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Bevacizumab in the treatment of ovarian cancer: a meta-analysis from four phase III randomized controlled trials

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Abstract
Background The aim of this meta-analysis was to summarize the efficacy and safety of bevacizumab in the treatment of ovarian cancer.
Methods We sought to identify randomised controlled trials (RCTs) by searching PubMed and Web of Science. Outcomes were objective response rate (ORR), progression-free survival (PFS), overall survival (OS), and adverse events.
Results Four studies with 4,246 patients were included. Combination of bevacizumab and chemotherapy resulted in a statistically significant improvement in ORR (OR 2.165, 95 % CI 1.511–3.103) and in PFS (HR 0.691, 95 % CI 0.517–0.865), compared with chemotherapy alone. There was no evidence of a significant improvement in OS (HR 0.934, 95 % CI 0.826–1.041). It also had significantly increased risk of gastrointestinal events (OR 2.743, 95 % CI 1.580–4.763; $P < 0.001$), hypertension (OR 4.630, 95 % CI 3.737 to 5.737; $P < 0.001$), proteinuria (OR 4.872, 95 % CI 2.617–9.069; $P < 0.001$), and arterial thromboembolism (OR 1.994, 95 % CI 1.210–3.286; $P = 0.007$).
Conclusion This meta-analysis suggests that the addition of bevacizumab to chemotherapy offers meaningful improvement in objective response rate and progression-free survival in ovarian cancer treatment, but does not benefit overall survival. It also significantly increased the occurrence of gastrointestinal events, hypertension, proteinuria, and arterial thromboembolism.

Keywords Ovarian cancer · Vascular endothelial growth factor · Monoclonal antibodies · Bevacizumab · Meta-analysis

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Introduction

According to Jemal and Bray [1], ovarian cancer is the eighth most common incident cancer in women worldwide, and the seventh most common cause of cancer death. Each year, worldwide, over 225,000 women are diagnosed with ovarian cancer and over 140,200 die, corresponding to an annual age-standardized incidence of 9.4 cases per 100,000 women, annual mortality rate of 5.1 deaths per 100,000 in developed areas. In the United States, ovarian cancer is the fifth most common cause of cancer death in women, accounting for nearly 22,280 estimated new cases and 15,500 estimated deaths annually [2]. Treatment strategies for ovarian cancer by stage include standard surgical therapy, intravenous chemotherapy with carboplatin plus a taxane, and systemic therapy [3]. New targeted biologic agents, particularly those involved with the vascular endothelial growth factor (VEGF) pathway, hold great promise for improving the outcome of ovarian cancer [4].

VEGF, a glycoprotein produced by both normal and neoplastic cells, is one of the key elements in the stimulation of angiogenesis. Numerous studies have demonstrated that VEGF over-expression plays an essential role in the growth, progression and metastatic potential of ovarian cancer [5–7]. VEGF became a fundamental target of antiangiogenic therapy for ovarian cancer.

Bevacizumab is a humanized recombinant monoclonal antibody that specifically blocks the binding of VEGF to high-affinity receptors [8]. Based on some phase III RCTs, the US Food and Drug Administration has approved bevacizumab for the treatment of metastatic HER2 negative breast cancer, metastatic renal cell carcinoma, second-line treatment of glioblastoma, first-line treatment of non-small cell lung cancer, second-line treatment of metastatic colorectal cancer, and first-line treatment of metastatic colorectal cancer [9].

Bevacizumab treatment for ovarian cancer in clinical trials appeared only in recent years. Some RCTs have reported the final results. In this article, we performed a meta-analysis to pool the results and summarize the efficacy and safety of bevacizumab in the treatment of ovarian cancer.

Methods

Database and literature search

We searched PubMed and Web of Science from their inception to 25 September 2012. The search terms included "ovarian cancer", "bevacizumab", and "avastin". The search detail in PubMed was "ovarian cancer" (Title/Abstract) AND ["bevacizumab" (Title/Abstract) OR "avastin" (Title/Abstract)]. In Web of Science citation database, we selected the science citation index expanded (SCI-EXPANDED) database and conference proceedings citation index science (CPCI-S) database. The search detail used was as follows: TS = (ovarian cancer) AND (TS = bevacizumab OR TS = avastin). We also looked at posters from the annual meetings of the American society of clinical oncology (ASCO) and the European society for medical oncology (ESMO) in the past 10 years.

Study selection

The following inclusion criteria had to be fulfilled: (1) types of studies: only randomised controlled trials (RCTs) were included. (2) Types of participants: adult women with histologically proven ovarian cancer were included. (3) Types of interventions: conventional chemotherapy plus Bevacizumab versus conventional chemotherapy plus placebo, and conventional chemotherapy plus Bevacizumab versus conventional chemotherapy alone. (4) Types of outcome: objective response rate (ORR) defined by according to the response evaluation criteria in solid tumors (RECIST) [10]; progression-free survival (PFS) defined as the time from randomization to disease progression or death from any cause; overall survival (OS) defined as the time from random assignment to death from any cause; adverse events, included gastrointestinal events (grade $\geq$ 2), hypertension (grade $\geq$ 2), proteinuria (grade $\geq$ 3), venous thromboembolism and arterial thromboembolism.

When the same trials were reported in different papers or meetings, only the most recent reports were included. We excluded case reports, case series, one arm phase I trials, retrospective case–control studies, and phase II non-randomized trials.

Quality assessment

We assessed the quality of included studies using the Cochrane Collaboration's tool for assessing risk of bias [11]. The tool included randomized sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. Items in the risk of bias assessment were judged "adequate" (+), "unclear" (?), or having the "potential for bias" (−) for each study. Two reviewers independently assessed the quality. Disagreements were resolved by discussion.

Data extraction

We collected information about methodological characteristics (study design, randomization method, allocation concealment, blinding, follow-up, baseline comparability, and other), study characteristics (study year, country, age, treatment schedule), and outcomes (ORR, median PFS and hazard ratios with 95 % CI, median OS and hazard ratios with 95 % CI, and the incidence of all kinds of adverse events). Data were extracted independently by two reviewers. Any differences of opinion were resolved by discussion.

Statistical analysis

Statistical heterogeneity was explored by χ^2 and inconsistency (I^2) statistics; an I^2 value of 50 %or more represented substantial heterogeneity [12]. If there was no heterogeneity, a fixed effects model was used for meta-analysis; otherwise, a random effect model based on the Der Simonian and Laird estimator was used [13]. Summary hazard ratios (HR) for time-to-event data or summary odds ratio (OR) for dichotomous data were calculated by taking a weighted average of individual study results. Two-sided $P < 0.050$ was considered statistically significant. Potential publication bias was tested by Begg's test and Egger's test. Subgroup meta-analyses were performed by patient inclusion criteria (first-line therapy patients or recurrent ovarian cancer patients). The risk of bias figure was drawn with

review manager (RevMan) software (version 5.0.21; Update Software Ltd, Oxford, Oxon, UK), and the pooling of data was performed with Stata software, version 12.0 (Stata Corp, College Station, Texas).

Results

Eligible studies and studies quality

We identified four studies [14–17] that met our inclusion criteria for meta-analysis. The detailed steps of our literature search are shown in Fig. 1. A total of 4,246 patients were used in the pooled analyses. Of the four studies, sample sizes ranged from 361 to 1873. They were all phase III RCTs. One of the studies was a three-arm trial; the remaining three studies were two-arm trials. Three studies have been published; another study has been reported in the 2012 ASCO annual meeting. Table 1 shows the main characteristics of the four included studies, and Table 2 shows the outcome results of the studies. Two published studies showed low risk of bias in randomized sequence generation, blinding, incomplete outcome data, selective reporting, and other bias; while allocation concealment was unclear in all these published studies. It was unclear in all six risk of bias items in the study reported in the meeting. Figure 2 illustrates a general risk of bias across the included studies.

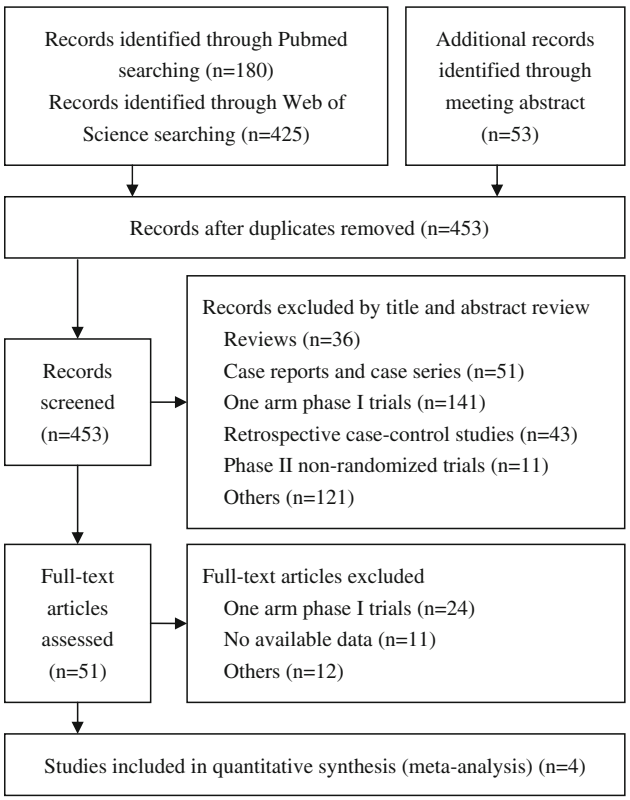


Fig. 1 Flow diagram showing selection of studies

Objective response rate

A total of four trials [14–17] reported this outcome representing 4,246 patients. The ORR ranged from 11.8 to 74.0 %. There was significant heterogeneity between the studies ($I^2 = 83.8$ %, $P < 0.001$). The pooled OR was 2.165 (95 % CI 1.511–3.103) by random-effects (Fig. 3). It shows the combination of bevacizumab and chemotherapy resulted in a statistically significant improvement in ORR compared with chemotherapy alone. The Begg's test ($z = 0.24$, $P = 0.806$) and the Egger's test ($t = 1.03$, $P = 0.378$) suggested there was no significant publication bias. The subgroup analysis based on patient inclusion criteria showed that the addition of bevacizumab to standard chemotherapy for ovarian cancer led to a statistically significant improvement in ORR, both as a first-line therapy (OR = 1.895, 95 % CI 1.172–3.064), and in patients with recurrent ovarian cancer (OR = 2.767, 95 % CI 1.999–3.830).

Progression-free survival

A total of four trials [14–17] reported this outcome representing 4,246 patients. The median of PFS ranged from 3.4 to 19.8 months. There was significant heterogeneity between the studies ($I^2 = 92.1$ %, $P < 0.001$). The pooled HR was 0.691 (95 % CI 0.517–0.865) by random-effects (Fig. 4). It shows the combination of bevacizumab and chemotherapy resulted in a statistically significant improvement in PFS compared with chemotherapy alone. The Begg's test ($z = 1.22$, $P = 0.221$) and the Egger's test ($t = 4.93$, $P = 0.016$) suggested there was no significant publication bias. The subgroup analysis based on patient inclusion criteria showed that the addition of bevacizumab to standard chemotherapy for ovarian cancer led to a statistically significant improvement in PFS, both as a first-line therapy (HR = 0.828, 95 % CI 0.710–0.946), and in patients with recurrent ovarian cancer (HR = 0.482, 95 % CI 0.405–0.559).

Overall survival

A total of three trials [14–16] reported this outcome representing 3,885 patients. The median of OS ranged from 33.3 to 39.7 months. There was no significant heterogeneity between the studies ($I^2 = 0.0$ %, $P = 0.553$). The pooled HR was 0.934 (95 % CI 0.826–1.041), using a fixed-effect model (Fig. 5). It shows the combination of

Table 1 Characteristics of phase III randomized controlled trials included in the meta-analysis

Reference (trial)	Country and enrolled pts	Arm	Schedule	Pts	Age (year)
Burger [14] (GOG-0218)	Country: 336 institutions in the USA, Canada, South Korea, and Japan Enrolled pts: Stage III (incompletely resectable) or stage IV epithelial ovarian cancer (first-line therapy)	P + C + PL (control arm)	Cycles 1–6: C, AUC 6; P, 175 mg/m^2; PL (starting in cycle 2) every 3 week Cycles 7–22: PL every 3 week	625	60 (25–86)
		P + C + Bev + PL (Bev initiation arm)	Cycles 1–6: C, AUC 6; P, 175 mg/m^2; Bev, 15 mg/kg (starting in cycle 2) every 3 week Cycles 7–22: PL every 3 week	625	60 (24–88)
		P + C + Bev + Bev (Bev throughout arm)	Cycles 1–6: C, AUC 6; P, 175 mg/m^2; Bev 15 mg/kg (starting in cycle 2) every 3 week Cycles 7–22: Bev 15 mg/kg, every 3 week	623	60 (22–89)
Perren [15] (ICON7)	Country: 263 centers in the UK, Germany, France, Canada, Australia, New Zealand, Denmark, Finland, Norway, Sweden, and Spain Enrolled pts: high-risk, early stage disease (FIGO stage I or IIA and clear-call or Grade 3 tumors) or advanced (FIGO stage IIB to IV) epithelial ovarian cancer, primary peritoneal cancer, or fallopian- tube cancer (First-line therapy)	P + C (control arm)	Cycles 1–6: C, AUC 5 or 6; P, 175 mg/m^2; every 3 week	764	57 (18–81)
		P + C + Bev (Bev arm)	Cycles 1–6: C, AUC 5 or 6; P, 175 mg/m^2; Bev 15 mg/kg (5 or 6 cycles); every 3 week Cycles 7–18: Bev 15 mg/kg, every 3 week	764	57 (24–82)
Aghajanian [16] (OCEANS)	Country: USA Enrolled pts: Platinum-sensitive Fallopian tube cancer (recurrence ≥6 months after front-line platinum-based therapy) (recurrent ovarian cancer)	G + C + PL (control arm)	Cycles 1–10: G, 1,000 mg/m^2 on days 1 and 8; C, AUC 4 mg/mL/min on day 1; PL, 15 mg/kg on day 1 every 3 week	242	61 (28–86)
		G + C + Bev (Bev arm)	Cycles 1–10: G, 1,000 mg/m^2 on days 1 and 8; C, AUC 4 mg/mL/min on day 1; Bev, 15 mg/kg on day 1 every 3 week	242	60 (38–87)
Pujade-Lauraine [17] (AURELIA)	Country: France, Germany, Spain, Norway, Italy, Belgium, Netherlands, Greece, Portugal, Denmark and Switzerland Enrolled pts: platinum-resistant ovarian cancer that had progressed ≤6 month after ≥4 cycles of platinum-based therapy (recurrent ovarian cancer)	Chemotherapy arm	Paclitaxel 80 mg/m^2 days 1, 8, 15, and 22 q4w; or Topotecan 4 mg/m^2 days 1, 8, and 15 q4w (or 1.25 mg/m2, days 1–5 q3w); or PLD 40 mg/m^2 day 1 q4w	182	61 (25–84)
		Chemotherapy + Bev arm	Chemotherapy + Bev 15 mg/kg q3w or 10 mg/kg q2w	179	62 (25–80)

Bev bevacizumab, *C* carboplatin, *G* gemcitabine, *P* paclitaxel, *PL* Placebo

bevacizumab and chemotherapy resulted in no significant improvement in OS compared with chemotherapy alone. The Begg's test ($z = 0.34$, $P = 0.734$) and the Egger's test ($t = 1.50$, $P = 0.273$) suggested there was no significant publication bias. The subgroup analysis based on patient inclusion criteria showed that the addition of bevacizumab to standard chemotherapy for ovarian cancer was not associated with a significant improvement in OS, either as a first-line therapy (HR = 0.916, 95 % CI 0.799–1.033), or in patients with recurrent ovarian cancer (HR = 1.027, 95 % CI 0.757–1.296).

Adverse events

Compared with controls, ovarian cancer patients treated with bevacizumab had a 2.743 times (95 % CI 1.580–4.763; $P < 0.001$) increased risk of grade ≥ 2 gastrointestinal events; 4.630 times (95 % CI 3.737–5.737; $P < 0.001$) increased risk of grade ≥2 hypertension; 4.872 times (95 % CI 2.617–9.069; $P < 0.001$) increased risk of grade ≥3 proteinuria; and 1.994 times (95 % CI 1.210–3.286; $P = 0.007$) increased risk of arterial thromboembolism. There was no evidence of a significant

Table 2 Outcome results of the included studies

Trials	Study arms	ORR	PFS (months)		OS (months)		Adverse events				
			Median PFS	HR (95 % CI)	Median OS	HR (95 % CI)	GI events (grade ≥ 2)	Hypertension (grade ≥ 2)	Proteinuria (grade ≥ 3)	Venous TE	Arterial TE
GOG-0218	Control arm	52.0 % (325/625)	10.3	1	39.3	1	1.2 % (7/601)	7.2 % (43/601)	0.7 % (4/601)	5.8 % (35/601)	0.8 % (5/601)
	Bev + Placebo maintenance arm	57.9 % (362/625)	11.2	0.908 (0.795 – 1.040)	38.7	1.036 (0.827–1.297)	2.8 % (17/607)	16.5 % (100/607)	0.7 % (4/607)	5.3 % (32/607)	0.7 % (4/607)
	Bev + Bev maintenance arm	74.0 % (461/623)	14.1	0.717 (0.625 – 0.824)	39.7	0.915 (0.727–1.152)	2.6 % (16/608)	22.9 % (139/608)	1.6 % (10/608)	6.7 % (41/608)	0.7 % (4/608)
ICON7	Control arm	48.0 % (118/247)	17.4	1	Not yet reached	1	0.4 % (3/753)	2.1 % (16/753)	0.1 % (1/753)	4.1 % (31/753)	1.5 % (11/753)
	Bev arm	67.0 % (168/257)	19.8	0.87 (0.77–0.99)	Not yet reached	0.85 (0.69–1.04)	1.3 % (10/745)	18.3 % (136/745)	0.5 % (4/745)	6.7 % (50/745)	3.6 % (27/745)
OCEANS	Control arm	57.4 % (139/242)	8.4 (8.3–9.7)	1	35.2 (29.9 –40.3)	1	0.0 % (0/233)	0.4 % (1/233)	0.9 % (2/233)	2.6 % (6/233)	0.9 % (2/233)
	Bev arm	78.5 % (190/242)	12.4 (11.4–12.7)	0.484 (0.388–0.605)	33.3 (29.8 –35.5)	1.027 (0.792 – 1.331)	0.0 % (0/247)	17.4 % (43/247)	8.5 % (21/247)	4.0 % (10/247)	2.8 % (7/247)
AURELIA	Control arm	11.8 % (21/182)	3.4 (2.2–3.7)	1	Not report	Not report	0.0 % (0/181)	6.6 % (12/181)	0.6 % (1/181)	4.4 % (8/181)	0.0 % (0/181)
	Bev arm	27.3 % (49/179)	6.7 (5.7–7.9)	0.48 (0.38–0.60)	Not report	Not report	2.2 % (4/179)	20.1 % (36/179)	10.6 % (19/179)	2.8 % (5/179)	2.2 % (4/179)

ORR objective response rate, *PFS* progression-free survival, *OS* overall survival, *HR* hazard ratio, *GI* gastrointestinal, *TE* thromboembolism

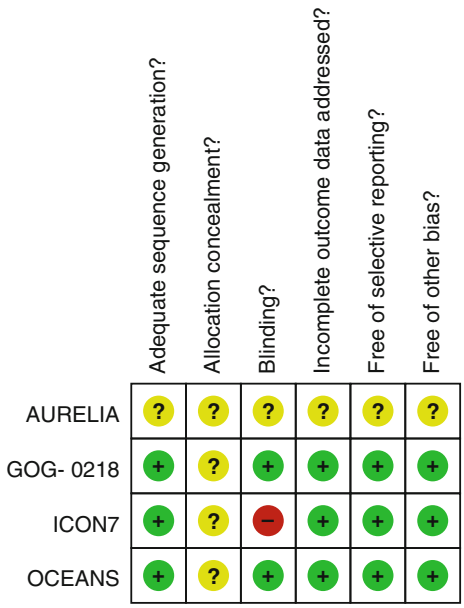


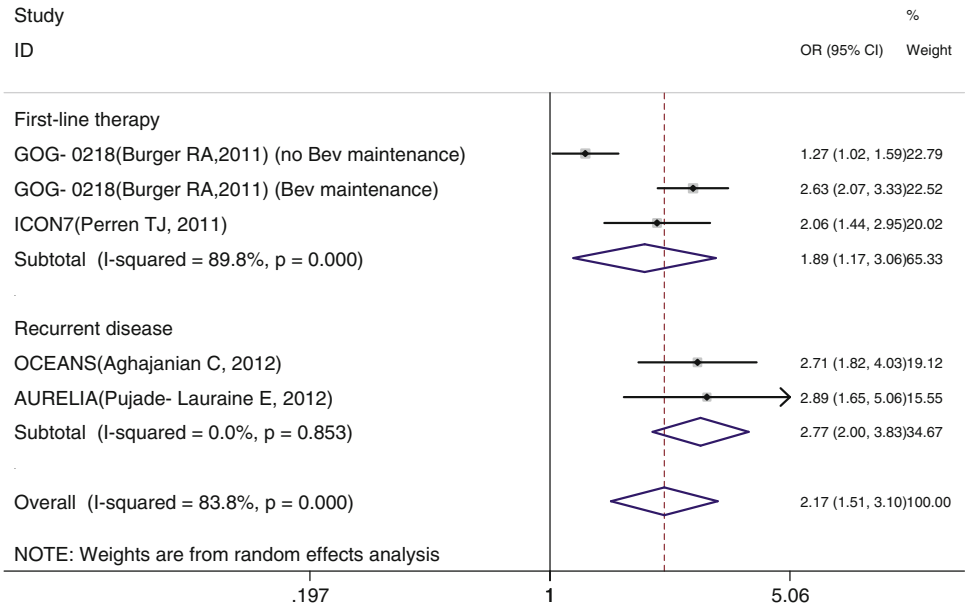
Fig. 2 Risk of bias summary of included studies

increased risk of venous thromboembolism (OR 1.205; 95 % CI 0.934–1.554; $P = 0.151$). The plots of meta-analysis for adverse events are listed in the Appendix.

Discussion

Tumor angiogenesis is critical for transition of a cancer from the avascular phase to the vascular phase. In the absence of neovascularization, most solid tumors stop growing when they are 2–3 mm in size and enter a dormant stage [18]. Work in animal models has shown that treatment with a VEGF-specific monoclonal antibody was associated with a decrease in the density of vessels, and inhibition of growth, for multiple tumor types, although there was no effect on the growth rate of the tumor cells in vitro [8, 19]. The US FDA has approved bevacizumab for the treatment of breast cancer, renal cell carcinoma, glioblastoma, non-small cell lung cancer, and colorectal cancer. In this meta-analysis, we pooled the results from four phase III RCTs. The results showed that the addition of bevacizumab to chemotherapy offers meaningful improvement in ORR and PFS in ovarian cancer treatment, but no significant improvement in OS. The treatment efficacy of bevacizumab in ovarian cancer is similar to that seen with other cancers. In breast cancer treatment, combination of bevacizumab and chemotherapy resulted in a statistically significant improvement in PFS (HR = 0.70, 95 % CI 0.60–0.82) and ORR (RR = 1.26, 95 % CI 1.17–1.37) compared with chemotherapy alone, there was no significant difference in OS [20]. In renal cell carcinoma treatment, bevacizumab can significantly prolong the PFS compared with the placebo group (HR 2.55; $P < 0.001$) [21]. In non-small cell lung cancer treatment, the addition of bevacizumab to chemotherapy resulted in a significantly longer OS (HR 0.89; 95 % CI 0.79–0.99), longer PFS (HR 0.73; 95 % CI 0.66–0.82) and higher response rates (OR 2.34; 95 % CI 1.89–2.89) [22]. In colorectal cancer treatment, there was a significant PFS benefit (HR = 0.66; $P < 0.01$) and OS benefit (HR = 0.77; $P < 0.01$) in favor of the bevacizumab combined treatment; the ORR was significantly higher on the bevacizumab-containing arm (RR = 1.5; $P = 0.021$) [23].

Fig. 3 Pooled data of objective response rate



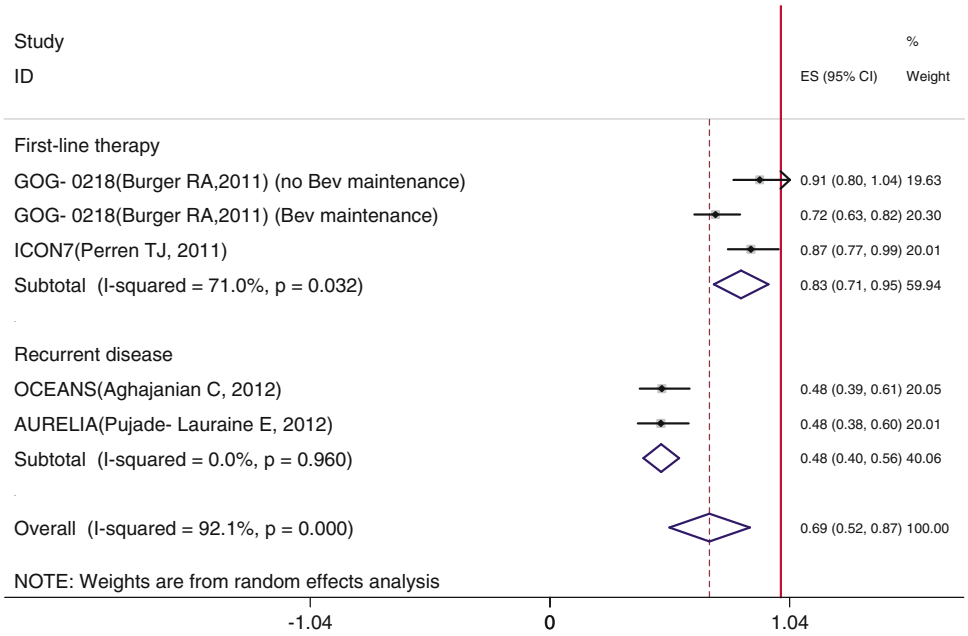


Fig. 4 Pooled data of progression-free survival

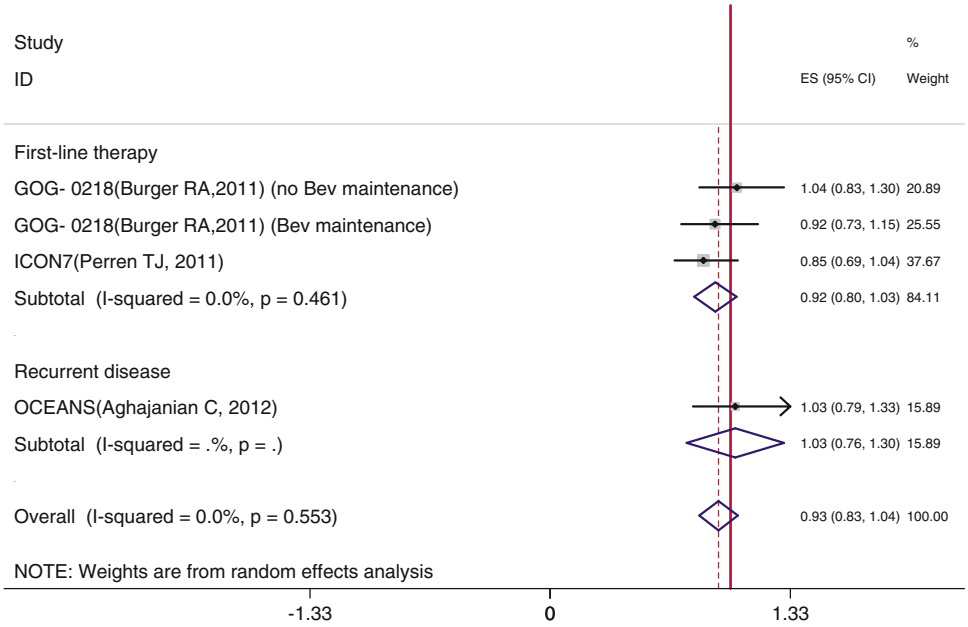


Fig. 5 Pooled data of overall survival

We also did subgroup analysis based on patient inclusion criteria (first-line therapy patients or recurrent patients). Two studies (GOG-0218 [14] and ICON7 [15]) enrolled patients for bevacizumab first-line therapy; another two studies (OCEANS [16] and AURELIA [17]) enrolled patients with recurrent ovarian cancer. For first-line therapy, some phase I/II trials have already shown evidence of efficacy for combined bevacizumab. A single-arm phase II trial of treatment with paclitaxel, carboplatin and bevacizumab (PCB), in 62 patients with stage ≥IC epithelial mullerian tumors, showed a radiographic response of 75 % (among 28 women with measurable disease), with CA-125 responses in 76 % of patients; the progression-free survival rate at 36 months was 58 % [24]. Micha et al. [25] reported, in 22 PCB treated advanced-stage ovarian cancer patients, the total response rate of 80 %, and the disease progression rate was 5 %. In our subgroup meta-analysis of bevacizumab versus standard chemotherapy as a first-line therapy, we found a significant improvement in ORR (OR = 1.942, 95 % CI 1.275–2.956), as well as PFS (HR = 0.828, 95 % CI 0.710–0.946). The GOG-0218 study also compared

bevacizumab maintenance with no bevacizumab maintenance in first-line therapy. The results showed relative to control treatment, the HR for progression or death was 0.908 (95 % CI 0.795–1.040; $P = 0.16$) with bevacizumab initiation and 0.717 (95 % CI 0.625–0.824; $P < 0.001$) with bevacizumab throughout [14]. Our meta-analysis showed no evidence of an improvement in OS associated with the addition of bevacizumab to standard therapy. However, in the ICON7 study, although there was no evidence of a difference in OS between the two treatment arms overall (HR 0.85, 95 % CI 0.69–1.04), the OS was significantly improved in the subgroup of patients at high risk for progression, with the median OS 28.8 months in the standard therapy group and 36.6 months in the bevacizumab group (HR 0.64; 95 % CI 0.48–0.85; $P = 0.002$) [15].

For recurrent ovarian cancer, some phase I/II trials also have already shown evidence of efficacy for combined bevacizumab. Garcia AA reported a single-arm trial of bevacizumab and cyclophosphamide, in 70 patients with recurrent ovarian cancer, in which, the probability of being alive and progression-free at 6 months was 56 % (±6 % SE); partial response rate was 24 %; median time to progression and survival were 7.2 and 16.9 months, respectively [26]. Chura et al. [27] reported a similar single-arm trial of bevacizumab and cyclophosphamide, in 15 patients with heavily pretreated recurrent ovarian cancer, 13.3 % of patients had a complete response after 4 months of therapy; 40.0 % patients had a partial response; the median duration of this response was 3.9 months (2.3–10.4). 20 % patients had stable disease of 4.0–5.5 months' duration, and 26.7 % patients had progressive disease. In our subgroup meta-analysis of bevacizumab versus standard chemotherapy for recurrent ovarian cancer, we found a significant improvement in ORR (OR = 2.767, 95 % CI 1.999–3.830), as well as PFS (HR = 0.482, 95 % CI 0.405–0.559). The two included studies enrolled platinum-sensitive patients (OCEANS [16]) and platinum-resistant patients (AURELIA [17]). Both studies showed an improvement in ORR and PFS, suggesting that bevacizumab may be used in both platinum-resistant and platinum-sensitive patients.

Bevacizumab has shown evidence of efficacy in ovarian cancer treatment as an addition to chemotherapy in first-line therapy or in recurrent disease. But we also should pay attention to the adverse events associated with bevacizumab. In our meta-analysis, we found ovarian cancer patients treated with bevacizumab had an increased risk of grade ≥2 gastrointestinal events, grade ≥2 hypertension, grade ≥3 proteinuria, and arterial thromboembolism. Patients should be monitored for these events throughout the course of bevacizumab therapy. Several other meta-analyses of bevacizumab therapy in cancer patients have found similar evidence of associated adverse events [28–31]. Shord recommended blood pressure should be routinely monitored, and hypertension should be medically managed with antihypertensive drugs as deemed appropriate during bevacizumab therapy; proteinuria should be monitored for every 3 to 4 weeks, and bevacizumab should be discontinued with persistent proteinuria of >2+; and thromboembolism events should be managed in accordance with guidelines established by the American College of Chest Physicians [32].

There are some limitations in this meta-analysis. First, there was significant heterogeneity between the studies. Second, only four phase III RCTs were included in the study. Further, some RCTs for accessing bevacizumab in treatment of ovarian cancer are ongoing such as NCT00262847, NCT00565851, NCT00951496, NCT01462890, NCT01081262, NCT00483782, NCT01239732 and NCT00434642. We are waiting for the results of these studies. Third, the data on overall survival are not complete for some studies (e.g. ICON7 and OCEANS). Fourth, we pooled summary HR for time-to-event data by generic inverse variance method. Individual patient data meta-analysis will make the results more accurate.

In conclusion, our meta-analysis suggested that addition of bevacizumab to chemotherapy offers a meaningful improvement in objective response rate and progression-free survival in first-line therapy for ovarian cancer, as well as in treatment of recurrent disease. But addition of bevacizumab does not benefit overall survival for ovarian cancer, and will significantly increase the occurrence of adverse events.

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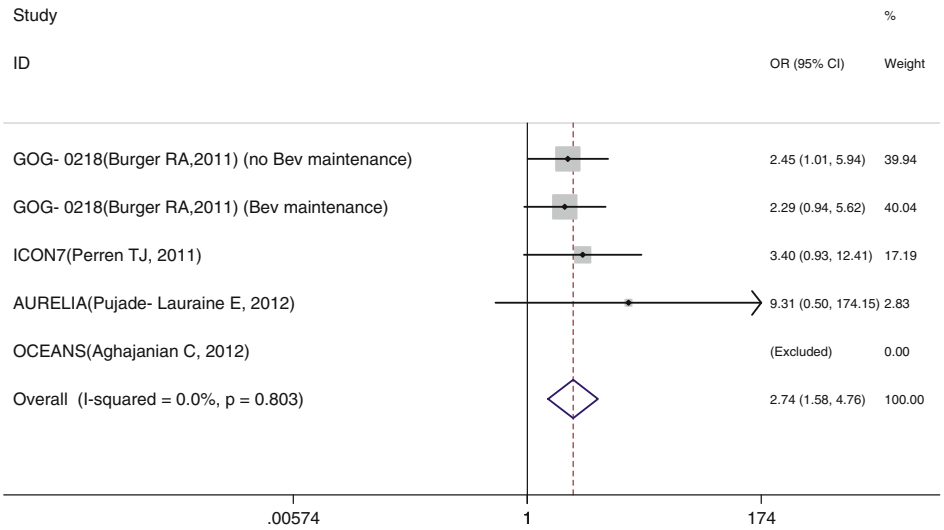
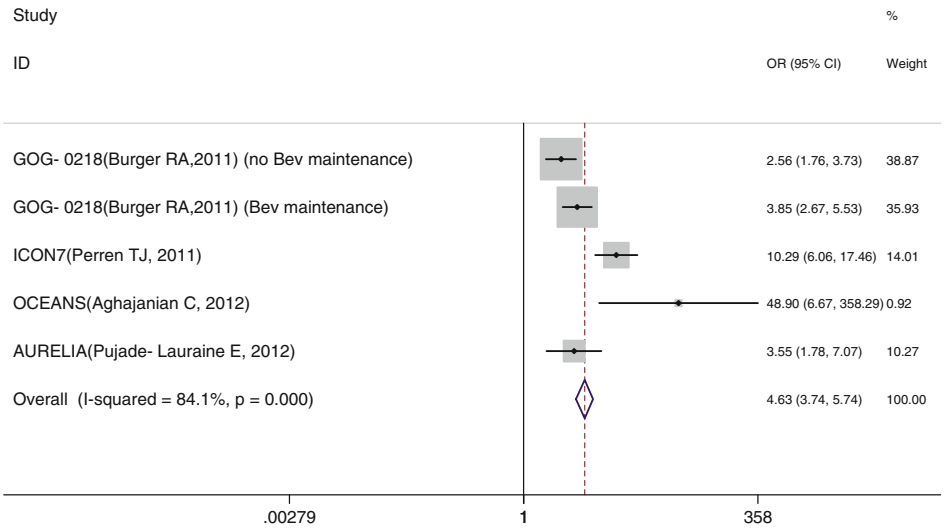
Conflicts of interest The authors have declared no conflicts of interest.

Appendix

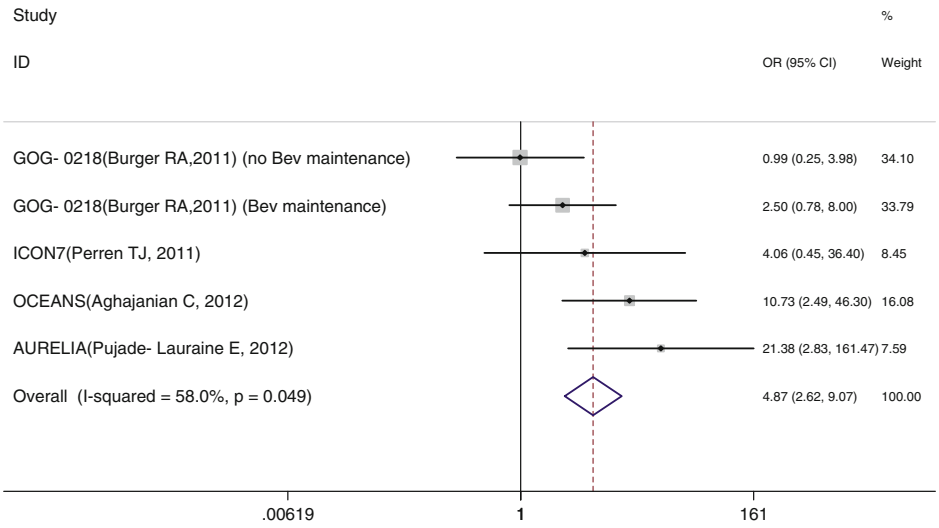
GI events



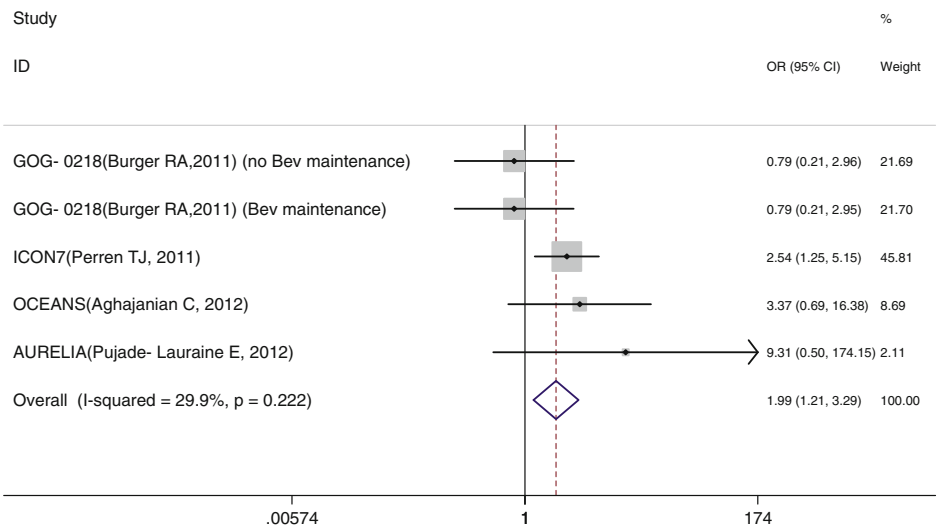
Hypertension



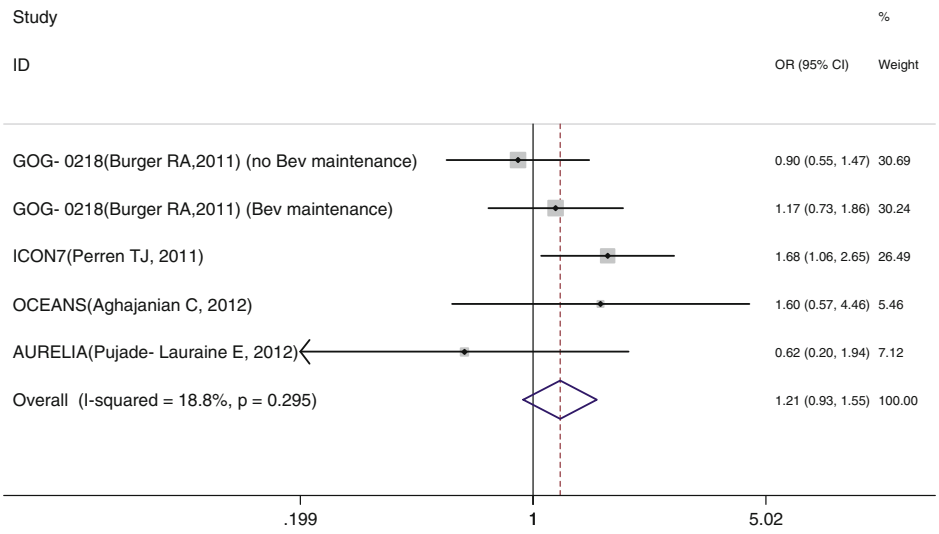
Proteinuria



Arterial TE



Venous TE



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