Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.0492-22
Intern Med 61: 3641-3649, 2022
http://internmed.jp

【 ORIGINAL ARTICLE 】

Impact of the COVID-19 Pandemic on the Management and End-of-life Care of Unresectable Pancreatic Cancer

Akiyoshi Kasuga[1], Masanori Nojima[2], Takeshi Okamoto[1], Takahiro Ishitsuka[1], Manabu Yamada[1], Hiroki Nakagawa[1], Shohei Udagawa[3], Chinatsu Mori[1], Takafumi Mie[1], Takaaki Furukawa[1], Yuto Yamada[1], Tsuyoshi Takeda[1], Masato Matsuyama[1], Takashi Sasaki[1], Masato Ozaka[1] and Naoki Sasahira[1]

Abstract:

Objective The coronavirus disease (COVID-19) pandemic has altered the delivery of medical care. The present study evaluated the impact of COVID-19 on the outcomes of unresectable pancreatic cancer (PC) patients who received end-of-life care.

Methods We retrospectively compared the management of PC patients during the COVID-19 pandemic (from April 2020 to March 2021) to the preceding year, which was unaffected by the pandemic (from April 2019 to March 2020), based on a prospectively maintained institutional database.

Results A total of 178 patients were included in the COVID-19-exposed group and 201 patients were included in the COVID-19-unexposed group. The median overall survival was similar between the groups (exposed vs. unexposed: 12.6 vs. 11.9 months, p=0.174). Treatment regimens and relative dose intensities and the progression-free survival of GnP (gemcitabine in combination with nab-paclitaxel) and mFOLFIRINOX as first- and second-line chemotherapy did not differ significantly between the two groups. Only 9.0% of patients died at home in the COVID-19-unexposed group, compared to 32.0% in the COVID-19-exposed group (p<0.001). A multivariate analysis revealed that death during the COVID-19 exposed period was independently associated with home death (odds ratio: 4.536, 95% confidence interval: 2.527-8.140, p<0.001).

Conclusions While the COVID-19 pandemic did not seem to influence chemotherapeutic treatment for PC patients at our institution, it had a large impact on end-of-life care. These findings may promote discussion about end-of-life care in Japan.

Key words: pancreatic cancer, COVID-19, chemotherapy, end-of-life care

(Intern Med 61: 3641-3649, 2022)
(DOI: 10.2169/internalmedicine.0492-22)

Introduction

Pancreatic cancer (PC) is one of the leading causes of cancer-related mortality worldwide (1). 5-fluorouracil, leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX) and gemcitabine in combination with nab-paclitaxel (GnP) has shown superior efficacy to gemcitabine monotherapy (2, 3). However, despite the increased availability of active agents as first- and second-line chemotherapy, the median overall survival (OS) in metastatic PC is less than one year (4-7).

The coronavirus disease (COVID-19) pandemic has impacted all areas of daily life, including medical care. Several reports have indicated that cancer patients have significantly increased severity and complications associated with COVID-19 infection compared with patients without cancer (8, 9). Most hospitals have curtailed in-person visits to minimize infection transmission, reducing the in-hospital

[1]Department of Hepato-Biliary-Pancreatic Medicine, Cancer Institute Hospital of Japanese Foundation for Cancer Research, Japan, [2]Division of Advanced Medicine Promotion, the Institute of Medical Science, the University of Tokyo, Japan and [3]Department of Medical Oncology, Cancer Institute Hospital of Japanese Foundation for Cancer Research, Japan
Received: June 13, 2022; Accepted: August 21, 2022; Advance Publication by J-STAGE: October 5, 2022
Correspondence to Akiyoshi Kasuga, akiyoshi.kasuga@jfcr.or.jp

quality of life for hospitalized patients as well as their families. Several statements, recommendations and guidelines on general care for patients with cancer, including PC, during the COVID-19 pandemic have been published (10-13). Lou et al. proposed recommendations concerning modifications of FOLFIRINOX or GnP to minimize risks to patients with unresectable PC in the United States (14).

PC patients frequently visit the emergency room and are usually hospitalized during the last few months of their lives (15). Our institution issued strict visitation policies from the end of March 2020. In-person visits were unrestricted only when death was imminent. Most hospitals in Japan issued similar restrictions, which radically changed in-hospital end-of-life care. The influence of the COVID-19 pandemic on treatment, including end-of-life care, for patients with unresectable PC remains unknown.

The present study evaluated the impact of the COVID-19 pandemic on the outcomes of PC patients who received end-of-life care.

Materials and Methods

Patients

We reviewed medical records of PC patients in a prospectively maintained institutional database. We retrospectively compared the management of patients during the COVID-19 pandemic (from April 2020 to March 2021) to that of the preceding year, which served as the control period (from April 2019 to March 2020). Patients with pathological and clinical diagnoses of unresectable pancreatic adenocarcinoma who received chemotherapy and died during each period were included in the study. Patients who met the inclusion criteria and were exposed to the pandemic between April 2020 and March 2021 were classified as cases (COVID-19-exposed group), and those meeting the same inclusion criteria between April 2019 and March 2020 were classified as controls (COVID-19-unexposed group) according to the date of the final outcome.

The data collection and evaluation

The pre-treatment evaluation included collection of data on the age, sex, Eastern Cooperative Oncology Group Performance Status (ECOG-PS), disease status, presence of biliary drainage, and laboratory variables, including carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9). Treatment regimens, efficacy and dose intensity of chemotherapy, place of death, and frequency of hospitalization were recorded. Quantitative data were expressed as medians (with ranges) and qualitative data as absolute numbers (with percentages). Continuous variables were later dichotomized based on the median or reference values of each variable for the analysis.

Relative dose intensities (RDIs) of GnP and modified FOLFIRINOX (mFOLFIRINOX) were calculated as the ratio of the actual dose intensity (ADI) to the standard dose intensity (SDI), where the ADI was the ratio of the actual dose to the actual duration of chemotherapy, and the SDI was the ratio of the standard dose to the standard duration of the regimen. The tumor response was assessed every two to three months using contrast-enhanced computed tomography, according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. The progression-free survival (PFS) was defined as the period from treatment initiation to disease progression, death, or the last follow-up, while the OS was defined as the period from treatment initiation to death or the last follow-up.

Statistical analyses

Continuous variables were compared using the Mann-Whitney U test. Categorial variables were evaluated using the chi-squared or Fisher's exact test, as appropriate. The OS and PFS were calculated using the Kaplan-Meier method and compared using the log-rank test. p values <0.05 were considered statistically significant.

The relationships between the place of death and clinical variables were investigated using univariate and multivariate analyses. Multivariate logistic regression was used to calculate the odds ratios (OR) and 95% confidence intervals (CIs) after controlling for potential confounders. Factors in the univariate analysis with p values <0.20, age, sex and performance status were included in the multivariate logistic regression analysis. All statistical analyses were performed using the SPSS statistical software program (version 20.0; SPSS, Chicago, USA).

Every patient gave their informed consent to receive chemotherapeutic treatment. This study was approved by the ethics committee of our institution (Institutional Review Board number: 2021-GA-1014). All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Results

Patient characteristics

A total of 430 PC patients were identified from the prospectively maintained institutional database. Of these, 32 patients who did not receive chemotherapy and 18 whose final outcome of death could not be confirmed were excluded from the analysis; the remaining 379 patients comprised the study cohort.

A total of 178 patients were included in the COVID-19-exposed group and the remaining 201 patients were included in the COVID-19-unexposed group (Fig. 1). Patient characteristics before chemotherapy in the two groups are shown in Table 1. The age, sex, ECOG-PS, number of treatment regimens, and status of biliary drainage did not differ significantly between the two groups. There was a tendency for locally-advanced PC to be more frequent and metastatic dis-

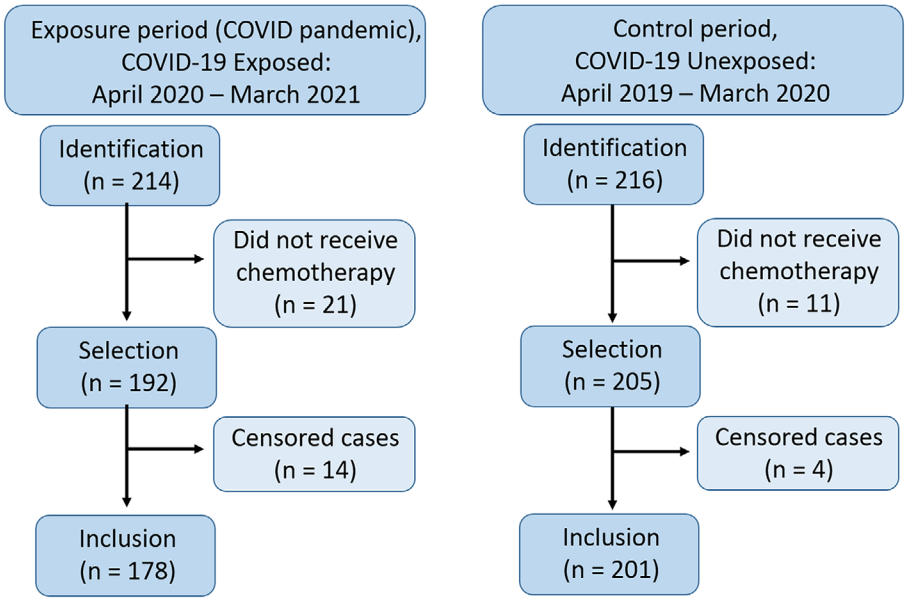

Figure 1. **Flowchart of patients included in the study.**

Table 1. **Baseline Patient Characteristics of COVID-19 Exposed and COVID-19 Unexposed Groups.**

	Exposed COVID-19 (n=178)	Unexposed COVID-19 (n=201)	p value
Age, years (range)	68 (22-86)	67 (37-87)	0.930
Sex, male (%)	94 (52.8%)	98 (48.8%)	0.472
Unresectable status, n (%)			
Locally advanced	46 (25.8%)	36 (17.9%)	0.081
Metastatic	90 (50.6%)	120 (59.7%)	0.074
Reccurrence after resection	42 (23.6%)	45 (22.4%)	0.780
ECOG PS, n (%)			
0	128 (71.9%)	156 (77.6%)	0.201
1	48 (27.0%)	38 (18.9%)	0.081
2	2 (1.1%)	7 (3.5%)	0.132
Number of treatment regimen, n (%)			
1	64 (36.0%)	71 (35.3%)	0.898
2	73 (41.0%)	90 (44.8%)	0.460
3	35 (19.7%)	31 (15.4%)	0.277
4	6 (3.4%)	9 (4.5%)	0.581
Biliary drainage, yes (%)	34 (19.1%)	31 (15.4%)	0.413
CEA, ng/mL	4.5 (0.5-357)	5 (0.7-612.9)	0.312
CA19-9, IU/mL	582 (2.0-50,000)	899 (2.0-50,000)	0.060

ECOG: Eastern Cooperative Oncology Group, PS: performance status, CEA: carcinoembryonic antigen, CA19-9: carbohydrate antigen 19-9

ease to be less frequent in the COVID-19-exposed group than in the COVID-19-unexposed group (p=0.081 and 0.074, respectively). CA19-9 also tended to be higher in the COVID-19-unexposed group than in the COVID-19-exposed group (p=0.060).

Kaplan-Meier curves for the OS between the two groups are illustrated in Fig. 2. The median OS did not differ significantly between the groups (12.6 months in COVID-19-exposed group vs. 11.9 months in the COVID-19-unexposed group, p=0.174).

Chemotherapy treatment

GnP and mFOLFIRINOX were frequently selected as first- and second-line chemotherapy, respectively, in both groups, with no significant difference in regimens noted between the two groups (Table 2). Nonoliposomal irinotecan was approved in 2020 in Japan, and nanoliposomal irinotecan and fluorouracil combination therapy was only used in the COVID-19-exposed group. The proportion receiving erlotinib in combination with gemcitabine (GE) as third-line

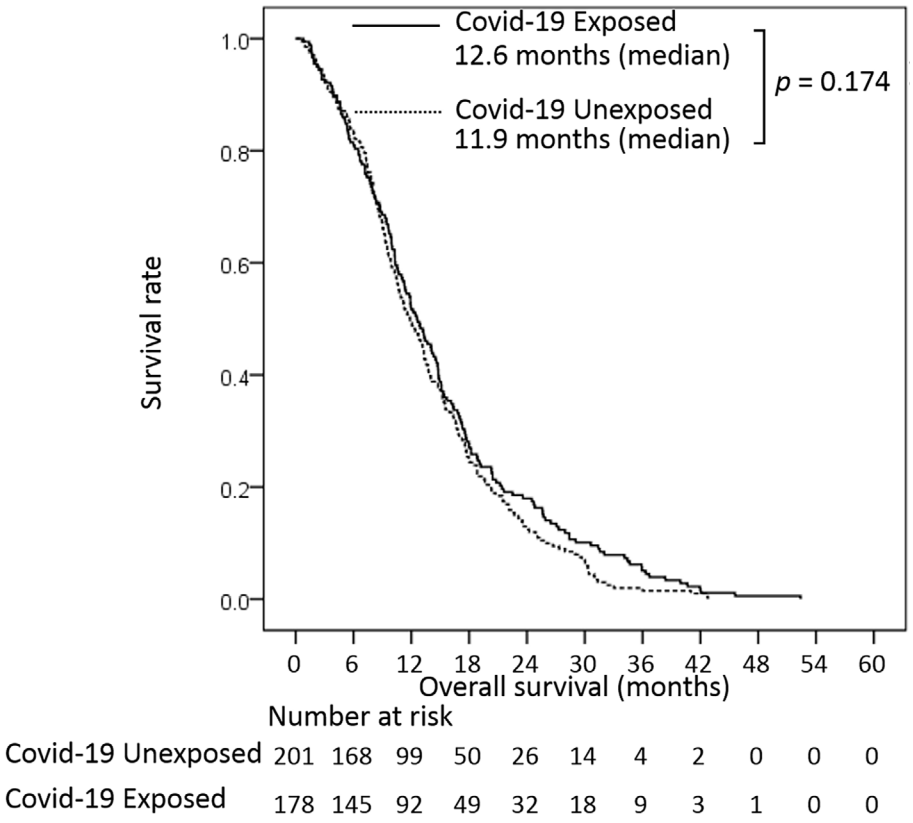

Figure 2. **The overall survival of the COVID-19-exposed and COVID-19-unexposed groups.**

Table 2. **Chemotherapy Regimens of COVID-19 Exposed and COVID-19 Unexposed Groups.**

	Exposed COVID-19 (n=178)	Unexposed COVID-19 (n=201)	p value
Treatment regimen			
1st line, n (%)			
Gemcitabine+nab-paclitaxel	125 (70.2%)	139 (69.2%)	0.821
mFOLFIRINOX	33 (18.5%)	35 (17.4%)	0.776
Gemcitabine monotherapy	11 (6.2%)	22 (10.9%)	0.101
Chemoradiotherapy	1 (0.6%)	3 (1.5%)	0.376
Others	8 (4.5%)	2 (1.0%)	0.072
2nd line, n (%)			
mFOLFIRINOX	34 (29.8%)	50 (38.5%)	0.157
S-1	40 (35.1%)	45 (34.6%)	0.938
Gemcitabine+nab-paclitaxel	25 (21.9%)	22 (16.9%)	0.322
Chemoradiotherapy	8 (7.0%)	9 (6.9%)	0.977
5FU/LV+nanoliposomal irinotecan	6 (5.3%)	0 (0.0%)	0.026
Others	1 (0.9%)	4 (3.1%)	0.226
3rd line, n (%)			
Gemcitabine+erlotinib	5 (12.2%)	17 (42.5%)	0.005
S-1	20 (48.8%)	16 (40.0%)	0.427
Gemcitabine+nab-paclitaxel	4 (9.8%)	1 (2.5%)	0.175
mFOLFIRINOX	4 (9.8%)	2 (5.0%)	0.414
5FU/LV+nanoliposomal irinotecan	4 (9.8%)	0 (0.0%)	0.043
Othres	4 (9.8%)	4 (10.0%)	0.971

mFOLFIRINOX: modified FOLFIRINOX, 5FU: fluorouracil, LV: leucovorin

Table 3. Relative Dose Intensity and Progression-free Survival of Patients Treated with mFOLFIRINOX or GnP.

	Exposed COVID-19 (n=178)		Unexposed COVID-19 (n=201)		p value
1st line					
Gemcitabine+nab-paclitaxel					
Gemcitabine, RDI (%)±SD	71.9%	±18.7%	70.6%	±21.4%	0.599
Nab-paclitaxel, RDI (%)±SD	70.0%	±19.5%	65.2%	±24.2%	0.159
PFS (median)	5.3 months		5.6 months		0.469
mFOLFIRINOX					
Fluorouracil, RDI (%)±SD	81.6%	±18.2%	79.9%	±18.6%	0.708
Oxaliplatin, RDI (%)±SD	73.5%	±23.8%	69.6%	±23.9%	0.507
Irinotecan, RDI (%)±SD	70.2%	±25.6%	72.2%	±23.2%	0.736
PFS (median)	5.6 months		6.2 months		0.602
2nd line					
Gemcitabine+nab-paclitaxel					
Gemcitabine, RDI (%)±SD	68.7%	±28.3%	73.4%	±20.5%	0.523
Nab-paclitaxel, RDI (%)±SD	68.7%	±28.3%	73.4%	±20.5%	0.523
PFS (median)	4.0 months		2.4 months		0.083
mFOLFIRINOX					
Fluorouracil, RDI (%)±SD	76.4%	±21.0%	81.0%	±20.1%	0.314
Oxaliplatin, RDI (%)±SD	67.7%	±21.5%	74.6%	±21.3%	0.151
Irinotecan, RDI (%)±SD	67.8%	±26.4%	71.9%	±23.6%	0.455
PFS (median)	4.9 months		3.1 months		0.464

RDI: relative dose intensity, SD: standard deviation, PFS: progression survival, mFOLFIRINOX: modified FOLFIRINOX

Table 4. Place of Death.

	Exposed COVID-19 (n=178)	Unexposed COVID-19 (n=201)	p value
Place of death, n, (%)			
Home	57 (32.0%)	18 (9.0%)	<0.001
Our hospital	61 (34.3%)	67 (33.3%)	0.847
General ward beds	15 (8.4%)	23 (11.4%)	0.329
Palliative care unit	46 (25.8%)	44 (21.9%)	0.367
Transferred hospital	58 (32.6%)	103 (51.2%)	<0.001
General ward beds	32 (18.0%)	61 (30.3%)	0.008
Palliative care unit	26 (14.6%)	42 (20.9%)	0.111
Not available (death confirmed by public inquiry)	2 (1.1%)	13 (6.5%)	0.016

therapy was significantly lower in the COVID-19-exposed group than in the COVID-19-unexposed group (p=0.005). The RDI and PFS of GnP and mFOLFIRINOX as first- and second-line treatment, respectively, did not differ significantly between the two groups (Table 3).

End-of-life situations

The place of death of the subjects is summarized in Table 4. A significantly larger number of patients died at home in the COVID-19-exposed group than in the COVID-19-unexposed group (32.0% vs. 9.0%, p<0.001). The proportion with our hospital's palliative-care unit (PCU) as the place of death did not differ significantly between the two groups. The proportion of patients who died after transfer to another hospital was significantly lower in the COVID-19-exposed group than in the COVID-19-unexposed group (32.6% vs. 51.2%, p<0.001). The frequency of hospitalization and total days spent at our hospital did not differ significantly between the two groups (Table 5). For the patients who died in our general wards, the duration of their last hospital stay was significantly shorter in the COVID-19-exposed group than in the COVID-19-unexposed group (7 vs. 15 days, p=0.006). For patients who died in our PCU, the duration of PCU stay tended to be shorter in the COVID-19-exposed group than in the COVID-19-unexposed group (11 vs. 15 days, p=0.227).

Table 5. End-of-life Situations.

	Exposed COVID-19 (n=178)		Unexposed COVID-19 (n=201)		p value
Finally biliary drainage, yes, n	66		75		0.962
Gastrointestinal stent, yes, n	19		17		0.463
Frequency of hospitalizaion (our hospital), n, range	3	0-14	3	0-13	0.485
Total days spent at our hospital, days, range	25	0-178	24	0-165	0.432
Days spent at our hospital (last stay), range	7	1-25	15	4-47	0.006
Days waiting for PCU (our hospital), range	6	1-43	5	1-38	0.537
Days spent at PCU (our hospital), range	11	1-58	15	1-62	0.227
Days spent at home with home doctors, range	32	1-213	23	2-397	0.402

PCU: palliative care unint

Clinical factors associated with death at home

The relationships between clinical factors and death at home are shown in Table 6. A univariate analysis revealed that death in the COVID-19-exposed era, a low CEA level (<10 ng/mL), and locally-advanced PC were significantly associated with death at home. In a multivariate analysis, death during the COVID-19 exposed era was independently associated with home death (OR: 4.536, 95% CI: 2.527-8.140, p<0.001).

Discussion

We performed a detailed analysis to evaluate the impact of the COVID-19 pandemic on chemotherapeutic treatment and end-of-life situations of patients with unresectable PC. The OS did not differ significantly between the COVID-19-exposed and COVID-19-unexposed groups. The PFS and RDI of the patients treated with GnP or mFOLFIRINOX as first- or second-line therapy also did not differ significantly between the two groups. However, more than three times as many patients died at home in the COVID-19-exposed group than in the COVID-19-unexposed group. A multivariate analysis revealed that death during the COVID-19-exposed era was an independent factor associated with home death.

Several recommendations and guidelines were issued concerning general care for patients with cancer during the COVID-19 pandemic (10-14). These statements suggested modifications of chemotherapy in patients with unresectable PC to reduce the high risk of neutropenia. The suggested modifications were to avoid FOLFIRINOX or to shift to bi-weekly injections of GnP. In this study, selection of GnP or mFOLFIRINOX regimens as first- or second-line chemotherapy and the dose intensities of these two chemotherapy regimens did not change after the spread of COVID-19. GnP and mFOLFIRINOX are established, well-tolerated chemotherapy regimens for Japanese patients with unresectable PC (16, 17). The management of classic FOLFIRINOX is considered difficult due to the high incidence of neutropenia, including febrile neutropenia (2, 18). The mFOLFIRINOX regimen is associated with similar outcomes and an improved safety profile compared with classic FOLFIRINOX (5, 17). The tolerability of these regimens for Japanese patients may be one of the reasons for maintaining a similar choice of chemotherapy after the onset of the pandemic. The RDI of GnP or mFOLFIRINOX was also similar between the two groups. The frequency of selection of GE as salvage-line chemotherapy was lower in the COVID-19-exposed group than in the COVID-19-unexposed group. We previously reported that the efficacy of GE as salvage treatment was limited (19). Concerns about interstitial lung disease as adverse events of GE have been particularly strong during the COVID-19 pandemic (20), leading to a decrease in the use of this regimen.

According to one study, almost half of Japanese cancer patients wished to receive end-of-life care or die at home (21). However, only 12.5% of Japanese people died at home in 2009, according to a Ministry of Health, Labour, and Welfare survey. Similar discrepancies were observed in other countries, such as the United Kingdom and Korea (22, 23). A Japan Public Health Center-based prospective study revealed that 14.1% of 17,546 deaths occurred at home (24). Regarding the cause of death, 8.1% of patients with cancer died at home, and cancer was not associated with home death compared with cardiovascular and cerebrovascular diseases. In our study, only 9.0% of patients died at home in the COVID-19-unexposed era, compared to 32.0% in the COVID-19-exposed era. Cancer patients who were concerned about the family burden or of being unable to respond to sudden changes in the patient's physical condition were less likely to choose home as the place of care (21). Loneliness due to strict hospital visitation policies may have led patients to realize the importance of face-to-face communications and of spending the end of their lives with their families.

PC patients visit the emergency department frequently and are usually hospitalized during end-of-life care (15). Obstructive jaundice and resulting cholangitis due to PC are common. Endoscopic biliary drainage is the intervention of choice for palliation of jaundice. Some PC patients develop gastric outlet or duodenal obstruction, which can be treated with endoscopic enteral stent placement. However, these procedures often require repeated hospitalizations and inter-

Table 6. Univariate and Multivariate Analysis of Clinical Factors Associated with Home Death.

	Univariate analysis		Multivariate analysis		
	Death at home (%)	p value	Odds ratio	95% CI	p value
Era					
Exposed COVID-19	32.0%	<0.001	4.536	2.527-8.140	<0.001
Unexposed COVID-19	9.0%		1.000		
Age					
<60	17.7%	0.554	0.840	0.444-1.589	0.592
60-	20.5%		1.000		
Sex					
Male	21.4%	0.438	1.208	0.703-2.075	0.494
Female	18.2%		1.000		
Overall survival					
<1 year	19.5%	0.877			
1 year-	20.1%				
CEA					
<10	22.3%	0.038	1.775	0.862-3.653	0.119
10-	12.5%		1.000		
CA19-9					
<1,000	22.0%	0.182	1.138	0.637-2.034	0.663
1,000-	16.4%		1.000		
ECOG PS					
0	18.9%	0.437	0.764	0.409-1.430	0.401
1, 2	22.6%		1.000		
Unresectable status					
Locally advanced	28.7%	0.024	1.639	0.881-3.048	0.119
Metastatic, recurrence	17.4%		1.000		
Number or treatment regimen					
1, 2	19.1%	0.535			
3-	22.2%				
Number of hospitalization					
1-3	21.0%	0.439			
4-	17.7%				
Finally biliary drainage					
Yes	19.1%	0.810			
No	20.2%				
Finally gastointestinal stent					
Yes	19.4%	0.957			
No	19.8%				

CEA: carcinoembryonic antigen, CA19-9: carbohydrate antigen 19-9, ECOG: European Cooperative Oncology Group, PS: performance status, 95% CI: 95% confidential interval

ventions. Although the frequency of hospitalization and the proportion of patients with biliary drainage or gastrointestinal stents did not differ markedly between the two groups in this study, the duration of the last stay at our hospital was significantly shorter in the COVID-19-exposed group than in the COVID-19-unexposed group. Some PC patients in the COVID-19-exposed group requiring hospitalization for end-of-life care may have been reluctant to be admitted because of the strict visitation policies, leading them to place a higher priority on spending time with their families at home than in the safety of the hospital setting in case of emergency.

Several limitations associated with the present study warrant mention. First, this was a retrospective study at a single institution, although the sample size was relatively large. Although the baseline patient characteristics of the two groups were well-balanced, the proportion of metastatic disease and CA19-9 levels were higher in the COVID-19-unexposed group than in the COVID-19-exposed group. Second, our study population was heterogeneous with regard to the timing of the initiation of systemic chemotherapy. Because survival outcomes are important for evaluating the efficacy of systemic chemotherapy and end-of-life care, we classified the patients according to the date of death. However, if patients had been classified into the two groups according to the date of the initiation of chemotherapy, it would have been difficult to evaluate the impact of the pandemic on patients who started chemotherapy in the COVID-19-

unexposed era but died in the COVID-19-exposed era. Extending the evaluation period to include more recent cases would also be difficult because of the impact of shortages in nab-paclitaxel due to manufacturing delays, which began in 2021. Third, environmental arrangements for spending the end of one's life in the COVID-19-exposed era are different from those in the COVID-19-unexposed era. These differences may have affected end-of-life care and choice about place of death. Many transfer hospitals have been facing bed and staff shortages, and some hospitals closed their PCU because COVID-19 hospitalizations increased. Therefore, the proportion of patients who died after hospital transfer was significantly lower in the COVID-19-exposed era than in the COVID-19-unexposed era. Although we also have been facing bed shortages, we have accepted all PC patients indicated for hospitalization. That is one of the reasons why the proportion of patients who died at our hospital was the same in the two groups. We started the pancreatic direct approach team (PANDA) program with a multi-disciplinary team in 2016. Information about palliative care and medical cooperation with home medical care and local health care is provided to patients with PC (25), starting from the time of their diagnosis with unresectable PC. We believe that all patients in both groups had opportunities to choose where to die, and strict hospital visitation policies influenced their preferred place of death.

In conclusion, although the COVID-19 pandemic did not seem to influence the management of chemotherapy for PC patients, it had a great impact on end-of-life care in this population. Face-to-face communication between patients and their families is a very important factor for PC patients receiving end-of-life care in order to allow them to make an informed decision about where they wish to die. These findings may promote discussion about end-of-life care in Japan.

This study was approved by the Institutional Review Board of the Cancer Institute Hospital of Japanese Foundation for Cancer Research (Institutional Review Board number: 2021-GA-1014) and was conducted in accordance with the Declaration of Helsinki.

The authors state that they have no Conflict of Interest (COI).

Acknowledgement

The authors wish to thank Kikuko Kaji for technical support.

References

1. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2021. CA Cancer J Clin **71**: 7-33, 2021.
2. Conroy T, Desseigne F, Ychou M, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med **364**: 1817-1825, 2011.
3. Von Hoff DD, Ervin T, Arena FP, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. N Engl J Med **369**: 1691-1703, 2013.
4. Wang-Gillam A, Li CP, Bodoky G, et al. Nanoliposomal irinotecan with fluorouracil and folinic acid in metastatic pancreatic cancer after previous gemcitabine-based therapy (NAPOLI-1): a global, randomised, open-label, phase 3 trial. Lancet **387**: 545-557, 2016.
5. Sawada M, Kasuga A, Mie T, et al. Modified FOLFIRINOX as a second-line therapy following gemcitabine plus nab-paclitaxel therapy in metastatic pancreatic cancer. BMC Cancer **20**: 449, 2020.
6. Kasuga A, Hamamoto Y, Takeuchi A, et al. Positive relationship between subsequent chemotherapy and overall survival in pancreatic cancer: meta-analysis of postprogression survival for first-line chemotherapy. Cancer Chemother Pharmacol **79**: 595-602, 2017.
7. Kasuga A, Hamamoto Y, Takeuchi A, et al. Post-progression survival following second-line chemotherapy in patients with advanced pancreatic cancer previously treated with gemcitabine: a meta-analysis. Invest New Drugs **36**: 939-948, 2018.
8. Lewis MA. Between Scylla and Charybdis - oncologic decision making in the time of COVID-19. N Engl J Med **382**: 2285-2287, 2020.
9. Yu J, Ouyang W, Chua MLK, Xie C. SARS-CoV-2 transmission in patients with cancer at a tertiary care hospital in Wuhan, China. JAMA Oncol **6**: 1108-1110, 2020.
10. Schrag D, Hershman DL, Basch E. Oncology practice during the COVID-19 pandemic. JAMA **323**: 2005-2006, 2020.
11. You B, Ravaud A, Canivet A, et al. The official French guidelines to protect patients with cancer against SARS-CoV-2 infection. Lancet Oncol **21**: 619-621, 2020.
12. Pinto C, Cagnazzo C. Indications regarding the management of interventional clinical trials with drugs during the current COVID-19 emergency in Italy. ESMO Open **5**: e000782, 2020.
13. Takahari D, Shinozaki E, Wakatsuki T, et al. Managing a gastrointestinal oncology practice in Japan during the COVID-19 pandemic: single institutional experience in the Cancer Institute Hospital of Japanese Foundation for Cancer Research. Int J Clin Oncol **26**: 335-344, 2021.
14. Lou E, Beg S, Bergsland E, et al. Modifying practices in GI oncology in the face of COVID-19: recommendations from expert oncologists on minimizing patient risk. JCO Oncol Pract **16**: 383-388, 2020.
15. Michael N, Beale G, O'Callaghan C, et al. Timing of palliative care referral and aggressive cancer care toward the end-of-life in pancreatic cancer: a retrospective, single-center observational study. BMC Palliative Care **18**: 13, 2019.
16. Ueno H, Ikeda M, Ueno M, et al. Phase I/II study of nab-paclitaxel plus gemcitabine for chemotherapy-naive Japanese patients with metastatic pancreatic cancer. Cancer Chemother Pharmacol **77**: 595-603, 2016.
17. Ozaka M, Ishii H, Sato T, et al. A phase II study of modified FOLFIRINOX for chemotherapy-naive patients with metastatic pancreatic cancer. Cancer Chemother Pharmacol **81**: 1017-1023, 2018.
18. Okusaka T, Ikeda M, Fukutomi A, et al. Phase II study of FOLFIRINOX for chemotherapy-naive Japanese patients with metastatic pancreatic cancer. Cancer Sci **105**: 1321-1326, 2014.
19. Mie T, Sasaki T, Takeda T, et al. Treatment outcomes of erlotinib plus gemcitabine as late-line chemotherapy in unresectable pancreatic cancer. Jpn J Clin Oncol **51**: 1416-1422, 2021.
20. Furuse J, Gemma A, Ichikawa W, Okusaka T, Seki A, Ishii T. Postmarketing surveillance study of erlotinib plus gemcitabine for pancreatic cancer in Japan: POLARIS final analysis. Jpn J Clin Oncol **47**: 832-839, 2017.
21. Yamagishi A, Morita T, Miyashita M, et al. Preferred place of care and place of death of the general public and cancer patients in Japan. Supportive Care Cancer **20**: 2575-2582, 2012.
22. Gao W, Ho YK, Verne J, Glickman M, Higginson IJ. Changing patterns in place of cancer death in England: a population-based study. PLoS Med **10**: e1001410, 2013.

23. Lee JK, Jang SN. Place of death and associated gender difference in Korea 2006-2014: evidence from exit interviews of the Korean longitudinal study of ageing. Arch Gerontol Geriatr **78**: 196-202, 2018.

24. Fujiwara N, Shimada N, Nojima M, et al. Exploratory research on determinants of place of death in a large-scale cohort study: the JPHC study. J Epidemiol 2021.

25. Nagasaki R, Hoshino K, Otomo Y, et al. Involvement of nursesin an outpatient chemotherapy center in the PANDA program for patients with advanced pancreatic cancer. Suizo **35**: 130-135, 2020 (in Japanese).