

Positive relationship between subsequent chemotherapy and overall survival in pancreatic cancer: meta-analysis of postprogression survival for first-line chemotherapy

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Abstract

Purpose To gain a better understanding of the impact of postprogression survival (PPS) and post-trial anticancer therapy on overall survival (OS) in first-line pancreatic cancer patients.

Methods A literature search identified 54 randomized trials, focusing on gemcitabine monotherapy to eliminate effects of heterogeneity of first-line regimens. We evaluated the relation between OS and either progression-free survival (PFS) or PPS. We also examined whether any association might be affected by the year of completion of trial enrollment.

Results For all 54 trials, PPS was strongly associated with OS ($r=0.844$), whereas PFS was moderately associated with OS ($r=0.623$). Average OS and PPS were significantly longer in recent trials than in older trials, (7.29 versus 6.15 months, $p<0.001$) and (3.64 versus 2.86 months, $p<0.001$), respectively. The correlation between OS and PPS in recent trials was much stronger than that in older trials ($r=0.846$ versus 0.729). The relation between OS and PFS in recent and older trials did not differ ($r=0.595$ versus 0.563). The percentage of patients with post-trial treatment was significantly higher in recent trials than in

older trials (52.7 versus 39.7%, $p<0.001$). The rate of post-trial anticancer therapy was significantly associated with OS ($r=0.910$).

Conclusions We found an increase in median PPS in accordance with an increase in median OS in recent trials compared with older trials and that rate of post-trial anticancer therapy was strongly associated with median OS. It is important that researchers be aware of these findings in designing clinical trials of first-line chemotherapy for pancreatic cancer patients.

Keywords Pancreatic cancer · Meta-analysis · Randomized controlled trial · Gemcitabine · Chemotherapy · Postprogression survival

Abbreviations

PC	Pancreatic cancer
GEM	Gemcitabine
OS	Overall survival
PFS	Progression-free survival
PPS	Postprogression survival
TTP	Time to progression
SE	Standard error

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Introduction

Pancreatic cancer (PC) is the fourth cause of cancer-related death in Europe and the United States [1]. Gemcitabine (GEM) monotherapy has been the standard first-line chemotherapy for patients with unresectable locally advanced or metastatic PC since 1997 [2]. Although various GEM-based combination regimens and GEM-free regimens have been evaluated, only nab-paclitaxel or erlotinib added to GEM or fluorouracil/leucovorin plus irinotecan plus

oxaliplatin (FOLFIRINOX) showed a survival benefit over GEM alone in phase III studies [3–5]. The median overall survival (OS) for patients with metastatic disease is less than 12 months, even when patients are treated with the most active chemotherapy regimens [4, 5].

Recent phase III studies CONKO-003 and NAPOLI-1 showed survival benefit of second-line treatment with an oxaliplatin-based regimen or a nanoliposomal irinotecan-based regimen in patients with GEM-refractory PC [6]. In view of the growing number of available drugs, any effect of first-line chemotherapy on OS might be confounded by several lines of subsequent therapy. Indeed, an improvement in progression-free survival (PFS) did not necessarily result in improved OS in a recent randomized phase III MAESTRO trial of evofosfamide in combination with GEM. The GEM arm performed better than the initial assumptions and the receipt of second-line therapy following disease progression was increased in the GEM arm compared with the experimental arm. In a phase III trial comparing GEM plus S-1 with GEM alone, S-1 failed to improve OS when added to GEM and second-line chemotherapy mainly with S-1 in the GEM group may be one reason for this discrepancy [7].

The duration of survival after disease progression (post-progression survival, PPS) and its association with OS have recently been investigated in advanced breast, colorectal, non-small cell lung and gastric cancers [8–11]. However, little is known about PPS in PC. First line chemotherapy regimens investigated in these meta-analysis of PPS were heterogeneous. GEM monotherapy had been the standard first-line chemotherapy for patients with unresectable PC for a long time and the effect of therapy after disease progression on survival in clinical trials of first-line GEM monotherapy is thus of interest. In the present study, we partitioned OS in randomized phase II and III trials for chemotherapy-naïve patients with advanced PC treated with GEM alone into PFS and PPS and assessed the association of each with OS.

Materials and methods

Search strategy and selection of trials

An independent review of Web of Science and Medline citations from 1 January 1997 to 31 April 2015 was carried out. Key words included in the search were ‘pancreatic cancer’, ‘randomized’ and ‘chemotherapy’. The search was limited to randomized controlled phase II and III trials with articles published in English. We reviewed each publication, and selected randomized studies comparing two or more first-line systemic chemotherapeutic agents (including treatment with molecular targeted agents) for unresectable

locally advanced or metastatic PC. To find any additional trials, we also searched unpublished data and abstracts from annual meetings of the American Society of Clinical Oncology (from 1997 to 2014) and the European Cancer Conference and European Society of Medical Oncology (from 1997 to 2014). We focused on PPS in patients who received first-line GEM monotherapy, and included randomized trials comparing GEM alone with other regimens for patients with histologically confirmed PC. Trials were eligible if they provided data for both OS and either PFS or time to progression (TTP), whether or not these parameters were explicitly defined. Exclusion criteria included trials designed to assess combined-modality therapy including radiation therapy or surgery (adjuvant or neoadjuvant chemotherapy), and those in which patients had previously been treated with chemotherapy. Two investigators (A.K. and Y.H.) independently abstracted the data from the trials to avoid bias.

We conducted a meta-analysis according to PRISMA. We did not use individual data but published data. The value of information has already been widely utilized in research and generally available. So we further confirm that any aspect of the work covered in this manuscript has been conducted with the ethical approval.

Data abstraction

We analyzed in detail the primary and secondary efficacy end points, following the definitions of the authors of each trial. When not specifically stated by the authors, we considered the primary endpoint to be used for 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 [8, 10, 11]. Median OS and median PFS were extracted from all trials that provided data for the GEM alone group. Median PPS was defined as median OS minus median PFS for each trial. We also obtained the following information from each report: year of completion of trial enrollment, number of patients in GEM alone group, median age of patients and proportion of patients who received second-line chemotherapy.

Data analysis

We summarized the survival data (median OS, median PFS, median PPS, and median PFS/median OS) as the average and standard error (SE) for the GEM alone arm. SE was calculated on the basis of previously described models [12]. We also calculated the percentage of OS accounted by PPS for the GEM alone arm as: $100 - (100 \times \text{median PFS} / \text{median OS})$. To assess the relation 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 the GEM alone arm. In addition, all trials were divided into two groups on the basis of the year in which trial enrolment was completed. Given the number of patients was nearly evenly split with a threshold between 2005 ($n=3329$) and 2006 ($n=3527$), we dichotomized at year 2005 (older trials, up to and including 2005; recent trials, 2006 and later) to evaluate a possible change in PPS and we assessed whether the evaluated relations might be dependent on the year of completion of trial enrolment. We examined differences in the survival data between older and recent trials by normal approximation of the average survival data (t test). All reported p values correspond to two-sided tests, and those of <0.05 were considered statistically significant. Analyses were carried out with SPSS (version 20.0, SPSS, Chicago, IL, USA) and SAS for Windows release 9.4 (SAS Institute, Cary, NC).

Results

Characteristics of trials

Our research yielded a total of 1648 potentially relevant publications. The selection process for the remaining randomized controlled trials is shown in Fig. 1. A total of 54 trials were finally considered to be highly relevant for the present study (see Supplementary Table 1). The main characteristics of the 54 trials included in the analysis are

listed in Table 1. A total of 6856 patients with advanced pancreatic cancer treated with GEM monotherapy were enrolled with a median rate of locally advanced disease

Table 1 Characteristics of 54 randomized trials for advanced pancreatic cancer included in present analysis

Trials characteristics	
Median no. of patients in GEM arm per trial (range)	69 (10–430)
Percentage of male patients (median)	58
Average of media age (years)	63
Percentage of patients with metastatic disease (median)	78.9
	No. of trials
Phase	
II	25
III	29
Primary end points (no of trials)	
OS	33
PFS or TTP	10
Response rate	3
Clinical benefit	2
Others	6
End point based on tumor assessment	
TTP	14
PFS	40
Post-trial treatment	
Data shown	20
Data not shown	34

GEM gemcitabine, *OS* overall survival, *PFS* progression-free survival, *TTP* time to progression

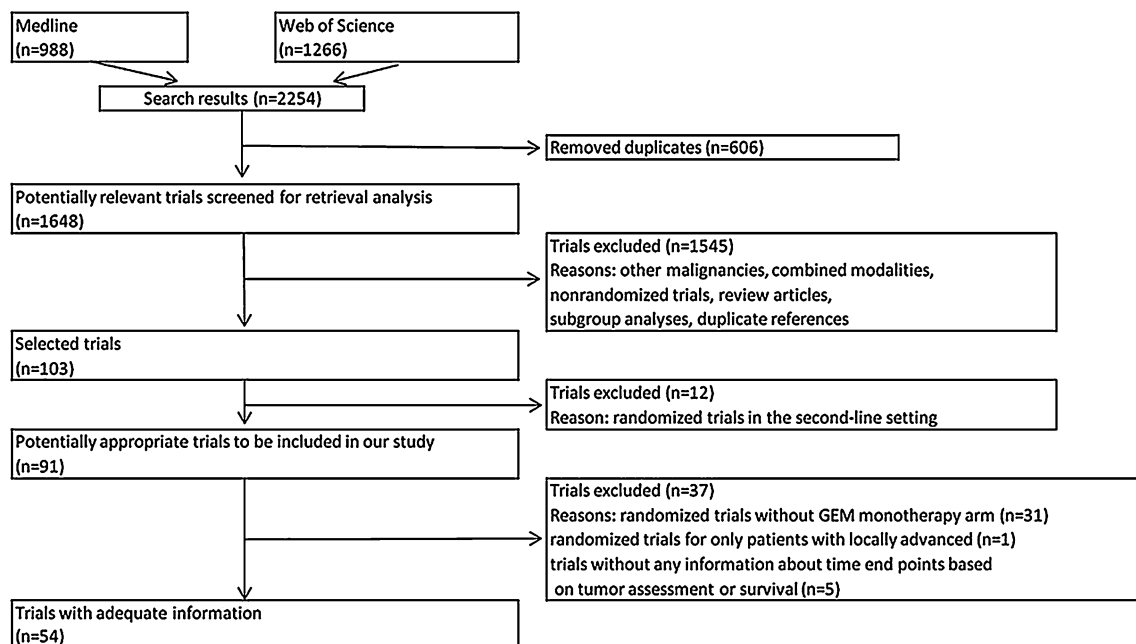


Fig. 1 PRISMA (preferred reporting items for systematic reviews) diagram for the meta-analysis

of 21% and a median rate of metastatic disease of 79%. Twenty-five of the trials were randomized phase II trials and 29 were phase III trials. Data of post-trial treatment were available in 20 of the trials.

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

Among the 54 trials, the average median OS, median PFS and median PPS were 6.73, 3.47 and 3.26 months (Table 2). The average median OS was significantly longer in recent trials than in older trials (7.29 versus 6.15 months, $p < 0.001$), and this improvement was accompanied by a significant increase in the average median PFS (3.65 versus 3.29 months, $p < 0.001$) and PPS (3.64 versus 2.86 months,

$p < 0.001$). The average proportion of median OS accounted for by median PFS was significantly larger in recent trials than in older trials (49.61 versus 46.49%, $p < 0.001$).

Relation between OS and either PFS or PPS

The relation between median OS and either median PFS or median PPS are shown in Figs. 2 and 3, respectively. We found that median PPS was strongly associated with median OS ($r = 0.844$, $p < 0.001$) on the basis of Spearman's correlation coefficient, whereas median PFS was moderately correlated with median OS ($r = 0.623$, $p < 0.001$). The association between median OS and median PPS in recent trials ($r = 0.846$, $p < 0.001$) was much stronger than that in older trials ($r = 0.729$, $p < 0.001$). The correlation between OS

Table 2 Average median PFS, OS and PPS for a GEM monotherapy arm in all trials according to year of completion of trial enrolment

Trials	No. of patients	No. of trials	Average of median (months)			Average PPS/OS (%)
			OS	PFS	PPS	
All	6856	54	6.73 (0.01)	3.47 (0.01)	3.26 (0.01)	48.10 (0.08)
Older (up to and including 2005)	3329	26	6.15 (0.01)	3.29 (0.01)	2.86 (0.01)	46.49 (0.13)
Recent (2006 and later)	3527	28	7.29 ^a (0.02)	3.65 ^a (0.01)	3.64 ^a (0.01)	49.61 ^a (0.09)

Values in brackets are standard errors

GEM gemcitabine, OS overall survival, PFS progression-free survival, TTP time to progression

^a $p < 0.001$ versus corresponding value for older trials (t test)

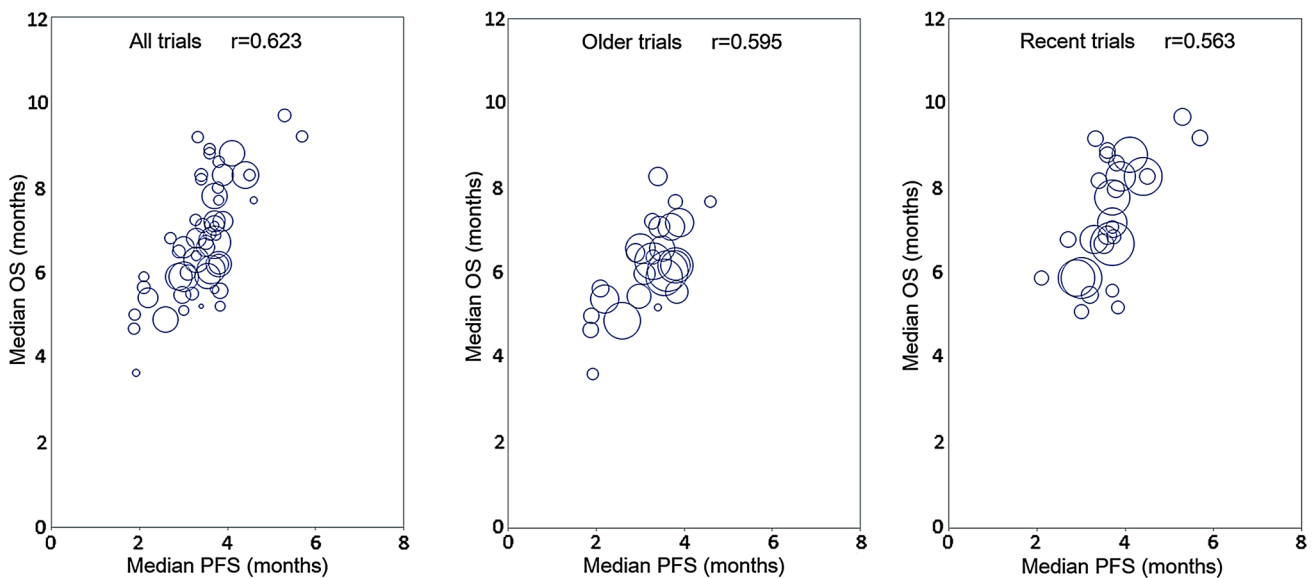


Fig. 2 Relation between median overall survival (OS) and median progression-free survival (PFS). **a** All trials. **b** Older trials (trial enrollment completed by 2005). **c** Recent trials (trial enrollment com-

pleted in 2006 or later). The area of each circle is proportional to the number of patients in each trial arm. The r values represent Spearman's rank correlation coefficient

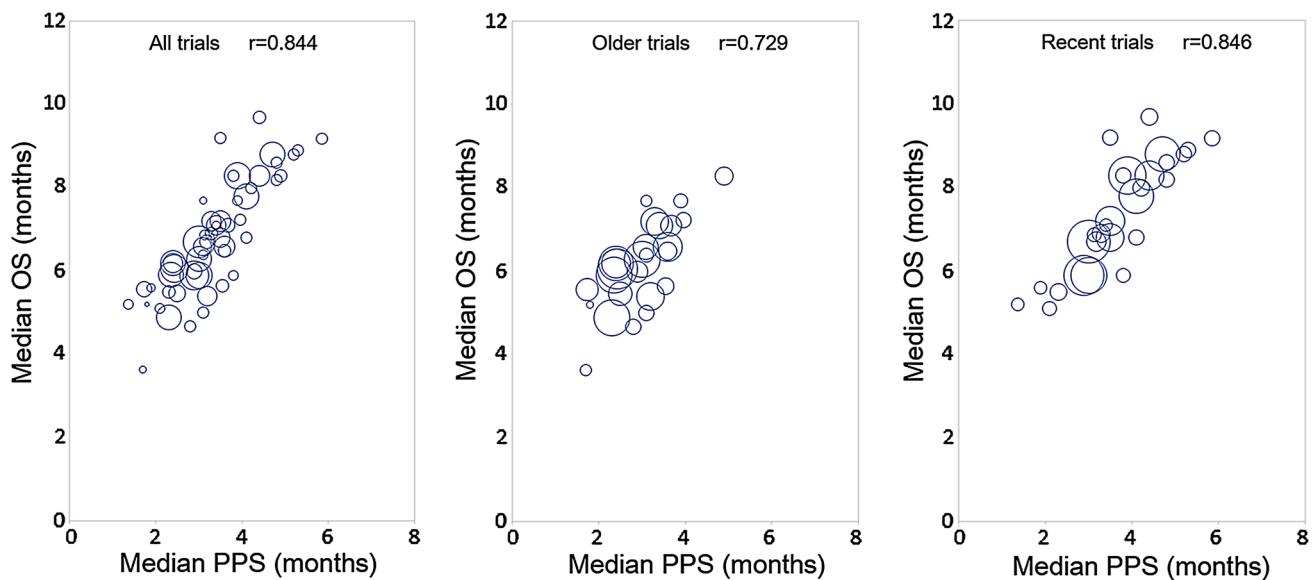


Fig. 3 Relation between median overall survival (OS) and median post progression survival (PPS). **a** All trials. **b** Older trials (trial enrollment completed by 2005). **c** Recent trials (trial enrollment com-

pleted in 2006 or later). The area of *each circle* is proportional to the number of patients in each trial arm. The *r* values represent Spearman's rank correlation coefficient

and PFS in recent and older trials did not differ ($r=0.595$ versus 0.563).

Relation between OS and post-trial treatment

Data of post-trial treatment were available in 20 of the 54 trials. Nine of the 20 trials were older trials and the remaining 11 were recent trials. The average median OS was significantly longer in recent trials than in older trials (7.59 versus 6.47 months, $p<0.001$), and this improvement was accompanied by a significant increase in average median PPS (3.92 versus 3.08 months, $p<0.001$) and average median PFS (3.67 versus 3.39 months, $p<0.001$). The percentage of patients with post-study treatment was

significantly higher in the recent trials than in the older trials (52.7 versus 39.7%, $p<0.001$) (Table 3). The rate of post-trial anticancer therapy was strongly associated with median OS in 20 trials ($r=0.910$, $p<0.001$) (Fig. 4).

Discussion

The present study examined the duration of PPS in randomized trials in patients with advanced pancreatic cancer treated with GEM monotherapy. Although first line chemotherapy regimens investigated in meta-analysis of postprogression survival in advanced breast, colorectal, non-small cell lung and gastric cancers were heterogeneous, we were

Table 3 Average median PFS, OS and PPS for a GEM monotherapy arm in trials with data of post-trial treatment according to year of completion of trial enrolment

Trials	No. of patients	No. of trials	Average rate of post-trial anticancer therapy (%)	Average of median (months)		
				OS	PFS	PPS
All	2715	20	46.5 (0.26)	7.05 (0.02)	3.54 (0.01)	3.52 (0.01)
Older (up to and including 2005)	1302	9	39.7 (0.34)	6.47 (0.01)	3.39 (0.01)	3.08 (0.01)
Recent (2006 and later)	1413	11	52.7 ^a (0.32)	7.59 ^a (0.03)	3.67 ^a (0.01)	3.92 ^a (0.02)

Values in parentheses are standard errors

GEM gemcitabine, OS overall survival, PFS progression-free survival, TTP time to progression

^a $p < 0.001$ versus the corresponding value for older trials (t test)

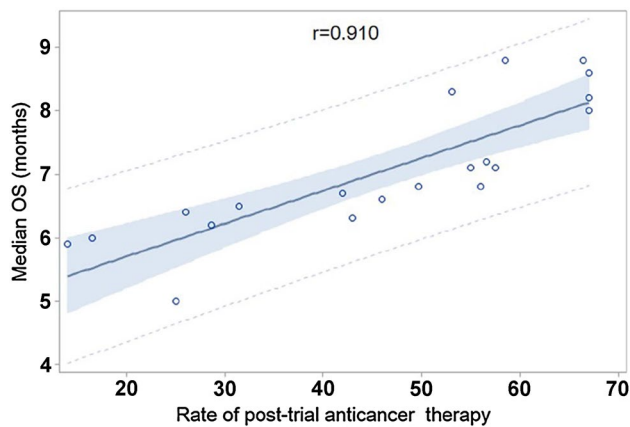


Fig. 4 Relation between median overall survival (OS) and rate of post-trial anticancer therapy. For GEM monotherapy arms of 20 randomized trials with data available for advanced pancreatic cancer. The r values represent Spearman's rank correlation coefficient

able to focus on only patients who received first-line GEM monotherapy because GEM monotherapy had been the standard first-line chemotherapy for patients with unresectable locally advanced or metastatic PC for a long time. We found that median OS was more strongly associated with median PPS than with median PFS. Moreover, we detected an increase in median PPS in accordance with an increase in median OS in recent trials compared with older trials. A similar prolongation of median PPS and median OS has also been described for breast cancer [8], colorectal cancer [9], non-small cell lung cancer [10, 13], and gastric cancer [11]. This is considered to be the result of subsequent active anticancer therapy. Given that the recent phase III studies CONKO-003 and NAPOLI-1 have shown a survival benefit of second-line chemotherapy after failure of GEM [6], increased provision of subsequent potentially active therapy for pancreatic cancers might be expected. In the MAESTRO trial the receipt of second-line therapy following disease progression was increased in the GEM arm compared with the experimental arm particularly for FOLFIRINOX and nab-paclitaxel in combination with GEM. In Japan, clinical trials of S-1 have been conducted since the early 2000s for patients with pancreatic cancer and there were four randomized trials comparing GEM monotherapy with GEM plus S1 [7, 14–16]. Median OS, PFS and PPS of the GEM monotherapy arm in these four trials were 8.0–8.8 months, 3.6–4.1 months and 4.2–5.2 months, respectively. The rate of post-trial anticancer therapy was 58.5–67.0%. The recent increasing number of active compounds used after failure of GEM monotherapy are likely to prolong median PPS as well as OS recently.

Although we focused only on patients who received first-line GEM monotherapy, PFS was significantly longer in recent trials than in older trials. Although the

correlation between OS and PFS in recent and older trials did not differ, screening programs may have potential biases. In lead-time bias, earlier detection of tumors via screening may appear to result in longer survival than that in subjects identified by clinical symptoms [17]. Earlier diagnosis of cancer is increasingly acknowledged as a key element of the drive to improve cancer outcomes, and the National Awareness and Early Diagnosis Initiative in UK is addressing this challenge and similar objectives are being pursued by a variety of national initiatives [18–20]. In UK, analysis of diagnostic intervals defined as the duration from the first occurrence of a symptom to the date of cancer diagnosis between the 2001–2002 and 2007–2008 cohorts in pancreatic cancer showed that there was a significant reduction in the interval of 12.6 days (0.42 months) [21]. In our study median PFS was 0.36 months longer in recent trials than in older trials. Lead to bias may be one reason for this prolongation of median PFS.

The present study has several limitations. First, our analysis was based on abstracted data. The use of individual patient data might be expected to allow better characterization of the relation between OS and other end points based on tumor assessment. However, such an 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 potentially have several confounders due to selection of many heterogeneous trials for analysis. We focused on patients treated with GEM monotherapy to minimize the heterogeneity. The results are generally unaccountable without appropriate adjustment for patient characteristics dependent on differences in predefined eligibility criteria for enrollment in the clinical trials. Third two endpoints (PFS and TTP) based on tumor assessment are considered as the same parameter, following the example of previous reports for advanced breast, non-small cell lung and gastric cancers [8, 10, 11]. TTP is the same as PFS if death does not occur during treatment. However, we also separately analyzed clinical trials providing PFS ($n=40$ trials) or TTP ($n=14$ trials), and found a consistent association between OS and PPS (data not shown). These data thus support our approach in which these two endpoints are collectively referred to as PFS in the present analysis. Finally, the clinical impact of PPS on OS in PC might be obscure because the duration of OS in patients with PC is much shorter than that in patients with advanced breast, colorectal, non-small cell lung and gastric cancers. Moore and colleagues reported a statistically significant OS benefit of 0.33 months for erlotinib added to GEM [3]. So significant increase in OS in the interval of one month between recent trials and older trials in this study suggest clinical value of PPS with the increasing number of available drugs. As PPS increases, OS can become skewed, and

a statistically significant benefit in terms of PFS will likely become masked with OS as the endpoint [22].

In conclusions, there was an apparent increase in median PPS accompanying an increase in median OS in recent trials compared with older trials for patients with advanced PC treated with GEM monotherapy. The rate of post-trial anticancer therapy was strongly associated with median OS and it was significantly higher in recent trials than in older trials. Although OS is the gold standard for efficacy evaluation in phase III trials for advanced PC, it is important that researchers be aware of these findings in designing clinical trials of first-line chemotherapy for patients with advanced PC.

Compliance with ethical standards

Conflict of interest None to declare.

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