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REVIEW

Post-progression survival following second-line chemotherapy in patients with advanced pancreatic cancer previously treated with gemcitabine: a meta-analysis

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Summary

Background Post-progression survival (PPS) could be a confounding element in interpreting data from clinical trials of second-line chemotherapy in patients with advanced pancreatic cancer (PC) previously treated with gemcitabine (GEM) because a recent meta-analysis of oxaliplatin combination therapy showed statistical heterogeneity for overall survival (OS) but not for progression-free survival (PFS). This study aimed to improve the understanding of the impact of PPS on OS in this setting. *Methods* Databases were searched to identify randomized controlled trials (RCTs) in the salvage setting. We evaluated relationships between OS and PFS, PPS, and other variables. *Results* Totally, 17 RCTs with 3253 patients were identified. Median OS was strongly and moderately associated with median PPS and PFS, respectively ($r = 0.913$; $p < 0.001$ and 0.780; $p < 0.001$, respectively). The proportion of patients with good performance status was significantly associated with both PPS and PFS ($r = 0.574$, $p < 0.001$ and 0.492, $p < 0.001$, respectively). The induction rate of subsequent chemotherapy was related to the duration of PPS and OS ($r = 0.640$, $p < 0.001$ and 0.647, $p < 0.001$, respectively). Median PPS and OS were significantly longer in recent trials than those in older trials (3.55 versus 2.78 months, $p < 0.001$ and 6.29 versus 5.02 months, $p < 0.001$). *Conclusions* Median PPS was strongly correlated with median OS. Given the recently increased opportunity for subsequent chemotherapy and supportive care, PPS may serve as an important element to clarify problems in this setting.

Keywords Pancreatic cancer · Meta-analysis · Randomized controlled trial · Second-line chemotherapy · Salvage chemotherapy · Post-progression survival

Introduction

Pancreatic cancer (PC) is the fourth leading cause of cancer-related deaths in the United States and Europe and the eighth leading cause of cancer-related mortality worldwide [1–3]. Conventional cytotoxic chemotherapy remains the standard treatment for patients with advanced PC. Gemcitabine (GEM)-based chemotherapy, including its combination with nab-paclitaxel, is a standard first-line treatment for metastatic PC because of the improved survival it confers [4]. Combined folinic acid (leucovorin (LV)), 5-fluorouracil (5-FU), irinotecan, and oxaliplatin (FOLFIRINOX) is also a standard first-line treatment, but only in patients with good performance status (PS) [5].

With the increased availability of active agents for PC, we have recently shown that survival after progression (post-progression survival, PPS) and the induction rate of subsequent anti-cancer therapies are significantly associated with overall survival (OS) after the first-line treatment of advanced PC [6]. A similar correlation between OS and PPS was reported in randomized trials of first-line treatment for many types of gastrointestinal cancers [6–9].

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A prematurely stopped RCT from the German CONKO-study group provided evidence of the benefit of second-line chemotherapy compared to best supportive care (BSC) [10]. Results from the recent NAPOLI-1 phase III trial showed significant improvements in both progression-free survival (PFS) and OS in patients with metastatic PC after previous GEM-based therapy and irinotecan liposomal injection combined with 5-FU/LV, indicating a new treatment option for this population [11]. Oxaliplatin combination therapy in this setting has also been investigated by three RCTs (CONKO-003, PANCREOX, and SOX [S-1 plus oxaliplatin]), with different and confounding results [12–14]. A meta-analysis of the three studies demonstrated a modest improvement in PFS (hazard ratio (HR), 0.81; 95% confidence interval (CI), 0.67–0.97; $I^2 = 5\%$; $p = 0.02$); however, this benefit in PFS did not translate to a survival advantage (HR, 1.03; 95% CI, 0.64–1.67; $I^2 = 83\%$; $p = 0.90$) [15]. The I^2 statistic describes the percentage of variation across studies that is due to heterogeneity rather than chance [16]. The statistical heterogeneity examined using the I^2 statistic for OS, but not for PFS, is suggestive of the significance of understanding PPS in the salvage setting in PC patients previously treated with GEM. PPS could be a confounding element in the interpretation of clinical trial data in this setting. Although a number of RCTs have been performed in patients with advanced PC previously treated with GEM-based therapy, little is known about PPS in this group of patients. Analysis of PPS may provide valuable insight for evaluation of chemotherapy in the salvage setting. Therefore, we conducted a systematic review and meta-analysis of currently available RCTs to assess the association between PPS with OS in the salvage setting of PC patients previously treated with GEM.

Methods

Registration

This study is registered in the PROSPERO database (CRD42017071274) and was conducted according to the Preferred Reporting Items for Systemic Reviews and Meta-Analysis (PRISMA) statement. We did not use individual data but published data. These data have been widely utilized in research and are generally available. Therefore, we confirm that any aspect of the work covered in this manuscript has been conducted with ethical approval.

Search strategy and trial selection

An independent review of PubMed, Embase, Web of Science, and Cochrane database citations through June 2017 was performed. The keywords included in the search were 'pancreatic cancer,' 'randomized,' and 'chemotherapy.' The search was limited to randomized controlled phase II and III trials published in English. We reviewed each publication and selected randomized studies comparing two or more first-line systemic chemotherapeutic agents for unresectable, locally advanced or metastatic PC. To find any additional trials, we also searched unpublished data and abstracts from the annual meetings of the American Society of Clinical Oncology (through 2017) and the European Cancer Conference and European Society of Medical Oncology (through 2017). Trials were eligible if they provided data for both OS and either PFS or time-to-progression (TTP), regardless of whether these parameters were explicitly defined. The exclusion criteria included trials in which patients had not previously been treated with GEM-based chemotherapy. Two investigators (A.K. and Y.H.) independently extracted the data from the trials in order to avoid bias.

Data abstraction

We analyzed the primary and secondary efficacy endpoints in detail based on the definitions provided in each trial. When not specifically stated, we considered the primary endpoint to be that used for the calculation of sample size. For the sake of simplicity, two endpoints (PFS and TTP) based on tumor assessment are collectively referred to as PFS in the present study, similar to the approach adopted in recent reports [6, 7, 17, 18]. Median OS and PFS were extracted from all trials and the median PPS was defined as the median OS minus the median PFS for each trial. We also obtained the following information from each report: year of completion of trial enrollment, number of patients, median age of patients, and proportion of patients who received second-line chemotherapy.

Statistical analysis

We summarized the survival data (median OS, PFS, PPS, and median PFS/median OS) as mean and standard error (SE). SE was calculated as previously described [19]. We also calculated the percentage of OS accounted for by PPS as: 100 – (100 × median PFS/median OS). To assess relationships between median OS and either median PFS or median PPS, we used Spearman's rank correlation coefficient. To account for differences in sample size among trials, we weighed all analyses by the number of patients. In addition, all trials were divided into two groups based on the year in which trial enrollment was completed. Thus, the number of patients was nearly evenly split using a threshold in order to evaluate the changes in PFS, PPS, and OS as described in previous studies [6, 7, 18]. We examined the differences between survival between older and recent trials by normal approximation of the average survival data (t-tests).

All reported p-values correspond to two-sided tests and those <0.05 were considered statistically significant.

Analyses were performed using IBM SPSS Statistics for Windows, version 20.0 (IBM Corp., Armonk, NY, USA) and SAS for Windows release 9.4 (SAS Institute, Cary, NC).

Results

Trials included in the analysis

Among the retrieved papers and abstracts, 17 randomized trials comprising 35 treatment arms and 3253 patients were identified (Fig. 1, Table 1) [11–14, 20–32]. Two randomized, placebo-controlled phase 3 studies of ruxolitinib plus capecitabine (JANUS 1 and JANUS 2) were excluded because the first-line regimens of some of the included patients were FOLFIRINOX [33].

Median OS, PFS, and PPS in all trials and in subgroups based on the year of trial enrollment completion

The average median OS was significantly longer in recent trials than that in older trials (6.29 versus 5.02 months, $p < 0.001$), and this improvement was accompanied by significant increases in the average median PFS (2.74 versus 2.24 months, $p < 0.001$) and PPS (3.55 versus 2.78 months, $p < 0.001$). The average proportion of median OS accounted for by the median PPS was significantly larger in recent trials than that in older trials (56.13 versus 54.25%, $p < 0.001$) (Table 2).

Association between median OS and median PFS or PPS

The relationships between the median OS and either median PFS or PPS are shown in Fig. 2. The median PPS was highly significantly associated with median OS ($r = 0.913$; $p < 0.001$), whereas the median PFS was moderately associated with median OS ($r = 0.780$; $p < 0.001$).

Correlation between performance status and median OS, PFS, or PPS

We analyzed the relationship between the percentage of patients with good performance status (PS) and the duration of PFS, PPS, and OS. The proportion of patients with Eastern Cooperative Oncology Group (ECOG) PS score of 0 or Karnofsky Performance Scale (KPS) score of 0 was more significantly associated with PPS than with PFS ($r = 0.574$ and 0.492; $p < 0.001$ and $p < 0.001$, respectively).

Relationship between the induction rate of subsequent chemotherapy and the duration of PPS and OS

The percentage of patients who received subsequent chemotherapy was available for 14 treatment arms. The characteristics of the patients in this subgroup were similar to those of all patients (data not shown). The duration of PPS and OS was related to the induction rate of subsequent chemotherapy ($r = 0.640$ and 0.647; $p < 0.001$ and $p < 0.001$, respectively) (Fig. 3).

Japanese and non-Japanese trials

Among the 17 trials, six were performed in Japan. In the randomized phase III study of TAS-118 versus S-1 in patients with gemcitabine-refractory advanced PC (GRAPE) trial conducted in Korea and Japan, 80% of the patients were Japanese; thus, it was regarded as a Japanese trial in the current study (Table 3). The average median OS, PFS, and PPS were

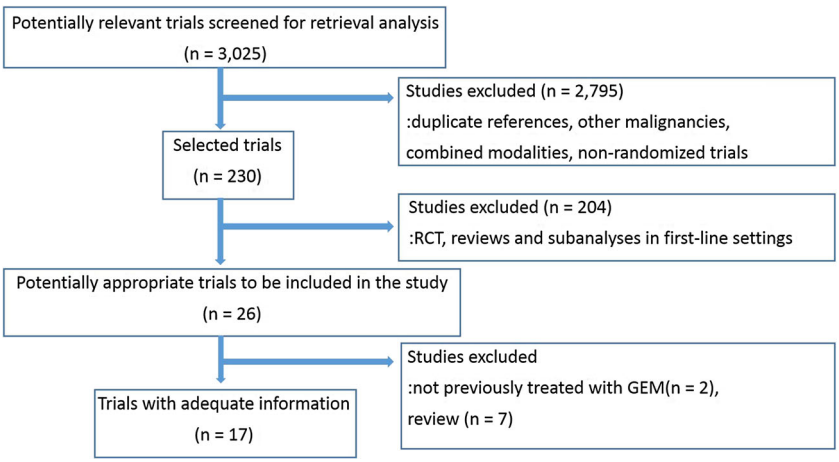

Fig. 1 PRISMA (Preferred Reporting Items for Systematic Reviews) diagram of the analysis

Table 1 Characteristics of the trials included in the analysis

Author	Reference	(Year)	Year of completion	Phase	Regimen	Performance status	Number of patients	Primary endpoint	PFS (months)	PFS HR (95% CI)	OS (months)	OS HR 95% CI	PPS (months)	Induction rate of post-trial treatment (%)
Ulrich-Pur	[20]	2003	2001	2	raltitrexed	KPS, 90–100: 21%	19	RR	2.50	NA	4.30	NA	1.80	NA
					raltitrexed plus irinotecan	KPS, 90–100: 21%	19		4.00		6.50		2.50	NA
Jacobs	[21]	2004	2004	3	physicians' best choice	NA	211	OS	1.60	NA	3.13	NA	1.53	NA
					rubitecan	NA	198		1.93		3.60		1.67	NA
Oettle	[12]	2014	2007	3	FF	KPS, 90–100: 47.6%	76	OS	2.00	0.68(0.50–0.94)	3.30	0.66(0.48–0.91)	1.30	23.7
					OFF	KPS, 90–100: 53.9%	84		2.90		5.90		3.00	26.2
Yoo	[22]	2009	2008	2	FOLFIRI	ECOG PS, 0: 16.1%	31	6-month SR	1.94	NA	3.87	NA	1.93	NA
					FOLFOX	ECOG PS, 0: 16.7%	30		1.40		3.48		2.08	NA
Ioka	[23]	2013	2008	2	fluoropyrimidine	NA	40	OS	3.80	NA	7.50	NA	3.70	NA
					GEM	NA	40		1.70		5.40		3.70	NA
Van Custem	[24]	2010	2009	3	5-FU or Cape	ECOG PS, 0: 37.7%	204	OS	1.91	1.02(0.83–1.26)	5.06	1.05(0.84–1.30)	3.15	NA
					larotaxel	ECOG PS, 0: 37.7%	204		2.04		4.80		2.76	NA
Ohkawa	[14]	2015	2010	2	S-1	ECOG PS, 0: 70.8%	135	PFS	2.80	0.84(0.65–1.08)	6.90	1.03(0.79–1.34)	4.10	55.6
					SOX	ECOG PS, 0: 69.4%	136		3.00		7.40		4.40	52.9
Ioka	[25]	2017	2011	2	S-1	ECOG PS, 0: 76.1%	67	PFS	1.90	0.77(0.53–1.11)	5.80	0.75(0.51–1.09)	3.90	62.7
					IRIS	ECOG PS, 0: 71.7%	60		3.50		6.80		3.30	63.3
Wang	[26]	2013	2012	2	S-1	ECOG PS, 0: 26.7%	30	PFS	2.50	NA	6.10	NA	3.60	NA
					S-1 CIK	ECOG PS, 0: 25.0%	28		2.90		6.60		3.70	NA
Ueno	[27]	2016	2012	2	S-1	ECOG PS, 0: 67.6%	71	PFS	2.70	0.56(0.37–0.85)	6.10	0.82(0.54–1.22)	3.40	42.3
					S-1/LV	ECOG PS, 0: 65.2%	69		3.80		6.30		2.50	39.1
Gill	[13]	2016	2012	3	FF	ECOG PS, 0: 18.9%	54	PFS	2.90	1.00(0.66–1.53)	9.90	1.78(1.08–2.93)	7.00	23.0
					FOLFOX	ECOG PS, 0: 13.0%	54		3.10		6.10		3.00	7.0
Ge	[28]	2014	2013	2	S-1	KPS, 90–100: 46.8%	47	6-month SR	1.90	0.86(0.66–1.63)	5.50	0.83(0.66–1.67)	3.60	NA
					S-1/LV	KPS, 90–100: 51.1%	45		3.00		6.30		3.30	NA
Hurwitz	[29]	2015	2013	2	Cape	KPS, 100: 12.7%	63	OS	1.50	0.75(0.52–1.10)	4.30	0.79(0.53–1.18)	2.80	NA
					Cape ruxolitnib	KPS, 100: 10.9%	64		1.70		4.50		2.80	NA
Wang-Gillam	[11]	2016	2013	3	FF	KPS, 100: 14.3%	149	OS	1.50	0.56(0.41–0.75)	4.20	0.67(0.49–0.92)	2.70	37.8
					nanoliposomal irinitecan	KPS, 100: 14.6%	151		2.70		4.90		2.20	NA
					nanoliposomal irinitecan plus FF	KPS, 100: 15.4%	117		3.10		6.10		3.00	30.8

Table 1 (continued)

Author	Reference	(Year)	Year of completion	Phase	Regimen	Performance status	Number of patients	Primary endpoint	PFS (months)	PFS HR (95% CI)	OS (months)	OS HR 95% CI	PPS (months)	Induction rate of post-trial treatment (%)
Chung	[30]	2016	2014	2	FOLFOX	ECOG PS, 0: 45.0%	62	OS	2.00	1.61(1.07–2.43)	6.70	1.37(0.90–2.08)	4.70	NA
					selumetinib MK2206	ECOG PS, 0: 41.5%	58		1.90		3.90		2.00	NA
Ueno	[31]	2017	2015	2	S-1	ECOG PS, 0: 28.0%	25	PFS	2.10	1.06(0.60–1.86)	5.50	1.02(0.57–1.81)	3.40	NA
					GS	ECOG PS, 0: 34.6%	26		2.00		3.80		1.80	NA
Ueno	[32]	2017	2015	2	S-1	ECOG PS, 0: 55.5%	290	OS	2.80	0.80(0.67–0.95)	7.90	0.98(0.82–1.16)	5.10	63.8
					TAS118	ECOG PS, 0: 57.1%	296		3.90		7.60		3.70	56.1

Abbreviations: Cape = Capecitabine; CI=Confidence interval; CIK=Cytokine-induced killer cells; ECOG PS = European Clinical Oncology Group Performance Status; FF = 5FU + folinic acid; FOLFIRI = 5FU + folinic acid+irinotecan; FOLFOX = 5FU + folinic acid+oxaliplatin; GEM = Gemcitabine; GS = Gemcitabine+S-1; HR = Hazard ratio; IRIS=Irinotecan+S-1; KPS=Karnofsky performance status; LV = Leucovorine; NA = not available; OFF = 5FU + folinic acid+irinotecan; OS=Overall survival; PFS=Progression-free survival; PPS = post-progression survival; SOX = S-1 + oxaliplatin; SR = survival rate

significantly longer in Japanese trials than those in non-Japanese trials. The induction rate of subsequent chemotherapy and the proportion of patients with ECOG PS score of 0 were significantly higher in Japanese trials than that in non-Japanese trials. The median PPS was moderately associated with the median OS ($r = 0.667$; $p < 0.001$), whereas the median PFS was weakly associated with the median OS ($r = 0.354$; $p < 0.001$).

Discussion

The present study examined the duration of PPS in RCTs of salvage chemotherapy in patients with advanced PC previously treated with GEM. An improved understanding of PPS may clarify the uncertainty in the interpretation of clinical trial data in this setting. We found that the median OS was more strongly associated with median PPS than with median PFS and that proportion of patients with a good PS was associated with PPS as well as PFS for patients with advanced PC in this setting. Moreover, the relatively long duration of average median PPS accounted for more than half of the average median OS derived from salvage chemotherapy. PPS accounted for a larger percentage of the OS in this setting than that in our previous study in a first-line setting [6]. Thus, it is reasonable to conclude that the high proportion of median OS accounted for by the median PPS in the present study contributed to the weakness of the association between the treatment benefits for PFS and OS.

Several factors might explain these findings. First, maintenance of a good PS could affect the duration of PPS even after the failure of standard chemotherapy. PS has been identified as a strong prognostic factor in terms of OS for patients with advanced PC in the second-line setting [34–36]. Systemic weakness and severe tumor condition are reflected by the PS [37]. Patients with a good PS are usually enrolled in clinical trials as a result of the inclusion criteria. Although information on changes in PS during disease progression was not available for the selected clinical trials, maintenance of a good PS may allow a patient to receive effective supportive and palliative care or additional lines of chemotherapy. Palliative care has played an important role in patients with advanced PC. According to the clinical data presenting the prognostic analysis of patients with advanced PC receiving palliative care without aggressive anti-tumor therapies, a good PS was an effective predictive factor of longer survival [38]. PS is also an important prognostic factor in patients undergoing palliative care. Mechanical obstruction or stenosis of the bile duct is very common in this

Table 2 Average median OS, PFS and PPS

Trials	Number of patients	Number of trials	Average median (months)			Average
			OS	PFS	PPS	PPS/OS (%)
All	3253	17	5.69 (0.03)	2.51 (0.01)	3.18 (0.02)	55.23 (0.00)
Older (up to and including 2011)	1554	8	5.02 (0.04)	2.24 (0.02)	2.78 (0.03)	54.25 (0.00)
Recent (2012 and later)	1699	9	6.29[a] (0.04)	2.74[a] (0.02)	3.55[a] (0.03)	56.13[a] (0.00)

Values in brackets are standard errors

OS Overall survival, *PFS* Progression-free survival, *PPS* post-progression survival

[a] $P < 0.001$ versus the corresponding value for older trials (t test)

setting; biliary drainage is an effective supportive method for these patients because obstruction may lead to the development of cholangitis. In patients with inoperable PC receiving chemotherapy who underwent biliary drainage, a good PS was independently associated with good prognosis [39]. Thus, patients maintaining a good PS could take advantage of opportunities for interventional supportive cares and benefit from palliative cares. Therefore, the maintenance of a good PS could contribute to the prolongation of PPS. Indeed, the proportion of patients with a good PS was associated with PPS in our study. Second, the recent increase in the number of available active compounds may have contributed to a more widespread clinical use of chemotherapy in this setting, although no further lines of chemotherapy (third line or later) have been shown to provide a survival benefit in comparison with best supportive care. A recent largest phase III trial comparing S-1 plus leucovorin and S-1 reported that FOLFIRINOX or nab-paclitaxel in combination with GEM as post-study treatment might dilute the contribution of the experimental therapy [32]. In the three abovementioned studies that examined the role of oxaliplatin in GEM-refractory PC, the induction rate of subsequent chemotherapy did not differ in each arm in the CONKO-003 and SOX trials [12, 14]. However, more than three times as many patients in the control arm received post-trial treatments as those in the experimental arm of the PANCREOX study. A larger proportion of patients with an ECOG PS of 0 were randomized to the control arm, which might have influenced the PPS in the control arm and was reflected in the percentage induction of subsequent chemotherapy in this study [13]. The induction of post-trial chemotherapy after the second line is related to the duration of PPS and OS in our study. These data suggest that the efficacy of late-line therapies might contribute, at least in part, to the prolongation of PPS.

The present study has several limitations. First, our analysis was based on abstracted data. The use of individual patient data might have allowed a better characterization of

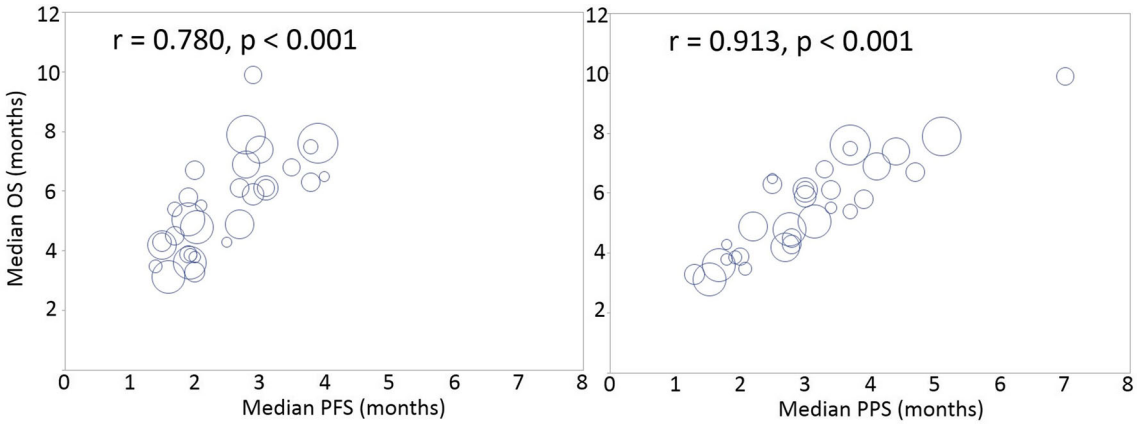

Fig. 2 Relationship between median overall survival (OS) and median progression-free survival (PFS) or post-progression survival (PPS). The area of each circle is proportional to the number of patients in each trial arm. The r values represent the Spearman's rank correlation coefficients

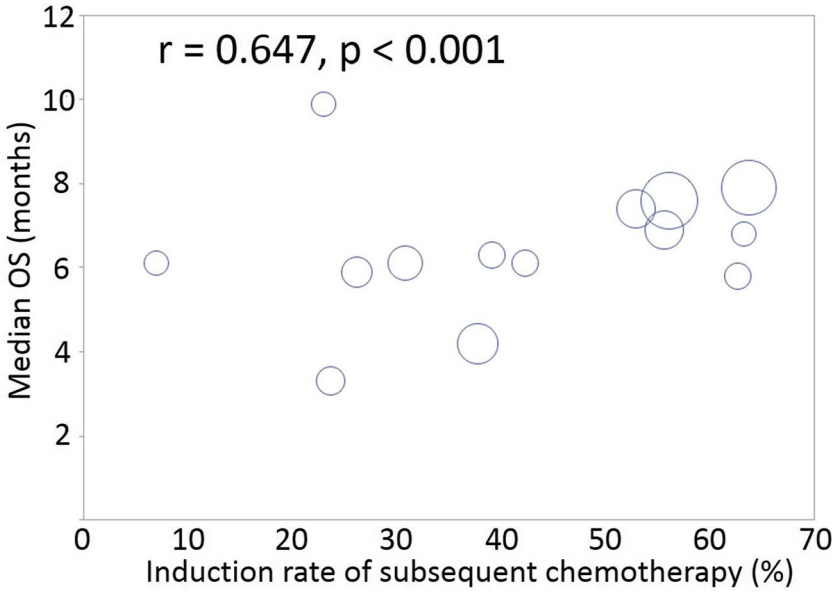

Fig. 3 Relationship between the median overall survival (OS) and the induction rate of post-trial anticancer therapy. The area of each circle is proportional to the number of patients in each trial arm. The r values represent the Spearman's rank correlation coefficients

the relationship between OS and other endpoints based on tumor assessment, including PFS and TTP. However, this approach would restrict the analysis to a small number of trials and would hinder its replication by independent researchers. Second, the results of our study may have several confounders due to the inclusion of a number of heterogeneous trials in the analysis. Indeed, our study revealed that the median PFS, OS, and PPS were significantly longer in Japanese trials than those in non-Japanese trials. Although the results are generally unaccountable without appropriate adjustment for patient characteristics dependent on differences in predefined eligibility criteria for enrollment in the clinical trials in different regions, the positive relationship between PPS and OS was apparent in Japanese trials as well as in non-Japanese trials. Finally, two endpoints (PFS and TTP) based on tumor assessment were grouped into the same parameter, following the example of previous studies [6, 7, 17, 18, 40]. PFS is defined as the time from randomization to tumor progression or death, whereas TTP is defined similarly but considers death as the time point at which censoring occurs. TTP is the same as PFS if death does not occur during treatment. We, therefore, considered PFS to be the same as TTP in our analyses.

Conclusions

To our knowledge, this is the first study to analyze PPS in randomized trials of patients with advanced PC previously treated with GEM who received second- or third-line chemotherapy. Our findings indicate that median PPS is strongly associated with median OS even in the salvage setting. Moreover, the proportion of good

Table 3 Average median OS, PFS, PPS, and average induction rate of subsequent chemotherapy and proportions of PS score of 0

Trials	Number of patients	Number of trials	Average median (months)			Average rate (%)	
			OS	PFS	PPS	Subsequent chemotherapy	PS 0
Japanese	1255	6	7.09 (0.02)	3.08 (0.02)	4.01 (0.02)	56.5 (0.21)	61.5 (0.28)
Non-Japanese	1998	11	4.81[a] (0.03)	2.14[a] (0.01)	2.67[a] (0.02)	27.8[a] (0.38)	25.0[a] (0.33)

Values in brackets are standard errors

OS Overall survival, *PFS* Progression-free survival, *PPS* post-progression survival, *PS* performance status

[a] $P < 0.001$ versus the corresponding value for Japanese trials (t-test)

PS was associated with both PPS and PFS. Given the recent increase in the opportunity for the subsequent chemotherapy and the effective supportive care, PPS could be an important element in the interpretation of clinical trials data in this setting. It is important that researchers are aware of these findings when designing clinical trials of salvage chemotherapy for patients with advanced PC.

Compliance with ethical standards

Conflict of interest All authors declare no Conflicts of Interests for this article.

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Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

We did not use individual data but published data. These data have been widely utilized in research and are generally available. Therefore, we confirm that any aspect of the work covered in this manuscript has been conducted with ethical approval. And this study is registered in the PROSPERO database (CRD42017071274) and was conducted according to the Preferred Reporting Items for Systemic Reviews and Meta-Analysis (PRISMA) statement.

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