patients, the diagnosis of peritoneal metastasis was confirmed by CT or PET/CT in 157 patients and by laparoscopy or laparotomy in 23 patients. The predominant site of distant organ metastasis other than the peritoneum was the liver (38%), followed by distant lymph node (21%) and lung (8%). During the follow-up period, 2 patients were continuing first-line chemotherapy, 12 patients were transferred to another hospital without disease progression, and the remaining 166 patients discontinued first-line chemotherapy. The reasons for first-line chemotherapy discontinuation were disease progression in 142 (86%), deterioration of general condition in 17 (10%), unacceptable toxicity in 5 (including 3 interstitial pneumonia, 1 peripheral neuropathy, and 1 acute kidney injury), and patients' decision in 2. The details of disease progression consisted of exacerbation of peritoneal metastasis in 65 (including 8 cases of ileus and 2 cases of gastrointestinal perforation due to peritoneal metastasis), exacerbation of the primary tumor or other metastatic sites in 43, exacerbation of malignant ascites in 19, rapid increase in tumor markers in 14, and death in 1.

Patient characteristics according to the period of diagnosis (group A vs. group B) are shown in Table 1. Although patients in group B had a worse PS ($p = 0.021$) and received a higher rate of combination chemotherapy using GnP or mFFX compared to patients in group A (83% vs. 3%, $p < 0.001$), other parameters such as the amount of ascites, the extent of peritoneal metastasis, metastatic site other than the peritoneum, mGPS, NLR, and tumor markers were not significantly different between the two groups.

On the other hand, patient characteristics and treatment efficacy according to the chemotherapy regimen (GnP or mFFX vs. other regimens) are illustrated in Table 2. Although patients who received GnP or mFFX were significantly younger compared to those who received other regimens (66 years vs. 70 years, $p < 0.001$), other parameters were well-balanced between the two groups. Regarding treatment efficacy, the objective response rate (28% vs. 5%, $p < 0.001$) and disease control rate (73% vs. 47%, $p < 0.001$) were significantly higher in patients receiving GnP or mFFX compared to patients receiving other regimens.

Survival outcomes

Kaplan-Meier curves of OS according to the period of diagnosis are illustrated in Fig. 2. Median OS was significantly longer in group B compared to group A (9.3 months vs. 6.7 months, $p < 0.001$). This finding indicates that the prognosis of PC with peritoneal metastasis has significantly improved over time.

Kaplan-Meier curves of PFS and OS according to the chemotherapy regimen (GnP or mFFX vs. other regimens) are shown in Fig. 3. Median PFS (6.1 months vs. 3.4 months, $p < 0.001$) and OS (10.1 months vs. 6.8 months, $p < 0.001$) were significantly longer in patients receiving GnP or mFFX compared to patients receiving other regimens.

Cox proportional hazards regression analysis for OS are shown in Table 3. Combination chemotherapy using GnP or mFFX (hazard ratio [HR], 0.32; 95% confidence interval [CI], 0.22–0.46; $p < 0.001$), ECOG PS of 0 (HR, 0.51; 95%CI, 0.33–0.78; $p = 0.002$), and NLR ≥ 5

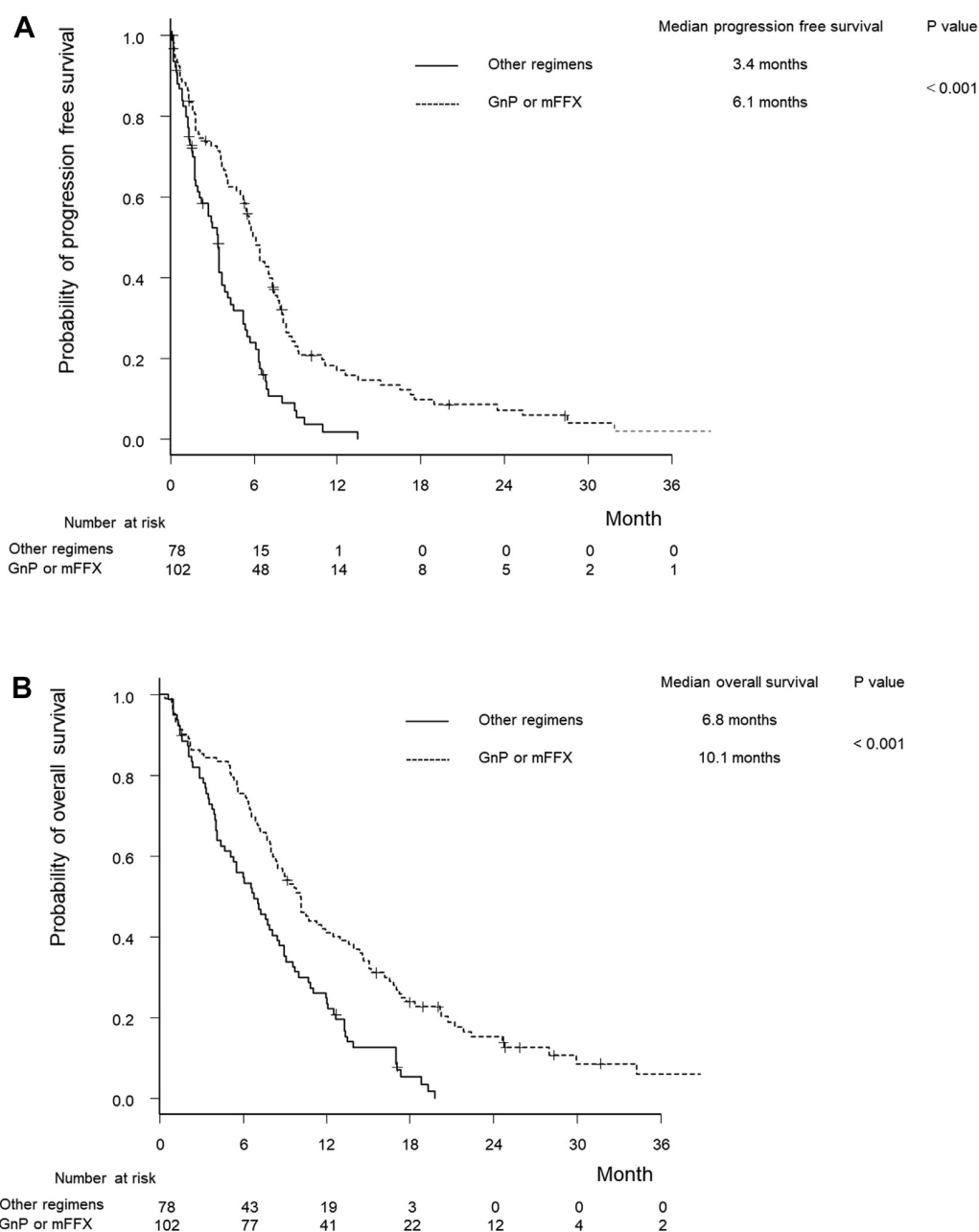


Fig. 3. Kaplan-Meier curves of (A) progression free survival and (B) overall survival according to the chemotherapy regimen. GnP, gemcitabine plus nab-paclitaxel; mFFX, modified FOLFIRINOX.

(HR, 1.68; 95%CI, 1.05–2.70; $p = 0.032$) were identified as independent prognostic factors for OS in PC patients presenting with peritoneal metastasis.

Subgroup analysis of patients with distant metastasis confined to the peritoneum

Kaplan-Meier curves of OS according to the amount of ascites and the extent of peritoneal metastasis are illustrated in Fig. 4. Median OS of patients with large volume of ascites (6.4 months vs. 12.4 months, $p = 0.003$) and advanced peritoneal metastasis (6.9 months vs. 15.2 months, $p = 0.001$) was significantly shorter compared to patients with small volume of ascites and limited

peritoneal metastasis. These findings suggest that patients with small volume of ascites and limited peritoneal metastasis could expect long-term survival and are good candidates for aggressive combination chemotherapy.

Subgroup analysis of patients who received recent combination chemotherapy (GnP or mFFX)

Patient characteristics and treatment efficacy according to the regimen of recent combination chemotherapy (GnP vs. mFFX) are illustrated in Supplementary Table 1. First, patients who received mFFX were significantly younger compared to patients receiving GnP (62 years vs. 67 years, $p = 0.028$). Second, the incidence of liver

Table 3

Cox proportional hazards regression analysis for overall survival.

		Univariate			Multivariate		
		HR	95% CI	P value	HR	95% CI	P value
Age, years	≥75	1.17	0.80–1.69	0.420			
Sex	Male	1.00	0.74–1.36	0.999			
Disease status	Metastatic	0.96	0.64–1.46	0.855			
Peritoneum as the sole distant metastatic site	Yes	0.57	0.42–0.78	* 0.001	0.79	0.56–1.11	0.169
Amount of ascites ^a	Moderate/Massive	1.87	1.33–2.65	* 0.001	0.96	0.62–1.48	0.853
Extent of peritoneal dissemination ^b	P2/P3	1.63	1.20–2.23	0.002	1.26	0.87–1.80	0.219
ECOG PS	0	0.46	0.33–0.64	* 0.001	0.51	0.33–0.78	0.002
CEA, ng/mL	≥10	1.43	1.04–1.97	0.028	0.86	0.60–1.23	0.402
CA19-9, IU/mL	≥1000	1.57	1.15–2.16	0.005	1.28	0.89–1.86	0.186
mGPS	0	0.46	0.33–0.63	* 0.001	0.68	0.45–1.03	0.071
NLR	≥5	1.97	1.39–2.79	* 0.001	1.68	1.05–2.70	0.032
Regimen of chemotherapy	GnP or mFFX	0.51	0.37–0.70	* 0.001	0.32	0.22–0.46	<0.001

HR, hazard ratio; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; mGPS, modified Glasgow prognostic score; NLR, neutrophil to lymphocyte ratio; GnP, gemcitabine plus nab-paclitaxel; mFFX, modified FOLFIRINOX.

^a Evaluated by computed tomography: none, ascites undetected by CT; small, ascites localized in only one area such as the pelvic cavity; moderate, ascites neither small nor massive; and massive, ascites extending throughout the abdominal cavity.

^b Evaluated by computed tomography or positron emission tomography: P1, metastatic nodule(s) limited to one area of the peritoneum; P2, multiple scattered metastatic nodules within the peritoneal cavity; P3, numerous metastatic nodules throughout the peritoneal cavity.

metastasis (44% vs. 14%, $p = 0.041$) was significantly higher and the level of CA19-9 (310 IU/mL vs. 3761 IU/mL, $p = 0.020$) was significantly lower in the mFFX group compared to the GnP group. Third, although the amount of ascites and the extent of peritoneal metastasis were not significantly different between the two groups, mFFX was contraindicated for patients with massive ascites. Finally, the objective response rate and disease control rate were similar between the two groups.

Comparison of treatment-related severe adverse events according to the regimen of recent combination chemotherapy are illustrated in [Supplementary Table 2](#). The incidence of severe hematologic and non-hematologic adverse events was not significantly different between the two groups except for leukopenia (36% vs. 7%, $p = 0.033$).

Kaplan-Meier curves of PFS and OS according to the regimen of recent combination chemotherapy (GnP vs. mFFX) are shown in [Figs1](#) and [Figs2](#). As mentioned above, although there were some differences in patient characteristics favoring patients receiving mFFX, the median PFS (6.0 months vs. 7.5 months, $p = 0.217$) and OS (9.2 months vs. 16.9 months, $p = 0.148$) were not significantly different between the two groups (GnP vs. mFFX).

Discussion

This retrospective study evaluated the improvements in treatment outcomes over time and examined the prognostic factors for advanced PC patients with peritoneal metastasis. We demonstrated that the prognosis of PC with peritoneal metastasis has significantly improved over time with the advent of intensified combination chemotherapy regimens, namely, GnP and mFFX. The objective response rate (28% vs. 5%, $p < 0.001$) and disease control rate (73% vs. 47%, $p < 0.001$) were also significantly higher in patients receiving GnP or mFFX compared to patients receiving other regimens. Furthermore, combination chemotherapy using GnP or mFFX (HR, 0.32; $p < 0.001$), ECOG PS of 0 (HR, 0.51; $p = 0.002$), and NLR ≥ 5 (HR, 1.68; $p = 0.032$) were identified as independent prognostic factors for OS in PC patients presenting with peritoneal metastasis. Taken together, these results suggest that patients with a good ECOG PS could significantly benefit from these two regimens even in the presence of peritoneal metastasis. Subgroup analysis of patients with distant metastasis confined to the peritoneum revealed that median OS of patients with large volume of ascites (6.4 months vs. 12.4 months, $p = 0.003$) and advanced peritoneal

metastasis (6.9 months vs. 15.2 months, $p = 0.001$) was significantly shorter compared to patients with small volume of ascites and limited peritoneal metastasis. To the best of our knowledge, this is one of the largest studies that exclusively focused on the treatment outcomes of PC patients with peritoneal metastasis. The assessment of the extent of peritoneal metastasis was also one of the strengths in this study.

Peritoneal metastasis is one of the most common forms of metastasis in PC. In this study, the incidence of synchronous peritoneal metastasis was 20% (180/920) among advanced PC patients, which was in line with previous studies [3,5]. One study reported that the incidence of synchronous peritoneal metastasis was 22% (88/409) among metastatic PC patients receiving gemcitabine-containing regimen [3], while the other population-based study reported that the incidence of synchronous peritoneal metastasis was 19% (265/1412) among metastatic PC patients with an increasing trend over time (16% [1995–2004] to 22% [2005–2009]) [5]. The increasing trend of the diagnosis of synchronous peritoneal metastasis could be attributed to the improvement in the diagnostic performance of multidetector CT and PET/CT in detecting small peritoneal nodules.

Peritoneal metastasis is often associated with intestinal obstruction, massive ascites, and reduced PS [4,15]. Therefore, it has been regarded as a devastating condition precluding most of the patients from receiving palliative chemotherapy. Indeed, only a minority of patients received palliative chemotherapy in the two retrospective studies focusing on peritoneal metastasis, 29% in one study and 18.5% in the other study, resulting in an extremely poor OS of 6–7 weeks in the entire cohort of each study [4,5]. Recently, several studies reported the improvements in the management of intestinal obstruction and massive ascites [16–21]. These procedures enable the patients to maintain their PS and offer the patients the chance to be candidates for chemotherapy. Furthermore, recent combination chemotherapy regimens, GnP and mFFX, have been shown to significantly improve the prognosis of metastatic PC patients with a good PS [8,9,22]. In this study, we demonstrated that the beneficial effect of GnP and mFFX was also observed in PC patients presenting with peritoneal metastasis. First, the objective response rate (28% vs. 5%, $p < 0.001$) and disease control rate (73% vs. 47%, $p < 0.001$) of these two regimens were significantly higher than those of other regimens. Second, these two regimens showed a somewhat satisfactory median OS of 10.1 months, whereas the other regimens showed a median OS of 6.8 months. Considering

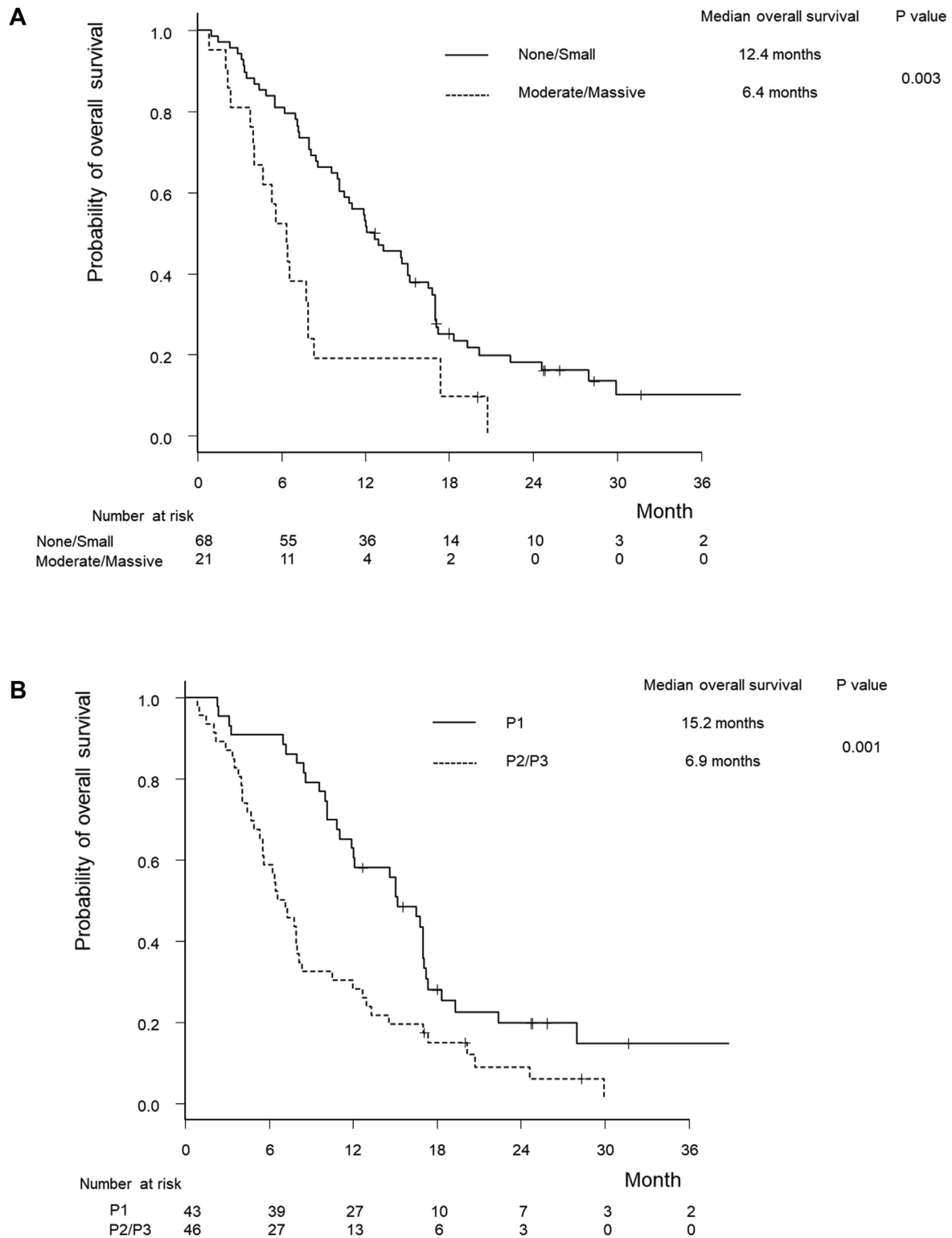


Fig. 4. Kaplan-Meier curves of overall survival according to (A) the amount of ascites and (B) the extent of peritoneal metastasis.

that PC patients with peritoneal metastasis are generally reported to have a poor prognosis, the survival outcomes of these two regimens are encouraging. Third, combination chemotherapy using these two regimens (HR, 0.32; $p < 0.001$) was identified as an independent prognostic factor for OS, together with ECOG PS of 0 and

NLR ≥ 5 . Subgroup analysis of patients with distant metastasis confined to the peritoneum was also conducted in this study. We revealed that the amount of ascites and the extent of peritoneal metastasis were significantly associated with OS. Patients with small volume of ascites and limited extent of peritoneal metastasis

showed a satisfactory median OS of 12.4 months and 15.2 months, respectively.

Although the prognosis of PC with peritoneal metastasis has moderately improved over time with the advent of intensified combination chemotherapy regimens, a novel treatment strategy focusing on peritoneal metastasis is needed to further improve its prognosis. Intraperitoneal chemotherapy has been developed to enhance the activity of antitumor drugs against peritoneal metastasis by maintaining a high drug concentration in the peritoneal cavity. Recently, promising results of intraperitoneal chemotherapy with paclitaxel have been reported in patients with peritoneal metastasis from several malignancies including PC [11,23–26]. The results of a phase II study evaluating the efficacy of intravenous GnP combined with intraperitoneal paclitaxel in PC patients with peritoneal metastasis (JRCTS031180095) is awaited to further validate the benefit of intraperitoneal chemotherapy. In this study, 88 patients received GnP as first-line chemotherapy for PC patients with peritoneal metastasis; the objective response rate, disease control rate, median PFS, and median OS were 28%, 73%, 6 months, and 9.2 months, respectively. As a result, we think that these data could be used as a standard reference for the above-mentioned phase II study evaluating intraperitoneal chemotherapy.

Our study has several limitations. First, this was a retrospective study with a limited sample size from a single institution. However, this is one of the largest studies focusing on PC patients with peritoneal metastasis. Second, since we only included patients who received chemotherapy and excluded patients who received best supportive care, the results of this study cannot be generalized to all PC patients with peritoneal metastasis. Third, the amount of ascites might be affected by factors other than peritoneal metastasis; for example, low albumin levels and/or portal hypertension could also influence the amount of ascites. Finally, the incidence of peritoneal metastasis could be underestimated in this study, because accurate diagnosis of peritoneal metastasis is sometimes difficult despite the improved diagnostic performance of CT and PET/CT.

In conclusion, we demonstrated that the prognosis of PC with peritoneal metastasis has significantly improved over time with the advent of the novel combination chemotherapy regimens (GnP and mFFX). These two regimens showed a satisfactory radiologic tumor response, PFS, and OS, and was identified as an independent prognostic factor for OS. The amount of ascites and extent of peritoneal metastasis were significantly associated with OS in patients with distant metastasis confined to the peritoneum. Furthermore, we consider that the results of this study could serve as a standard reference for future studies evaluating PC patients with peritoneal metastasis.

Declaration of competing interest

The authors declare no conflict of interests.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.pan.2021.03.006>.

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