Real-world treatment outcomes among patients with metastatic pancreatic cancer in Japan: The Tokushukai real-world data project

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Received August 4, 2023; Accepted September 7, 2023

DOI: 10.3892/mco.2023.2694

Abstract. The present study aimed to investigate temporal trends in treatment patterns and prognostic factors for overall survival (OS) among patients with metastatic pancreatic cancer. From the Tokushukai REAl-world Data project, 1,093 patients with metastatic pancreatic cancer treated with gemcitabine, tegafur/gimeracil/oteracil (S-1), gemcitabine plus S-1, gemcitabine plus nab-paclitaxel, or fluorouracil, folic acid, oxaliplatin and irinotecan (FOLFIRINOX) between April 2010 and March 2020 were identified. Stratified/conventional Cox regression analyses were conducted to examine associations between patient- and tumor-related factors, study period, hospital volume, hospital type and first-line chemotherapy regimens. Overall, 846 patients were selected (503 male patients; median age, 70 years) after excluding ineligible patients. Over a median follow-up of 5.4 months, the median OS was 6.8 months (95% confidence interval, 6.3-7.4). The median OS for gemcitabine, S-1, gemcitabine plus S-1, gemcitabine plus nab-paclitaxel and FOLFIRINOX regimens was 5.9, 5.3, 7.7, 9.0 and 9.5 months, respectively. The median OS for 2010-2013, 2014-2017 and 2017-2020 was 6.2, 7.1 and 7.8 months, respectively. Performance status, body mass index and first-line chemotherapy regimens were identified to be significant prognostic factors. In summary, the real-world data indicated that standard care, including chemotherapy, for metastatic pancreatic cancer was widely used in hospitals throughout Japan and verified the survival benefits of gemcitabine plus nab-paclitaxel and FOLFIRINOX observed in prior clinical trials. This trial has been registered in the University Hospital Medical Information Network Clinical Trials Registry as UMIN000050590 on April 1, 2023.

Introduction

Pancreatic cancer is one of the most aggressive cancers, with an extremely low five-year survival rate of 10% in the US and Japan, and its incidence continues to increase (1,2). Diabetes (3), obesity (4,5), smoking (6), heavy drinking (7) and chronic pancreatitis (8) are listed as risk factors for the development of pancreatic cancer. Although increase in the incidence of these lifestyle-related factors and aging have been cited as causes of the increased incidence of pancreatic cancer, not all the mechanisms of onset have been elucidated. In most cases, pancreatic cancer is detected at an advanced stage, representing the fourth leading cause of cancer-related mortality in both the U.S. and Japan (1,2). Surgical resection is the only potentially curative treatment, but only 20% of cases are resectable at diagnosis, and most patients have unresectable disease (1,2). Furthermore, the recurrence rate is very high even in patients who have undergone radical resection, and the 5-year survival rate does not reach 30% (2).

Before 2010, only 5-fluorouracil (5-FU), gemcitabine, and tegafur/gimeracil/oteracil (S-1) regimens had been approved for use in cases of advanced/recurrent pancreatic cancer in Japan. Gemcitabine has been used worldwide for many years because of its demonstrated improvement in quality of life

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Abbreviations: AIC, Akaike Information Criterion; BMI, body mass index; CI, confidence interval; FOLFIRINOX, fluorouracil, folic acid, oxaliplatin and irinotecan; HRs, hazard ratios; OS, overall survival; PS, performance status; RWD, real-world data; S-1, tegafur/gimeracil/oteracil; TREAD, Tokushukai real-world data; TTF, treatment failure

Key words: chemotherapy, metastatic pancreatic cancer, RWD, FOLFIRINOX, gemcitabine plus nab-paclitaxel

and prolongation of overall survival (OS) in a gold-standard phase III trial (vs. 5-FU) (9) and was approved for use in Japan in 2001. S-1 is an oral 5-FU derivative developed in Japan and was approved for use in 2006 based on the results of phase II studies in patients with advanced pancreatic cancer (10,11). In 2007, the results of a phase III trial examining the efficacy of gemcitabine in combination with erlotinib were reported and showed a statistically significant improvement in survival, but the difference was small and did not have enough impact to change actual clinical practice (12).

Recently, some additional regimens for chemotherapy-naïve pancreatic cancer, proven to be effective in gold-standard clinical trials have been approved and are now in widespread use, including fluorouracil, folinic acid, oxaliplatin, and irinotecan (FOLFIRINOX) (approved in Japan since 2013) (13-15) and gemcitabine plus nab-paclitaxel (approved in Japan since 2014) (16). In addition, a Japanese phase III study in 2013 demonstrated the non-inferiority of S-1, but not the superiority of gemcitabine plus S-1 therapy compared to gemcitabine (17). Notably, previous clinical trials have shown that each combination therapy prolongs OS when compared with gemcitabine alone; NCCN guidelines recommend FOLFIRINOX and gemcitabine plus nab-paclitaxel for metastatic pancreatic cancer with good performance status (PS) (18). Japanese guidelines for pancreatic cancer also recommend the same two regimens (19), and they are widely used as standard treatments for metastatic pancreatic cancer. Other approved regimens include liposomal irinotecan plus 5-FU and leucovorin for patients who have failed gemcitabine-based therapy (20) and olaparib as maintenance therapy after platinum-based chemotherapy for *BRCA* mutation-positive patients (21) (approved in Japan since 2020). The history of approved agents in Japan is shown in Fig. 1.

On the other hand, patients enrolled in clinical trials are highly selected patients with good general condition and organ functions. Therefore, there is often a discrepancy between the treatment results shown in clinical trials and actual clinical practice due to this selection bias (22). In recent years, cohort studies based on large-scale databases have been conducted to fill these gaps (23-26). Fortunately, real-world data (RWD) regarding the health and treatment status of patients receiving daily medical care are collected within standard organizational processes (e.g., electronic medical records and hospitalization data) (27). To evaluate whether the results of clinical trials are carried over to the real-world, we conducted an exploratory cohort study using RWD to investigate temporal trends in treatment patterns for metastatic pancreatic cancer as well as treatment outcomes and prognostic factors that influence OS.

Materials and methods

Study overview. This nationwide retrospective cohort study was conducted as part of the TREAD project, the outline of which has been described elsewhere (28). This project was approved by the Ethics Committee of the Tokushukai Group in April 2020 (No. TGE01427-024) and was conducted following the principles of the Declaration of Helsinki, and patients were provided with information using opt-out methods. This study was registered in the UMIN Clinical Trial Registry (http://www.umin.ac.jp/ctr/index.htm) and clinical trial number was UMIN000050590.

Objective patients. We evaluated patients with pathologically or radiologically confirmed metastatic pancreatic cancer who were started on first-line chemotherapy at Tokushukai Medical Group hospitals, which included 46 hospitals with 14829 beds, using the same medical record system (e-Karte and Newtons2; Software Service Inc., Osaka, Japan) and chemotherapy protocol system (srvApmDrop; Software Service Inc., Osaka, Japan) between April 1, 2010, and March 31, 2020.

All patients were administered gemcitabine, S-1, gemcitabine plus S-1, gemcitabine plus nab-paclitaxel, or FOLFIRINOX as first-line treatment. Pathological diagnoses including adenocarcinoma, adenosquamous carcinoma, and carcinoma/malignant neoplasms were included in the current study, but patients with acinar and neuroendocrine carcinoma were excluded (see Fig. 2 for more information). Additional key exclusion criteria were the presence of active double cancer, inadequate treatment history, and missing fundamental patient data, such as body weight and height.

Data collection. In the current study, we evaluated eligible patients identified from electronic medical records. Patient information such as age, sex, body mass index (BMI), the latest data on survival confirmation, survival outcomes, and diagnosis on medical receipt were extracted from the medical record system. Treatment information related to chemotherapy regimens, start and end dates of chemotherapy, and PS was extracted from the chemotherapy protocol system. The linked cancer registry information including diagnostic information (site, pathology, stage), treatment details (surgery, endoscopic procedure, radiotherapy, chemotherapy), and prognosis (final date of survival confirmation, date of death, cause of death) was extracted from the National Cancer Registry Data in Japan (29). Hospital volume and hospital type (government designated cancer hospital, prefectural designated cooperative cancer hospital, or non-designated general hospital) were also noted.

The treatment history was organized based on the extracted chemotherapy information, and when discrepancies or missing information were detected, the missing data were investigated by directly checking the medical records at Tokushukai Information Inc. (Osaka, Japan). Patients with inadequate treatment history (i.e., previous or subsequent cancer treatment outside of Tokushukai Medical Group hospitals or no detailed treatment information available) were excluded from the study. The study was divided into three periods for the elucidation of secular trends (A, 2010-2013; B, 2014-2016; C, 2017-2020).

Statistical analysis. The primary endpoint evaluated in the current study was OS, which is defined as the time from the start date of initial palliative chemotherapy to the date of death or final survival confirmation. The secondary endpoint was time to treatment failure (TTF), which is defined as the time from the start date of the first-line chemotherapy treatment to discontinuation of the treatment for any reason.

Basic statistics (absolute and relative frequencies for categorical variables; quartiles, maximum values, minimum values, and means for continuous variables; and quartiles

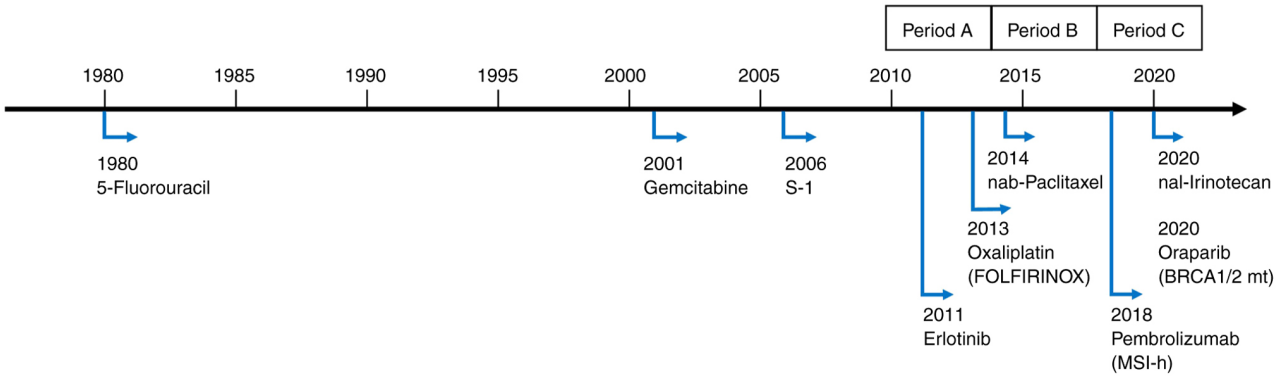

Figure 1. Year of approval for multiple agents used to treat pancreatic cancer in Japan. FOLFIRINOX, fluorouracil, folic acid, oxaliplatin and irinotecan; MSI-h, microsatellite instability-high; mt, mutation; nab, nanoparticle albumin-bounded; nal, nanoliposomal; S-1, tegafur/gimeracil/oteracil.

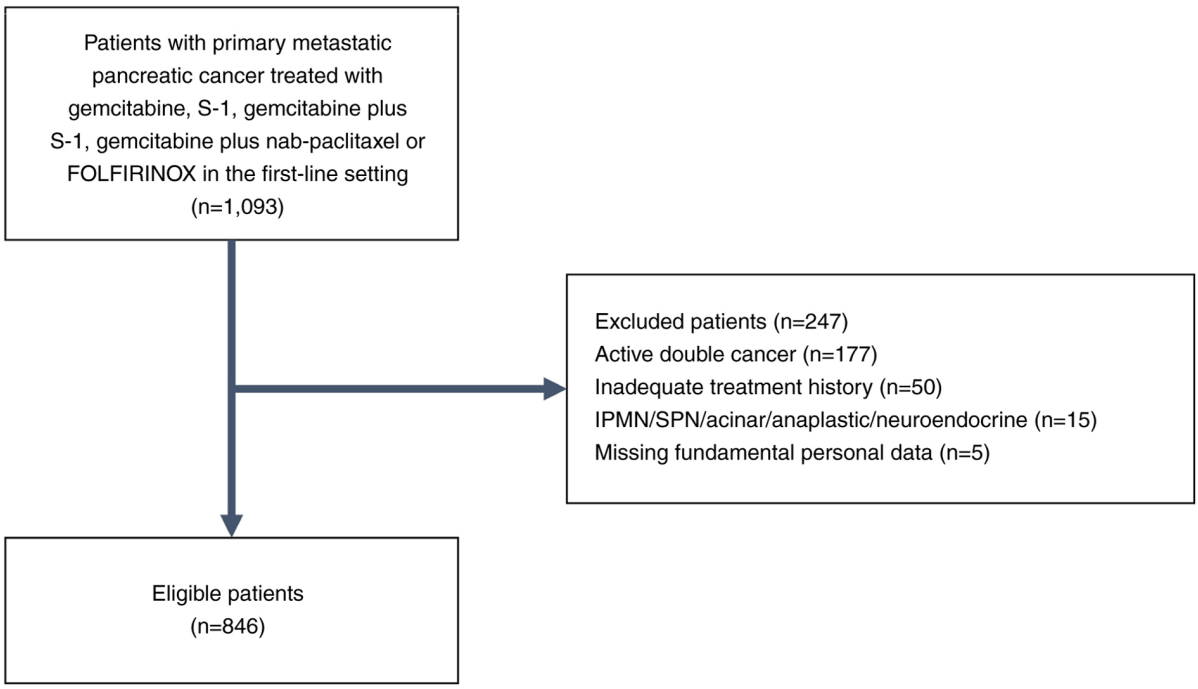

Figure 2. Flow chart of the patient recruitment and selection process in the current survival analysis. FOLFIRINOX, fluorouracil, folic acid, oxaliplatin and irinotecan; IPMN, intraductal papillary mucinous neoplasms; nab, nanoparticle albumin-bounded; S-1, tegafur/gimeracil/oteracil; SPN, solitary pulmonary nodules.

and relative frequencies for discrete variables) were obtained to summarize the distribution of variables related to patient background factors, complications, other prognostic factors, and primary and secondary endpoints. Survival analyses were performed using OS as the primary endpoint. The start date of the study was April 1, 2010, and the study end date was March 31, 2020. The time variable represents the number of days from the start date of the first-line chemotherapy treatment to the date of death. The censored cases included patients who were alive at the study end date or who dropped out of the study for any reason.

Kaplan-Meier curves (univariate analyses) and log-rank test were applied for each stratum, defined according to the patient background and prognostic factors (age at the start of first-line chemotherapy, sex, PS, BMI, smoking status, pathology, primary disease site, study period, hospital volume, hospital type, and first-line chemotherapy regimen) for the occurrence of events associated with study endpoints (OS, TTF).

In addition, several hierarchical predictive models were constructed by combining explanatory variables that were expected to contribute to the evaluated endpoints, and single- and multi-tiered proportional hazard models were established by incorporating each predictive model. Stratified/conventional Cox multiple regression analyses were performed. Conventional Cox regression was applied when the proportional hazards hypothesis was valid; otherwise, a stratified Cox regression was applied.

The Akaike Information Criterion (AIC), based on partial likelihood, was used to explore the optimal model in the current study (i.e., when the number of eligible cases differed between models, the average AIC per case was substituted). Hazard ratios (HRs) and 95% confidence intervals (CIs) were

obtained for each category of OS-related prognostic factors selected in the optimal model, and the impact of prognostic factors in the optimal model was examined using likelihood tests with associated p-values for each item. All analyses were performed using R, version 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria). All statistical analyses were two-sided, and probability values of <0.05 were considered statistically significant.

Results

Patient flow. A total of 1,093 patients were detected using the procedures described above, and 846 patients were found to be eligible according to the study inclusion and exclusion criteria specified above, as shown in Fig. 2.

Patient characteristics. Patient medical and demographic characteristics were typical for metastatic pancreatic cancer (Table I). Approximately 30% of the patients were over 75 years of age. Over 90% of the included patients had an Eastern Cooperative Oncology Group PS of 0 or 1. Most patients had pathologically proven disease. Patient characteristics by treatment regimen are shown in Table II. There was a trend toward fewer patients over 75 years of age and PS 2 or higher for combination chemotherapy. Patient backgrounds were generally similar among the three time periods, but the proportion of patients receiving combination therapy increased over time to 11.2, 37.8, and 67.8% in study periods A, B, and C, respectively (Table III). The patient background between hospital volume and type is also presented in Table SI.

Trends in the implementation of chemotherapy regimens. Trends in the implementation of first-line chemotherapy are shown in Fig. 3. In 2010, when the study began, gemcitabine was the most commonly used drug, but its percentage gradually decreased, while that of nab-paclitaxel increased after 2014, when nab-paclitaxel was approved. However, the use of FOLFIRINOX remained consistently low during the study period, even after its approval in 2013.

Kaplan-Meier survival curves. The crude (before adjusting for background factors) survival curves evaluating OS and TTF using the Kaplan–Meier method are shown in Fig. 4. The median follow-up duration was 5.4 months (95% confidence interval [CI], 4.8-6.0). The median OS of all included patients was 6.8 months (95% CI, 6.3-7.4), and the median TTF was 2.5 months (95% CI, 2.3-2.7). In addition, crude Kaplan-Meier OS curves according to the first-line chemotherapy regimen and study period are shown in Fig. 5. The median OS for gemcitabine, S-1, gemcitabine plus S-1, gemcitabine plus nab-paclitaxel, and FOLFIRINOX was 5.9, 5.3, 7.7, 9.0, and 9.5 months, respectively, and the median OS according to study period (A, B, C) was 6.2, 7.1, and 7.8 months, respectively.

Cox regression analyses. Cox regression analyses evaluating prognostic factors for OS are presented in Table IV. In a univariate analysis, age, PS, BMI, study period, and first-line systemic therapy regimens were found to affect OS. However, a multivariate analysis showed that study period did not affect OS (P=0.989). Based on first-line systemic therapy, patients who received gemcitabine plus nab-paclitaxel or FOLFIRINOX demonstrated significantly longer survival times (with HRs of 0.622 and 0.608, respectively) than those who received gemcitabine monotherapy.

The details of treatment regimens with gemcitabine plus nab-paclitaxel and FOLFIRINOX, are shown in Table V. Both regimens are recommended as first-line therapy in the Japanese and NCCN guidelines (18,19). In total, 11% of patients treated with gemcitabine plus nab-paclitaxel crossed over to FOLFIRINOX, and 46% of patients treated with FOLFIRINOX crossed over to a gemcitabine plus nab-paclitaxel regimen. During the study period, erlotinib, nal-irinotecan, pembrolizumab, and olaparib were not used for subsequent systemic therapy in this population. The adjusted Kaplan-Meier OS curves for each prognostic factor are shown in Fig. 6, based on the results of the stratified Cox regression analyses provided in Table IV.

Discussion

In this large retrospective cohort study of patients with metastatic pancreatic cancer, we clarified the actual state of treatment in clinical practice in a large representative hospital system. Although there is concern that treatment outcomes for the portion of the patient population that fulfills the eligibility criteria for clinical trials do not apply to older adults or the clinical population of patients experiencing complications (22), this RWD study demonstrated that most patients could be administered standard treatment and obtained survival benefits.

As of 2010, only gemcitabine and S-1 had been approved for use in Japan, and consistent with previous Japanese RWD study (30), nearly 80% of our study population received gemcitabine. Although FOLFIRINOX became available in 2013, it was not frequently used in our study population; the use of this regimen remained at approximately 10% through 2020. One of the reasons why FOLFIRINOX therapy is not widely used is its serious adverse events, including myelosuppression. A phase II study of FOLFIRINOX in Japan showed that 77.8% of patients had Grade 3 or higher neutropenia and 22.2% of patients had febrile neutropenia, which was much higher than the 45.7 and 5.4% in the global Phase III study (13). Therefore, it is recommended only for selected patients in good general condition (19). On the contrary, since less toxic gemcitabine plus nab-paclitaxel regimen became available in 2014, the frequency of its use has increased rapidly, and the use of this regimen in our study population exceeded 60% as of 2020. According to a previous paper published by Terashima *et al* (31), as of 2015, the frequency of the use of gemcitabine plus nab-paclitaxel was approximately 25%. According to the latest clinical practice guidelines (18,19), both gemcitabine plus nab-paclitaxel and FOLFIRINOX regimens were recommended as first-line treatments for metastatic pancreatic cancer. However, gemcitabine and S-1 were given weak recommendations; these regimens were recommended only for patients who are unsuitable for the aforementioned treatment regimens. Moreover, gemcitabine plus S-1 was only recommended in the neoadjuvant setting (19). Our work provides a timely follow-up to previously reported data and suggests that the

Table I. Patient medical and demographic characteristics (n=846).

Characteristics	Value
Age (at start of first-line treatment)	
Median age, years (quantile)	70 (36, 64, 70, 76, 90)
≥75 years, n (%)	266 (31.4)
Sex, n (%)	
Male	503 (59.5)
Female	343 (40.5)
PS, n (%)	
0	232 (27.4)
1	290 (34.3)
≥2	53 (6.3)
Not available	271 (32.0)
Median BMI, kg/m^2 (quantile)	19.7 (11.2, 17.4, 19.7, 21.9, 35.4)
Smoking status, n (%)	
Current or former (BI>0)	217 (25.7)
Never smoked (BI=0)	562 (66.4)
Not available	67 (7.9)
Diagnosis, n (%)	
Pathologically confirmed	745 (88.1)
Adenocarcinoma	418
Adenosquamous	7
Carcinoma/malignant neoplasm	320
Radiological diagnosis only	101 (11.9)
Primary disease site, n (%)	
Pancreas head	359 (42.4)
Pancreas body	232 (27.4)
Pancreas tail	220 (26.0)
Not evaluable	35 (4.1)
Previous procedures[a], n (%)	
Surgery	123 (14.5)
Endoscopic procedure	44 (5.2)
Radiotherapy	47 (5.6)
None of the above	678 (80.1)
Study period, n (%)	
Period A (2010-2013)	268 (31.7)
Period B (2014-2016)	251 (29.7)
Period C (2017-2020)	327 (38.7)
Hospital volume, n (%)	
High volume (n≥50)	509 (60.2)
Low volume (n<50)	337 (39.8)
Hospital type, n (%)	
Government designated cancer hospital	218 (25.7)
Prefectural designated cooperative cancer hospital	316 (37.4)
General hospital	312 (36.9)
First-line systemic therapy, n (%)	
Gemcitabine monotherapy	302 (35.7)
S-1 monotherapy	197 (23.3)
Gemcitabine plus S-1	66 (7.8)
Gemcitabine plus nab-paclitaxel	229 (27.1)
FOLFIRINOX	52 (6.1)

[a]The sum does not equal 100% because certain cases involved two or more procedures. BI, Brinkman index; BMI, body mass index; FOLFIRINOX, fluorouracil, folic acid, oxaliplatin and irinotecan; nab, nanoparticle albumin-bounded; S-1, tegafur/gimeracil/oteracil; PS, performance status.

Table II. Patient medical and demographic characteristics by regimen.

Characteristics	Gem (n=302)	S-1 (n=197)	GS (n=66)	GnP (n=229)	FOLFIRINOX (n=52)
Age (at start of first-line treatment)					
Median age, years (quantile)	71 (36, 65, 71, 77, 89)	71 (45, 66, 71, 78, 90)	67 (39, 61, 67, 73, 84)	70 (37, 64, 70, 75, 86)	65 (42, 57, 65, 69, 82)
≥75 years, n (%)	113 (37.4)	75 (38.1)	14 (21.1)	60 (26.2)	4 (6.2)
Sex, n (%)					
Male	162 (53.6)	122 (61.9)	42 (63.6)	141 (61.6)	36 (69.2)
Female	140 (46.4)	75 (38.1)	24 (36.4)	88 (38.4)	16 (30.3)
Performance status, n (%)					
0	100 (33.1)	19 (9.6))	25 (37.9)	69 (30.1)	19 (36.5)
1	124 (41.1)	20 (10.2))	12 (18.2)	112 (48.9)	22 (42.3)
≥2	28 (9.2)	8 (4.1))	1 (1.5)	16 (7.0)	11 (21.2)
Not available	50 (16.6)	150 (76.1)	28 (42.4)	32 (14.0)	0 (0.0)
Median body mass index, kg/m^2 (quantile)	19.7 (12.0, 17.5, 19.7, 22.0, 34.8)	19.3 (11.6, 17.3, 19.3, 21.5, 35.4)	19.4 (13.6, 17.3, 19.4, 21.8, 29.9)	20.1 (11.2, 17.5, 20.1, 22.1, 34.8)	20.2 (13.3, 17.4, 20.2, 22.6, 34.5)
Smoking status, n (%)					
Current or former (BI>0)	71 (23.5)	49 (24.9)	17 (25.8)	62 (27.0)	18 (34.6)
Never smoked (BI=0)	198 (65.6)	132 (67.0)	46 (69.7)	157 (68.6)	29 (55.8)
Not available	33 (10.9)	16 (8.1)	3 (4.5)	10 (4.4)	5 (9.6)
Diagnosis, n (%)					
Pathologically confirmed	241 (79.8)	181 (91.9)	55 (83.3)	221 (96.5)	47 (90.4)
Adenocarcinoma	129 (42.7)	87 (44.2)	22 (33.3)	147 (64.2)	33 (63.5)
Adenosquamous	1 (0.3)	1 (0.5)	0 (0.0)	4 (1.7)	1 (1.9)
Carcinoma/malignant neoplasm	111 (36.8)	93 (47.2)	33 (50.0)	70 (30.6)	13 (25.0)
Radiological diagnosis only	61 (20.2)	16 (8.1)	11 (16.7)	8 (3.5)	5 (9.6)
Primary site of disease, n (%)					
Pancreas head	130 (43.0)	81 (41.1)	25 (37.9)	100 (43.7)	23 (44.2)
Pancreas body	84 (27.8)	55 (27.9)	20 (30.3)	59 (25.8)	14 (26.9)
Pancreas tail	78 (25.8)	54 (27.4)	20 (30.3)	54 (23.5)	14 (26.9)
Not evaluable	10 (3.3)	7 (3.5)	1 (1.5)	16 (7.0)	1 (1.9)
Previous procedure[a], n (%)					
Surgery	51 (16.9)	39 (19.8)	13 (19.7)	18 (7.9)	2 (3.8)
Endoscopic procedure	21 (7.0)	13 (6.6)	5 (7.6)	5 (2.2)	0 (0.0)
Radiotherapy	12 (4.0)	17 (8.6)	6 (9.1)	8 (3.5)	4 (7.7)
None of the above	240 (79.5)	141 (71.6)	47 (71.2)	203 (88.6)	47 (90.4)
Study period, n (%)					
Period A (2010-2013)	179 (59.3)	59 (29.9)	30 (45.5)	0 (0.0)	0 (0.0)
Period B (2014-2016)	79 (26.1)	77 (39.1)	22 (33.3)	54 (23.6)	19 (36.5)
Period C (2017-2020)	44 (14.6)	61 (31.0)	14 (21.2)	175 (76.4)	33 (63.5)
Hospital volume, n (%)					
High-volume hospital (≥50)	184 (60.9)	115 (58.4)	30 (45.5)	156 (68.1)	24 (46.2)
Low-volume hospital (<50)	118 (39.1)	82 (41.6)	36 (54.4)	73 (31.9)	28 (53.8)
Hospital type, n (%)					
Government designated cancer hospital	94 (31.1)	39 (19.8)	0 (0.0)	77 (33.6)	8 (15.4)
Prefectural designated cooperative cancer hospital	102 (33.8)	76 (38.6)	25 (37.9)	94 (41.0)	19 (36.5)
General hospital	106 (35.1)	82 (41.6)	41 (62.1)	58 (25.3)	25 (48.1)

[a]The sum does not equal 100% because certain cases involved two or more procedures. BI, Brinkman index; FOLFIRINOX, fluorouracil, folic acid, oxaliplatin and irinotecan; Gem, gemcitabine; GnP, gemcitabine plus nanoparticle albumin-bounded-paclitaxel; GS, gemcitabine + S-1; S-1, tegafur/gimeracil/oteracil.

Table III. Patient medical and demographic characteristics by study period.

Characteristics	Period A (2010-2013) (n=268)	Period B (2014-2016) (n=251)	Period C (2017-2020) (n=327)
Age (at start of first-line treatment)			
Median age, years (quantile)	69 (36, 63, 69, 76, 90)	69 (37, 62, 69, 75, 89)	71 (44, 66, 71, 76, 86)
≥75 years, n (%)	80 (29.9)	69 (27.5)	117 (35.8)
Sex, n (%)			
Male	157 (58.6)	153 (61.0)	193 (59.0)
Female	111 (41.4)	98 (39.0)	134 (41.0)
PS, n (%)			
0	89 (33.2)	63 (25.1)	80 (24.5)
1	83 (30.0)	78 (31.1)	129 (39.4)
≥2	19 (7.1)	15 (6.0)	19 (5.8)
Not available	77 (28.7)	95 (37.8)	99 (30.3)
Median BMI, kg/m^2 (quantile)	19.5 (12.0, 17.6, 19.5, 21.9, 30.6)	19.7 (11.6, 17.5, 19.7, 21.9, 35.4)	19.8 (11.2, 17.2, 19.8, 22.1, 34.8)
Smoking status, n (%)			
Current or former (BI>0)	63 (23.5)	57 (22.7)	97 (29.7)
Never smoked (BI=0)	173 (64.6)	173 (68.9)	216 (66.1)
Not available	32 (11.9)	21 (8.4)	14 (4.2)
Diagnosis, n (%)			
Pathologically confirmed	204 (76.1)	232 (92.4)	309 (94.5)
Adenocarcinoma	106 (39.6)	157 (62.5)	174 (53.2)
Adenosquamous	1 (0.3)	3 (1.2)	3 (0.9)
Carcinoma/malignant neoplasm	97 (36.2)	72 (28.7)	132 (40.4)
Radiological diagnosis only	64 (23.9)	19 (7.6)	18 (5.5)
Primary disease site, n (%)			
Pancreas head	127 (47.4)	89 (35.5)	143 (43.7)
Pancreas body	61 (22.8)	79 (31.5)	89 (27.2)
Pancreas tail	68 (25.4)	72 (28.7)	80 (24.5)
Not evaluable	9 (3.4)	11 (4.3)	15 (4.6)
Previous procedures[a], n (%)			
Surgery	67 (25.0)	37 (12.0)	19 (5.8)
Endoscopic procedure	24 (9.0)	18 (7.2)	2 (0.6)
Radiotherapy	5 (1.9)	22 (8.8)	20 (6.1)
None of the above	197 (73.5)	192 (76.5)	289 (88.4)
Hospital volume, n (%)			
High volume (n≥50)	173 (64.6)	149 (59.4)	187 (57.2)
Low volume (n<50)	95 (35.4)	102 (40.6)	140 (42.8)
Hospital type, n (%)			
Government designated cancer hospital	63 (23.5)	69 (27.4)	86 (26.3)
Prefectural designated cooperative cancer hospital	112 (41.8)	89 (35.5)	115 (35.2)
General hospital	93 (34.7)	93 (37.1)	126 (38.5)
First-line systemic therapy, n (%)			
Gemcitabine monotherapy	179 (66.8)	79 (31.5)	44 (13.5)
S-1 monotherapy	59 (22.0)	77 (30.7)	61 (18.7)
Gemcitabine plus S-1	30 (11.2)	22 (8.8)	14 (4.2)
Gemcitabine plus nab-paclitaxel	0 (0.0)	54 (21.5)	175 (53.5)
FOLFIRINOX	0 (0.0)	19 (7.5)	33 (10.1)

[a]The sum does not equal 100% because certain cases involved two or more procedures. BI, Brinkman index; BMI, body mass index; FOLFIRINOX, fluorouracil, folic acid, oxaliplatin and irinotecan; nab, nanoparticle albumin-bounded; S-1, tegafur/gimeracil/oteracil; PS, performance status.

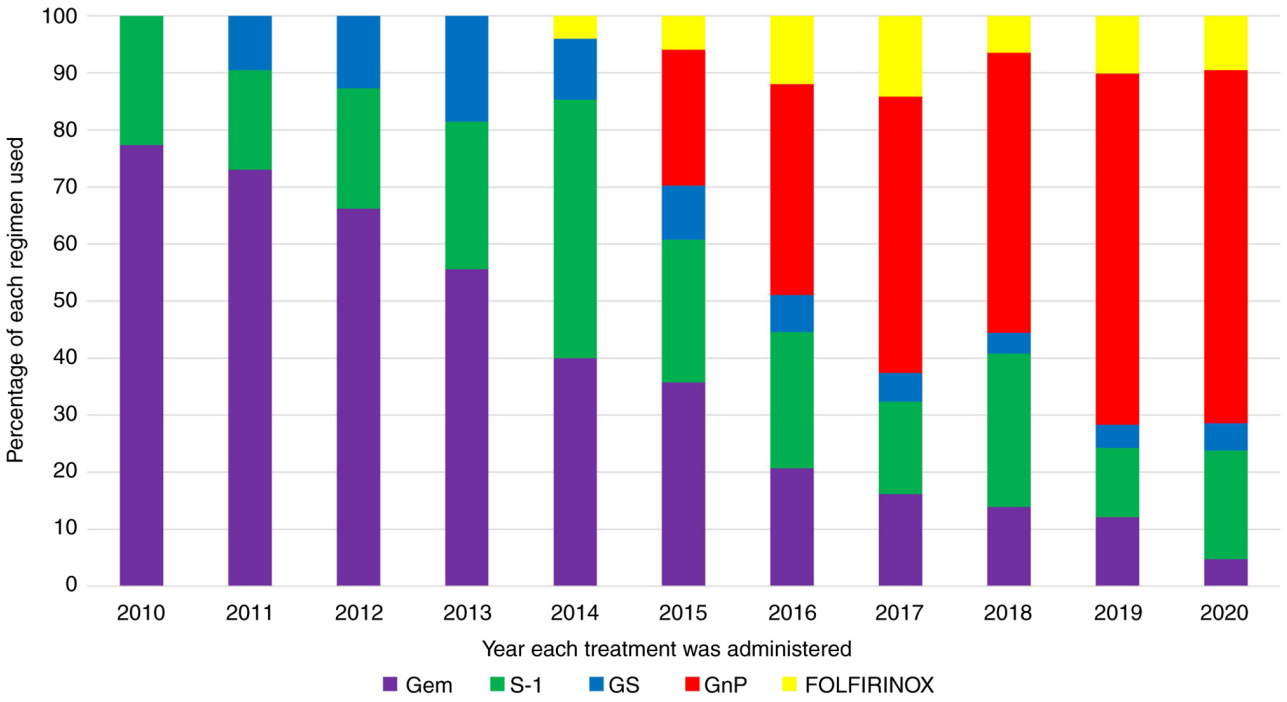

Figure 3. Trends in the administration of first-line chemotherapy regimens in Japan during the study follow-up period. FOLFIRINOX, fluorouracil, folic acid, oxaliplatin and irinotecan; Gem, gemcitabine; GnP, gemcitabine plus nanoparticle albumin-bounded-paclitaxel; GS, gemcitabine + S-1; S-1, tegafur/gimeracil/oteracil.

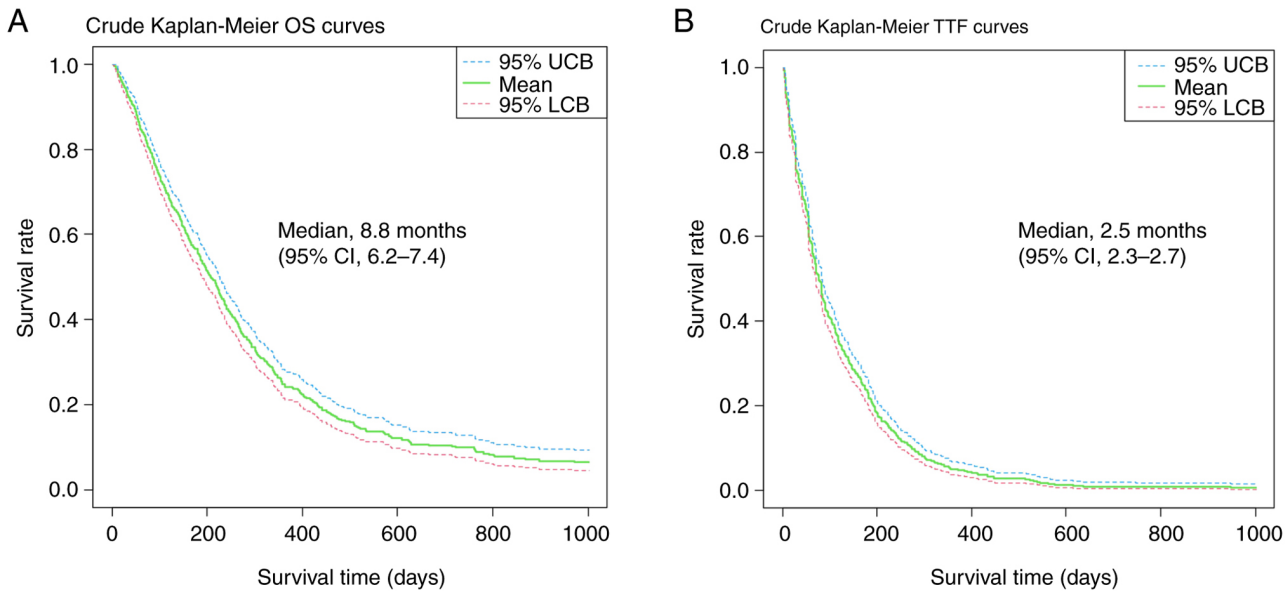

Figure 4. Crude Kaplan-Meier curves for (A) OS and (B) TTF. CI, confidence interval; LCB, lower confidence bound; OS, overall survival; TTF, time to treatment failure; UCB, upper confidence bound.

treatment strategies selected by physicians in actual clinical practice adhere closely to these guidelines.

Univariate and multivariate analyses in our study showed a greater survival benefit of gemcitabine plus nab-paclitaxel and FOLFIRINOX than that of gemcitabine alone. On the other hand, no survival benefits of S-1 monotherapy or S-1 + gemcitabine over gemcitabine monotherapy was demonstrated. These results are consistent with the results of previous clinical trials and RWD studies. The results of previous clinical trials and RWD studies are shown in Table V. In addition, our univariate analyses revealed a prolongation of OS in the late study period. However, this effect was not confirmed by multivariate analyses after adjusting for other prognostic factors, such as treatment regimen. Furthermore, our univariate analyses did not suggest a hospital volume-outcome relationship, unlike a previous report from the Netherlands accounting for patients diagnosed with metastatic pancreatic cancer between 2007 and 2011 (30). Indeed, in our study, the

Table IV. Stratified Cox regression analyses evaluating prognostic factors for OS.

	Univariate analysis		Multivariate analysis	
Characteristics	HR (95% CI)	P-value	HR (95% CI)	P-value
Sex				
Male (Ref.)	1.000	[0.444]	1.000	[0.140]
Female	0.940 (0.802-1.102)	0.444	0.883 (0.748-1.042)	0.140
Age, years				
<75 (Ref.)	1.000	[0.010]	1.000	[0.249]
≥75	1.243 (1.053-1.466)	0.010	1.109 (0.931-1.321)	0.249
PS				
0 (Ref.)	1.000	[<0.001]	1.000	[<0.001]
1	1.195 (0.976-1.462)	0.084	1.268 (1.031-1.559)	0.025
≥2	2.154 (1.540-3.011)	<0.001	2.159 (1.526-3.054)	<0.001
Unknown	1.523 (1.245-1.862)	<0.001	1.527 (1.218-1.915)	<0.001
BMI, kg/m^2				
≥18.5 and <25.0 (Ref.)	1.000	[0.050]	1.000	[0.018]
<18.5	0.866 (0.733-1.024)	0.092	0.839 (0.707-0.996)	0.045
≥25.0	1.205 (0.916-1.586)	0.182	1.250 (0.942-1.657)	0.122
Primary disease site				
Pancreas head (Ref.)	1.000	[0.500]	1.000	[0.736]
Pancreas body	0.885 (0.731-1.071)	0.209	0.905 (0.743-1.101)	0.318
Pancreas tail	1.032 (0.851-1.252)	0.747	1.047 (0.859-1.277)	0.647
Not evaluable	0.951 (0.626-1.444)	0.813	0.961 (0.627-1.472)	0.855
Smoking status				
Never smoked (Ref.)	1.000	[0.900]	1.000	[0.926]
Current or former	1.046 (0.875-1.250)	0.622	1.036 (0.850-1.261)	0.729
Unknown	1.046 (0.756-1.447)	0.786	0.978 (0.704-1.360)	0.896
Study period				
Period A (2010-2013) (Ref.)	1.000	[0.001]	1.000	[0.989]
Period B (2014-2016)	0.858 (0.710-1.037)	0.114	0.928 (0.754-1.142)	0.482
Period C (2017-2020)	0.754 (0.623-0.912)	0.004	0.948 (0.746-1.204)	0.659
Hospital volume				
High volume (n≥50)	1.000	[0.610]	1.000	[0.132]
Low volume (n<50)	1.040 (0.889-1.221)	0.610	0.872 (0.729-1.042)	0.132
Hospital type				
Government designated cancer hospital (Ref.)	1.000	[0.522]	1.000	[0.187]
Prefectural designated cooperative cancer hospital	1.118 (0.915-1.367)	0.277	1.134 (0.922-1.394)	0.235
General hospital	1.097 (0.897-1.342)	0.367	0.952 (0.765-1.185)	0.659
First-line systemic therapy				
Gemcitabine (Ref.)	1.000	[<0.001]	1.000	[0.006]
S-1	0.929 (0.762-1.133)	0.466	0.839 (0.669-1.053)	0.130
Gemcitabine + S-1	0.826 (0.613-1.113)	0.209	0.829 (0.609-1.128)	0.232
Gemcitabine + nab-paclitaxel	0.592 (0.489-0.729)	<0.001	0.622 (0.480-0.806)	<0.001
FOLFIRINOX	0.556 (0.387-0.799)	0.002	0.608 (0.410-0.902)	0.013

The numbers in the square brackets represent the 'P-value of the item', an indicator of the type I error rate for rejecting the null hypothesis regarding the evaluated item's effect on OS. BMI, body mass index; CI, confidence interval; FOLFIRINOX, fluorouracil, folic acid, oxaliplatin and irinotecan; HR, hazard radio; nab, nanoparticle albumin-bounded; OS, overall survival; PS, performance status; S-1, tegafur/gimeracil/oteracil.

Table V. Treatment data for first-line gemcitabine plus nab-paclitaxel and FOLFIRINOX regimens.

Characteristics	Gemcitabine + nab-paclitaxel (n=229)	FOLFIRINOX (n=52)
Duration of chemotherapy		
Median no. of cycles (range)	4 (1-28)	6 (1-22)
Median duration, days (range)	90 (2-748)	76 (6-391)
Sequential surgical procedure, n		
Yes	2	0
Sequential radiotherapy, n		
Yes	3	1
Sequential systemic therapy		
Median no. (range)	0 (0-4)	1 (0-6)
0, n (%)	123 (53.7)	16 (30.8)
1, n (%)	75 (32.8)	19 (36.5)
≥2, n (%)	31 (13.5)	17 (32.7)
Sequential regimens, n (%)		
Gemcitabine	23 (10.0)	5 (9.6)
S-1	46 (20.1)	6 (11.5)
Gemcitabine + S-1	12 (5.2)	1 (1.9)
Gemcitabine + nab-paclitaxel	-	24 (46.2)
FOLFIRINOX	25 (10.9)	-

FOLFIRINOX, fluorouracil, folic acid, oxaliplatin and irinotecan; nab, nanoparticle albumin-bounded; S-1, tegafur/gimeracil/oteracil.

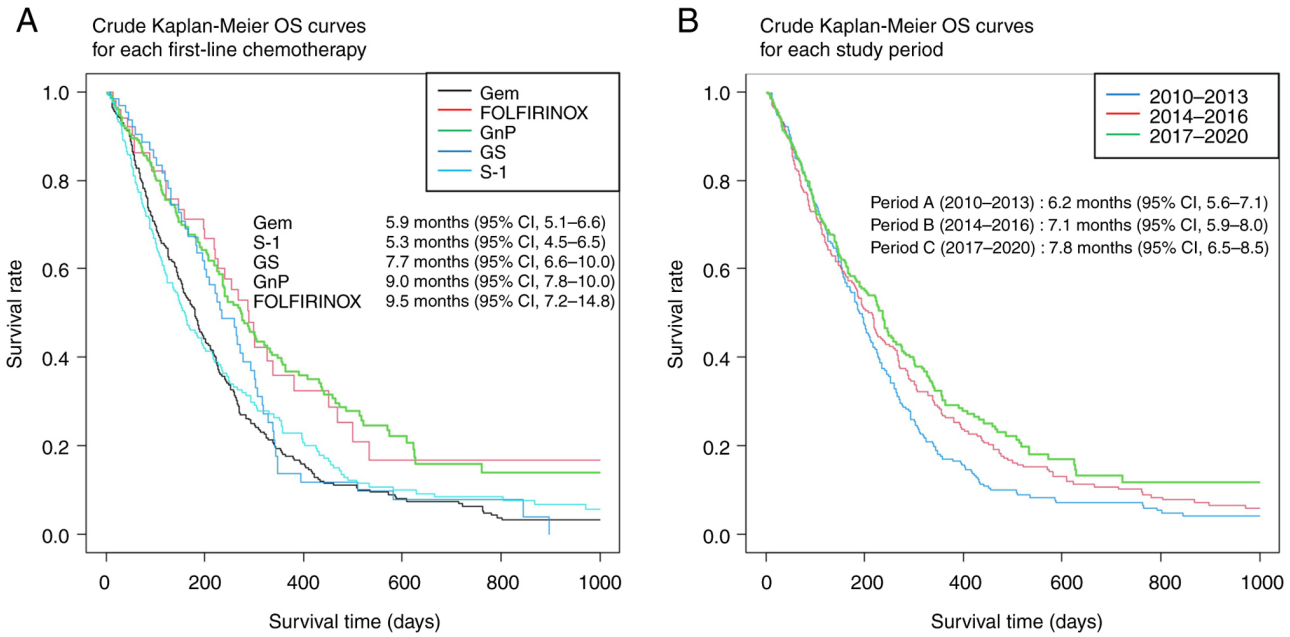

Figure 5. OS for (A) each first-line chemotherapy regimen and (B) each study period. CI, confidence interval; FOLFIRINOX, luorouracil, folic acid, oxaliplatin and irinotecan; Gem, gemcitabine; GnP, gemcitabine plus nanoparticle albumin-bounded-paclitaxel; GS, gemcitabine + S-1; OS, overall survival; S-1, tegafur/gimeracil/oteracil.

variances in chemotherapy regimens administered categorized by hospital volume and type exhibited uniformity, with combination therapy consistently accounting for approximately 40% (Table SI). These results suggested that improvement in survival over time may be primarily due to the approval of new treatment regimens, even though other factors such as advances in diagnostic imaging and supportive care could also have improved survival, and the widespread use of more effective standard treatments may have reduced differences by hospital volume and type.

In two prior pivotal phase III studies, the median survival following the administration of FOLFIRINOX

Table VI. Overall survival data from recent clinical trials and RWD investigations evaluating treatment regimens for advanced/metastatic pancreatic cancer.

First author/s, year	No. of patients	Disease status	Study design	Overall survival, months								
				5-FU	S-1	Gem	GE	GS	GnP	FOLFIRINOX	P-value[a]	(Refs.)
Burris *et al*, 1997	126	laPC; mPC	Phase III	4.5	-	5.7	-	-	-	-	0.0025	(9)
Ueno *et al*, 2005	19	mPC	Phase II	-	5.6	-	-	-	-	-	-	(10)
Moore *et al*, 2007	569	laPC; mPC	Phase III	-	-	5.9	6.2	-	-	-	0.038	(12)
Okusaka *et al*, 2008	40	mPC	Phase II	-	9.2	-	-	-	-	-	-	(11)
Conroy *et al*, 2011	342	mPC	Phase III	-	-	6.8	-	-	-	11.1	<0.001	(13)
Ueno *et al*, 2013	835	laPC; mPC	Phase III	-	13.8	12.7	-	15.9	-	-	0.15[b], <0.001[c]	(17)
Von Hoff *et al*, 2013	861	mPC	Phase III	-	-	6.7	-	-	8.5	-	<0.001	(16)
Okusaka *et al*, 2014	36	mPC	Phase II	-	-	-	-	-	10.7	-	-	(14)
Ozaka *et al*, 2018	69	mPC	Phase II	-	-	-	-	-	11.2	-	-	(15)
Terashima *et al*, 2018	1,085	laPC; mPC	RWD	-	8.5	7.5	8.2	10.3	9.9	10.3	-	(31)
Sasaki *et al*, 2019	321	mPC	RWD	-	-	-	-	-	11.5	17.1	-	(32)
Javed *et al*, 2019	1,056	mPC	RWD	-	-	4.9	-	-	7.9	9.9	-	(33)
Cho *et al*, 2020	167	mPC	RWD	-	-	-	-	-	12.1	10.7	0.157	(34)
Chan *et al*, 2020	1,130	mPC	RWD	-	-	-	-	-	6.1	8.2	<0.0001	(35)
Franco *et al*, 2021	119	mPC	RWD	-	-	-	-	-	10.2	12.7	0.912	(36)
Pijnappel *et al*, 2021	1,586	mPC	RWD	-	-	2.9	-	-	4.7	6.6	-	(37)
Present study	846	mPC	RWD	-	5.3	5.9	-	7.7	9.0	9.5	-	-

[a]These P-values were reported in the previous studies. [b]GS did not demonstrate superiority over Gem. [c]S-1 demonstrated non-inferiority compared with Gem. 5-FU, 5-fluorouracil; Gem, gemcitabine; GE, gemcitabine + erlotinib; GS, gemcitabine + S-1; FOLFIRINOX, fluorouracil, folic acid, oxaliplatin and irinotecan; GnP, gemcitabine plus nanoparticle albumin-bounded-paclitaxel; laPC, locally advanced unresectable pancreatic cancer; mPC, metastatic pancreatic cancer; RWD, real-world data; S-1, tegafur/gimeracil/oteracil.

was 11.1 months (13), while the median survival following the administration of gemcitabine plus nab-paclitaxel was 8.5 months (16). A phase II study on modified FOLFIRINOX, in which irinotecan was reduced from 180 to 150 mg/m^2 and bolus 5-FU was omitted, showed favorable results with a median survival of 11.2 months in 2018, and it is now widely used in Japan (15). In the present study, the median survival times following the administration of gemcitabine plus nab-paclitaxel and FOLFIRINOX were 9.0 and 9.5 months, respectively, which are comparable to the median survival associated with gemcitabine plus nab-paclitaxel reported in prior clinical trials but approximately 1.6 months shorter than that associated with FOLFIRINOX (13,16). No data were extracted on the dose of FOLFIRINOX in this study; hence, there are no data on whether FOLFIRINOX or modified FOLFIRINOX was administered or how withdrawal or dose reduction was performed. In several recent RWD studies on gemcitabine plus nab-paclitaxel and FOLFIRINOX in metastatic pancreatic cancer, OS varied; moreover, OS tended to be shorter with FOLFIRINOX treatment in RWD studies compared to that in clinical trials (31-37) (Table VI). As mentioned above, actual analysis of dose intensity is needed, but it is possible that FOLFIRINOX dose reduction may have led to the shorter OS. We await the results of the trials currently underway in Japan comparing gemcitabine plus nab-paclitaxel, modified FOLFIRINOX, and S-1 plus irinotecan and oxaliplatin for final conclusions (38).

The present study had several limitations. First, this study had a retrospective design, and hence, the choice of the first-line treatment regimen administered to each patient was left to the attending physician, and no clear criteria have been established yet. As shown in Table II, the background of each regimen differs greatly. Therefore, it is possible that FOLFIRINOX was selected by the attending physician for patients with large tumors and extensive metastases, resulting in a shorter OS. Second, as discussed before, although dose intensity is a factor that may contribute significantly to OS, data on dose intensity were not extracted in this analysis. Third, several prognostic factors, such as metastatic sites, tumor markers, prognostic scores based on laboratory data, comorbidities, and complications, were not examined. Finally, in the current study, treatment data were extracted from the protocol system; hence, only data on treatment duration could be extracted, and it was not possible to distinguish between treatment discontinuation due to disease progression or adverse events (28). As this is an RWD study, periodic imaging assessment were

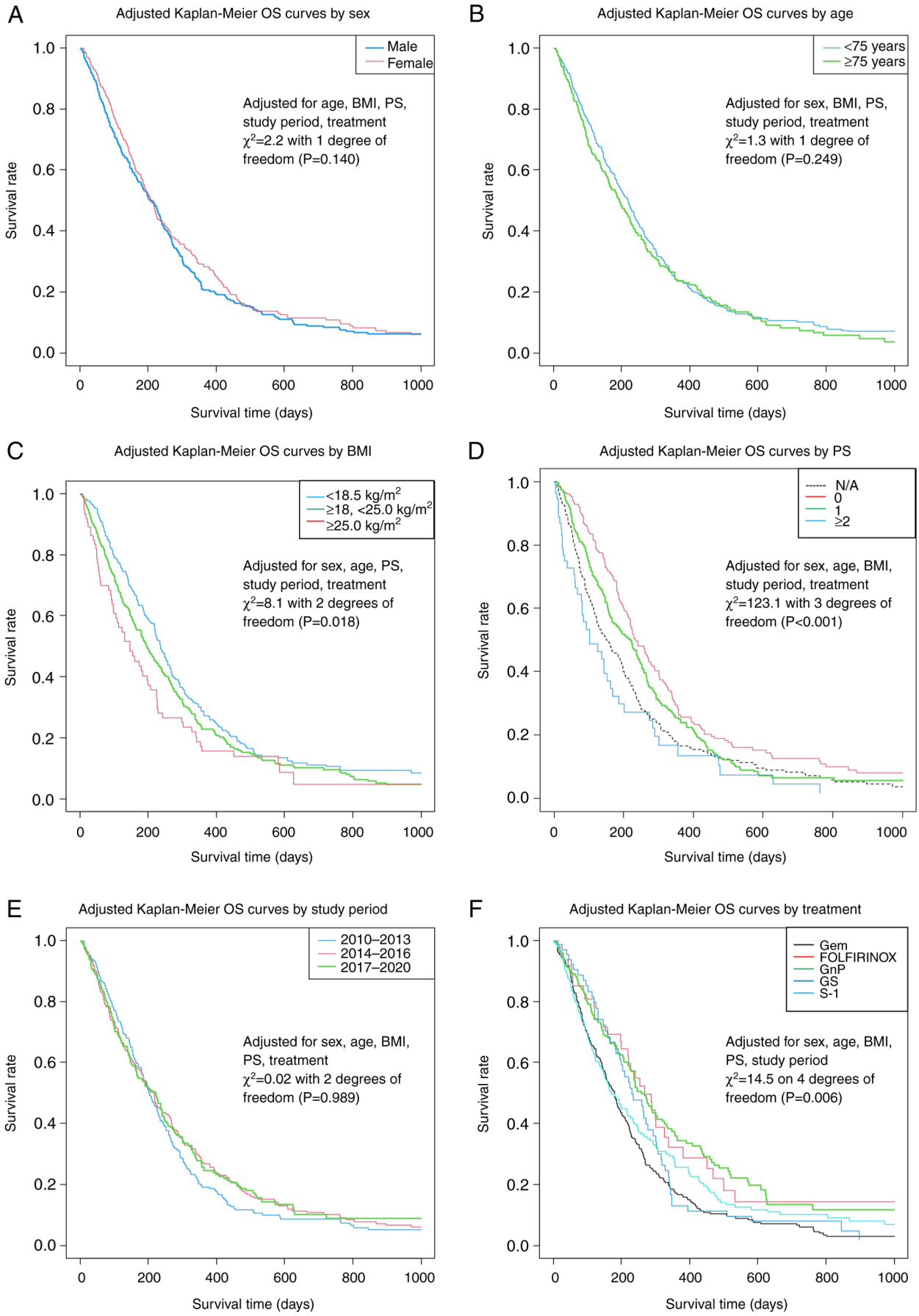

Figure 6. Adjusted OS curves based on stratified Cox multiple regression analyses for patient groups based on (A) sex, (B) age, (C) BMI, (D) PS, (E) study period and (F) treatment. BMI, body mass index; FOLFIRINOX, fluorouracil, folic acid, oxaliplatin and irinotecan; Gem, gemcitabine; GnP, gemcitabine plus nanoparticle albumin-bounded-paclitaxel; GS, gemcitabine + S-1; N/A, not available; OS, overall survival; PS, performance status; S-1, tegafur/gimeracil/oteracil.

not performed, and descriptions of disease progression were not mandatory. In addition, it is not possible to extract data on subjective adverse events, because physicians are not required to state their judgment of intolerance.

Allowing for these limitations, however, the strength of this study is that we included a large population and the evaluation of RWD for many treatment regimens that reflect current population trends.

In conclusion, our RWD analyses demonstrated that a standard care for metastatic pancreatic cancer was largely available in hospitals across Japan and verified the survival benefits of gemcitabine plus nab-paclitaxel and FOLFIRINOX regimens observed in previous clinical trials. As such, our findings provide important information for future research directions, policy initiatives, medical guidelines, and clinical decision-making.

Acknowledgements

The authors acknowledge the dedication of Dr. Hisaaki Afuso (chair of Medical Corporation Tokushukai, Tokyo, Japan and General Incorporated Association Tokushukai, Tokyo, Japan) for their support in conducting clinical research within the Tokushukai Group, and Ms. Megumi Shiragami (software development department, Tokushukai Information System, Inc., Osaka, Japan) and Mr. Katsuhiko Ozaki (President of Tokushukai Information System, Inc., Osaka, Japan) for their assistance in using the medical database.

Funding

No funding was received.

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

RS, YI and MO made substantial contributions to the study design and conception. RS, YF and MH were responsible for data acquisition. RS and YI interpreted the data and drafted the manuscript. KU, TM, KO, NS and HM provided advice on research design and aided in the critical interpretation of this research for critical content. RS and YI confirm the authenticity of all the raw data. NS and HM comprehensively reviewed and approved the final version of this manuscript. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

This project was approved by the Ethics Committee of the Tokushukai Group (Tokyo, Japan) in April 2020 (no. TGE01427-024) and was conducted following the principles of the Declaration of Helsinki. Patients were provided with information using opt-out methods and no patient declared not to participate.

Patient consent for publication

Patient consent for publication was obtained through opt-out methods.

Competing interests

Some of the authors have received research funding, honoraria, or scholarship donations from various pharmaceutical companies and other organizations outside of the submitted work, none of which construe actual or potential conflicts of interest. RS received speakers' bureau fees/honoraria from Daiichi-Sankyo, Ono Pharm, Taiho Pharma and Chugai outside of the submitted work. YI received speakers' bureau fees/honoraria from Bayer, Bristol-Myers Squibb, Daiichi-Sankyo, Pfizer and Ono Pharm outside of the submitted work. HM has received speakers' bureau fees/honoraria from Daiichi-Sankyo and Ono Pharm, research funding from Astelas-Amgen Biopharma, Bayer, Bristol Myers Squibb, Chugai, Daiichi-Sankyo, Incite, Novartis, Ono Pharm, Pfizer and Rakuten-Medical, and scholarship donations from Bayer, Chugai, Daiichi-Sankyo, Eisai, Kyowa-Kirin, Lilly, Ono Pharmaceutical, Pfizer, Taiho Pharma and Takeda outside of the submitted work. These organizations had no role in the design, conduct, or reporting of this work. All other authors declare that they have no competing interests.

References

1. Siegel RL, Miller KD, Fuchs HE and Jemal A: Cancer statistics, 2021. CA Cancer J Clin 71: 7-33, 2021.
2. Cancer statistics. https://ganjoho.jp/reg_stat/statistics/data/dl/en.html. Accessed June 30 2022 Cancer Information Service, Natl Cancer Cntr, Japan. Vital Statistics of Japan Ministry of Health, Labour and Welfare.
3. Ben Q, Xu M, Ning X, Liu J, Hong S, Huang W, Zhang H and Li Z: Diabetes mellitus and risk of pancreatic cancer: A meta-analysis of cohort studies. Eur J Cancer 47: 1928-1937, 2011.
4. Stolzenberg-Solomon RZ, Adams K, Leitzmann M, Schairer C, Michaud DS, Hollenbeck A, Schatzkin A and Silverman DT: Adiposity, physical activity, and pancreatic cancer in the National Institutes of Health-AARP Diet and Health Cohort. Am J Epidemiol 167: 586-597, 2008.
5. Aune D, Greenwood DC, Chan DS, Vieira R, Vieira AR, Navarro Rosenblatt DA, Cade JE, Burley VJ and Norat T: Body mass index, abdominal fatness and pancreatic cancer risk: A systematic review and non-linear dose-response meta-analysis of prospective studies. Ann Oncol 23: 843-852, 2012.
6. Matsuo K, Ito H, Wakai K, Nagata C, Mizoue T, Tanaka K, Tsuji I, Tamakoshi A, Sasazuki S, Inoue M, *et al*: Cigarette smoking and pancreas cancer risk: An evaluation based on a systematic review of epidemiologic evidence in the Japanese population. Jpn J Clin Oncol 41: 1292-1302, 2011.
7. Tramacere I, Scotti L, Jenab M, Bagnardi V, Bellocco R, Rota M, Corrao G, Bravi F, Boffetta P and La Vecchia C: Alcohol drinking and pancreatic cancer risk: A meta-analysis of the dose-risk relation. Int J Cancer 126: 1474-1486, 2010.
8. Raimondi S, Lowenfels AB, Morselli-Labate AM, Maisonneuve P and Pezzilli R: Pancreatic cancer in chronic pancreatitis; aetiology, incidence, and early detection. Best Pract Res Clin Gastroenterol 24: 349-358, 2010.
9. Burris HA III, Moore MJ, Andersen J, Green MR, Rothenberg ML, Modiano MR, Cripps MC, Portenoy RK, Storniolo AM, Tarassoff P, *et al*: Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: A randomized trial. J Clin Oncol 15: 2403-2413, 1997.
10. Ueno H, Okusaka T, Ikeda M, Takezako Y and Morizane C: An early phase II study of S-1 in patients with metastatic pancreatic cancer. Oncology 68: 171-178, 2005.

11. Okusaka T, Funakoshi A, Furuse J, Boku N, Yamao K, Ohkawa S and Saito H: A late phase II study of S-1 for metastatic pancreatic cancer. Cancer Chemother Pharmacol 61: 615-621, 2008.
12. Moore MJ, Goldstein D, Hamm J, Figer A, Hecht JR, Gallinger S, Au HJ, Murawa P, Walde D, Wolff RA, *et al*: Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: A phase III trial of the National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol 25: 1960-1966, 2007.
13. Conroy T, Desseigne F, Ychou M, Bouché O, Guimbaud R, Bécouarn Y, Adenis A, Raoul JL, Gourgou-Bourgade S, de la Fouchardière C, *et al*: Folfirinox versus gemcitabine for metastatic pancreatic cancer. N Engl J Med 364: 1817-1825, 2011.
14. Okusaka T, Ikeda M, Fukutomi A, Ioka T, Furuse J, Ohkawa S, Isayama H and Boku N: Phase II study of FOLFIRINOX for chemotherapy-naïve Japanese patients with metastatic pancreatic cancer. Cancer Sci 105: 1321-1326, 2014.
15. Ozaka M, Ishii H, Sato T, Ueno M, Ikeda M, Uesugi K, Sata N, Miyashita K, Mizuno N, Tsuji K, *et al*: A phase II study of modified folfirinox for chemotherapy-naïve patients with metastatic pancreatic cancer. Cancer Chemother Pharmacol 81: 1017-1023, 2018.
16. Von Hoff DD, Ervin T, Arena FP, Chiorean EG, Infante J, Moore M, Seay T, Tjulandin SA, Ma WW, Saleh MN, *et al*: Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. N Engl J Med 369: 1691-1703, 2013.
17. Ueno H, Ioka T, Ikeda M, Ohkawa S, Yanagimoto H, Boku N, Fukutomi A, Sugimori K, Baba H, Yamao K, *et al*: Randomized phase III study of gemcitabine plus S-1, S-1 alone, or gemcitabine alone in patients with locally advanced and metastatic pancreatic cancer in Japan and Taiwan: GEST study. J Clin Oncol 31: 1640-1648, 2013.
18. National Comprehensive Cancer Network (NCCN): NCCN clinical practice guidelines in oncology pancreatic adenocarcinoma. Version 1.2022. https://www.nccn.org/guidelines/category_1. Accessed June 30, 2022.
19. Okusaka T, Nakamura M, Yoshida M, Kitano M, Uesaka K, Ito Y, Furuse J, Hanada K and Okazaki K; Committee for Revision of Clinical Guidelines for Pancreatic Cancer of the Japan Pancreas Society: Clinical practice guidelines for pancreatic cancer 2019 from the Japan Pancreas Society: A synopsis. Pancreas 49: 326-335, 2020.
20. Wang-Gillam A, Hubner RA, Siveke JT, Von Hoff DD, Belanger B, de Jong FA, Mirakhur B and Chen LT: NAPOLI-1 phase 3 study of liposomal irinotecan in metastatic pancreatic cancer: Final overall survival analysis and characteristics of long-term survivors. Eur J Cancer 108: 78-87, 2019.
21. Golan T, Hammel P, Reni M, Van Cutsem E, Macarulla T, Hall MJ, Park JO, Hochhauser D, Arnold D, Oh DY, *et al*: Maintenance olaparib for germline BRCA-mutated metastatic pancreatic cancer. N Engl J Med 381: 317-327, 2019.
22. Averitt AJ, Weng C, Ryan P and Perotte A: Translating evidence into practice: Eligibility criteria fail to eliminate clinically significant differences between real-world and study populations. NPJ Digit Med 3: 67, 2020.
23. Hilgers RD, König F, Molenberghs G and Senn S: Design and analysis of clinical trials for small rare disease populations. J Rare Dis Res Treat 1: 53-60, 2016.
24. Latimer NR: Survival analysis for economic evaluations alongside clinical trials-extrapolation with patient-level data: Inconsistencies, limitations, and a practical guide. Med Decis Making 33: 743-754, 2013.
25. Corrigan-Curay J, Sacks L and Woodcock J: Real-world evidence and real-world data for evaluating drug safety and effectiveness. JAMA 320: 867-868, 2018.
26. Katkade VB, Sanders KN and Zou KH: Real world data: An opportunity to supplement existing evidence for the use of long-established medicines in health care decision making. J Multidiscip Healthc 11: 295-304, 2018.
27. Makady A, de Boer A, Hillege H, Klungel O and Goettsch W; (on behalf of GetReal Work Package 1): What is real-world data? A review of definitions based on literature and stakeholder interviews. Value Health 20: 858-865, 2017.
28. Shimoyama R, Imamura Y, Uryu K, Mase T, Fujimura Y, Hayashi M, Ohtaki M, Ohtani K, Shinozaki N and Minami H: Real-world outcomes of systemic therapy in Japanese patients with cancer (Tokushukai REAl-world Data project: TREAD): Study protocol for a nationwide cohort study. Healthcare (Basel) 10: 2146, 2022.
29. National Cancer Registry (Ministry of Health, Labour and Welfare), tabulated by Cancer Information Service, National Cancer Center, Japan. https://ganjoho.jp/med_pro/cancer_control/can_reg/index.html. Accessed June 30, 2022.
30. Haj Mohammad N, Bernards N, Besselink MG, Busch OR, Wilmink JW, Creemers GJ, De Hingh IH, Lemmens VE and van Laarhoven HW: Volume matters in the systemic treatment of metastatic pancreatic cancer: A population-based study in the Netherlands. J Cancer Res Clin Oncol 142: 1353-1360, 2016.
31. Terashima T, Yamashita T, Sakai A, Ohta H, Hinoue Y, Toya D, Kawai H, Yonejima M, Urabe T, Noda Y, *et al*: Treatment patterns and outcomes of unresectable pancreatic cancer patients in real-life practice: A region-wide analysis. Jpn J Clin Oncol 48: 966-973, 2018.
32. Sasaki T, Kanata R, Yamada I, Matsuyama M, Ozaka M and Sasahira N: Improvement of treatment outcomes for metastatic pancreatic cancer: A real-world data analysis. In Vivo 33: 271-276, 2019.
33. Javed MA, Beyer G, Le N, Vinci A, Wong H, Palmer D, Morgan RD, Lamarca A, Hubner RA, Valle JW, *et al*: Impact of intensified chemotherapy in metastatic pancreatic ductal adenocarcinoma (PDAC) in clinical routine in Europe. Pancreatology 19: 97-104, 2019.
34. Cho IR, Kang H, Jo JH, Lee HS, Chung MJ, Park JY, Park SW, Song SY, An C, Park MS and Bang S: Folfirinox vs gemcitabine/nab-paclitaxel for treatment of metastatic pancreatic cancer: Single-center cohort study. World J Gastrointest Oncol 12: 182-194, 2020.
35. Chan KKW, Guo H, Cheng S, Beca JM, Redmond-Misner R, Isaranuwatchai W, Qiao L, Earle C, Berry SR, Biagi JJ, *et al*: Real-world outcomes of FOLFIRINOX vs gemcitabine and nab-paclitaxel in advanced pancreatic cancer: A population-based propensity score-weighted analysis. Cancer Med 9: 160-169, 2020.
36. Franco F, Camara JC, Martín-Valadés JI, López-Alfonso A, Marrupe D, Gutiérrez-Abad D, Martínez-Amores B, León A, Juez I, Pérez M, *et al*: Clinical outcomes of folfirinox and gemcitabine-nab paclitaxel for metastatic pancreatic cancer in the real world setting. Clin Transl Oncol 23: 812-819, 2021.
37. Pijnappel EN, Dijksterhuis WPM, van der Geest LG, de Vos-Geelen J, de Groot JWB, Homs MYV, Creemers GJ, Mohammad NH, Besselink MG, van Laarhoven HWM, *et al*: First- and second-line palliative systemic treatment outcomes in a real-world metastatic pancreatic cancer cohort. J Natl Compr Canc Netw 20: 443-450.e3, 2021.
38. Mizusawa J, Ohba A, Ozaka M, Katayama H, Okusaka T, Kobayashi S, Ikeda M, Terashima T, Sasahira N, Okano N, *et al*: Protocol of a randomized phase II/III study of gemcitabine plus nab-paclitaxel combination therapy versus modified FOLFIRINOX versus S-IROX for metastatic or recurrent pancreatic cancer: JCOG1611 (GENERATE). Jpn J Clin Oncol 53: 80-84, 2023.