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Effect of Angiogenesis Inhibitor Bevacizumab on Survival in Patients with Cancer: A Meta-Analysis of the Published Literature

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Abstract

Bevacizumab is a recombinant humanized monoclonal antibody against vascular endothelial growth factor which has been used in conjunction with other anti-cancer agents in the treatment of patients with many cancers. It remains controversial whether bevacizumab can prolong survival in cancer patients. This meta-analysis was therefore performed to evaluate effect of bevacizumab on survival in cancer patients. PubMed, EMBASE, and Web of Science databases were searched for English-language studies of randomized controlled trials comparing bevacizumab with control therapy published through February 8, 2012. Progression-free survival, overall survival, and one-year survival rate were analyzed using random- or fixed-effects model. Thirty one assessable randomized controlled trials were identified. A significant improvement in progression-free survival in cancer patients was attributable to bevacizumab compared with control therapy (hazard ratio, 0.72; 95% confidence interval, 0.68 to 0.76; $p<0.001$). Overall survival was also significantly longer in patients were treated with bevacizumab (hazard ratio, 0.87; 95% confidence interval, 0.83 to 0.91; $p<0.001$). The significant benefit in one-year survival rate was further seen in cancer patients receiving bevacizumab (odds ratio, 1.30; 95% confidence interval, 1.20 to 1.41; $p<0.001$). Current evidences showed that bevacizumab prolong progression-free survival and overall survival, and increase one-year survival rate in cancer patients as compared with control therapy.

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Introduction

Angiogenesis is a universal requirement for the growth of solid tumors beyond the limits of oxygen diffusion from the existing vasculature, and plays a crucial role in the growth and metastasis of cancer [1]. Vascular endothelial growth factor (VEGF), a key mediator of angiogenesis, is overexpressed in many tumor types, and has been associated with poor prognosis [1,2]. The experimental *in vivo* inhibition of the VEGF pathway results in tumor growth inhibition and improves delivery of chemotherapeutic drugs by reducing tumor interstitial fluid pressure and by changing vessel diameter, density, and permeability in response to treatment [3]. These data prompted the clinical investigation of bevacizumab (Avastin; Genentech, South San Francisco, CA), a humanized anti-VEGF monoclonal IgG_1 antibody in the treatment of cancer patients.

Bevacizumab has shown benefits in the treatment of many types of malignancy including colorectal cancer, non–small cell lung cancer, renal cell carcinoma, breast cancer, and glioblastoma [4]. Bevacizumab monotherapy has been notably less studied in cancer patients than bevacizumab combined with chemotherapy, and fatal adverse events have been reported in cancer patients treated with bevacizumab in combination with chemotherapy [5]. In a recent meta-analysis, Ranpura et al [6] have reported that bevacizumab in combination with chemotherapy or biological therapy was associated with increased treatment-related mortality as compared with chemotherapy alone. To better understand the overall impact of bevacizumab on survival of patients with cancer, we conducted a systematic review and meta-analysis of published randomized controlled trials (RCTs) to evaluate the effect of bevacizumab on progression-free survival (PFS), overall survival (OS), and one-year survival rate (OYSR) in patients with cancer.

Methods

Data sources and searches

Two investigators searched PubMed, EMBASE, and Web of Science databases for relevant articles published until February 8, 2012; no lower date limit was applied. We used the following Medical Subject Heading terms and keywords: "bevacizumab", "Avastin", and "carcinoma/cancer", and the searches were limited initially to English publications of RCTs in humans. The search strategy also used text terms such as "progression-free survival", "overall survival", "one-year survival rate" and "vascular endothelial growth factor" to identify relevant information. We screened the reference lists of included studies and related

publications. The results were then hand searched for eligible trials. Results were double-checked and arbitrated by a second investigator.

Study selection

We included full-text publications that investigated patients with cancer during treatment with bevacizumab compared with placebo, or bevacizumab-containing chemotherapy regimen with the same regimen either without bevacizumab or with bevacizumab replaced by a placebo, or with different doses of bevacizumab. We excluded studies that were not published as full reports, such as conference abstracts and letters to editors.

Data extraction and quality assessment

To avoid bias in the data-abstraction process, 2 investigators independently abstracted the data from the trials and subsequently compared the results. The following information was obtained from each report: the first author, the year of publication, the period and location of study, and the numbers of patients enrolled, randomized and analyzed, the proportion of patients who were men, the therapy regimen, the duration of follow up, hazard ratios (HRs) for PFS and OS, and odds ratios (ORs) for OYSR comparing bevacizumab-based therapies with control arms. When studies compared 2 or more doses of bevacizumab with a control, we used data from the group with the highest dose. All data were checked for internal consistency, and disagreements were resolved by discussion among the investigators.

Quality assessment of the publications included was done unblinded by three investigators using a 10 point scoring system as described in a previous meta-analysis [7].

Statistical analysis

If HRs for PFS or/and OS were not reported in the original publications, we calculated HR values and their 95% confidence intervals (CIs) in each RCT using the abstracted survival probabilities in the Kaplan-Meier curve at specific time points according to the methods proposed by Parmar et al [8]. Minimum and maximum follow-up times were used to estimate censored subjects under the assumption that censoring happens constantly throughout follow-up. If the minimum follow-up time was not available, time zero was substituted for it. HRs were calculated to show how many times higher the probability of death from any cause in patients receiving bevacizumab as compared with those receiving control therapies.

We calculated ORs to assess OYSR advantage of bevacizumab as compared with control therapy. We constructed 2×2 tables from abstracted data for OYSR. ORs and their 95% CIs for the subjects who received bevacizumab relative to those receiving control therapy were calculated from the tables. For OR calculations we excluded ineligible subjects from each evaluation.

A general variance-based method was used to estimate the summary HRs, ORs, and their 95% CIs. We assessed heterogeneity between studies with the I^2 statistic [9] as a measure of the proportion of total variation in estimates that is due to heterogeneity, where I^2 value of 50% correspond to cut-off point for a significant heterogeneity. Based on the statistical significance of heterogeneity test, we applied a random-effects model or fixed-effects model to perform meta-analyses. We also used Egger's test [10] to detect possible publication bias.

All statistical analyses were conducted with Comprehensive Meta-Analysis version 2.2.055 software (Englewood, NJ, USA).

Results

Eligible RCTs

After independent review, seventy-nine publications [11–89] reporting RCT results with bevacizumab in patients with various cancers were considered to be eligible for inclusion in the analysis (Figure 1). Of 79 publications, 11 were excluded because the same authors published several reports on the same patients, and only the best-quality study was considered [41–51], 18 were excluded because they did not provide acquired data for calculating HR and OR values [52–69], 20 were excluded because they did not include suitable control groups [70–89]. Subsequently, 30 publications [11–40] were available for analyzing the effect of bevacizumab on survival in patients with cancer.

Study characteristics and quality

Baseline characteristics of the 31 RCTs included in the present meta-analysis are listed in Table S1. These RCTs include 10 phase 2 and 21 phase 3 studies, and they were all published since 2003. Eleven RCTs were from USA, 1 from Germany, 1 from Greece, the remaining 18 from multiple countries (more than 3 countries, including Europe and USA). We noted that the mean of quality scores was 7.6, with a range between 5 and 10 (Table S1). Therefore, the overall quality of all trials was quite good.

Survival in overall population

The meta-analysis of PFS was based on 29 publications with 30 RCT s [11–23,25–30,31–40], involving 18,132 cancer patients. A statistically significant improvement in PFS was observed favoring bevacizumab groups compared with control groups (pooled HR, 0.72; 95% CI, 0.68 to 0.76; $p<0.001$; random-effects model) (Figure 2). Overall test for heterogeneity showed that $I^2 = 51.30$ ($p<0.001$), indicating a significant heterogeneity between studies. Evaluation of publication bias showed that the Egger test was not significant ($p = 0.669$). The funnel plots for publication bias also showed an apparent symmetry (data not shown). These results indicated that there was no publication bias.

The meta-analysis of OS was based on 27 publications with 28 RCTs [11–13,15–30,32–33,35–40], involving 16,462 cancer patients. Bevacizumab had improvement in OS as compared with control therapy (HR, 0.87; 95% CI, 0.83 to 0.91; $p<0.001$; fixed-effects model) (Figure 3). Overall test for heterogeneity showed that $I^2 = 1.11$ ($p = 0.448$), indicating no heterogeneity between studies. We recorded no evidence of publication bias with the Egger test ($p = 0.540$).

The OR values of OYSR for meta-analysis were available or have been computed from 24 publications with 25 RCTs [11–13,16–24,26–30,32,33,35,36,38–40]. The analysis showed significant improvement in OYSR for bevacizumab versus control (OR = 1.30; 95% CI, 1.20 to 1.41; $p<0.001$; fixed-effects model) (Figure 4). Overall test for heterogeneity showed that $I^2 = 15.03$ ($p = 0.250$), indicating no heterogeneity between studies. We recorded no evidence of publication bias with the Egger test ($p = 0.559$).

Bevacizumab monotherapy was administered in only one RCT [32], in the remaining 30 RCTs, bevacizumab was combined with chemotherapy. After excluding the RCT with bevacizumab monotherapy, HRs of PFS and OS with bevacizumab remained similar and was 0.72 (95% CI, 0.67 to 0.76; $p<0.001$) and 0.87 (95% CI, 0.83 to 0.91; $p<0.001$), respectively; OR of OYSR also remained similar and was 1.30 (95% CI, 1.20 to 1.42; $p<0.001$).

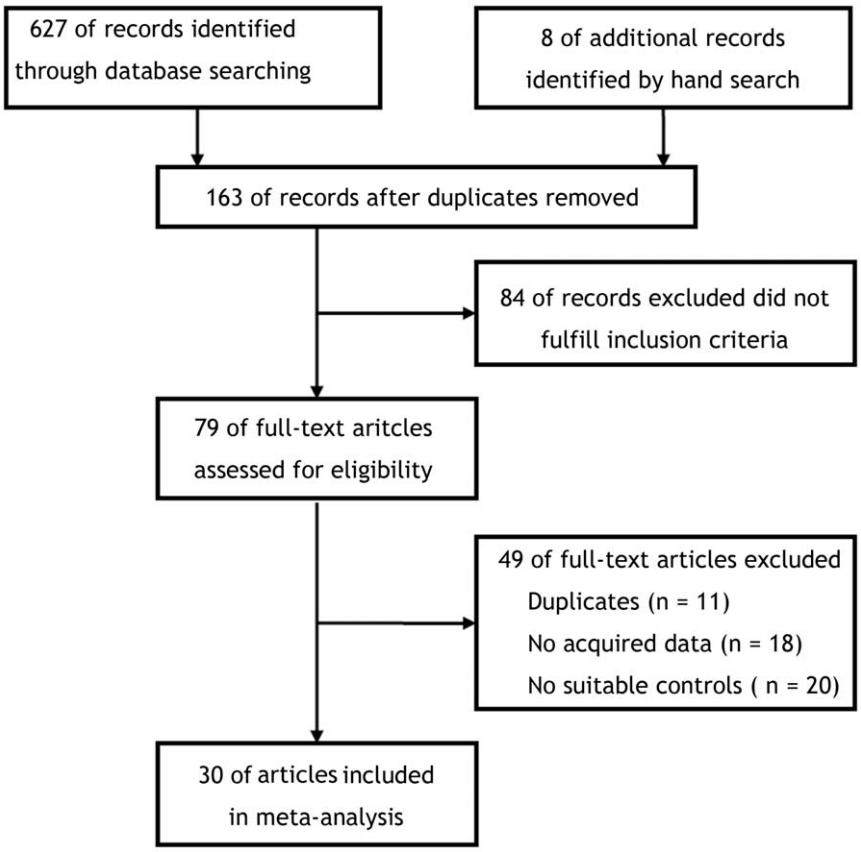

Figure 1. A flow chart showing the progress of trials through the review.
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Subgroup analyses

Based on the statistical significance of heterogeneity test, a random-effects model or fixed-effects model was used to alalyze the effects of bevacizumab on survival in patients with cancers in following subgroups.

From 7 RCTs with lung cancer [11–17], 7 with colorectal cancer [18–23,25], 7 with breast cancer [26–30,31], 3 with renal cell carcinoma [32–34], 2 with pancreatic cancer [35,36], 2 with ovarian cancer [37,38], and 2 with the other cancers (liver cancer and gastric cancer) [39,40], data could be obtained for analyzing PFS. Our data showed that bevacizumab was associated with significant improvement in PFS in patients with all kinds of cancers, except for liver cancer and gastric cancer (Table S2). From 6 RCTs with lung cancer [11–13,15–17], 8 with colorectal cancer [18–25], 6 with breast cancer [26–30(1, 2)], 2 with renal cell carcinoma [32–33], and 2 with pancreatic cancer [35,36], 2 with ovarian cancer [37–38],1 liver cancer and 1 gastric cancer [39,40], data could be obtained for analyzing OS. From 5 RCTs with lung cancer [11–13,16–17], 7 with colorectal cancer [18–24], 6 with breast cancer [26–30(1, 2)], 2 with renal cell carcinoma [32–33], and 2 with pancreatic cancer [35,36], 1 with ovarian cancer [38], 1 liver cancer and 1 gastric cancer [39,40], data could be obtained for analyzing OYSR. Also as shown in Table S2, bevacizumab improved OS in patients with lung cancer and colorectal cancer, but not with renal cell carcinoma, breast cancer, pancreatic cancer, ovarian cancer, liver cancer and gastric cancer. It was found that bevacizumab had benefit in improvement of OYSR in patients with colorectal cancer, breast cancer and ovarian cancer, but not with lung cancer, renal cell carcinoma, pancreatic cancer, liver cancer and gastric cancer.

From 22 RCTs [11–17,20,22,26–30,31–34,36–37,39] of bevacizumab at an equivalent of 5.0 mg/kg per week or more (high dose) and 12 RCTs [11,14,18–19,21,23,25,28,32,35,38,40] of bevacizumab at 2.5 mg/kg per week (low dose), data could be obtained for analyzing PFS. From 19 RCTs [11–13,15–17,20,22,26–30,32–33,36–37,39] of high-dose bevacizumab and 12 RCTs [11,18–19,21,23–25,28,32,35,38,40] of low dose bevacizumab, data could be obtained for analyzing OS. From 17 RCTs [11–13,16–17,20,22,26–30,32–33,36,39] of high-dose bevacizumab and 11 RCTs [11,18–19,21,23–24,28,32,35,38,40] of low dose bevacizumab, data could be obtained for analyzing OYSR. Our analysis revealed that the cancer patients treated with both high and low doses of bevacizumab showed better PFS and OS benefits compared with those treated with control therapies (Table S2). Similar to PFS and OS results, the cancer patients treated with both high and low doses of bevacizumab also showed a better benefit on OYSR compared with those treated with control therapies (Table S2). Overall, no statistically significant difference was found for the effect of bevacizumab on PFS, OS and OYSR between the high and low doses of bevacizumab (all $p>0.05$).

To determine whether the type of chemotherapeutic agent may alter the impact of bevacizumab on patients' survival, we performed a subgroup analysis stratified according to drug class such as platinum (cisplatin, carboplatin, or oxaliplatin) and taxanes (paclitaxel or docetaxel) [11–15,17,20–21,27–30,31,37–38,40] versus others (nonplatinum- and nontaxane-based chemotherapies

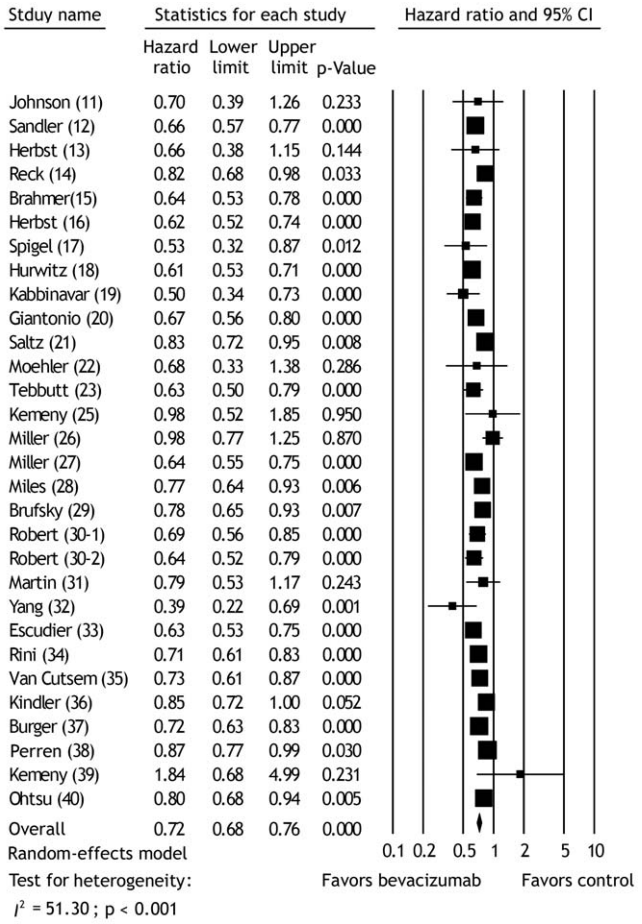

Figure 2. Meta-analysis of the hazard ratios of progression-free survival between bevacizumab and control therapy using random effect model. Bars, 95% confidence intervals (CI) of hazard ratio in patients receiving bevacizumab versus controls. The areas of the squares are proportional to the weights used for combining the data. The center of the lozenge gives the combined hazard ratio. The hazard ratio was considered statistically significant if the 95% CI for the overall hazard ratio did not overlap one.
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including fluorouracil, irinotecan, and gemcitabine) [16,18–19,22–26,30,33–36,39]. Also shown in Table S2, the HR values of PFS and OS, and the OR value of OYSR for bevacizumab with platinum- or taxane-containing regimens were similar to those for nonplatinum- or nontaxane-based regimens. This difference in risk of PFS, OS and OYSR with bevacizumab among these chemotherapeutic classes was not statistically significant (all $p>0.05$).

Discussion

Most cancers are diagnosed with unresectable advanced disease [90]. Systemic chemotherapy or radiotherapy is indicated for the cancer patients with advanced disease to prolong survival, control symptoms and maintain or improve quality of life. However, the benefit of chemoradiotherapy is counterbalanced by increased and prohibitive toxicity, particularly among cancer patients with coexisting medical conditions and decreased performance status. Therefore, novel therapeutic strategies are needed. Bevacizumab can bind selectively circulating VEGF, and thus inhibits the binding of VEGF to its cell surface receptors. This inhibition leads to a reduction in microvascular growth of tumor blood vessels and thus limits the blood supply to tumor tissues [91]. As a matter of fact, bevacizumab has been used in conjunction with other anti-cancer agents in the treatment of patients with many cancers.

Recently, several meta-analyses revealed that the use of bevacizumab was associated with increased risks of arterial thromboembolism [92], venous thromboembolism [93], gastrointestinal perforation [94], severe proteinuria [95], and high-grade hypertension [96], and treatment-related mortality [6]. Although the inhibition of VEGF by bevacizumab has been noted to cause serious adverse events, evidence has continued to accumulate that bevacizumab is a powerful anti-angiogenic agent that has efficacy in the treatment of a wide variety of cancers. The present meta-analysis has shown the benefit of bevacizumab in the treatment of patients with cancer. A significant improvement in PFS, OS and OYSR was seen in overall population with cancer receiving bevacizumab-based therapies when compared with control therapies.

We failed to perform the meta-regression analysis to assess the effect of bevacizumab monotherapy or combination with chemotherapy on cancer patients' survival, since bevacizumab monotherapy was studied in only one RCT [32]. After excluding the RCT with bevacizumab monotherapy, HRs of PFS and OS with bevacizumab remained similar and were all significant improved. Therefore, according to the results of the present meta-analysis, the addition of bevacizumab to first-line chemotherapy regimens would provide a significant advantage in terms of PFS, OS, and OYSR.

We evaluated impact of bevacizumab on cancer patients' survival according to tumor type, and noted that bevacizumab improved in PFS in patients with most of cancers studied except for liver cancer and gastric cancer, but did not improve OS in patients with renal cell carcinoma, breast cancer, pancreatic cancer, ovarian cancer, liver cancer and gastric cancer, did not improved OYSR in patients with lung cancer, renal cell carcinoma pancreatic cancer, ovarian cancer, liver cancer and gastric cancer. These data suggested that patients with some kinds of cancers, such as lung cancer and colorectal cancer, would obtain more survival benefit from bevacizumab therapy compared with the other kinds.

Our subgroup analysis revealed that the cancer patients treated with both high and low doses of bevacizumab showed better PFS, OS, and OYSR benefits compared with those treated with control therapies. Overall, no statistically significant difference was found for the effect of bevacizumab on PFS, OS and OYSR between the high and low doses of bevacizumab. These data suggested that cancer patients treated with higher dose of bevacizumab did not have more favorable benefit in PFS, OS, as well as OYSR than those treated with lower dose. Since lower dose were as effective as higher doses, and higher dose is associated with significantly increased risk with serious adverse events [6], and thus should be the recommended for patients with cancer in case of need.

Although the primary aim of the present meta-analysis was to to evaluate effect of bevacizumab on survival in cancer patients, one should also pay attention to the adverse events risk associated with bevacizumab. Recent meta-analyses have shown that bevacizumab could increase the risk of left ventricular dysfunction and hemorrhagic events, and even were associated with fatal adverse events, including treatment-related mortality [6,97]. The interaction between bevacizumab and certain chemotherapeutic agents might also affect the effects of bevacizumab on cancer patients' survival. However, our further subgroup analysis showed HR values of PFS and OS, and the OR values of OYSR for bevacizumab with platinum- or taxane-containing regimens were

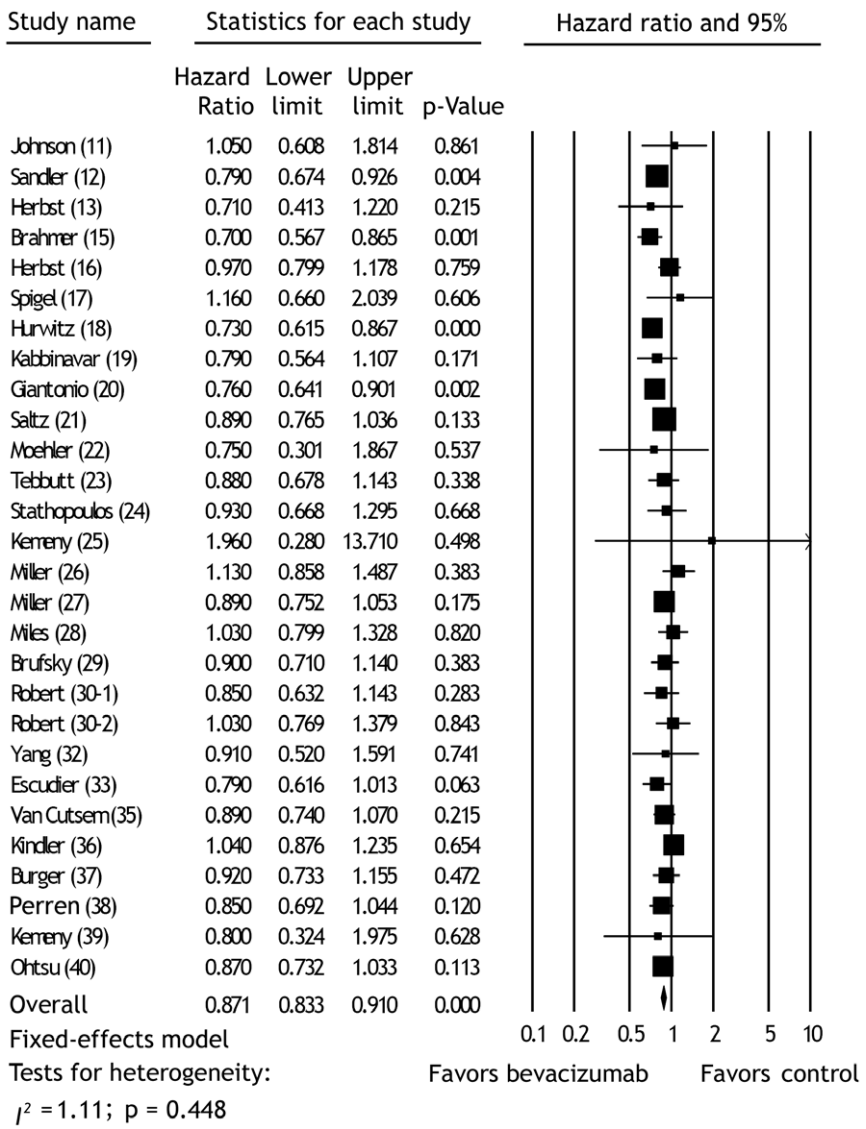

Figure 3. Meta-analysis of the hazard ratios of overall survival between bevacizumab and control therapy using random effect model. Bars, 95% confidence intervals (CI) of hazard ratio in patients receiving bevacizumab versus controls. The areas of the squares are proportional to the weights used for combining the data. The center of the lozenge gives the combined hazard ratio. The hazard ratio was considered statistically significant if the 95% CI for the overall hazard ratio did not overlap one.
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similar to those for nonplatinum- or nontaxane-based regimens. The difference in risk of PFS, OS and OYSR with bevacizumab among these chemotherapeutic classes was not statistically significant.

Several technical issues have to be mentioned in relation to this meta-analysis. This meta-analysis was not based on individual patient data and was not subjected to an open external evaluation procedure. Meta-analyses based on published data tend to overestimate treatment effects compared with individual patient data analyses. However, analyses using individual patient data may include fewer studies if all authors do not agree to submit their full databases to the analyzing group. Another drawback of analyses based on individual patient data is the time-consuming review process. The results must therefore be interpreted cautiously, as an individual patient data-based meta-analysis would give more reliable estimation than one based on abstracted data [98]. Publication bias is a significant threat to the validity of the results, however, such a situation did not exist in the present meta-analysis. Heterogeneity among trials may be another limitation of our meta-analysis, even though we applied a random-effects model that takes possible heterogeneity into consideration. The accuracy of the values of HR and OR estimated from the Kaplan-Meier curves is another important issue. We obtained fairly good correlation between the HRs and ORs reported in this article and those obtained based on the Kaplan-Meier curves, suggesting that curve-based HRs or/and ORs can be substituted in cases where the HRs or/and ORs are not available.

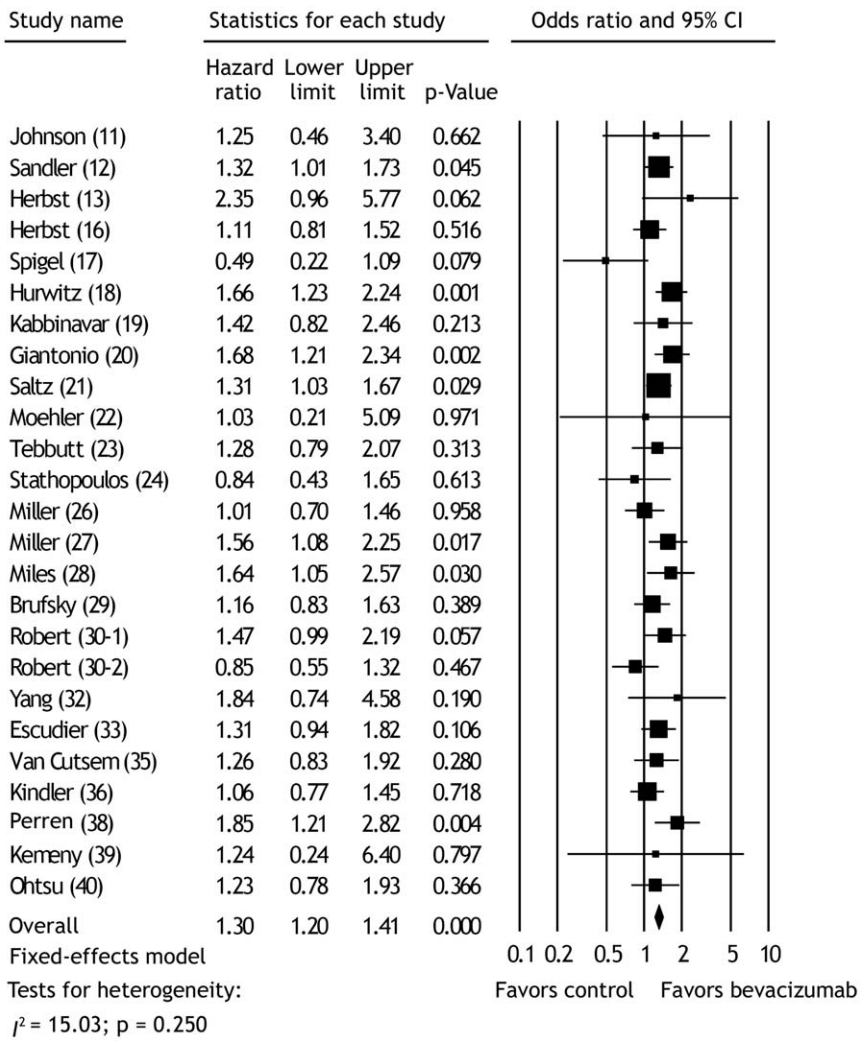

Figure 4. Meta-analysis of the odds ratios of one-year survival rate between bevacizumab and control therapy. Bars, 95% confidence intervals (CI) of odds ratio in patients receiving bevacizumab versus controls. The areas of the squares are proportional to the weights used for combining the data. The center of the lozenge gives the combined odds ratio. The odds ratio was considered statistically significant if the 95% CI for the overall odds ratio did not overlap one.
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In conclusion, our results have demonstrated that PFS, OS, as well as OYSR was significantly improved in cancer patients treated with bevacizumab as compared with control therapies.

Supporting Information

Table S1 Characteristics of the trials included in this meta-analysis.
(DOC)

Table S2 Subgroup analyses.
(DOC)

Author Contributions

Conceived and designed the experiments: YS WBY HZS QZ. Performed the experiments: YS WBY. Analyzed the data: YS WBY SL ZJY. Contributed reagents/materials/analysis tools: YS WBY SL ZJY. Wrote the paper: HZS QZ.

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