Post-progression survival and progression-free survival in patients with advanced hepatocellular carcinoma treated by sorafenib

Post-progression survival and progression-free survival in patients with advanced hepatocellular carcinoma treated by sorafenib

Authors: Takeshi Terashima[1], Tatsuya Yamashita[1], Noboru Takata[1], Hidetoshi Nakagawa[1], Tadashi Toyama[2], Kuniaki Arai[1], Kazuya Kitamura[1], Taro Yamashita[1], Yoshio Sakai[1], Eishiro Mizukoshi[1], Masao Honda[1], Shuichi Kaneko[1]

Affiliations: [1] Department of Gastroenterology, Kanazawa University Hospital, Kanazawa, Ishikawa 920-8641, Japan

[2] Department of Nephrology, Kanazawa University Hospital, Kanazawa, Ishikawa 920-8641, Japan

Corresponding author: Tatsuya Yamashita, M.D., Ph.D.

Postal address: 13-1, Takara-machi, Kanazawa, Ishikawa 920-8641, Japan

Email: ytatsuya@m-kanazawa.jp

Phone: +81-76-265-2235

Fax: +81-76-234-4250

Short title: PPS in advanced HCC treated by sorafenib

Abstract

Aim: Although sorafenib is a standard drug for advanced hepatocellular carcinoma (HCC), little is known about a patient's clinical course after treatment. We investigated the effect of post-progression survival (PPS) and progression-free survival (PFS) on overall survival (OS) in patients whose advanced HCC was treated by sorafenib.

Methods: We searched in the PubMed database for reports with survival data of patients with HCC treated with sorafenib monotherapy, and selected reports with ≥ 20 patients each that provided data for both OS and PFS or time to progression (TTP). Median PPS (mPPS) was defined as the period obtained by subtracting median PFS or TTP (mPFS/TTP) from median OS (mOS). We identified 56 reports with 5803 patients. We investigated the correlation of mOS and either mPPS or mPFS/TTP using weighted linear regression.

Results: Median PPS correlated with mOS (r=0.834) very strongly, whereas mPFS/TTP did not correlate with mOS as highly as PPS did (r=0.546). When we stratified survival data by Child-Pugh classification, a significantly greater average percentage of mPPS to mOS was seen in Child-Pugh class A (54.4±17.6 %) than in Child-Pugh class B (32.0±11.6 %) (P=0.015).

Conclusions: PPS highly correlated with OS, and its importance should be more emphasized for advanced HCC patients treated after sorafenib therapy, whereas we need to take more care in interpreting the results of PFS to evaluate treatment efficacy in clinical trial of advanced HCC.

Key Words: post-progression survival, progression-free survival, hepatocellular carcinoma,

sorafenib, subsequent therapy

Introduction

Some anti-cancer therapies are effective even for disease that is refractory to first-line chemotherapy agents. The duration of disease progression from first-line treatment to death is defined as post-progression survival (PPS), and can be prolonged as active agents become available at subsequent treatment [1-4]. Consequently overall survival (OS), which is considered to be the optimal endpoint for cancer patients who could not receive curative therapy, has been strongly correlated with PPS in non-small-cell lung cancer, gastric cancer, colorectal cancer, and breast cancer [1-4], and this tendency has been stronger in recent trials than that in older trials [1-3]. The association between progression-free survival (PFS) and OS is moderate at best in these malignancies because it becomes weaker as the proportion of PPS to OS increases [5]. Conversely, PFS supposedly correlates well with OS in some malignancies, such as pancreatic cancer, melanoma and older trials of colorectal cancer [6, 7], in which PPS remains short because the advantage of second-line chemotherapy is limited [8] and the biological malignancy is very potent.

Hepatocellular carcinoma (HCC) is the sixth most common cancer and the third leading cause of cancer-related mortality worldwide [9]. A variety of new imaging techniques have enabled early-stage detection of HCC [10], and advances in various therapeutic procedures such as liver transplantation and radiofrequency ablation have improved its curability [11]. However, patients with HCC who can be treated curatively have unsatisfactory prognosis because of frequent recurrence even after curative therapy. The prognosis of patients whose advanced HCC has

spread over the liver or invaded major vessels remains very poor [12].

Sorafenib, an oral multi-kinase inhibitor that blocks tumor cell proliferation and angiogenesis, is the only systemic therapy that has significantly improved OS compared with placebo for patients with advanced HCC [13, 14]. It is recognized as standard first-line chemotherapy for advanced HCC [15, 16]. Alternative systemic chemotherapies using cytotoxic agents or novel targeted drugs have been attempted in patients with advanced HCC. Some of agents significantly prolonged PFS compared to that of control group; however, they did not improve OS in phase III trials [17].

Under such circumstances, better understanding of PPS and PFS will clarify any problems of those failed trials and lead new agents to successful development. The present study reviewed clinical literature to investigate the effect of PPS and PFS on OS for patients with advanced HCC treated by sorafenib.

Materials and Methods

Search and selection of literatures

We searched medline database through PubMed citations up to 20 December, 2013. Key words included in the search were “hepatocellular carcinoma” and “sorafenib.” The search was limited to reports describing clinical data of patients with HCC treated by a single-medication sorafenib and published in English. We selected all reports that provided analyzed intent-to-treat data for OS and either PFS or time-to-progression (TTP), whether or not these parameters were

explicitly defined. We included reports in which primary endpoints were not OS or PFS and reports of prospective clinical trials or retrospective clinical practice, and single arms of multi-arm studies if each arm dealt with at least 20 patients. We excluded review articles, case reports, letters or commentaries, interim analysis, subgroup analyses of previously reported trials, or duplicates. Reports in which all or some patients were treated as adjuvant setting or neoadjuvant setting, or with concomitant treatment, including resection, transplantation, transarterial chemoembolization, or radiation therapy in addition to sorafenib were also excluded. To avoid bias, two specialists in HCC (T.T. and N.T.) independently reviewed and selected the articles and extracted the data from the reports.

Data collection

For the sake of simplicity, TTP data were also collectively referred to as that of PFS in the present analysis if PFS was not addressed; similar to an approach adopted in a recent reposts [1-4]. Median OS (mOS) and median PFS or median TTP (mPFS/TTP) were extracted from all reports that provided data. Median PPS (mPPS) was defined as the period obtained by subtracting mPFS/TTP from mOS for each report [1-4]. Survival data were converted to months; 30.45 days were converted to 1 month in reports that described survival data in days or weeks. We also obtained the following information from each report: number of arms in each report, characteristics of the reports, number of patients in each arm, criteria of radiological responses, and patients' characteristics as far as we could obtain.

Data analysis

We summarized the survival data (mOS, mPFS/TTP, and proportion of mPPS/mOS) as the average for all treatment arms. The relationship between mOS and either mPFS/TTP or mPPS was estimated using weighted linear regression, with weights equal to the sample size of the arms from which the data were derived [18]. If the reports described the survival data stratified by Child-Pugh classification, we obtained the respective data. Student's *t*-test was used to assess differences in proportions of mPPS to mOS stratified by Child-Pugh classification. All reported *P*-values correspond to two-sided tests, with $P < 0.05$ considered to be statistically significant. Data analyses used Stata 12.1 (College Station, TX, USA).

Results

Characteristics of the trials

We found a total of 1171 publications from the search for medline database through PubMed, but excluded 780 reports for at least one of the following reasons: not in English (n=104), case report (n=127), preclinical assessment (n=261), study of other treatment modalities, neoadjuvant setting, adjuvant setting, with concomitant treatment (n=200), review articles, letters, commentaries, conference records, and other assessment of sorafenib (n=338), interim analysis, subgroup analyses of previously reported trial duplicates (n=12), consisted of 19 or less patients (n=30), without information about mOS and/or mPFS/TTP (n=38), and/or not intention-to-treat

analyses (n=5). The remaining 56 reports met the inclusion criteria of the present study (Figure 1). Characteristics of the 56 reports in our study, with 61 arms and 5803 patients with advanced HCC, are shown in Table 1 and Supplementary Table 1.

Survival data and relations between OS and either PFS/TTP or PPS

The mPPS of all trials had a range of 0.4–18.1 months; mPPS was 4.8±3.2 months (mean ± standard deviation; SD). The mOS and the mPFS/TTP had a range of 2.7–26.1 months and 1.9–12.0 months, respectively, and 8.9±3.8 months and 4.0±1.9 months (mean ±SD), respectively. The average proportion (±SD) of mPPS to OS for all patients was 51.8±17.4%.

The mOS among the 61 arms were plotted against mPPS (Figure 2), and mPFS/TTP (Figure 3). We found mPPS was strongly correlated with mOS (r=0.834, P<0.001) based on weighted linear regression (Figure 2). However, mPFS/TTP did not correlate with mOS as highly as PPS did (r=0.546, P<0.001; Figure 3).

Similar tendencies were observed among the reports in which tumor progression was assessed by PFS (Supplementary Figure 1) and TTP (Supplementary Figure 2), and in which radiological responses were assessed by Response Evaluation Criteria In Solid Tumors (RECIST) (Supplementary Figure 3) and modified RECIST (Supplementary Figure 4).

Survival data according to Child-Pugh classification

Survival data stratified by Child-Pugh classification were obtained from only 10 arms in

Child-Pugh class A and 6 arms in Child-Pugh class B. Average PPS and OS (±SD) were significantly longer in Child-Pugh class A (4.8±1.6 months and 9.3±2.4 months) than in Child-Pugh class B (1.6±1.0 months; *P*=0.0011 and 4.5±1.9 months; *P*=0.0005, respectively). Average PFS tended to be longer, but not significantly so, in Child-Pugh class A (4.5±3.1 months) than in Child-Pugh class B (3.0±1.0 months) (*P*=0.28). The average proportion of mPPS against mOS was significantly higher in Child-Pugh class A than in Child-Pugh class B (54.4±17.6 % vs. 32.0±11.6 %, *P*=0.015) (Figure 4).

Discussion

Our analysis demonstrated that PPS is highly correlated with OS, whereas PFS is less correlated with OS in this patient population. This result was unexpected and interesting because PFS rather than PPS has been considered to correlate strongly with OS in advanced HCC patients from the perspective of the fact that no treatment has shown to be effective after sorafenib in prospective study [17]. While in patients with other cancers such as breast cancer, colorectal cancer, or non-small-cell lung cancer for which several effective agents are available after first-line chemotherapy, PPS strongly correlated with OS [1-4].

Although the precise reason for this strong correlation between PPS and OS was unclear, a possible reason was the role of multidisciplinary therapy in HCC. Such alternative therapies as hepatic arterial infusion chemotherapy [19] and radiation [20] as well as continuous administration of sorafenib beyond progression [21] have been conventionally conducted as subsequent therapy because they have been thought to be efficacious even after sorafenib therapy [22, 23] although such opinions had not been established in proper prospective trials. Although this study could not analyze the effect of subsequent therapies on PPS and OS because of the absence of individual information about subsequent therapies, multidisciplinary approaches may have the impact of PPS on HCC, as seen in other cancers for which many effective agents have been successfully developed.

Another consideration was most subjects in this study had good hepatic reserve, as the feasibility and efficacy of sorafenib for patients with Child-Pugh class B/C is unclear [24], and

sorafenib is usually administrated in patients with Child-Pugh class A cirrhosis or without liver cirrhosis. Our results, the proportion of mPPS against mOS was higher in Child-Pugh class A than in Child-Pugh class B, also suggested good hepatic reserve may enable patients to benefit more from subsequent therapy after sorafenib and to have longer PPS than our assumption [25]. In addition to contribution to PPS prolongation of subsequent therapy after sorafenib itself, better natural prognosis which may affect the strong correlation between PPS and OS in this study.

Our result, which clarified the strong correlation between PPS and OS in advanced HCC treated with sorafenib, showed the necessity of considering PPS. For example, survival time of the patients in control group was actually longer than that of hypothesis in recent randomized control trials which was conducted as second-line setting after sorafenib therapy [26], which may lead these trials to insufficient difference in OS because it was reported that long PPS diminishes the effect of agents on OS in clinical trials [5]. Some reports showed that PPS depended on patterns of tumor progression, clinical stage, reasons of discontinuation of sorafenib [27, 28]. Successful development of novel therapies needs better understanding of such factors as different hazard ration of PPS according to tumor progression patterns, clinical stage, or hepatic reserve in trial design, and additional information including subsequent therapy or progression pattern should be checked in trial analysis.

Conversely, the following reasons were speculated to explain the weak correlation between PFS and OS in these patients. First, HCC progression is assessed heterogeneously; although radiology and other imaging is used to judge response to anti-cancer drugs in solid tumors,

clinical criteria or follow-up intervals were not standardized in this study [29]. Determining tumor progressions unlike tumor responses were reported to be corresponding in conventional RECIST and modified RECIST [30, 31], and similar results were observed in this study in subgroup analysis among the reports in which conventional RECIST and modified RECIST were used as tool of radiological assessments (Supplementary Figure 3 and 4), which suggested that the variation of assessment tool had minimal effects. Second, hepatic reserve affects survival in HCC [25, 32]. Hepatic reserve often restricts OS independently of PFS which is purely restricted by antitumor effect. To minimalize the effect of the death without tumor progression for understanding these results, we conducted subgroup analyses separately among the reports dealt with PFS and TTP, and confirmed that similar results were observed (Supplementary Figure 1 and 2). Third, the present study showed that, among patients with Child-Pugh class A, PPS was more than half of OS, which accords with recent findings for breast cancer and colon cancer, although the average PPS of 4.8 months was not long compared with those cancers. Weaker correlation between PFS and OS may thus be induced from the greater proportion of PPS to OS in patients with better hepatic reserve [5].

OS is usually set as the primary endpoint for the pivotal study in advanced HCC area because it is considered that the primary endpoint should be the endpoint which can directly evaluate purpose of the treatment for study patients, and true purpose for the patients with advanced HCC was longer survival. This attitude in advanced HCC area is corresponded to that of regulating authority which was assigned to evaluation of the efficacy of novel agents. On the

other hand, PFS is commonly recognized as an alternative endpoint especially for early-phase studies to evaluate the efficacy of novel agents for advanced HCC over a short time [27, 33]. In this study, however, the correlation between OS and PFS seemed to be too weak to establish PFS as surrogate endpoint of OS. This is consistent with a perspective that PFS had favorable tendency whereas prolongation of OS weren't observed in recent clinical trials [34], therefore we need to take more care in interpreting the results of PFS to evaluate the efficacy of new agents or treatments and judging whether it has efficacy to proceed to phase III trial based not only PFS/TTP but also that of OS especially in early-phase studies of advanced HCC. Of course, sorafenib prolonged TTP as well as OS compared with placebo in large phase III trials [13, 14], and we did not deny the significance of PFS prolongation obtained by sorafenib therapy in advanced HCC patients from our findings that median PFS was also correlated with median OS statistically. The prolongation of PFS obtained by sorafenib therapy probably contributes that of OS, and the prolongation of PPS may also contribute that of OS based on our results.

There had been few reports of randomized control trial in advanced HCC, therefore we collected all reports which met our inclusion criteria; however, we could not fully ensure the quality of these reports. Then some phase III trials have been reported after the time of our analysis, and we additionally investigated the correlation of OS and PPS or TTP using information of these trials describing about survival data of sorafenib monotherapy because they were similar design (Supplementary Table 2). In consequence, median PPS correlated with mOS strongly (r=0.804), whereas mTTP did not correlate with mOS as highly as PPS did (r=0.396)

as shown in Figure 5, which supported our results of all reports although still limited number of trials did not allow reaching any definite conclusion. Other limitations included lack of detail of individual patient data, potential confounders because of the inclusion of many heterogeneous trials, and selection and publication bias. Further investigation with information of individual patients including subsequent therapy and progression pattern is needed to confirm our findings.

Conclusion

In conclusion, among patients with advanced HCC patients treated with sorafenib, PPS highly correlates with OS, which should be noticeable for these patients in the design and analysis of clinical trials and in daily practice. However, PFS appears not to be a suitable surrogate endpoint for OS for advanced HCC.

Acknowledgments: The authors thank Mikako Araki and Mio Tanaka for data collection.

Conflicts of interest: none to declare

References

1. Hayashi H, Okamoto I, Morita S, Taguri M, Nakagawa K. Postprogression survival for first-line chemotherapy of patients with advanced non-small-cell lung cancer. Ann Oncol 2012; 23: 1537-41.

2. Kawakami H, Okamoto I, Hayashi H, Taguri M, Morita S, Nakagawa K. Postprogression survival for first-line chemotherapy in patients with advanced gastric cancer. Eur J Cancer 2013; 49: 3003-9.

3. Petrelli F, Barni S. Correlation of progression-free and post-progression survival with overall survival in advanced colorectal cancer. Ann Oncol 2013; 24: 186-92.

4. Saad ED, Katz A, Buyse M. Overall survival and post-progression survival in advanced breast cancer: a review of recent randomized clinical trials. J Clin Oncol 2010; 28: 1958-62.

5. Broglio KR, Berry DA. Detecting an overall survival benefit that is derived from progression-free survival. J Natl Cancer Inst 2009; 101: 1642-9.

6. Buyse M, Burzykowski T, Carroll K, Michiels S, Sargent DJ, Miller LL, et al. Progression-free survival is a surrogate for survival in advanced colorectal cancer. J Clin Oncol 2007; 25: 5218-24.

7. Tang PA, Bentzen SM, Chen EX, Siu LL. Surrogate end points for median overall survival in metastatic colorectal cancer: literature-based analysis from 39 randomized controlled trials of first-line chemotherapy. J Clin Oncol 2007; 25: 4562-4568.

8. Rahma OE, Duffy A, Liewehr DJ, Steinberg SM, Greten TF. Second-line treatment in advanced pancreatic cancer: a comprehensive analysis of published clinical trials. Ann Oncol 2013; 14: 1972-9.

9. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer 2010; 127: 2893-917.

10. Lee JM, Yoon JH, Kim KW. Diagnosis of hepatocellular carcinoma: newer radiological tools. Semin Oncol 2012; 39: 399-409.

11. Song MJ, Chun HJ, Song do S, Kim HY, Yoo SH, Park CH, et al. Comparative study between doxorubicin-eluting beads and conventional transarterial chemoembolization for treatment of hepatocellular carcinoma. J Hepatol 2012; 57: 1244-50.

12. Takizawa D, Kakizaki S, Sohara N, Sato K, Takagi H, Arai H, et al. Hepatocellular carcinoma with portal vein tumor thrombosis: clinical characteristics, prognosis, and patient survival analysis. Dig Dis Sci 2007; 52: 3290-5.

13. Cheng AL, Kang YK, Chen Z, Tsao CJ, Qin S, Kim JS, et al. Efficacy and safety of sorafenib in patients in the 12Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. Lancet Oncol 2009; 10: 25-34.

14. Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, et al; SHARP Investigators Study Group. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 2008; 359: 378-90.

15. Bruix J, Sherman M. Management of hepatocellular carcinoma: an update. Hepatology 2011; 53: 1020-2.

16. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol 2012; 56: 908-43.

17. Villanueva A, Llovet JM. Targeted therapies for hepatocellular carcinoma. Gastroenterology 2011; 140: 1410-26.

18. Sargent DJ, Wieand HS, Haller DG, Gray R, Benedetti JK, Buyse M, et al. Disease-free survival versus overall survival as a primary end point for adjuvant colon cancer studies: individual patient data from 20,898 patients on 18 randomized trials. J Clin Oncol 2005; 23: 8664-70.

19. Yamashita T, Arai K, Sunagozaka H, Ueda T, Terashima T, Yamashita T, et al. Randomized, phase II study comparing interferon combined with hepatic arterial infusion of fluorouracil plus cisplatin and fluorouracil alone in patients with advanced hepatocellular carcinoma. Oncology 2011; 81: 281-90.

20. Soliman H, Ringash J, Jiang H, Singh K, Kim J, Dinniwell R, et al. Phase II trial of palliative radiotherapy for hepatocellular carcinoma and liver metastases. J Clin Oncol 2013; 31: 3980-6.

21. Miyahara K, Nouso K, Morimoto Y, Takeuchi Y, Hagihara H, Kuwaki K, et al. Efficacy of sorafenib beyond first progression in patients with metastatic hepatocellular carcinoma. Hepatol Res 2014; 44: 296-301

22. Terashima T, Yamashita T, Arai K, Sunagozaka H, Kitahara M, Nakagawa H, et al. Feasibility and efficacy of hepatic arterial infusion chemotherapy for advanced hepatocellular carcinoma after sorafenib. Hepatol Res 2014; 44: 1179-85.

23. Shao YY, Liang PC, Wu YM, Huang CC, Huang KW, Cheng JC, et al. A pilot study of hepatic arterial infusion of chemotherapy for patients with advanced hepatocellular carcinoma who have failed anti-angiogenic therapy. Liver Int 2013; 33: 1413-9.

24. Pressiani T, Boni C, Rimassa L, Labianca R, Fagiuoli S, Salvagni S, et al. Sorafenib in patients with Child-Pugh class A and B advanced hepatocellular carcinoma: a prospective feasibility analysis. Ann Oncol 2013; 24: 406-11.

25. Kaseb AO, Shindoh J, Patt YZ, Roses RE, Zimmitti G, Lozano RD, et al. Modified cisplatin/interferon α-2b/doxorubicin/5-fluorouracil (PIAF) chemotherapy in patients with no hepatitis or cirrhosis is associated with improved response rate, respectability, and survival of initially unresectable hepatocellular carcinoma. Cancer 2013 119: 3334-42.

26. Zhu AX, Kudo M, Assenat E, Cattan S, Kang YK, Lim HY, et al. Effect of everolimus on survival in advanced hepatocellular carcinoma after failure of sorafenib: the EVOLVE-1 randomized clinical trial. JAMA 2014; 312: 57-67.

27. Reig M, Rimola J, Torres F, Darnell A, Lope CR, Forner A, et al. Post-progression survival of patients with advanced hepatocellular carcinoma. Rationale for second line trial design. Hepatology 2013; 58: 2023-31.

28. Iavarone M, Cabibbo G, Biolato M, Corte CD, Maida M, arbara M, et al. Predictors of survival of patients with advanced hepatocellular carcinoma who permanently discontinued sorafenib. Hepatology. doi: 10.1002/hep.27729.

29. Edeline J, Boucher E, Rolland Y, Vauléon E, Pracht M, Perrin C, et al. Comparison of tumor response by Response Evaluation Criteria in Solid Tumors (RECIST) and modified RECIST in patients treated with sorafenib for hepatocellular carcinoma. Cancer 2012; 118: 147-56.

30. Kawaoka T, Aikata H, Murakami E, Nakahara T, Naeshiro N, Tanaka M, et al. Evaluation the mRECIST and α-fetoprotein ratio for stratification of the prognosis of advanced-hepatocellular-carcinoma patients treated with sorafenib. Oncology 2012; 83: 192-200.

31. Edeline J, Boucher E, Rolland Y, Vauléon E, Pracht M, Perrin C, et al. Comparison of tumor response by Response Evaluation Criteria in Solid Tumors (RECIST) and modified RECIST in patients treated with sorafenib for hepatocellular carcinoma. Cancer 2012; 118: 147-56.

32. D'Amico G, Garcia-Tsao G, Pagliaro L. Natural history and prognostic indicators of survival in chrrhosis: a systematic review of 118 studies. J Hepatol 2006; 44: 217-31.

33. Chen PJ, Furuse J, Han KH, Hsu C, Lim HY, Moon H, et al. Issues and controversies of hepatocellular carcinoma-targeted therapy clinical trials in Asia: experts' opinion. Liver Int 2010; 30: 1427-38.

34. Llovet JM, Hernandez-Gea V. Hepatocellular carcinoma: reasons for phase III failure and novel perspectives on trial design. Clin Cancer Res 2014; 20: 2072-9.

Figure legends

Figure 1: Study flow diagram

Figure 2: Relationship between median overall survival and median post-progression survival among all reports. Each arm is represented by a circle, with a size proportional to the number of patients. Median post-progression survival was strongly correlated with median overall survival (r=0.834, P<0.001) on the basis of weighted linear regression.

Figure 3: Relationship between median OS and median progression-free survival among all reports. Each arm is represented by a circle, with a size proportional to the number of patients. Median PFS/TTP was moderately correlated with median OS (r=0.546, P<0.001) on the basis of weighted linear regression.

Figure 4: Average proportion of median PPS to median OS according to Child-Pugh class. The average of median PPS/median OS in Child-Pugh class A (54.4±17.6 %) was significantly higher than in Child-Pugh class B (32.0±11.6 %) (P=0.015).

Figure 5: Relationship between median overall survival median post-progression survival or progression-free survival among phase III trials. **(A)** Relationship between median overall survival (OS) and median post-progression survival (PPS), and **(B)** relationship between median

OS and median progression-free survival (PFS) or median time to progression (TTP) among reports of phase III trials. Each arm is represented by a circle, with a size proportional to the number of patients. Median PPS was strongly correlated with median OS (r=0.804), and median PFS/TTP was moderately correlated with median OS (r=0.396) on the basis of weighted linear regression.

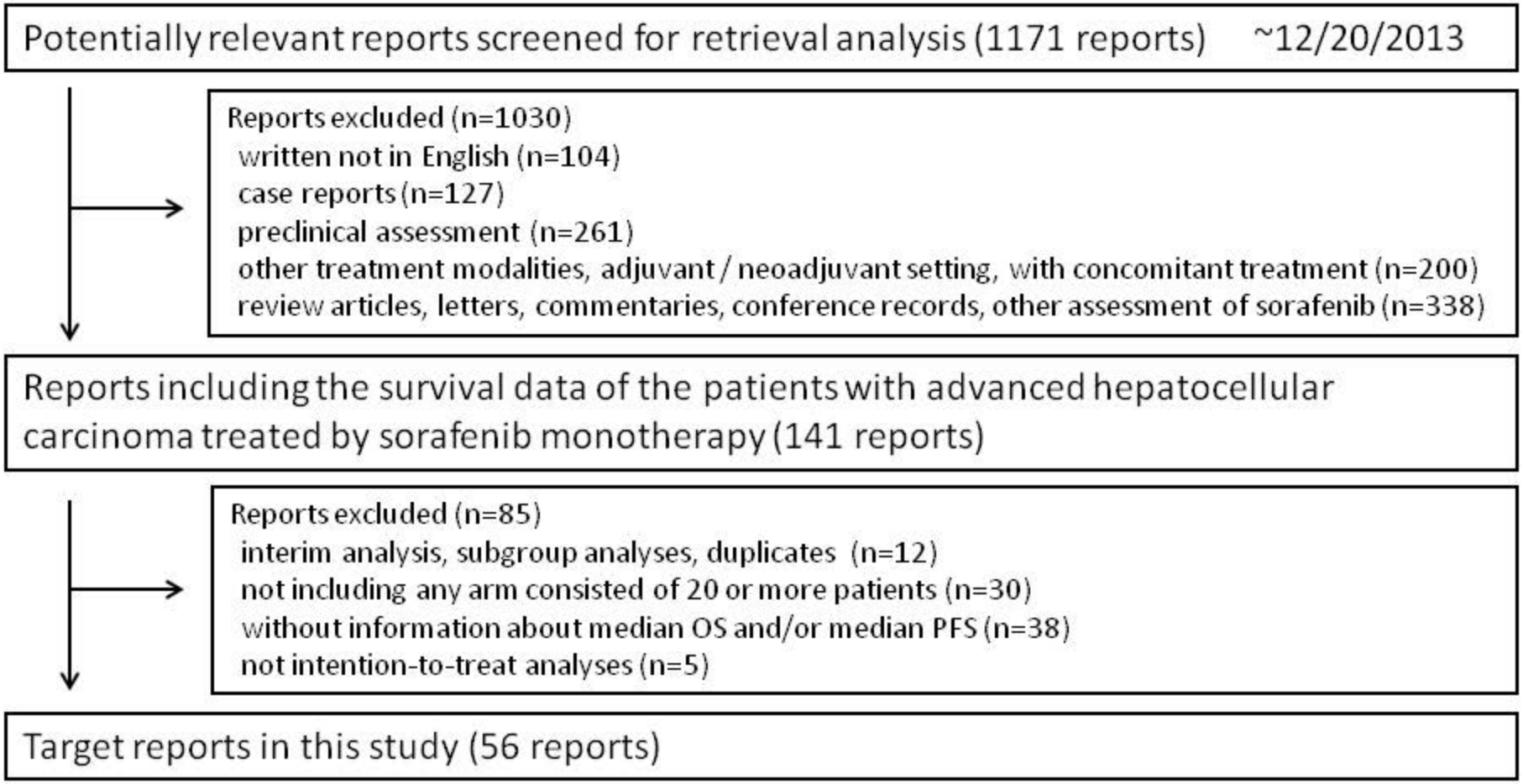
Supplementary Figure 1: (A) Relationship between median overall survival (OS) and median post-progression survival (PPS) and **(B)** relationship between median OS and median progression-free survival (PFS) among the reports in which tumor progression was assessed by PFS. Each arm is represented by a circle, with a size proportional to the number of patients. Median PPS was strongly correlated with median OS (r=0.952, P<0.001) on the basis of weighted linear regression. On the other hand, median PFS had no correlation with median OS (r=0.064, P=0.773).

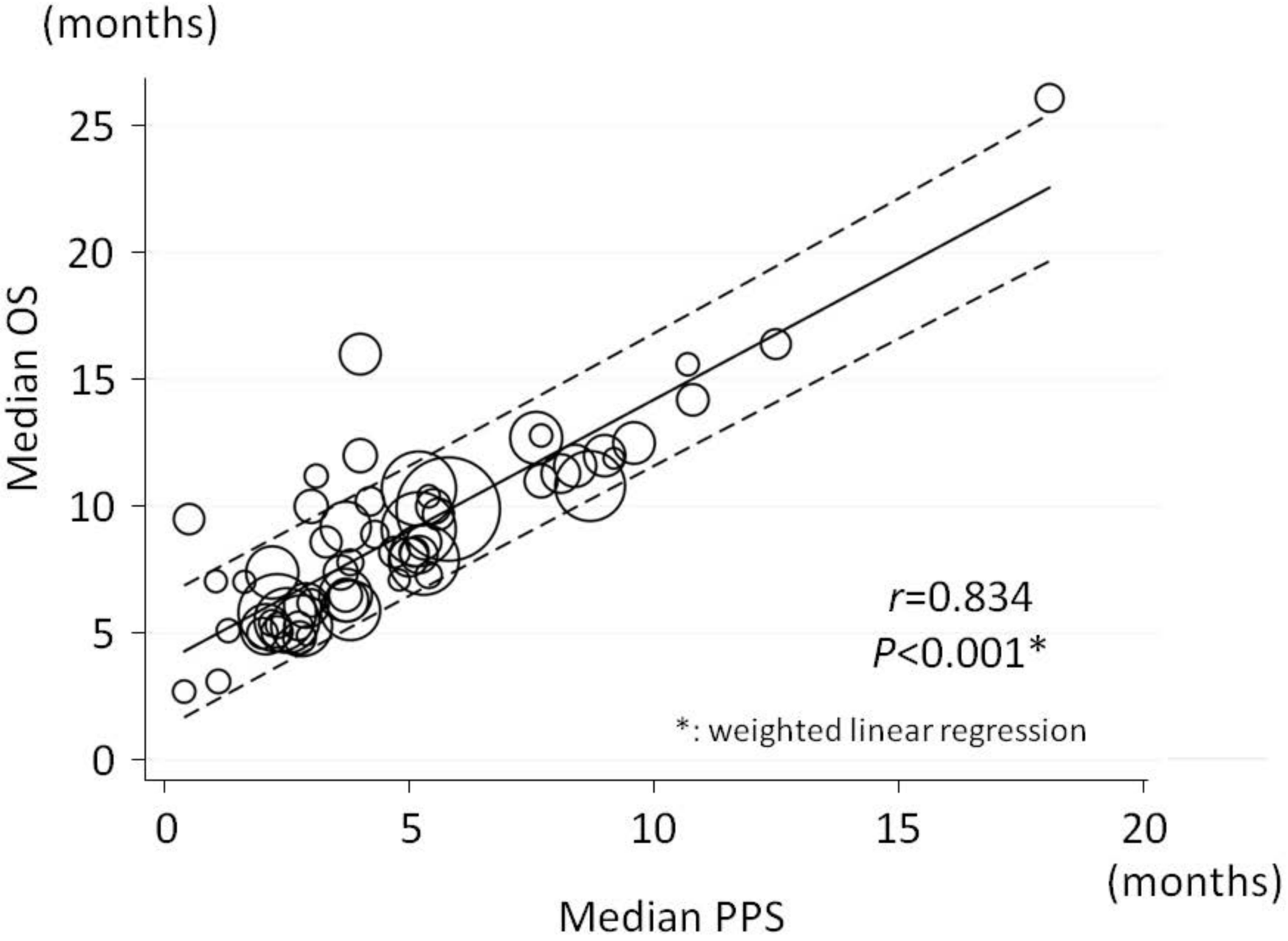
Supplementary Figure 2: (A) Relationship between median overall survival (OS) and median time to progression (TTP) and **(B)** relationship between median OS and median progression-free survival (PFS) among the reports in which tumor progression was assessed by TTP. Each arm is represented by a circle, with a size proportional to the number of patients. Median PPS was strongly correlated with median OS (r=0.795, P<0.001) on the basis of weighted linear regression. On the other hand, median TTP was moderately correlated with

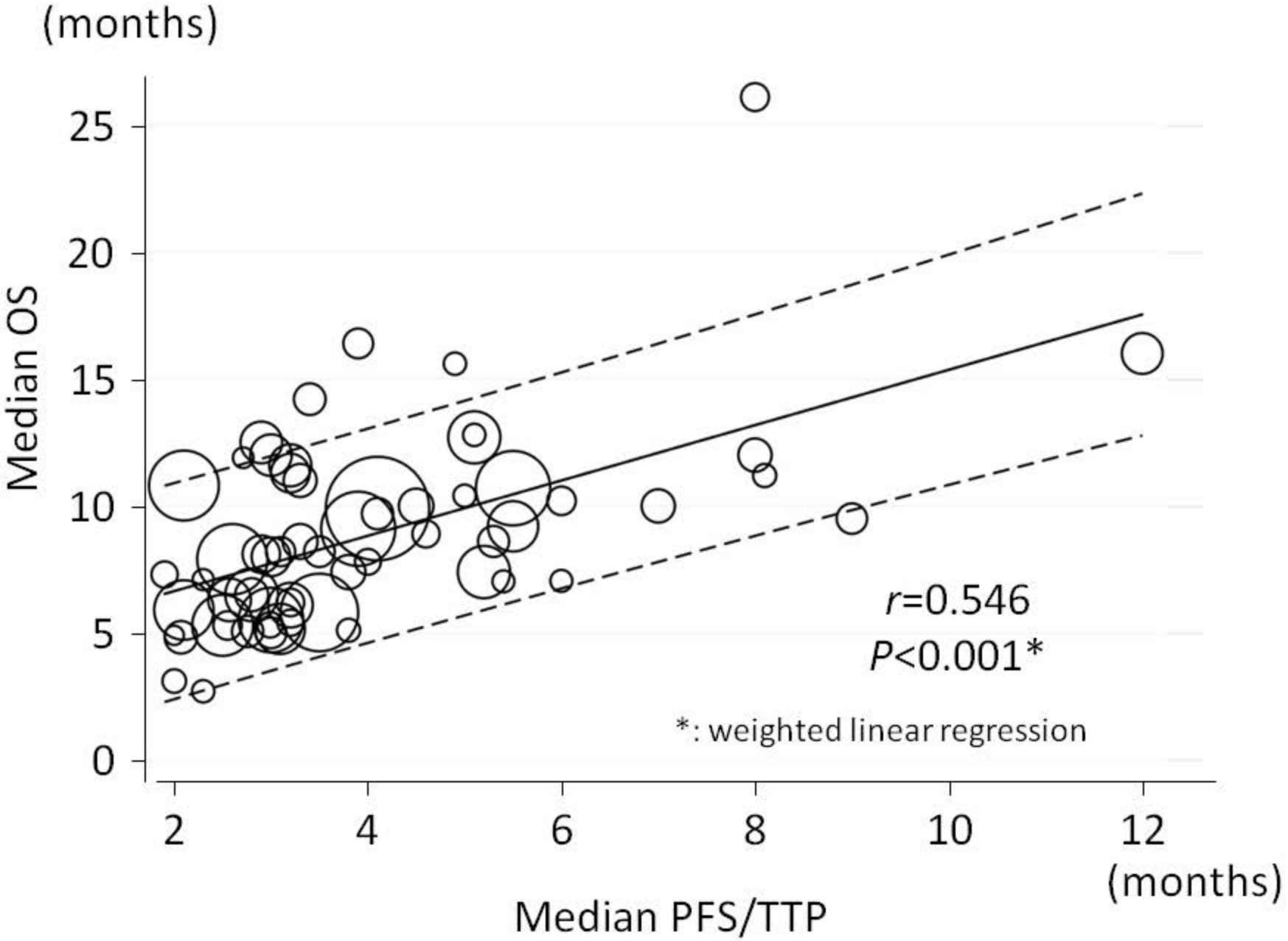
median OS (r=0.575, P<0.001).

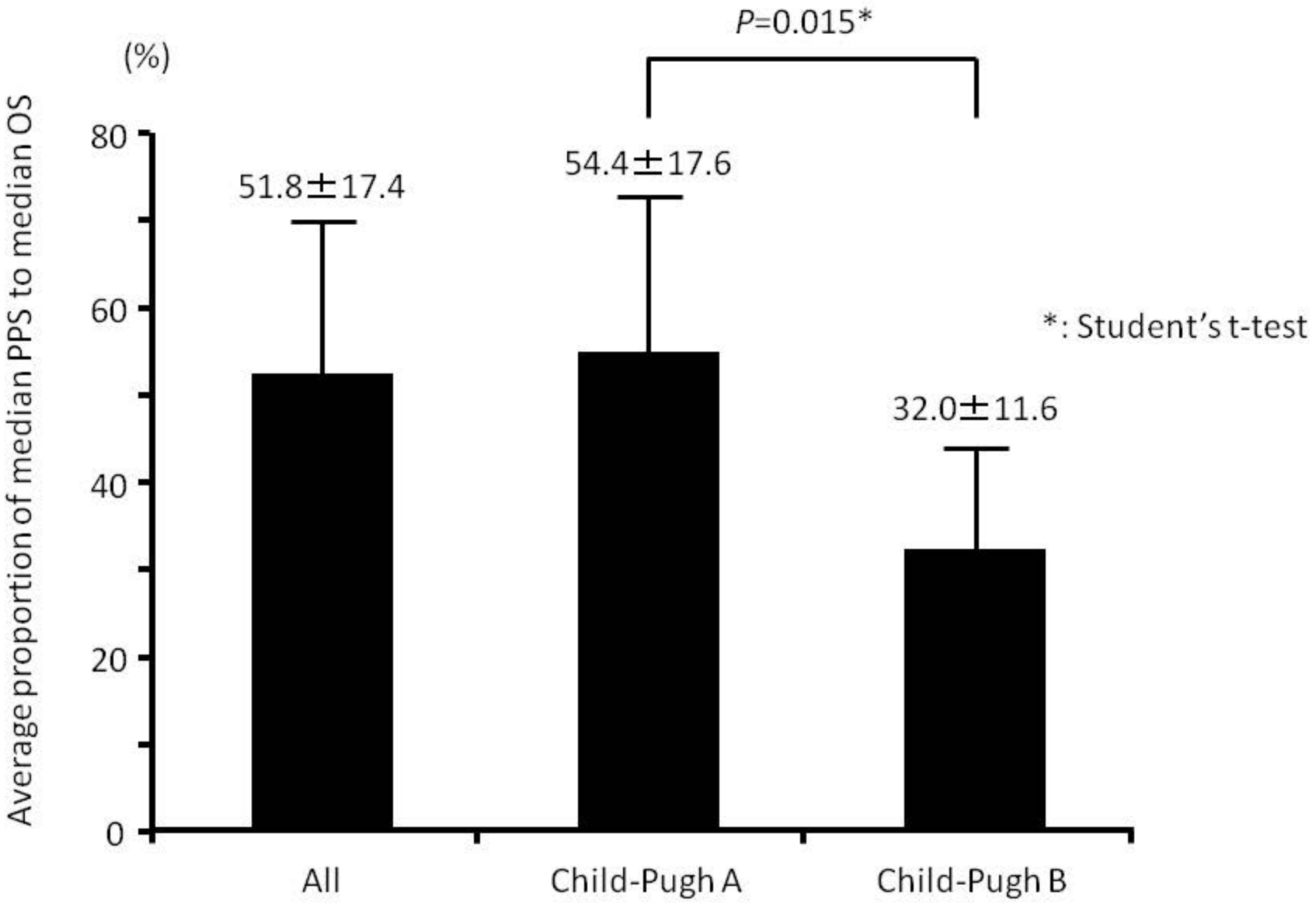
Supplementary Figure 3: (A) Relationship between median overall survival (OS) and median post-progression survival (PPS) and **(B)** relationship between median OS and median progression-free survival (PFS) or median time to progression (TTP) among the reports in which radiological responses were assessed by Response Evaluation Criteria In Solid Tumors (RECIST). Each arm is represented by a circle, with a size proportional to the number of patients. Median PPS was strongly correlated with median OS (r=0.870, P<0.001) on the basis of weighted linear regression. On the other hand, median PFS/TTP was weekly correlated with median OS (r=0.385, P=0.006).

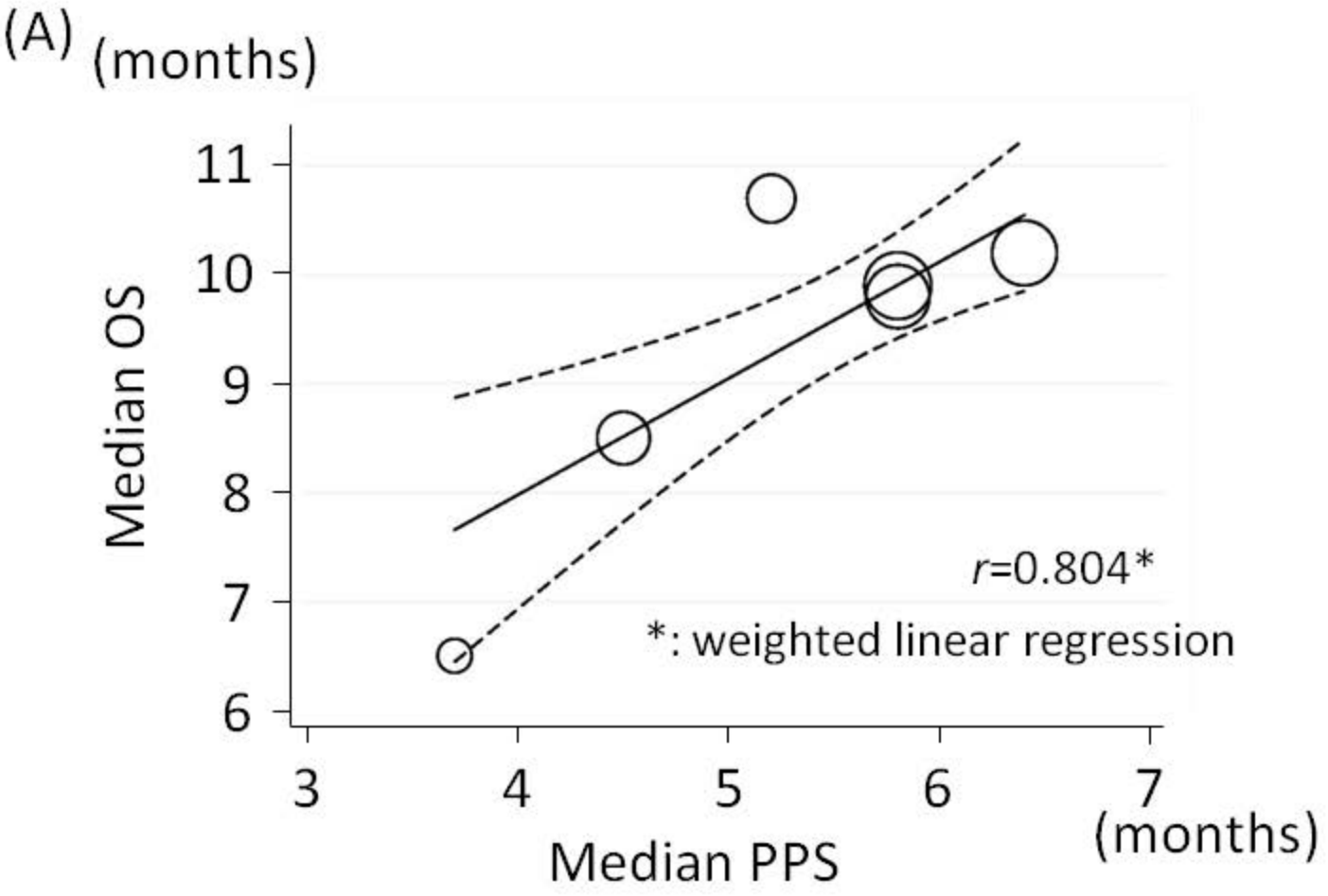
Supplementary Figure 4: (A) Relationship between median overall survival (OS) and median post-progression survival (PPS) and **(B)** relationship between median OS and median progression-free survival (PFS) or median time to progression (TTP) among the reports in which radiological responses were assessed by modified Response Evaluation Criteria In Solid Tumors. Each arm is represented by a circle, with a size proportional to the number of patients. Median PPS was strongly correlated with median OS (r=0.802, P<0.001) on the basis of weighted linear regression. On the other hand, median PFS/TTP was moderately correlated with median OS (r=0.728, P=0.007).

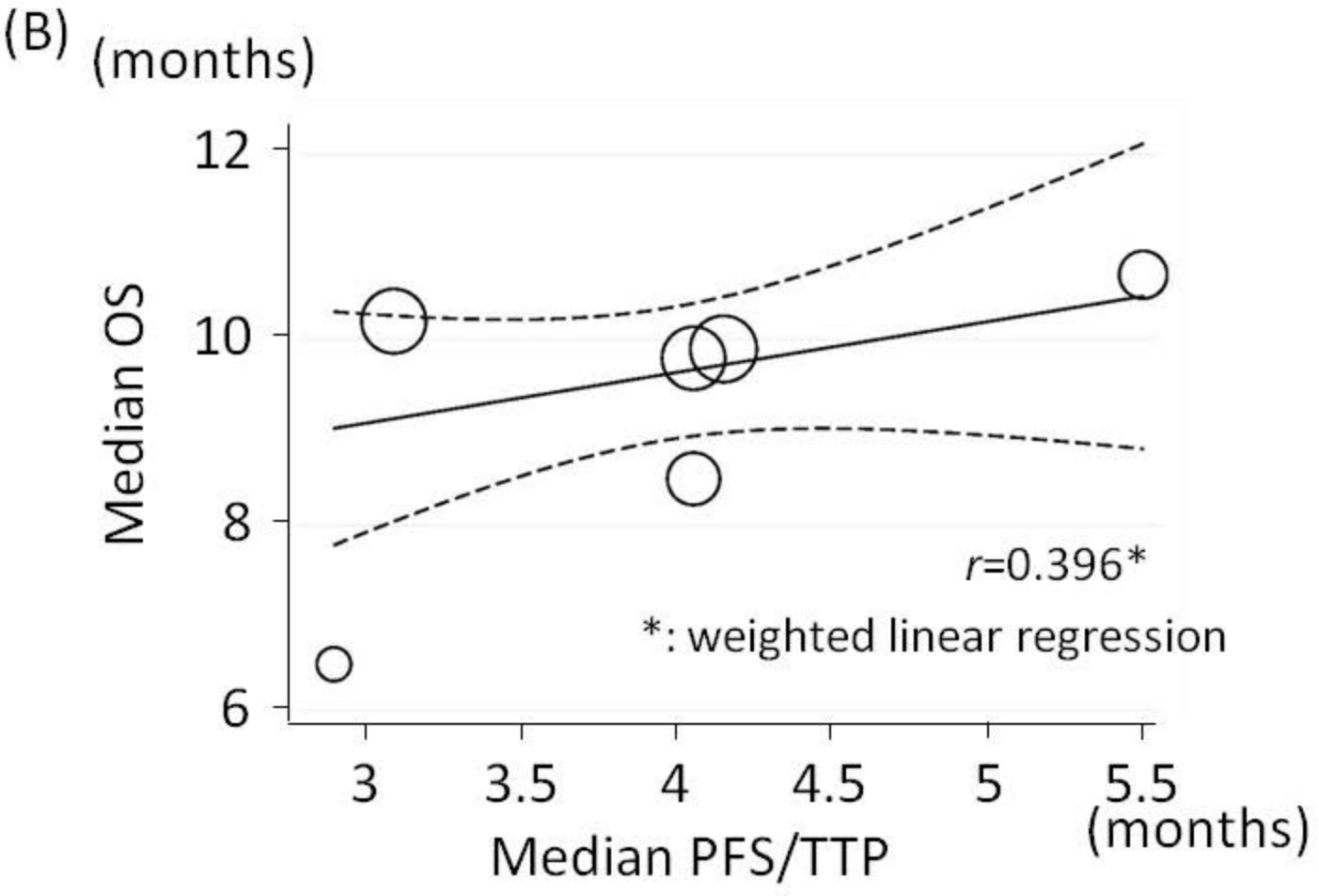

Potentially relevant reports screened for retrieval analysis (1171 reports) ~12/20/2013
Reports excluded (n=1030)
written not in English (n=104)
case reports (n=127)
preclinical assessment (n=261)
other treatment modalities, adjuvant / neoadjuvant setting, with concomitant treatment (n=200)
review articles, letters, commentaries, conference records, other assessment of sorafenib (n=338)
Reports including the survival data of the patients with advanced hepatocellular carcinoma treated by sorafenib monotherapy (141 reports)
Reports excluded (n=85)
interim analysis, subgroup analyses, duplicates (n=12)
not including any arm consisted of 20 or more patients (n=30)
without information about median OS and/or median PFS (n=38)
not intention-to-treat analyses (n=5)
Target reports in this study (56 reports)

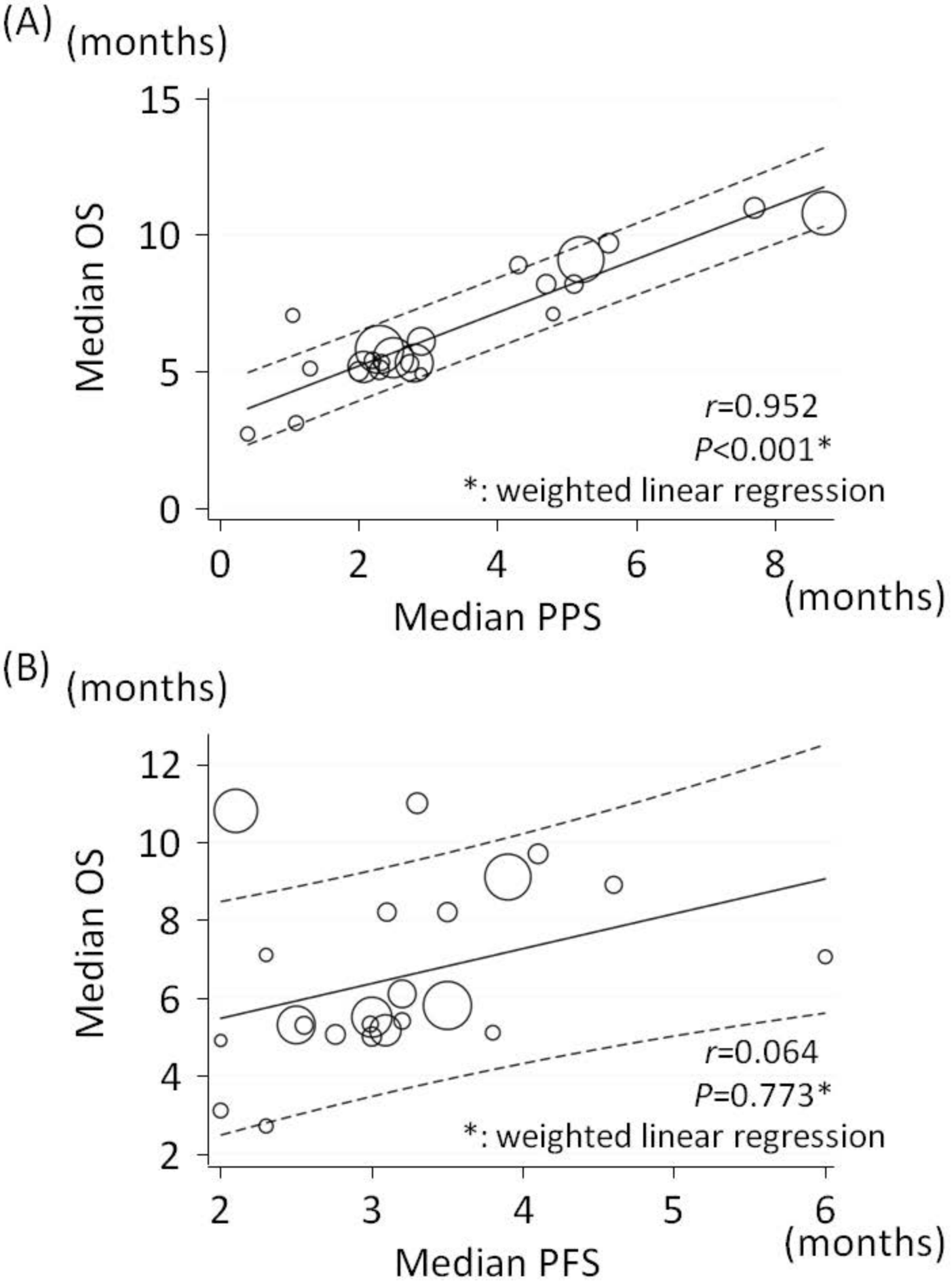

(months)
25
20
15
10
5
0
Median OS
r=0.834
P<0.001*
*: weighted linear regression
0
5
10
15
20
(months)
Median PPS

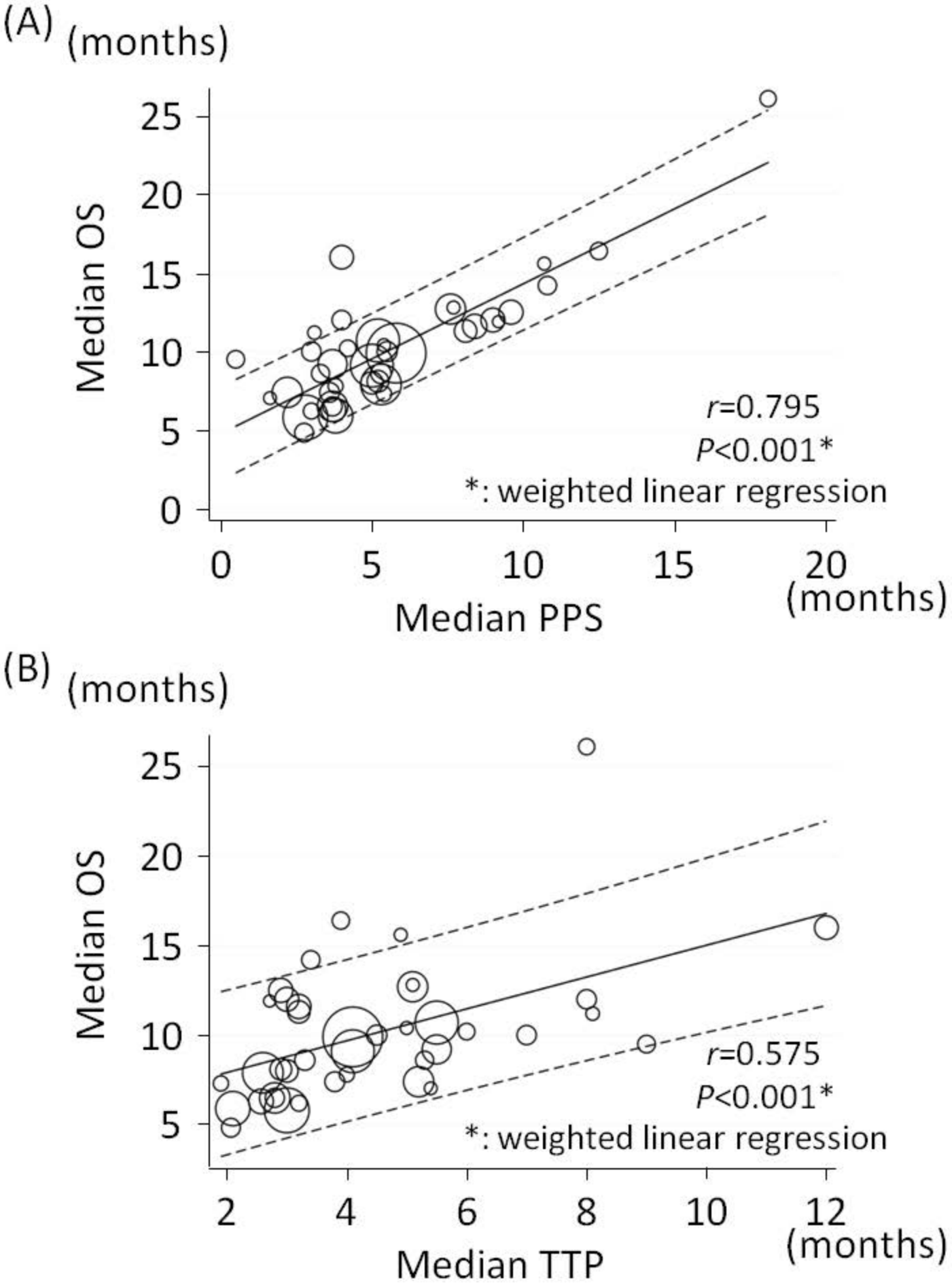

(months)
25
20
15
10
5
0
Median OS
r=0.546
P<0.001*
*: weighted linear regression
2
4
6
8
10
12
(months)
Median PFS/TTP

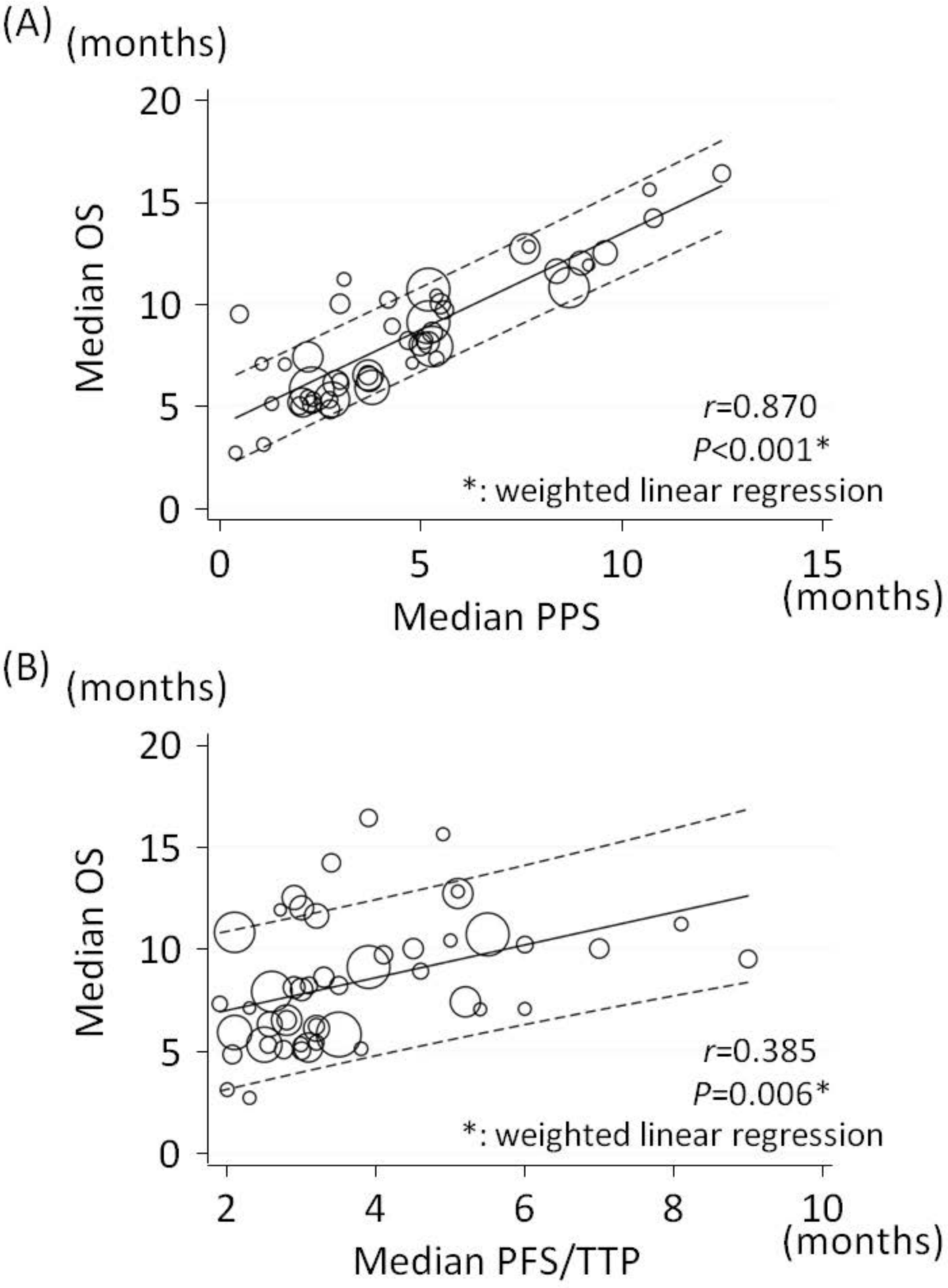

P=0.015*
(%)
Average proportion of median PPS to median OS
80
60
40
20
0
51.8±17.4
54.4±17.6
32.0±11.6
*: Student's t-test
All
Child-Pugh A
Child-Pugh B


(A)
(months)
11
10
9
8
7
6
Median OS
r=0.804*
*: weighted linear regression
3
4
5
6
7
(months)
Median PPS


(B)
(months)
12
10
8
6
Median OS
r=0.396*
*: weighted linear regression
3
3.5
4
4.5
5
5.5
(months)
Median PFS/TTP


(A)
(months)
15
10
5
0
Median OS
r=0.952
P<0.001*
*: weighted linear regression
0
2
4
6
8
(months)
Median PPS
(B)
(months)
12
10
8
6
4
2
Median OS
r=0.064
P=0.773*
*: weighted linear regression
2
3
4
5
6
(months)
Median PFS


(A)
(months)
Median OS
25
20
15
10
5
0
r=0.795
P<0.001*
*: weighted linear regression
0
5
10
15
20
(months)
Median PPS
(B)
(months)
Median OS
25
20
15
10
5
r=0.575
P<0.001*
*: weighted linear regression
2
4
6
8
10
12
(months)
Median TTP


(A)
(months)
20
15
10
5
0
Median OS
r=0.870
P<0.001*
*: weighted linear regression
0
5
10
15
(months)
Median PPS
(B)
(months)
20
15
10
5
0
Median OS
r=0.385
P=0.006*
*: weighted linear regression
2
4
6
8
10
(months)
Median PFS/TTP

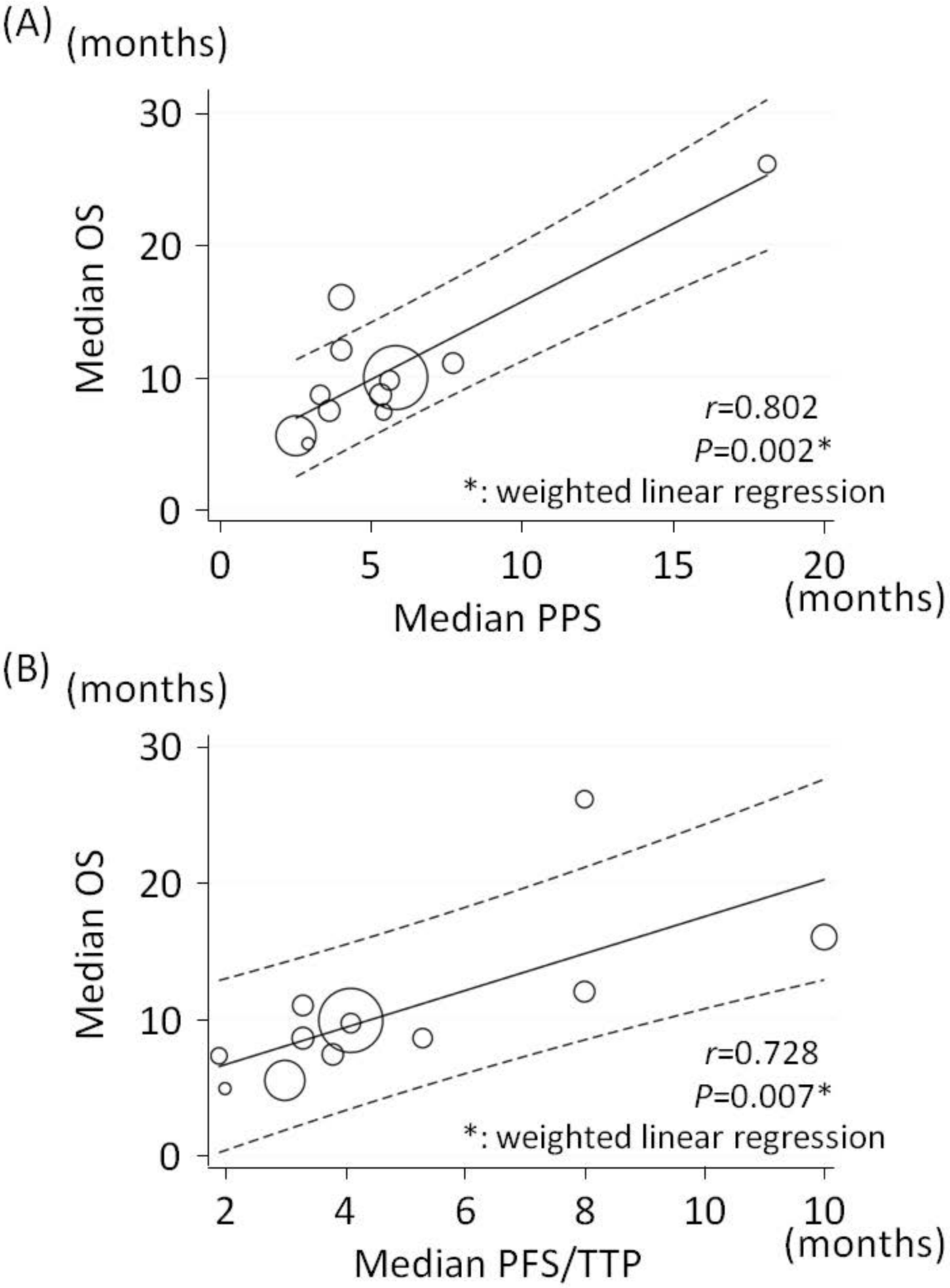

(A)
(months)
30
20
10
0
Median OS
r=0.802
P=0.002*
*: weighted linear regression
0
5
10
15
20
(months)
Median PPS
(B)
(months)
30
20
10
0
Median OS
r=0.728
P=0.007*
*: weighted linear regression
2
4
6
8
10
10
(months)
Median PFS/TTP

Table Characteristics of the reports used in this study

Number of reports	56
Number of arms in each report	
1	52
2	3
3	1
Characteristics of the reports	
Clinical trials	10
Clinical practice	46
Number of arms	61
Number of patients in each arm	
Median (Range)	57 (20-578)
Assessment of tumor progression	
PFS	21
TTP	38
Both PFS and TTP	2
Criteria of radiological responses	
RECIST	46
Modified RECIST	9
Both of RECIST and Modified RECIST	3
Not described or other criteria	3

Supplementary Table 1 List of reports and patients characteristics used in this study

Author	Journal. Year	n	Age * (years)	Male (n)	Child-Pugh class (n)				MVI [b] (n)	EHS [c] (n)	Criteria of radiological assessment	PFS (months)	TTP (months)	OS (months)
					A	B	C	ND[a]						
Jeong SW	Gut Liver. 2013;7:696-703.	30	57.6	21	17	13	0	0	30	19	RECIST	2.1	ND [a]	3.1
Zheng YB	Asian Pac J Cancer Prev. 2013;14:5527-31.	65	55	51	35	16	0	0	ND [a]	34	RECIST	ND [a]	4.5	10
Lee S	PLoS One. 2013;8:e77240.	226	57	188	161	65	0	0	ND [a]	147	mRECIST	3	ND [a]	5.5
Shin SY	Int J Clin Pharmacol Ther. 2013;51:837-46.	99	55.57	87	83	16	0	0	ND [a]	ND [a]	RECIST	ND [a]	2.57	6.3
Johnson PJ	J Clin Oncol. 2013;31:3517-24.	578	60	484	531	47	0	0	158	ND [a]	mRECIST	ND [a]	4.1	9.9
Choi GH	Radiology. 2013;269:603-11.	191	54	166	136	55	0	0	34	ND [a]	RECIST	ND [a]	2.1	5.9
Chen D	Eur J Surg Oncol. 2013;39:974-80.	54	ND [a]	46	44	10	0	0	ND [a]	ND [a]	RECIST	ND [a]	3.4	14.2
Abdel-Rahman O	Med Oncol. 2013;30:655.	26	53.5	ND	8	18	0	0	10	6	RECIST	6	ND [a]	7.05
Miyaki D	J Gastroenterol Hepatol. 2013;28:1834-41.	27	66	169	25	2	0	0	ND [a]	ND [a]	RECIST	ND [a]	5	10.4
Kim HY	J Gastroenterol Hepatol. 2013;28:1756-61.	325	56	289	245	80	0	0	176	170	RECIST	3.5	3	5.8
Ikeda M	J Gastroenterol. 2014;49:932-40	48	71	43	32	16	0	0	ND [a]	0	RECIST	ND [a]	3.9	16.4
Reig M	Hepatology. 2013;58:2023-31.	147	64.1	124	125	22	0	0	ND [a]	27	RECIST	ND [a]	5.1	12.7
Miyahara K	Hepatol Res. 2014;44:296-301.	23	68	20	0	0	0	23	4	ND [a]	RECIST	ND [a]	11.8 weeks	11.9
Personeni N	J Cancer Res Clin Oncol. 2013;139:1179-87.	44	ND [a]	41	36	8	0	0	ND [a]	16	RECIST	ND [a]	6	10.2
Montella L	Oncology. 2013;84:265-72.	60	76	47	44	13	3	0	ND [a]	12	RECIST	ND [a]	7	10
Nakazawa T	Eur J Gastroenterol Hepatol. 2013;25:683-9.	59	69	49	59	0	0	0	19	18	mRECIST	3.3	ND [a]	11
Di Costanzo GG	Med Oncol. 2013;30:446.	90	62	79	71	19	0	0	45	33	mRECIST	ND [a]	12	16
		60	73	47	54	6	0	0	32	20	mRECIST	ND [a]	8	12
Sugimoto K	Liver Int. 2013;33:605-15.	37	69.1	31	37	0	0	0	15	11	RECIST mRECIST	ND [a]	1.9	7.3
Berretta M	Anticancer Drugs. 2013;24:212-8.	27	46	26	16	10	1	0	ND [a]	ND [a]	RECIST	ND [a]	5.1	12.8

Nakano M	Oncology. 2013;84:108-14.	96	70.4	76	88	8	0	0	ND [a]	ND [a]	RECIST	ND [a]	3.2	11.6
Santini D	Expert Rev Anticancer Ther. 2012;12:1283-8.	93	63	77	14	70	9	0	ND [a]	ND [a]	RECIST	ND [a]	3	12
Koschny R	Oncology. 2013;84:6-13.	46	67	39	42	4	0	0	ND [a]	18	RECIST	3.1	ND [a]	8.2
Pressiani T	Ann Oncol. 2013;24:406-11.	297	ND [a]	232	234	63	0	0	ND [a]	217	RECIST	3.9	4.1	9.1
Yang Y	Exp Ther Med. 2012;3:171-180.	52	52.6	47	43	9	0	0	52	ND [a]	mRECIST	ND [a]	5.3	8.6
Kawaoka T	Oncology. 2012;83:192-200.	66	63	58	58	8	0	0	ND [a]	38	RECIST mRECIST	ND [a]	3.3	8.6
Zugazagoitia J	Clin Transl Oncol. 2013;15:146-53.	51	68	38	30	18	0	3	ND [a]	9	RECIST	3.5	ND [a]	8.2
Sacco R	Expert Rev Anticancer Ther. 2012;12:869-75.	42	70.1	30	41	1	0	0	38	9	mRECIST	ND [a]	8	26.1
Mir O	PLoS One. 2012;7:e37563.	40	62.5	0	40	0	0	0	ND [a]	ND [a]	RECIST	4.6	ND [a]	8.9
Kaneko S	Hepatol Res. 2012;42:523-42.	264	70	ND [a]	0	0	0	264	ND [a]	ND [a]	RECIST	2.1	ND [a]	10.8
Woo HY	Scand J Gastroenterol. 2012;47:809-19.	57	55	64	43	14	0	0	ND [a]	32	RECIST	ND [a]	63 days	147 days
Estfan B	Am J Clin Oncol. 2013;36:319-24.	41	58	35	25	16	0	0	ND [a]	ND [a]	RECIST	ND [a]	3.2	6.2
Jeong SW	Asia Pac J Clin Oncol. 2012;8:164-71.	20	59.5	11	14	6	0	0	17	10	mRECIST	2.0	ND [a]	4.9
Chiu J	Cancer. 2012;118:5293-301.	108	57	91	108	0	0	0	ND [a]	ND [a]	RECIST	3.2	ND [a]	6.1
		37	58	35	0	37	0	0	ND [a]	ND [a]	RECIST	3.2	ND [a]	5.4
		27	61	21	0	27	0	0	ND [a]	ND [a]	RECIST	2.3	ND [a]	2.7
Otsuka T	Hepatol Res. 2012;42:879-86.	94	75	77	78	16	0	0	29	40	RECIST	ND [a]	2.9	12.5
Pinter M	Radiology. 2012;263:590-9.	63	ND [a]	48	28	35	0	0	39	32	mRECIST	ND [a]	3.8	7.4
Kim JE	Oncology. 2012;82:119-25.	267	ND [a]	234	199	68	0	0	ND [a]	245	RECIST	ND [a]	2.6	7.9
Morimoto M	Anticancer Res. 2012;32:619-23.	81	75	60	68	13	0	0	18	17	ND	ND [a]	3.2	11.3
Wong H	Oncologist. 2011;16:1721-8.	137	55	122	86	51	0	0	ND [a]	ND [a]	RECIST	3.09	ND [a]	5.16
		35	73	25	22	13	0	0	ND [a]	ND [a]	RECIST	2.99	ND [a]	5.32
Trojniak MP	Immunopharmacol Immunotoxicol. 2012;34:419-22.	81	65	66	77	4	0	0	ND [a]	ND [a]	RECIST	ND [a]	3	8
Yau T	Oncologist. 2011;16:1270-9.	53	58	44	31	20	1	0	ND [a]	ND [a]	RECIST	12 weeks	ND [a]	22 weeks
Pinter M	Aliment Pharmacol Ther. 2011;34:949-59.	148	65	121	77	56	15	0	68	57	RECIST	ND [a]	5.2	7.4
Ueshima K	Dig Dis. 2011;29:321-5.	50	ND [a]	0	0	0	0	50	9	17	RECIST	ND [a]	9.0	9.5

Lee JH	Liver Int. 2011;31:1144-9.	29	57.5	22	17	12	0	0	ND [a]	ND [a]	RECIST	3.8	ND [a]	5.1
Edeline J	Cancer. 2012;118:147-56.	53	ND [a]	48	41	12	0	0	ND [a]	13	RECIST mRECIST	4.1	ND [a]	9.7
Baek KK	Oncology. 2011;80:167-74.	201	54.3	163	165	34	2	0	ND [a]	ND [a]	RECSIT	2.5	ND [a]	5.3
Morimoto M	Hepatol Res. 2011;41:296-302.	76	70.3	63	71	5	0	0	24	19	RECIST	ND [a]	2.9	8.1
Lee S	Invest New Drugs. 2012;30:1150-1157.	44	58	32	29	15	0	0	21	40	RECIST	11.1 weeks	ND [a]	23.0 weeks
Balsom SM	Oncology. 2010;78:210-2.	26	56	23	0	0	0	26	ND	ND	RECIST	ND [a]	5.40	7.03
Kim JW	Am J Clin Oncol. 2011;34:125-9.	24	53	19	20	4	0	0	10	ND	RECIST	2.3	ND [a]	7.1
Vincenzi B	Oncologist. 2010;15:85-92.	29 36	69	42	0 0	0 0	0 0	29 36	ND	17	RECIST ND [a]	ND [a] ND [a]	8.1 4.0	11.2 7.8
Pinter M	Oncologist. 2009;14:70-6.	59	64	46	26	23	10	0	ND	ND	RECIST	ND [a]	2.8	6.5
Yau T	Cancer. 2009;115:428-36.	51	56	45	36	13	2	0	24	ND	RECIST	3	ND [a]	5
Cheng AL	Lancet Oncol. 2009;10:25-34.	150	51	127	146	4	0	0	54	103	RECIST	ND [a]	2.8	6.5
Llovet JM	N Engl J Med. 2008;359:378-90.	299	64.9	260	284	14	0	1	209	108	RECIST	ND [a]	5.5	10.7
Furuse J	Cancer Sci. 2008;99:159-65.	27	70	25	13	14	0	0	ND	7	RECIST	ND [a]	4.9	15.6
Abou-Alfa GK	J Clin Oncol. 2006;24:4293-300.	137	69	97	98	38	0	1	ND	ND	modified WHO	ND [a]	5.5	9.2

*. Mean or median, a. ND: not described, b. MVI: Macroscopic vascular invasion, c. EHS: Extrahepatic spread

Supplementary Table 2 List of phase III trials and those patients characteristics used in additional analysis

Author	Journal. Year	n	Age * (years)	Male (n)	Child-Pugh class (n)				MVI [b] (n)	EHS [c] (n)	Criteria of radiological assessment	PFS (months)	TTP (months)	OS (months)
					A	B	C	ND[a]						
Llovet JM	N Engl J Med. 2008; 359: 278-90.	299	64.9	260	284	14	0	1	209	108	RECIST	ND [a]	5.5	10.7
Cheng AL	Lancet Oncol 2009; 10: 25-34.	150	51	127	146	4	0	0	54	103	RECIST	ND [a]	2.8	6.5
Johnson PJ	J Clin Oncol 2013; 31: 3517-24.	578	60	484	531	47	0	0	158	ND [a]	mRECIST	ND [a]	4.1	9.9
Cheng AL	J Clin Oncol 2013; 31: 4067-75.	544	59.0	459	541	1	0	2	415 [**]		RECIST	3.0	4.1	10.2
Cainap C	J Clin Oncol 2015; 33: 172-9.	521	60	436	493	26	0	2	211	296	RECIST	ND [a]	4.0	9.8
Zhu AX	J Clin Oncol 2015; 33: 559-66.	358	60.0	286	345	0	0	13	153	219	RECIST	ND [a]	4.0	8.5

*. Median, **: Vascular invasion and/or extrahepatic spread

a. ND: not described, b. MVI: Macroscopic vascular invasion, c. EHS: Extrahepatic spread