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<https://hdl.handle.net/2324/2236077>

出版情報 : Kyushu University, 2018, 博士 (医学) , 課程博士
バージョン :
権利関係 :





Efficacy of S-1 monotherapy for older patients with unresectable pancreatic cancer: A retrospective cohort study

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ARTICLE INFO

Article history:

Received 15 April 2018

Received in revised form 10 July 2018

Accepted 6 September 2018

Available online 17 September 2018

ABSTRACT

Objectives: Pancreatic cancer is a fatal malignancy that frequently occurs in older patients. However, limited evidence is available on the effects of chemotherapy on older patients with unresectable pancreatic cancer. Here we explored the efficacy of S-1, an oral fluorouracil drug, compared with gemcitabine, as first-line chemotherapy.

Materials and Methods: We conducted a retrospective cohort study of patients with unresectable pancreatic cancer aged ≥ 75 years. For this purpose, we used the claims and master databases of the Fukuoka Prefecture Wide-Area Association of Latter-Stage Elderly Healthcare between April 1, 2010 to March 31, 2017. According to first-line chemotherapy, we divided patients into gemcitabine and S-1 groups to compare three-year survival from the date of diagnosis and time to second-line chemotherapy as a surrogate indicator of progression-free survival. We analyzed the data using multivariate Cox proportional hazards method.

Results: The study comprised 680 patients, of which 92.5% ($N = 629$) died within three years of diagnosis. The S-1 group had a significantly lower risk of death within three years of diagnosis (hazard ratio (HR) 0.695, 95% CI: 0.588–0.821, $p < .001$). There were no significant differences (HR 0.968, 95% CI: 0.708–1.324, $p = .838$) in time to second-line chemotherapy. Two sensitivity analyses excluding study subjects who received radiation therapy or second-line chemotherapy yielded consistent results (HR 0.746, 95% CI: 0.622–0.895, $p = .002$, HR 0.628, 95% CI: 0.509–0.776, $p < .001$, respectively).

Conclusion: S-1 can serve as a first-line chemotherapeutic option of patients aged ≥ 75 years with unresectable pancreatic cancer.

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1. Introduction

Pancreatic cancer has the lowest survival rate among all cancers [1]. During its early stages, it is usually asymptomatic and challenging to detect. Therefore, the majority of pancreatic carcinoma are diagnosed as unresectable and/or metastatic. The five-year survival rates have been reported to range between 6% and 10% [2,3]. The mortality rate is higher in developed countries, compared with developing countries [4]. For example, in the United States, pancreatic cancer accounts for approximately 7% of the estimated cancer deaths in both sexes [5]. In Japan, pancreatic cancer is the fifth most common cause of cancer death in males and third in females [6]. The average age at diagnosis is ≥ 70 years, and pancreatic cancer most frequently occurs in older individuals [3,7]. In general, anticancer treatments of older patient population are restricted by their weakened physical or cognitive function. Especially, older patients with pancreatic cancer were reported to be reluctant to undergo aggressive interventions or treatments such as

laparotomy and/or chemotherapy with possible significant side effects [8,9].

Surgical resection is the only curative treatment for pancreatic cancer. However, fewer than 20% of patients with pancreatic cancer are diagnosed as resectable cases [5]. Patients with unresectable pancreatic cancer are typically offered chemotherapy and/or radiation as a palliative treatment option. Gemcitabine has been the most frequently administered drug as the first-line chemotherapy [10]. Recently, Gemcitabine and nab-paclitaxel and FOLFIRINOX (a combination of 5-fluorouracil, oxaliplatin, irinotecan, and leucovorin) have been proposed as optimal first-line options for patients with metastatic pancreatic cancer based on the compelling results of randomized controlled trials (RCT) that these treatments resulted in significantly prolonged overall survival (OS), compared with gemcitabine monotherapy [11,12]. However, FOLFIRINOX and gemcitabine and nab-paclitaxel were much less commonly administered to older Japanese patients with unresectable/metastatic pancreatic cancer because of the concern for serious adverse effects of FOLFIRINOX and delayed approval of nab-paclitaxel in Japan [13]. S-1, an anticancer agent with indications of gastrointestinal and breast cancer, has been used for older patients with unresectable pancreatic cancer since it received approval based

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on a phase II trial in 2006 [14–17]. The GEST study, a RCT conducted in Japan and Taiwan, found that S-1 has shown non-inferiority to gemcitabine for advanced pancreatic cancer [18,19]. However, its efficacy for older patients has not been fully elucidated. Imaoka et al. conducted a subgroup analysis in the GEST study of study participants aged ≥ 70 years [20]. They concluded that S-1 could be a reasonable first-line treatment option for older patients with unresectable pancreatic cancer. However, as the authors wrote in the limitation of their article, the analysis lacked statistical power because they studied as few as 171 study participants. Although the GEST study was a RCT, trials with a small sample size may be biased by confounding factors [21]. Furthermore, the study lacked detailed descriptions of the study participants' comorbidities such as diabetes mellitus.

The aim of the present study is to explore an additional evidence of the efficacy of S-1 compared with gemcitabine as first-line therapy for older patients with unresectable pancreatic cancer.

2. Method and Materials

2.1. Data Source

We conducted a retrospective cohort study using healthcare claims database and master database of Fukuoka Prefecture Wide-Area Association of Latter-Stage Elderly Healthcare between April 1, 2010 and March 31, 2017. The majority of people aged ≥ 75 years enrolls in this public health insurance. The number of the insured belonging to that age group was reported to be approximately 580,000, as of March 2017 [22]. The healthcare claims database included data of International Classification of Diseases 10th Revision (ICD-10), date of the diagnosis, drug prescriptions, and medical procedures such as surgery and radiation therapy. The master database records the date of admission, withdrawal, and death. The majority of this healthcare insured population have sustainable long-term eligibility once they enrolled, and therefore, there are few study subjects lost to follow-up. The majority of these databases are computer-administered. According to a report by Japanese Ministry of Health, Labour and Welfare, the penetration rate of computer-administered claims database was 98.6% at April 2015 [23]. Japanese Health Insurance Claims Review & Reimbursement services has a responsibility of the quality control. The Institutional Review Board of Kyushu University (Clinical Bioethics Committee of the Graduate School of Healthcare Sciences, Kyushu University) approved this study.

2.2. Study Population

We identified patients diagnosed with pancreatic cancer (ICD-10 code = C25) in the healthcare database who were aged ≥ 75 years between from April 1, 2010 through March 31, 2014. Patients with unresectable tumors were identified by excluding those who underwent surgery. We classified the patients into the gemcitabine and S-1 groups by cross-referencing the date of first-line chemotherapy and drug identification codes. We excluded patients treated with other first-line chemotherapy regimens who were identified according to the drug identification codes as follows: cisplatin, paclitaxel, fluorouracil (5-FU), irinotecan, oxaliplatin, etoposide, and erlotinib. To calculate loss to follow-up, we analyzed the medical record on physicians' visits and drug prescription of subjects alive at the end of the observation, March 31, 2017.

2.3. Outcomes

The primary outcome was all-cause mortality within three years after the diagnosis, and secondary outcome was the time to second-line treatment. Chemotherapy against pancreatic cancer is recommended to continue as long as it was deemed effective [24]. Transition to second-line chemotherapy occurs mainly due to either significant adverse effects or disease progression. Gemcitabine was administered on

days 1, 8, and 15 of a 28-day cycle; and S-1 was orally administered on days 1 through 28 of a 42-day cycle [18]. Considering both regimens, disease progression was typically evaluated 28 days after initiation of first-line chemotherapy. Therefore, we used time to second-line chemotherapy of the patients who tolerated their first-line chemotherapy longer than 28 days as a surrogate indicator of progression free survival (PFS).

2.4. Statistical Analysis

We conducted survival analyses to compare survival between the S-1 and the gemcitabine groups within older patients with unresectable pancreatic cancer. At first, we generated Kaplan–Meier plots to estimate time to event distributions of each group. The differences between groups were tested for statistical significance using the log-rank test. Furthermore, we used a multivariate Cox proportional hazards method to control for the potential confounding effects of the patients' sex, age, and comorbidities. We checked Schoenfeld residuals to investigate the validity of each proportional hazards assumption [25]. To evaluate patients' comorbidities, we used the Charlson Comorbidity Index (CCI) at the time of diagnosis as an explanatory variable [26–28]. The CCI includes an item for a variable designated “any cancer”. We calculated the CCI without the item and classified the CCI into tertiles. A two-sided P value $< .05$ was considered statistically significant. Analyses were conducted using Stata software, version 14. (Stata Corp, College Station, Texas).

2.5. Sensitivity Analysis

To confirm the robustness of our study, we performed two sensitivity analyses. At first, we examined overall survival (OS) for study population, excluding patients treated with combination therapy of chemotherapy and radiation to examine effects of the radiation therapy. Secondly, we applied analyses for study population receiving only first-line chemotherapy to examine contributions of second-line chemotherapy to OS.

3. Result

3.1. Patient Characteristics

Following screening according to our inclusion and exclusion criteria (Fig. 1), the final number of study subjects was 680, with 440 patients undergoing treatment with gemcitabine and 240 patients treated with S-1. Six patients were lost to follow-up. Three patients transferred to the public assistance system: another social security system managed by the Japanese government. The other three patients moved to another prefecture. Thus, the completeness of follow-up was as much as 99.1%.

The proportion of males was 49.4% ($N = 336$). The mean age upon diagnosis was 79.8 ± 3.78 . The S-1 and gemcitabine groups represented 35.1% ($N = 240$) and 64.9% ($N = 440$) of the patient population, respectively. The percentages of patients in the S-1 and gemcitabine groups who underwent chemoradiotherapy were 22.1% ($N = 53$) and 6.59% ($N = 29$), respectively. Patients' baseline characteristics are shown in Table 1.

3.2. Overall Survival

The percentages of all-cause mortality within three years from the diagnosis was 92.5% ($N = 629$), and 87.9% ($N = 211$) in the S-1 group and 95.0% ($N = 418$) in the gemcitabine group, respectively (Table 2). The median OS was 10.8 months (95% confidence interval [CI], 9.46–12.5) in the S-1 group and 7.36 months (95% CI, 6.87–8.01) in the gemcitabine group. There were significant differences between the Kaplan–Meier plots ($p < .0001$) (Fig. 2). Multivariate Cox proportional hazards analysis adjusted for sex, age, and the CCI revealed that the

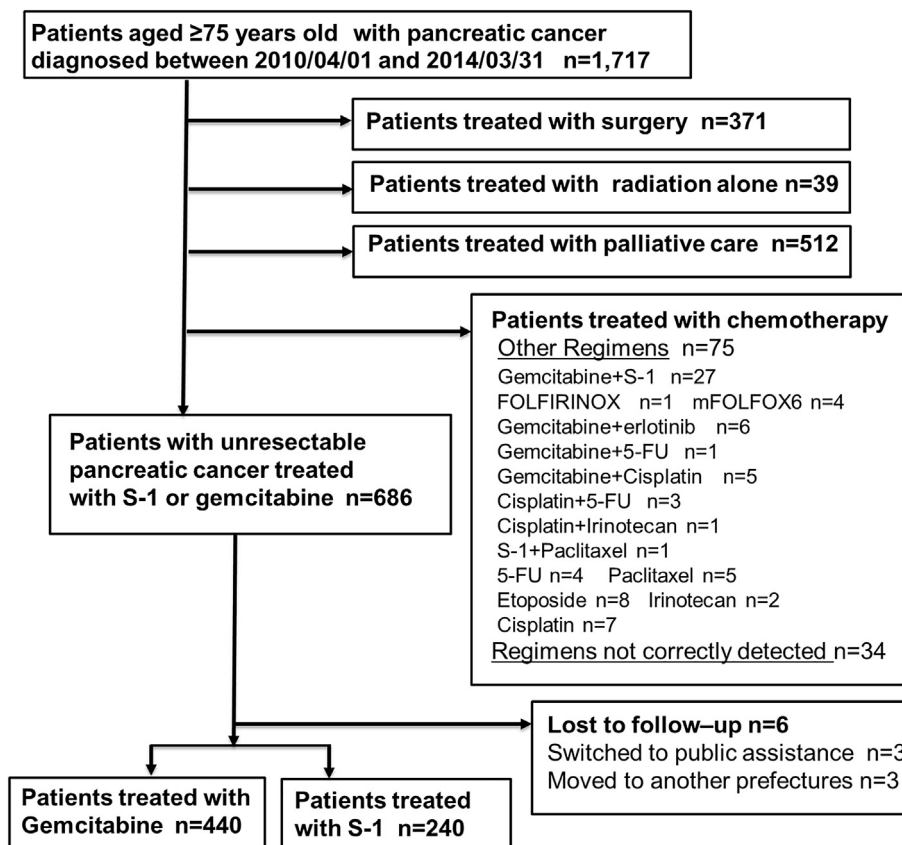


Fig. 1. Flow diagram of inclusion/exclusion criteria 5-FU: Fluorouracil.

Table 1
Baseline characteristics of patients in the present study.

	S-1 (n = 240)		Gemcitabine (n = 440)		p value
	Number		Number		
Gender: Male	119	49.6%	217	49.3%	0.506
Mean age (SD)	80.1	(±4.07)	79.5	(±3.60)	
Median age	79		80		
Age categories					0.345
75 ≤ <80	119	49.6%	239	54.3%	
80 ≤ <85	87	36.3%	153	34.8%	
85 ≤	34	14.2%	48	10.9%	
CCI categories					0.689
Low (≤1)	84	35.0%	166	37.7%	
Intermediate (2 ≤ ≤6)	78	32.5%	133	30.2%	
High (7 ≤)	78	32.5%	141	32.0%	
Comorbidities					
Acute myocardial infarction	4	1.7%	4	0.9%	0.462
Congestive heart failure	23	9.6%	24	5.5%	0.057
Peripheral vascular disease	12	5.0%	21	4.8%	0.515
Cerebral vascular disease	21	8.8%	57	13.0%	0.104
Dementia	8	3.3%	14	3.2%	1.00
Chronic pulmonary disease	29	12.1%	39	8.9%	0.184
Connective tissue disorder	2	0.8%	4	0.9%	1.00
Peptic ulcer	66	27.5%	133	30.2%	0.481
Mild liver disease	26	10.8%	32	7.3%	0.116
Diabetes	67	27.9%	123	28.0%	1.00
Hemiplegia	0	0.0%	3	0.7%	0.556
Moderate to severe renal disease	11	4.6%	17	3.9%	0.688
Diabetes with end-organ damage	16	6.7%	42	9.5%	0.250
Leukemia	1	0.4%	0	0.0%	0.353
Lymphoma	1	0.4%	3	0.7%	1.00
Moderate to severe liver disease	6	2.5%	12	2.7%	1.00
Metastatic solid tumor	107	44.6%	197	44.8%	1.00
AIDS	0	0.0%	0	0.0%	

P value was calculated by Fisher exact test.

SD: Standard deviation CCI: Charlson comorbidity index AIDS: Acquired immune deficiency syndrome.

S-1 group had a significant lower risk of death within three years from the diagnosis (hazard ratio (HR) 0.695, 95% CI: 0.588–0.821, $p < .001$). The result of Schoenfeld residuals revealed no violation of the proportional hazards assumption.

3.3. Time to Second-Line Chemotherapy

The percentages of patients receiving second-line chemotherapy was 34.6% ($N = 235$); 38.8% ($N = 93$) in the S-1 group and 32.3% ($N = 142$) in the gemcitabine group (Table 3). Among the patients in the S-1 and gemcitabine groups, 68.8% ($N = 64$) and 91.5% ($N = 130$), respectively, switched to second-line chemotherapy after they continued their first-line chemotherapy longer than 28 days. The median time to second-line chemotherapy in this population were 4.90 months (95%CI, 2.83–6.57) in the S-1 group and 4.60 months (95%CI: 4.01–5.78) in the gemcitabine group. There were no significant differences in the Kaplan–Meier plots ($p = .881$) as well as in the multivariate Cox proportional hazards analysis adjusted for sex, age, and the CCI (HR 0.968, 95% CI: 0.708–1.324, $p = .838$) (Fig. 3). The result of Schoenfeld residuals revealed no violation of the proportional hazards assumption.

3.4. Sensitivity Analysis

In the first sensitivity analysis, we analyzed OS in each group receiving chemotherapy alone (Table 4). In this population, there were 187 persons in the S-1 group and 411 persons in the gemcitabine group, respectively. Median OS was 9.46 months (95% CI, 7.72–10.78) in the S-1 group and 7.16 months (95% CI, 6.28–7.66) in the gemcitabine group. There were significant differences in the Kaplan–Meier plots ($p = .002$) (Fig. 4). The results of multivariate Cox proportional hazards analysis with adjustments for sex, age, and the CCI were consistent with the original analysis (HR 0.746, 95% CI: 0.622–0.895, $p = .002$). The second sensitivity analysis included the same variables of each group

Table 2

OS and results of univariate and multivariate Cox proportional hazard analyses.

		S-1		Gemcitabine	
Total of number patients		240		440	
Death within 3 years (%)		211(87.9%)		418(95.0%)	
Median OS (95% CI) [months]		10.8(9.46–12.5)		7.36 (6.87–8.01)	
		Univariate HR(95% CI)	p-value	Adjusted HR(95% CI)	p-value
Sex	Male	REF		REF	
	Female	0.907(0.776–1.061)	0.222	0.893(0.762–1.045)	0.158
Age	75 ≤ <80	REF		REF	
	80 ≤ <85	1.057(0.892–1.253)	0.522	1.080(0.909–1.283)	0.381
	85 ≤	0.917(0.713–1.180)	0.502	0.941(0.728–1.214)	0.638
CCI	Low (≤1)	REF		REF	
	Intermediate (2 ≤ <6)	0.831(0.685–1.008)	0.061	0.838 (0.690–1.018)	0.075
	High (7 ≤)	1.068(0.886–1.287)	0.488	1.094 (0.905–1.323)	0.353
Regimen	Gemcitabine	REF		REF	
	S-1	0.694 (0.588–0.820)	<0.001	0.695(0.588–0.821)	<0.001

Adjusted HR was estimated according to age, sex, and comorbidities(Charlson comorbidity index).

OS: Overall survival CI: confidence interval REF: reference HR: hazard ratio CCI: Charlson comorbidity index.

receiving first-line chemotherapy alone (Table 4). There were 147 and 298 subjects in the S-1 and gemcitabine groups, respectively. The median OS was 8.87 months (95% CI, 7.10–10.51) in the S-1 group and 5.65 months (95% CI, 4.86–6.18) in the gemcitabine group. There were significant differences in the Kaplan–Meier plots ($p < .0001$) (Fig. 4). Multivariate Cox proportional hazards analysis yielded results consistent with the original analysis (HR 0.628, 95% CI: 0.509–0.776, $p < .001$). The results of Schoenfeld residuals revealed no violation of the proportional hazards assumptions of both sensitivity analyses.

4. Discussion

Pancreatic cancer has the poorest prognosis among cancers because it often lacks recognizable symptoms until its advanced stages. When detected, the majority of the patients have advanced to unresectable clinical stages. Such patients are offered the options of chemotherapy, radiation, or both. Gemcitabine has been one of the most effective chemotherapeutic agents since Burris et al. reported the efficacy compared with 5-FU in 1997 [10]. During the last decade, combination therapies comprising gemcitabine and erlotinib, gemcitabine and nab-paclitaxel, and FOLFIRINOX have been proposed as better first-line options for patients with unresectable pancreatic cancer [11,12,29,30]. In particular, RCTs showed that FOLFIRINOX and combination therapy with gemcitabine and nab-paclitaxel achieved much longer OS [11,12]. In

Japan, FOLFIRINOX is not recommended for older patients because of a higher incidence of neutropenic fever [13]. Nab-paclitaxel was approved for treating unresectable pancreatic cancer as late as 2014. Therefore, treatment with either FOLFIRINOX or combination therapy with gemcitabine and nab-paclitaxel were much less commonly administered to Japanese older patients with unresectable pancreatic cancer. S-1 was developed in Japan as an anticancer drug that combines three pharmacological agents: tegafur, a prodrug of 5-FU; 5-chloro-2,4-dihydropyridine, an inhibitor of dihydropyrimidine dehydrogenase; and potassium oxonate, which inhibits the phosphorylation of 5-FU and ameliorates gastrointestinal toxicity [31]. It has been approved as a chemotherapeutic agent for gastrointestinal cancers, breast cancer, and non-small-cell lung cancer. S-1 has been frequently used for older patients because the oral administration route imposes less physical burden such as physician visits or puncturing for vascular access. The efficacy of S-1 for treating pancreatic cancer was demonstrated in the GEST study for unresectable patients with cancer as well as in the JASPAC-1 study for resectable patients with cancer [18,19,32]. However, almost all articles on efficacy of S-1 monotherapy investigated patients with gemcitabine resistant pancreatic cancer [16,33]. There is limited evidences of the clinical value and efficacy of S-1 monotherapy as first-line systemic chemotherapy in the management of older patients with pancreatic cancer. Although a research conducted by Imaoka et al. was the one that investigated the efficacy of S-1 monotherapy on older patients with unresectable pancreatic cancer, it focused on the efficacy of combination gemcitabine and S-1 therapy and the authors could not devote sufficient focus to assess the efficacy of S-1 monotherapy [20].

In the present study, the OS of the S-1 group was longer than that of the gemcitabine group. The HR associated with death within three years from the diagnosis was significantly lower in the S-1 group than the gemcitabine group. On the other hand, the percentage of patients who also received radiation was higher in the S-1 group. This could contribute to prolonging survival. Therefore, in the first sensitivity analysis, we analyzed the population, excluding the patients treated with both radiation and chemotherapy. Although the median OS was reduced, the sensitivity analysis revealed consistent results. This result demonstrated that the combination therapy of S1 and radiation might partially improve the survival but S-1 monotherapy without radiation could achieve improved efficacy when administered to older patients with unresectable pancreatic cancer. This sensitivity analysis also suggested that a combination therapy with S-1 and radiation might be an effective therapeutic option, though the population that received S-1 and radiation was under-represented. Furthermore, the percentage of patients receiving second-line chemotherapy was higher in the S-1 group than the

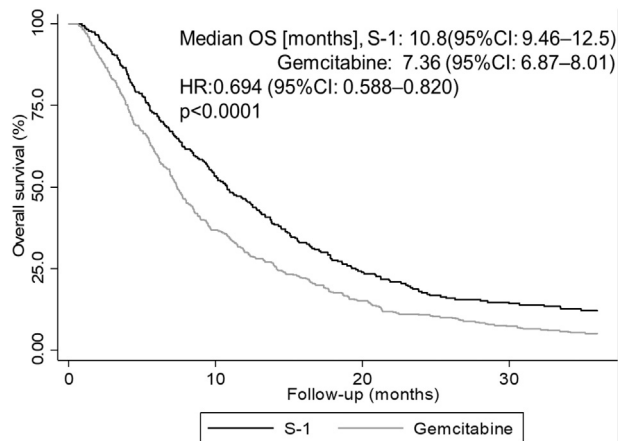


Fig. 2. Kaplan-Meier curves comparing overall survival. P value was calculated with the use of the stratified log-rank test. OS: overall survival CI: confidence interval HR: hazard ration.

Table 3
Time to second-line treatment and results of univariate and multivariate Cox proportional hazard analyses.

		S-1	Gemcitabine		p-Value
Patients receiving second-line chemotherapy		93	142		0.0923
Second-line chemotherapy	Gemcitabine	44 (47.3%)	S-1	78 (54.9%)	
	S-1 + Gemcitabine	39 (41.9%)	S-1 + Gemcitabine	58 (40.8%)	
	S-1 + Cisplatin	3 (3.2%)	Cisplatin	3 (2.1%)	
	Paclitaxel	2 (2.2%)	Etoposide	2 (1.4%)	
	5-FU	2 (2.2%)	Paclitaxel	1 (0.7%)	
	Cisplatin + Irinotecan	1 (1.1%)			
	Gemcitabine + Paclitaxel	1 (1.1%)			
	Gemcitabine + 5-FU	1 (1.1%)			
Switching to second-line chemotherapy	<28 days	29(31.2%)	12(8.5%)	<0.001	
	≥28 days	64(68.8%)	130(91.5%)	0.477	
Median interval between first-line and second-line therapy (95% CI) [months]		4.90 months (95%CI: 2.83–6.57)	4.60 months (95%CI: 4.01–5.78)		
		Univariate HR(95% CI)	p-Value	Adjusted HR(95% CI)	p-Value
Sex	Male	REF		REF	
	Female	0.906(0.682–1.204)	0.496	0.902(0.669–1.215)	0.497
Age	75≤ <80	REF		REF	
	80≤ <85	1.039(0.718–1.321)	0.865	0.974(0.749–1.442)	0.819
	85≤	0.842(0.489–1.450)	0.535	0.907(0.513–1.602)	0.736
	Low (≤1)	REF		REF	
CCI	Intermediate (2 ≤ ≤6)	1.025(0.713–1.475)	0.893	1.014(0.702–1.467)	0.938
	High (7≤)	1.178(0.845–1.642)	0.335	1.194(0.844–1.690)	0.317
	Gemcitabine	REF		REF	
Regimen	S-1	1.023(0.757–1.382)	0.882	0.968 (0.708–1.324)	0.838

P value of upper case was calculated by Fisher exact test.

Adjusted HR was estimated according to age, sex, and comorbidities(Charlson comorbidity index).

Patients switching to second-line chemotherapy within 28 days were excluded from this analysis.

CI: confidence interval REF: reference HR: hazard ratio CCI: Charlson comorbidity index.

gemcitabine group. We conducted the second sensitivity analysis to investigate whether the improved survival was affected by treatments after first-line chemotherapy. In the analysis of patients receiving first-line chemotherapy alone, the results were consistent with the original analysis.

Regarding time to second-line chemotherapy as a surrogate indicator of PFS, there was no significant difference between the S-1 group and the gemcitabine group, after excluding those who switched to second-line chemotherapy within 28 days. The investigation of the secondary outcome revealed that the percentage of patients who switched to other regimens within 28 days was higher in the S-1 group than the gemcitabine group. This finding suggested that adverse events might occur at higher rates in the S-1 group. The preceding studies suggested

that there were more patients discontinued treatment due to treatment-related adverse events in the S-1 group than the gemcitabine group [20]. This result may warrant careful attention and further characterization of the tolerability of S-1 administered to older patients with pancreatic cancer.

The present study has strengths and limitations. One strength is that study was based on a healthcare claims database with long-term sustainable eligibility for the majority of older adults. In general, loss to follow-up in cohort studies could introduce selection bias [34]. The structure of this public insurance enabled us to achieve a high rate of complete follow-up. Another strength is that the healthcare insurance covered almost all people aged ≥75 years. Sampling from this insurance database made a study population large enough for multivariate survival analyses with adjustments for sex, age, and comorbidities.

As this study was performed exclusively in Japan, there was limited ethnic diversity. Therefore, whether our findings apply to other populations remains to be determined. Another limitation was that the study design was a retrospective cohort for which potential selection bias could exist. Furthermore, this study was based on a claims database which information concerning cancer stages upon diagnosis and tumor morphology was not always well-documented, although the CCI included metastasis. This claims database could have input and coding errors, which are more likely to be random errors and not to have crucial influence on the statistical inferences. There was also a limitation regarding the use of time-to-second-line chemotherapy as a surrogate indicator of PFS; however, this was based on prior literature that demonstrated time-to-second-line chemotherapy correlated with PFS [35]. Finally, we excluded study subjects switching to another regimen within 28 days because they were likely to shift to an alternative regimen because of adverse events of their first-line chemotherapy rather than disease progression. This would not exclude study subjects who switched to another regimen because of late adverse reactions.

In conclusion, the present study revealed that S-1 could significantly prolong the survival of patients aged ≥75 years with unresectable

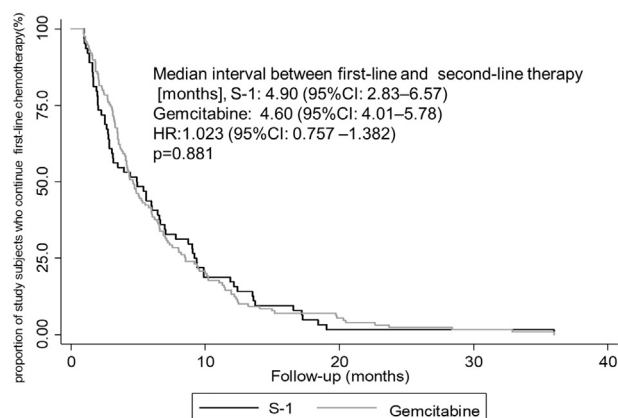


Fig. 3. Kaplan-Meier curve comparing time to second-line chemotherapy. In this analysis, patients switching to second-line chemotherapy within 28 days were excluded. P values was calculated with the use of the stratified log-rank test. CI: confidence interval HR: hazard ratio.

Table 4

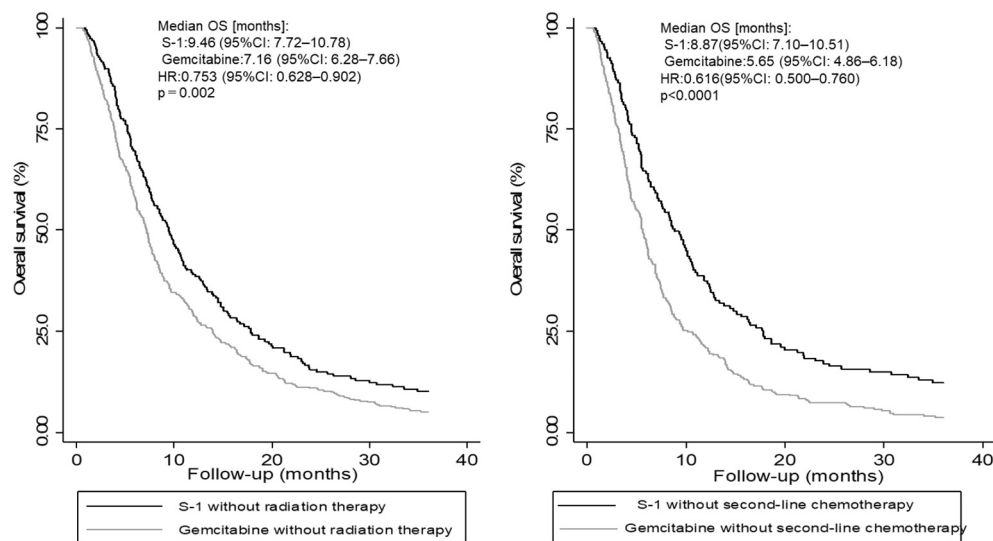
Sensitivity analysis. Upper case: analyses for study subjects receiving chemotherapy alone.

		S-1		Gemcitabine	
Patients treated with chemotherapy alone (%)		187		411	
Death within 3 years (%)		168 (89.8%)		390 (94.9%)	
Median OS (95% CI) [months]		9.46 (7.72–10.78)		7.16 (6.28–7.66)	
		Univariate HR(95% CI)	p-Value	Adjusted HR(95% CI)	p-Value
Sex	Male	REF		REF	
	Female	0.891(0.755–1.053)	0.175	0.873(0.738–1.032)	0.112
Age	75≤ <80	REF		REF	
	80≤ <85	1.027(0.858–1.230)	0.768	1.082(0.901–1.299)	0.401
	85≤	0.897(0.685–1.173)	0.427	0.941(0.716–1.234)	0.660
CCI	Low (≤1)	REF		REF	
	Intermediate (2 ≤ ≤6)	0.840(0.685–1.030)	0.094	0.837(0.681–1.028)	0.089
	High (7≤)	1.093(0.896–1.332)	0.380	1.115(0.911–1.364)	0.292
Regimen	Gemcitabine	REF		REF	
	S-1	0.753(0.628–0.902)	0.002	0.746(0.622–0.895)	0.002

		S-1		Gemcitabine	
Patients treated with first-line chemotherapy alone(%)		147		298	
Death within 3 years(%)		129(87.8%)		287(96.3%)	
Median OS (95% CI)[months]		8.87(7.10–10.51)		5.65 (4.86–6.18)	
		Univariate HR(95% CI)	p-Value	Adjusted HR(95% CI)	p-Value
Sex	Male	REF		REF	
	Female	0.917(0.756–1.111)	0.376	0.898(0.739–1.091)	0.279
Age	75≤ <80	REF		REF	
	80≤ <85	1.086(0.881–1.340)	0.439	1.101(0.892–1.361)	0.369
	85≤	0.774(0.578–1.037)	0.086	0.807(0.601–1.084)	0.155
CCI	Low (≤1)	REF		REF	
	Intermediate (2 ≤ ≤6)	0.839(0.667–1.057)	0.136	0.860(0.681–1.086)	0.206
	High (7≤)	1.201(0.953–1.528)	0.118	1.204(0.948–1.530)	0.127
Regimen	Gemcitabine	REF		REF	
	S-1	0.616(0.500–0.760)	<0.001	0.629(0.509–0.776)	<0.001

Lower case: analyses for study subjects receiving first-line chemotherapy alone.

OS: Overall survival REF: reference CI: confidence interval HR: hazard ratio CCI: Charlson comorbidity index.

**Fig. 4.** Kaplan-Meier curve for sensitivity analyses. LEFT: analyses for study receiving chemotherapy alone. RIGHT: analyses for study subjects receiving first-line chemotherapy alone. P values were calculated with the use of the stratified log-rank test. OS: overall survival CI: confidence interval HR: hazard ratio.

pancreatic cancer, compared with gemcitabine. The present study further showed that the S-1 group switched to other regimen within 28 days at higher rates than the gemcitabine group. This finding suggests that adverse events might occur more frequently in the S-1 group. However, regarding the time to second-line chemotherapy, there was no significant difference between each group who could continue

their first-line chemotherapy over 28 days. This finding suggests S-1 could serve as a first-line chemotherapeutic option for older patients with unresectable pancreatic cancer, if they could tolerate the S-1 regimen longer than 28 days. The present study was a retrospective cohort, which selection bias could not be denied in spite of the high rate of complete follow-up. However, our findings suggested the promising efficacy

of S-1 as an alternative for first-line chemotherapy of older patients with unresectable pancreatic cancer and therefore warrant further evaluation in RCTs to establish higher quality evidence.

Disclosures and Conflicts of Interest Statement

None

Role of the Funding Source

None

Acknowledgement

We appreciated Fukuoka Prefecture Wide-Area Association of Latter-Stage Elderly Healthcare for providing health claims database and master data. We thank Edanz Group (www.edanzediting.com/ac) for editing a draft of this manuscript.

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