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RESEARCH ARTICLE

Bevacizumab Combined with Chemotherapy Improves Survival for Patients with Metastatic Colorectal Cancer: Evidence from Meta Analysis

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Abstract

Background

Colorectal cancer is one of the leading causes of cancer deaths in both sexes in the world. Improvement of existing therapy modalities and implementing new ones in order to improve survival of patients with colorectal cancer represents a great challenge for medicine. The aim of this paper was to assess the impact that adding bevacizumab to chemotherapy has on survival in patients with metastatic colorectal cancer, compared to the use of chemotherapy alone.

Methods

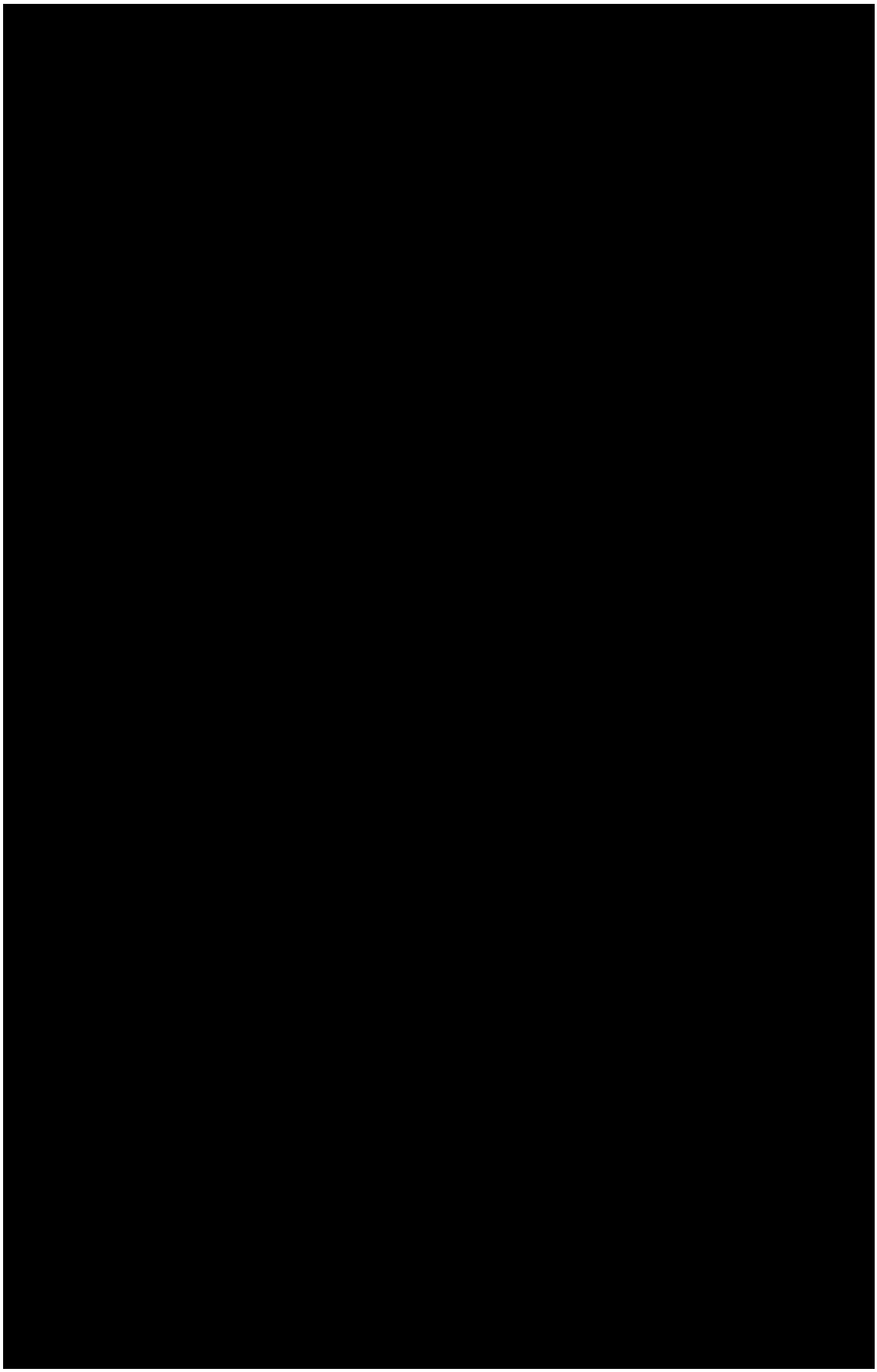
Hazard ratios (HRs) with their 95% confidence intervals (CI) were determined from the studies and pooled. Two-sided *p* values were reported and considered to indicate statistical significance if less than 0.05.

Results

A total of 12 studies that meet the inclusion criteria were identified in the literature search, 3 phase II studies and 9 phase III studies. Based on the random effects meta-analysis, a statistically significant improvement was identified for both overall survival (HR = 0.84; 95% CI: 0.74–0.94; $p = 0.003$) and progression free survival (HR = 0.64; 95% CI: 0.55–0.73; $p<0.00001$) in patients with metastatic colorectal cancer when bevacizumab was added to chemotherapy, compared to chemotherapy treatment alone.

Conclusion

The findings of this meta analysis confirm the benefit of adding bevacizumab to chemotherapy in terms of survival and progression free survival, but the magnitude of this effect is not consistent throughout the included studies. This suggests the need for further research of



Search strategy

A systematic review of the literature was carried out according to a predefined protocol, in order to identify studies assessing and comparing survival of patients with colorectal cancer who are receiving chemotherapy alone or along with bevacizumab [10]. The PubMed database was searched for eligible articles (up to the end of March 2015). The following keywords were used in the search: "bevacizumab", "metastatic colorectal cancer" and "overall survival". Keywords were formed using the MeSH database (Medical Subject Headings Database). In case of duplicate publications, the most recent papers and those with the most data provided were selected. Finally, the "snowball" method was used, which involved tracking references and citations of found articles in order to identify additional relevant studies.

Study eligibility criteria

Clinical trials investigating the associations between bevacizumab and overall survival in patients with metastatic colorectal cancer were initially reviewed. Two review authors (II and MI), working independently and in parallel, scanned the abstracts and then obtained and reviewed in full only studies that appeared to meet predefined inclusion and not exclusion criteria.

Inclusion criteria: clinical studies including patients with metastatic colorectal cancer, patient randomization to a group of bevacizumab + chemotherapy and chemotherapy-only group for comparison, survival as an outcome, papers in English language.

Exclusion criteria: types of paper such as meta-analyses, systematic reviews, case reports, observational studies, letters to the editor, studies that didn't have patients assigned to a bevacizumab + chemotherapy and chemotherapy only group and didn't measure survival as an outcome, studies not performed on humans, papers not in English language.

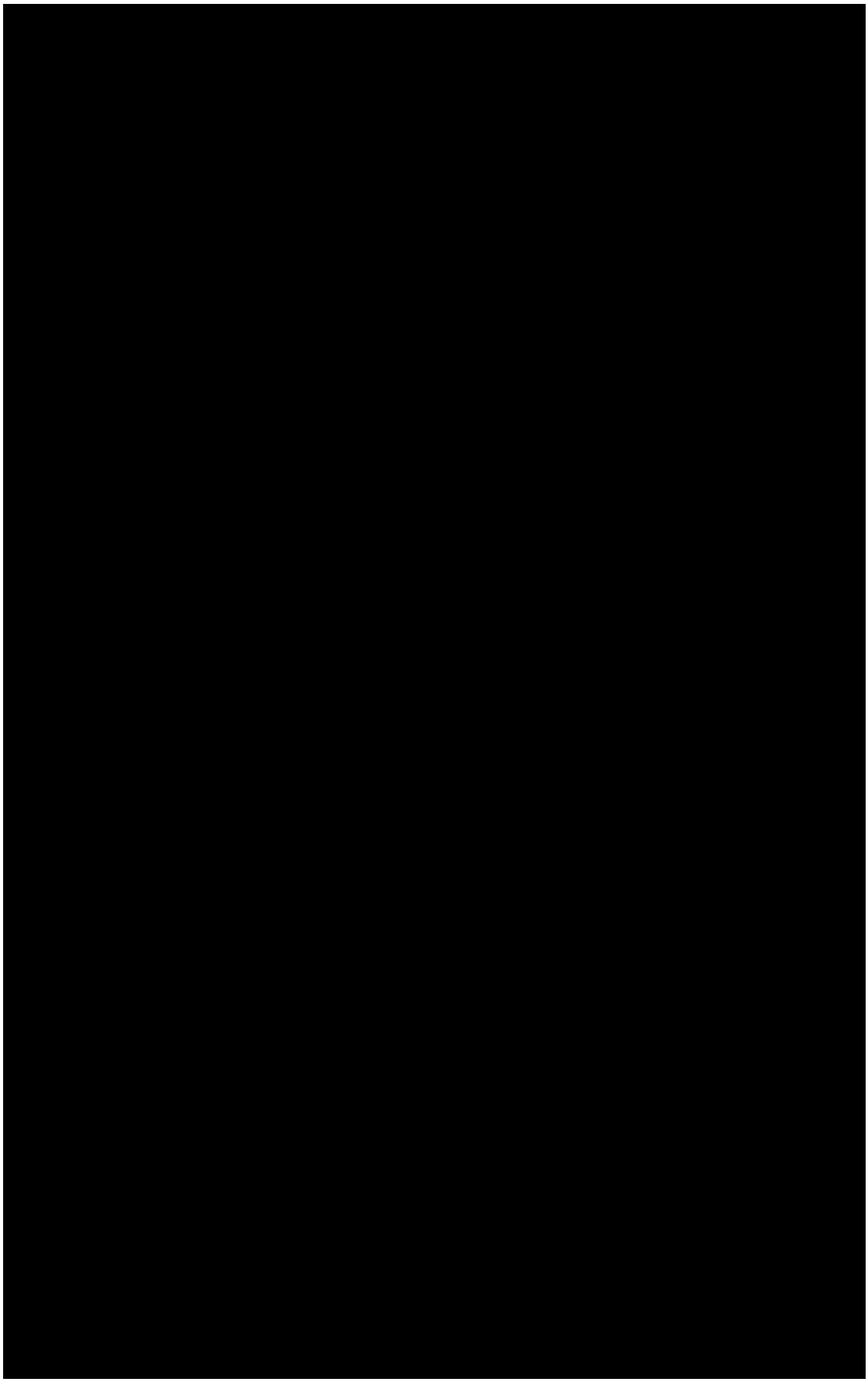
Quality assessment of included studies

Methodological validity and significance was assessed for every study that met the inclusion criteria. All reviewers independently detected studies for inclusion and then separately assessed validity and significance. Any disagreements were resolved through consensus-based discussion. Quality assessment of included studies was based on the recommendations given by Higgins et al [11] and their principles for assessing risk of bias. Guidance for Assessing the Quality of Controlled Intervention Studies by National Institutes of Health [12] was also used. Methodology of studies was evaluated using available information regarding randomization, blinding, follow up–whether all patients that entered the study were properly accounted for and attributed at its conclusion, whether the groups were treated in the same way apart from the tested treatment, whether groups were similar in the beginning.

Clinical significance of included studies was evaluated by calculating Number Needed to Treat (NNT), as suggested by Altman and Andersen [13] for studies in which outcome is the time to an event. Number needed to treat was calculated using relative risk of response and absolute risk of response [14]. The NNT shows the number of patients needed to treat with the particular drug to see one additional response.

Statistical analyses

Meta analysis was performed using the generic inverse variance method. Review Manager software Version 5.3 [15] was used. The data for ratio measures of intervention effect were entered as natural logarithms and their standard errors. The weight given to each study is the inverse of the variance of the effect estimate. Presented effect estimates were calculated using the random effects model based on the method of DerSimonian and Laird [16]. Outcome of interest, overall



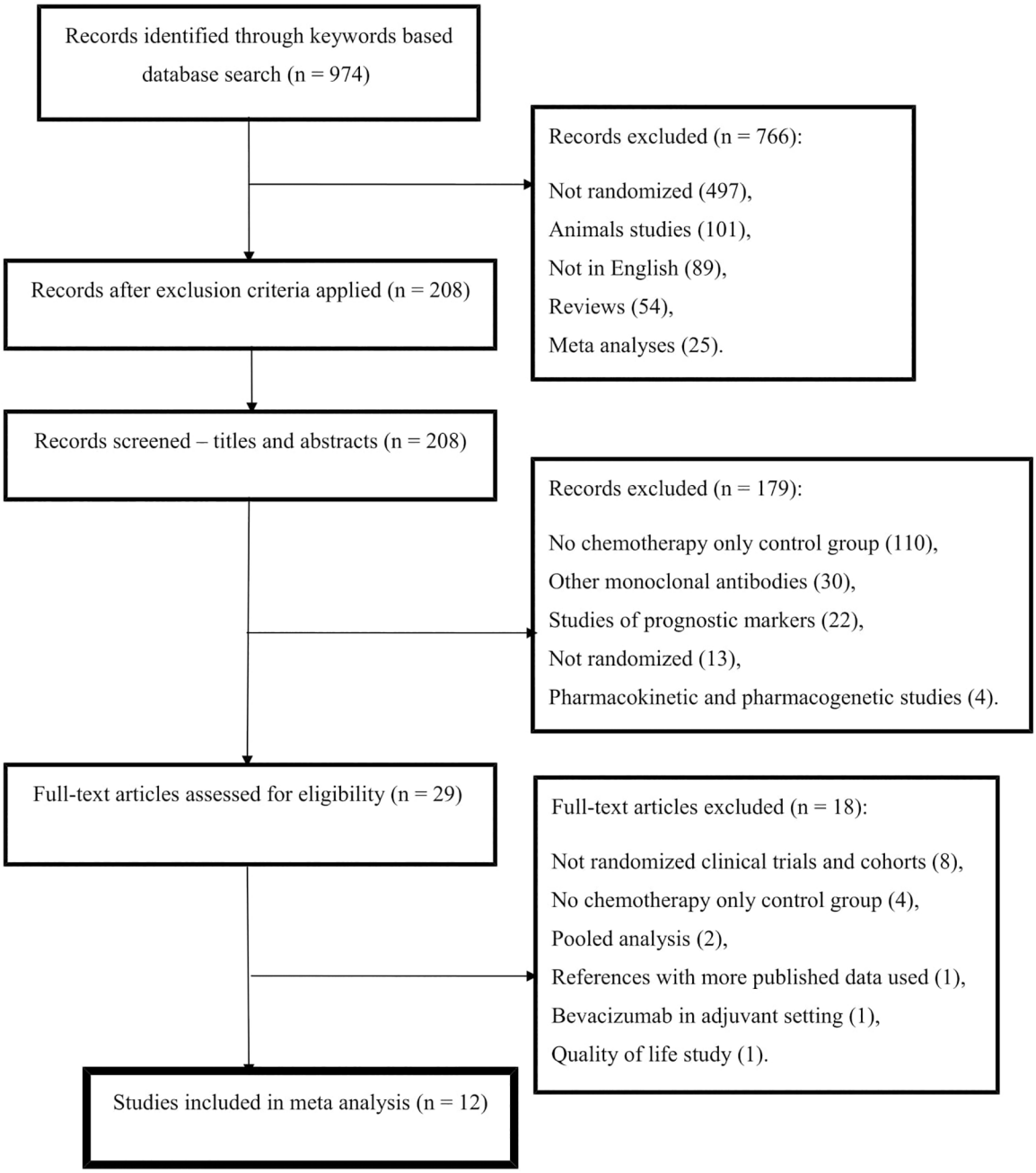


Fig 1. Flow diagram of study selection process.

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distribution differences between study's arms through adjustments in analysis and with one study [23] showing that differences in gender distribution were not statistically significant. Characteristics and main findings of included trials are shown in Tables 1 and 2.

Number needed to treat

Number needed to treat calculated using response rates given in the included studies is shown in Table 3. This table also shows the Number needed to treat to benefit (NNTB) and Number

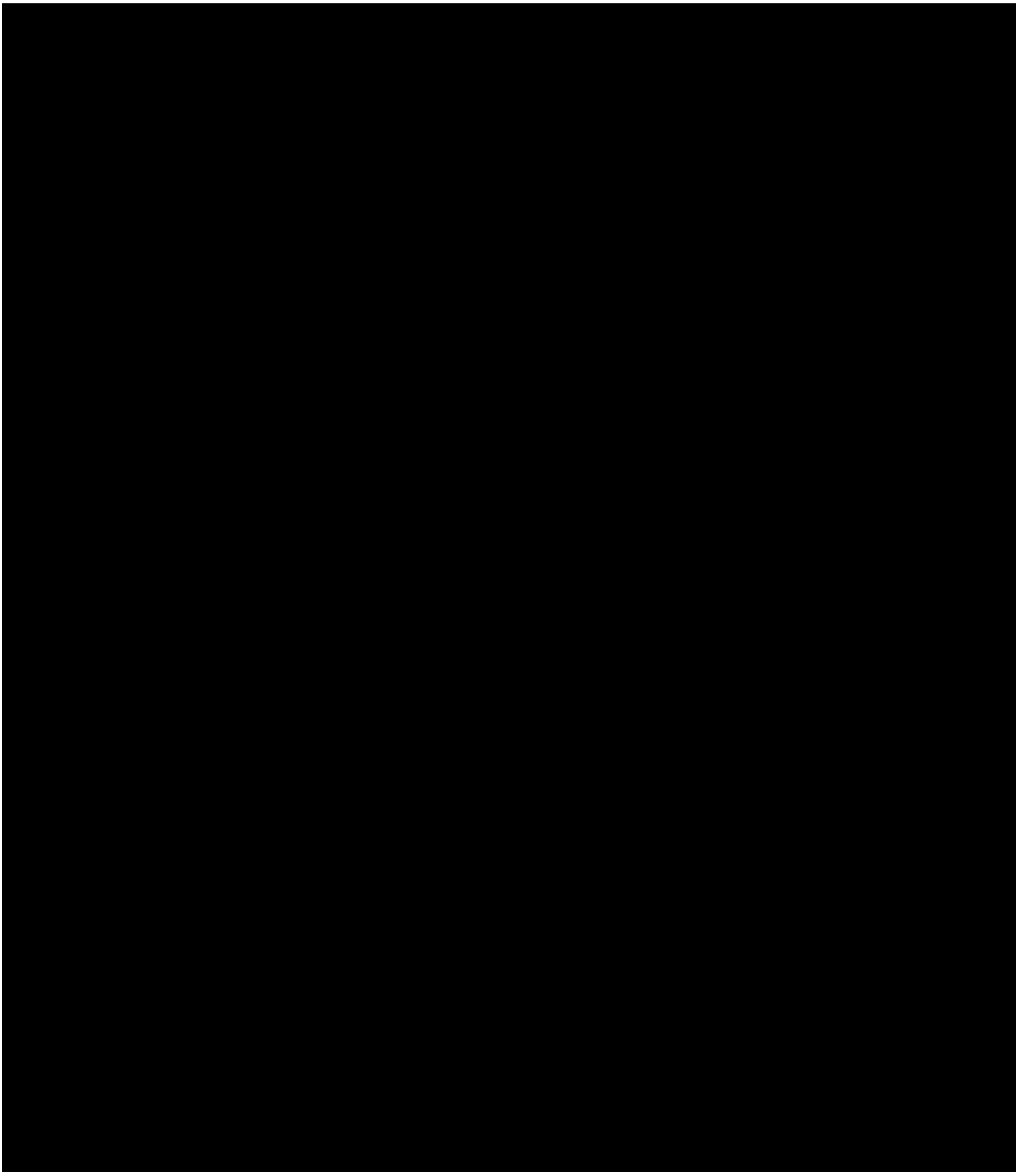

Table 3. Number needed to treat throughout studies.

Researcher, year of publication (reference)	Bevacizumab dose	NNT for response	NNTB and NNTH–survival	
			At 12 months	At 24 months
Kabbinavar et al., 2003 (22)	5 mg/kg; 10 mg/kg	4; 14	NNTB 9 (6–20)	NNTB 6 (5–11)
Moehler et al., 2009 (23)	7.5 mg/kg	20	NNTH 100 (NNTH 4 to ∞ to NNTB 4)	NNTB 7 (NNTB 2 to ∞ to NNTH 6)
Hurwitz et al., 2005 (24)	5 mg/kg	33	NNTB 10 (NNTB 4 to ∞ to NNTH 29)	NNTB 10 (NNTB 4 to ∞ to NNTH 34)
Hurwitz et al., 2004 (25)	5 mg/kg	10	-	-
Saltz et al., 2008 (26)	7.5 mg/kg; 5 mg/kg	RR equal (38%)	NNTB 16 (9–63)	NNTB 34 (NNTB 12 to ∞ to NNTH 43)
Stathopoulos et al., 2010 (27)	7.5 mg/kg	63	NNTH 40 (NNTH 8 to ∞ to NNTB 13)	NNTH 9 (NNTB 48 to ∞ to NNTH 4)
Kabbinavar et al., 2005 (28)	5 mg/kg	9	NNTB 10 (NNTH 31 to ∞ to NNTB 4)	NNTB 21 (NNTH 28 to ∞ to NNTB 7)
Guan et al., 2011 (29)	5 mg/kg	6	NNTB 7 (NNTB 4 to ∞ to NNTH 1250)	NNTB 34 (NNTB 6 to ∞ to NNTH 10)
Giantonio et al., 2007 (30)	10 mg/kg	7	NNTB 8 (5–21)	NNTB 14 (7–158)
Tebutt et al., 2010 (31)	7.5 mg/kg	13; 6	NNTB 15 (NNTB 6 to ∞ to NNTB 27); NNTB 1000 (NNTB 9 to ∞ to NNTH 10)	NNTB 167 (NNTB 9 to ∞ to NNTB 10); NNTH 43 (NNTH 8 to ∞ to NNTB 12)
Cunningham et al., 2013 (32)	7.5 mg/kg	11	NNTB 8 (4–53)	NNTB 10 (5–57)
Passardi et al., 2015 (33)	5 mg/kg	167	NNTH 13 (NNTH 6 to ∞ to NNTB 101)	NNTH 35 (NNTH 8 to ∞ to NNTB 14)

Abbreviations: NNT = Number needed to treat; RR = Response rate; NNTB = Number needed to treat to benefit; NNTH = Number needed to treat to harm.

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fluorouracil monotherapy (HR = 0.71; 95% CI: 0.61–0.83; $p<0.0001$) and oxaliplatin based chemotherapy regimens (HR = 0.83; 95% CI: 0.74–0.93; $p = 0.001$), while the results for irinotecan based and capecitabine regimens did not reach statistical significance. Sensitivity analysis aimed to detect the influence of three phase II studies showed results to remain stable when these studies were included or excluded from analysis (Fig 3).

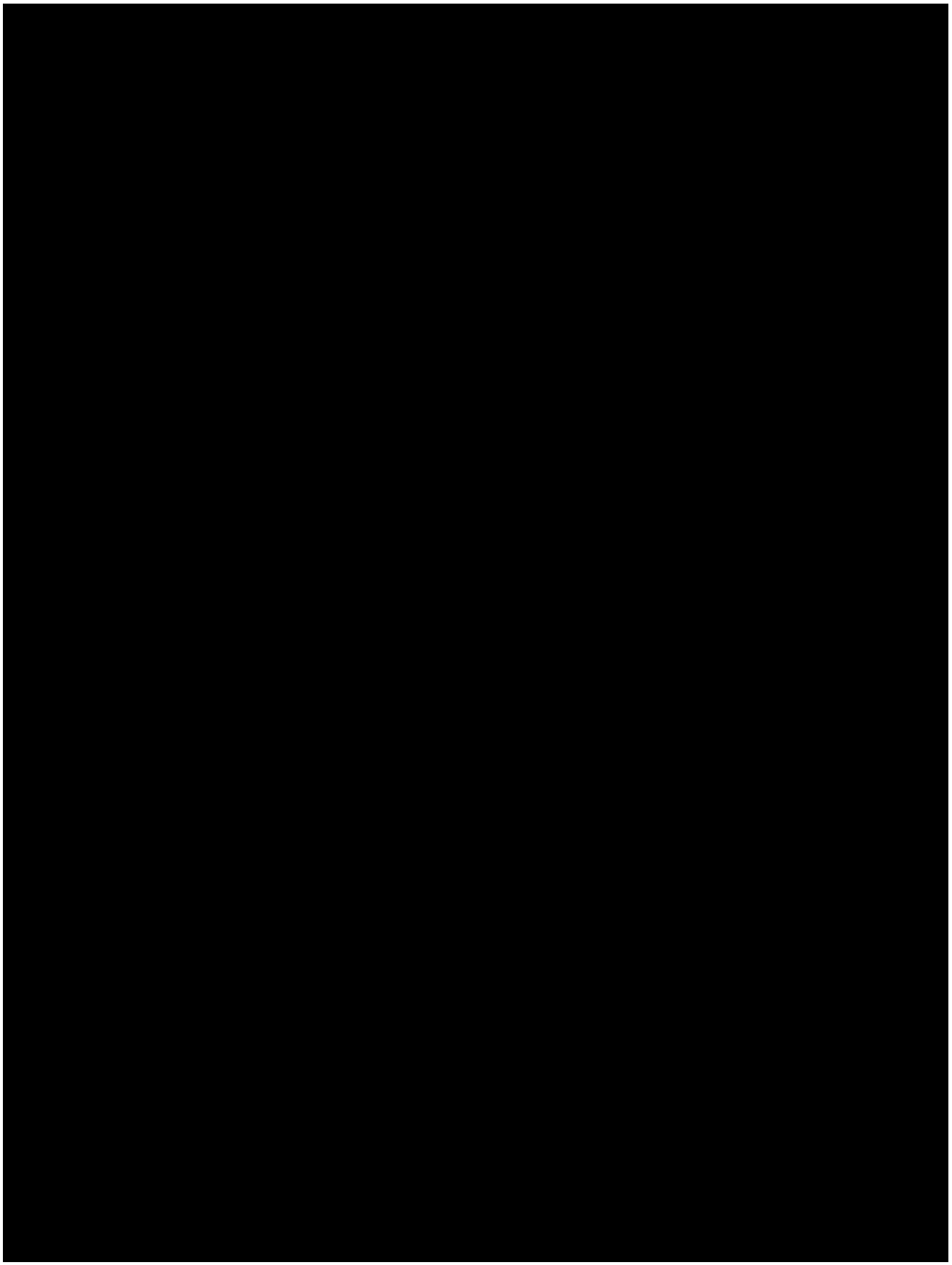
Progression free survival

Benefit in progression free survival was evident when bevacizumab was added to chemotherapy (HR = 0.64; 95% CI: 0.55–0.73; $p<0.00001$), but with high heterogeneity ($I^2 = 63\%$; $p = 0.002$) (Fig 4). However, subgroup analysis showed that the increment in PFS was persistent throughout all chemotherapy regimens to which bevacizumab was added, with oxaliplatin based regimens showing the least but still significant benefit (HR = 0.73; 95% CI: 0.54–0.98; $p = 0.04$) and addition to fluorouracil monotherapy showing the most benefit (HR = 0.52; 95% CI: 0.38–0.70; $p< 0.0001$) (Fig 5).

Funnel plots (Fig 6 and Fig 7) were used for assessing publication bias. The lines representing 95% confidence intervals for each summary effect show the expected distribution of studies in the absence of selection bias or heterogeneity [34]. Funnel plots are relatively symmetrical for both OS (Fig 6) and PFS (Fig 7), and since the asymmetry is not pronounced, it is not likely that the amount of publication bias is substantial.

Discussion

Bevacizumab is a drug that targets vascular endothelial growth factor and, as such, is widely investigated in clinical trials with cancer patients. Studies that included patients with metastatic colorectal cancer have tested it alongside different chemotherapy protocols, and this research yielded various results. These variations could find a possible explanation in studies' settings, their methodological quality and in interactions of bevacizumab with chemotherapeutic agents. Our meta-analysis showed that the addition of bevacizumab to chemotherapy in patients with metastatic colorectal cancer prolongs overall survival and progression free survival.



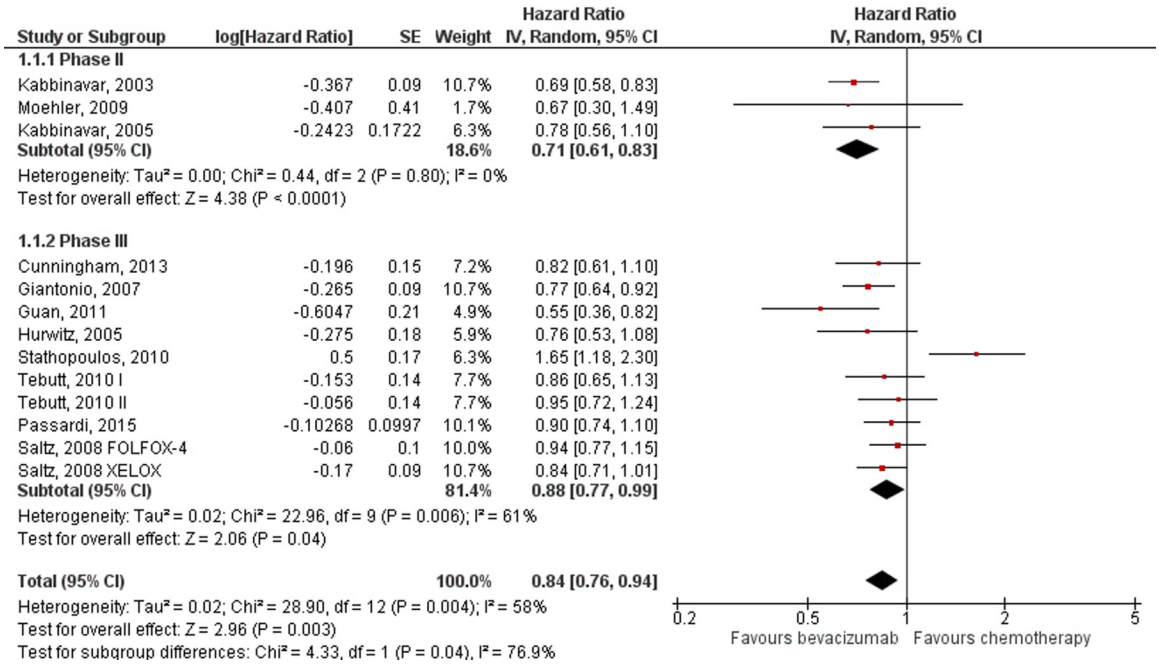


Fig 3. Meta-analysis of overall survival data by trial phase. Abbreviations: SE = Standard Error; 95% CI = 95% Confidence Interval; Chi^2 = Chi-squared test; df = degree of freedom; Tau^2 = Tau-squared; I^2 = I- squared; P = Probability.

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predefined criteria. The effect of bevacizumab on survival in patients with various cancer localizations, compared to control treatment, was assessed in meta-analyses [35,36–38] which showed that the use bevacizumab in patients with metastatic colorectal cancer was linked with

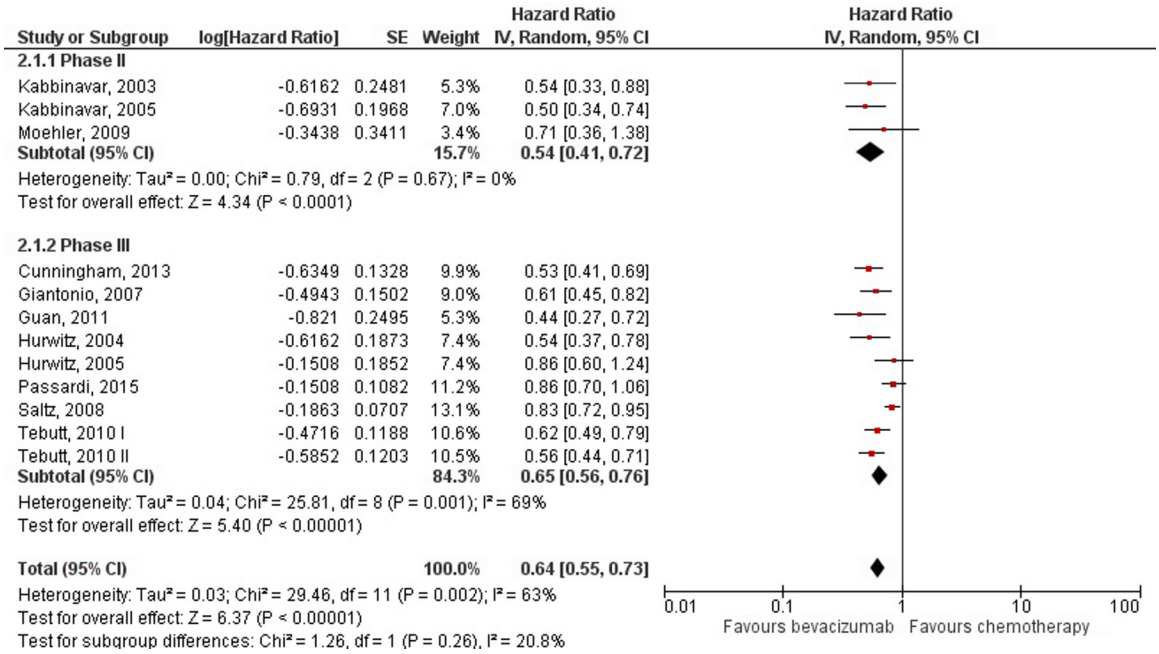

Fig 4. Meta-analysis of progression free survival data by trial phase. Abbreviations: SE = Standard Error; 95% CI = 95% Confidence Interval; Chi^2 = Chi-squared test; df = degree of freedom; Tau^2 = Tau-squared; I^2 = I- squared; P = Probability.

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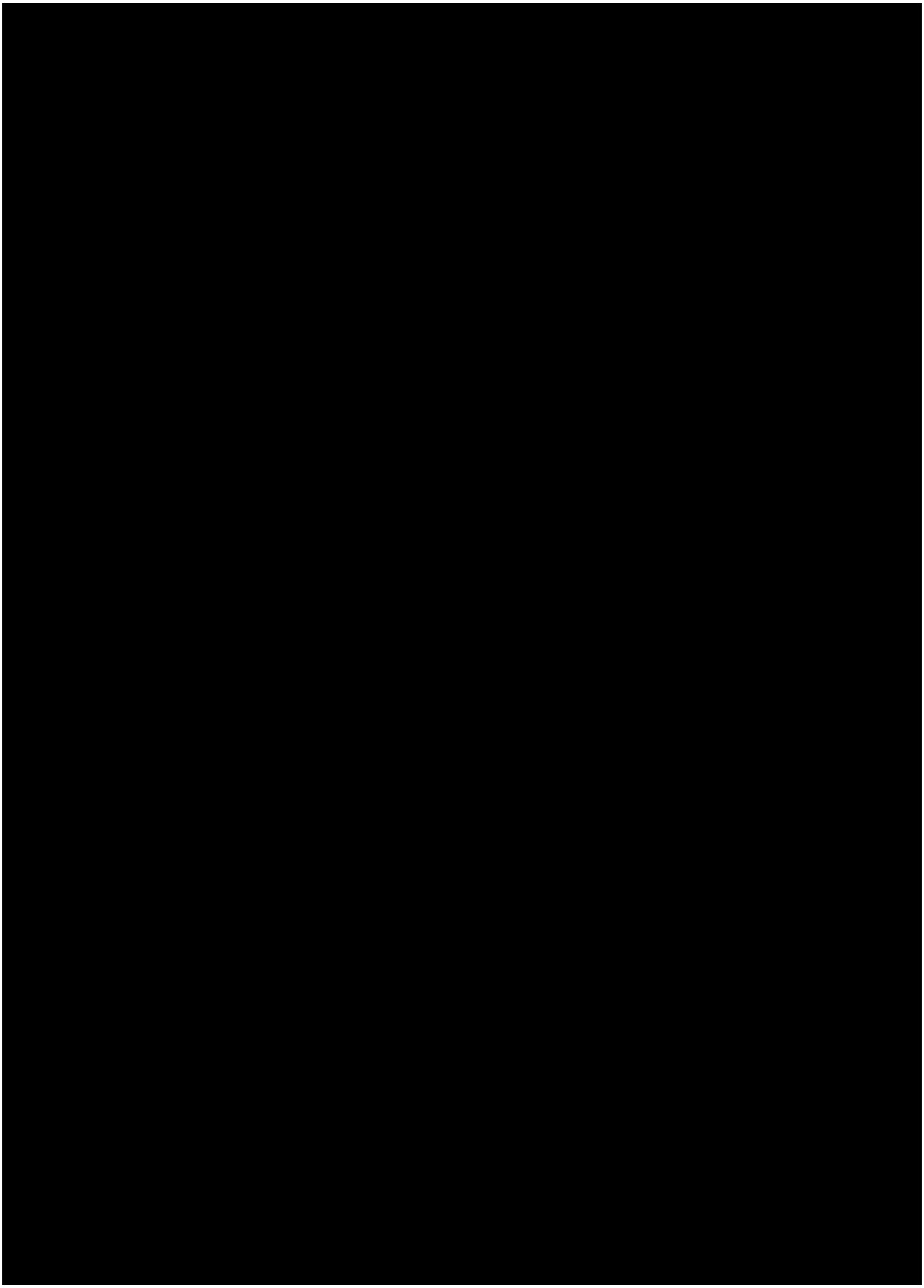

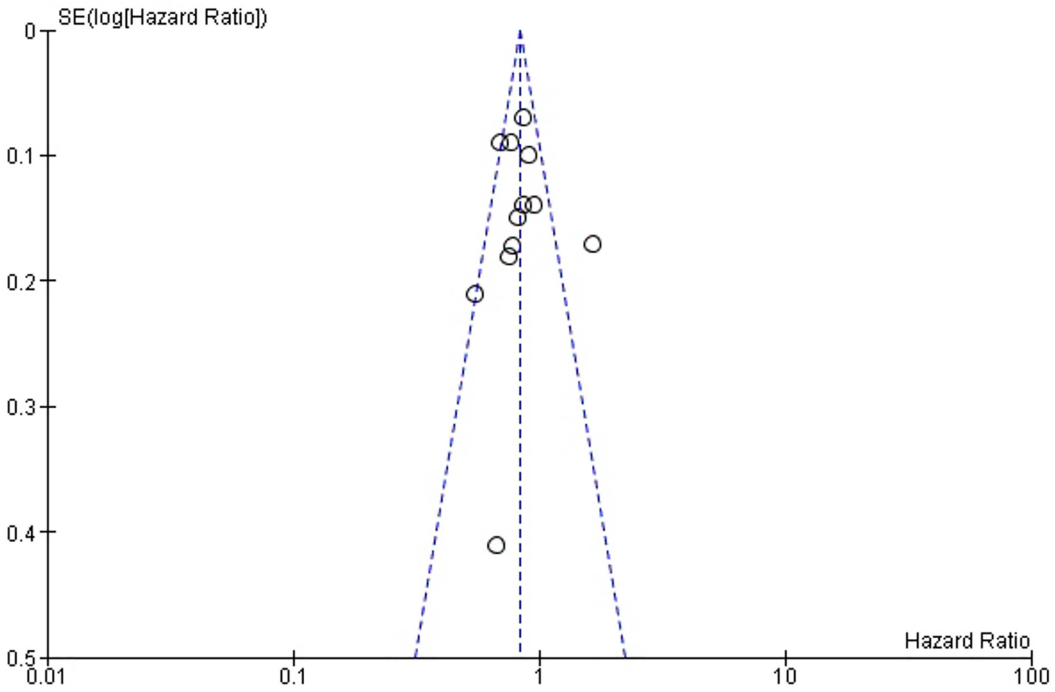

Fig 6. Funnel plot for publication bias assessment regarding overall survival. Abbreviation: SE = Standard Error.

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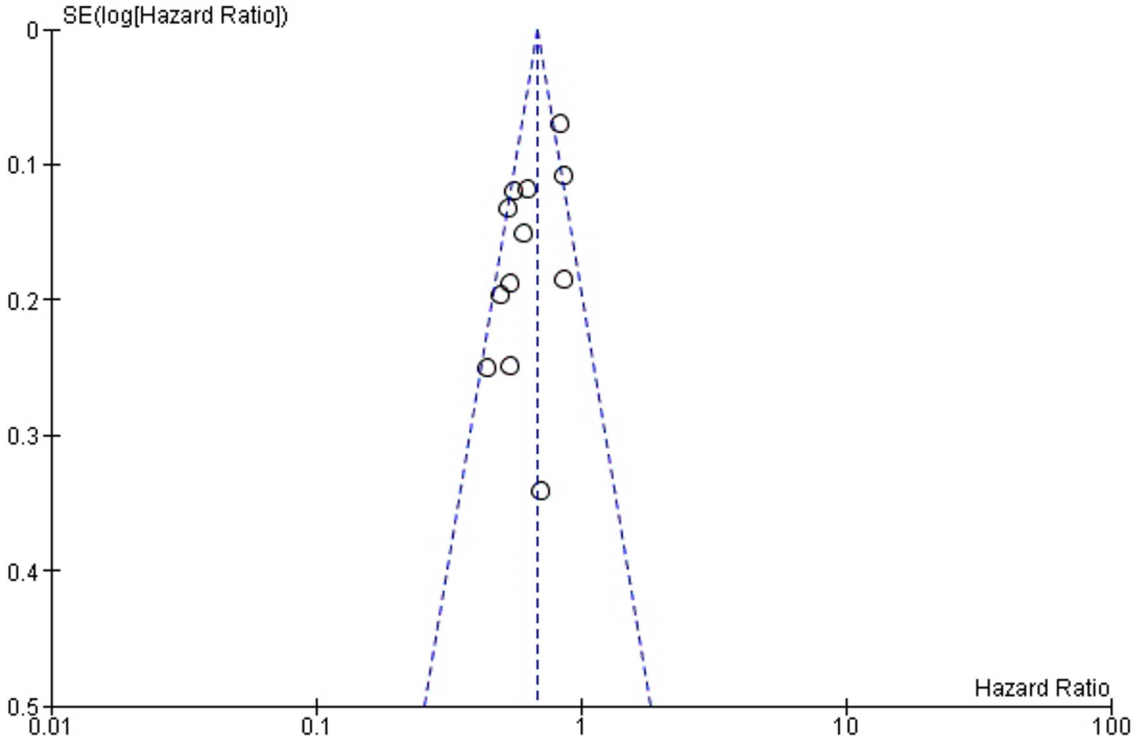

Fig 7. Funnel plot for publication bias assessment regarding progression-free survival. Abbreviation: SE = Standard Error.

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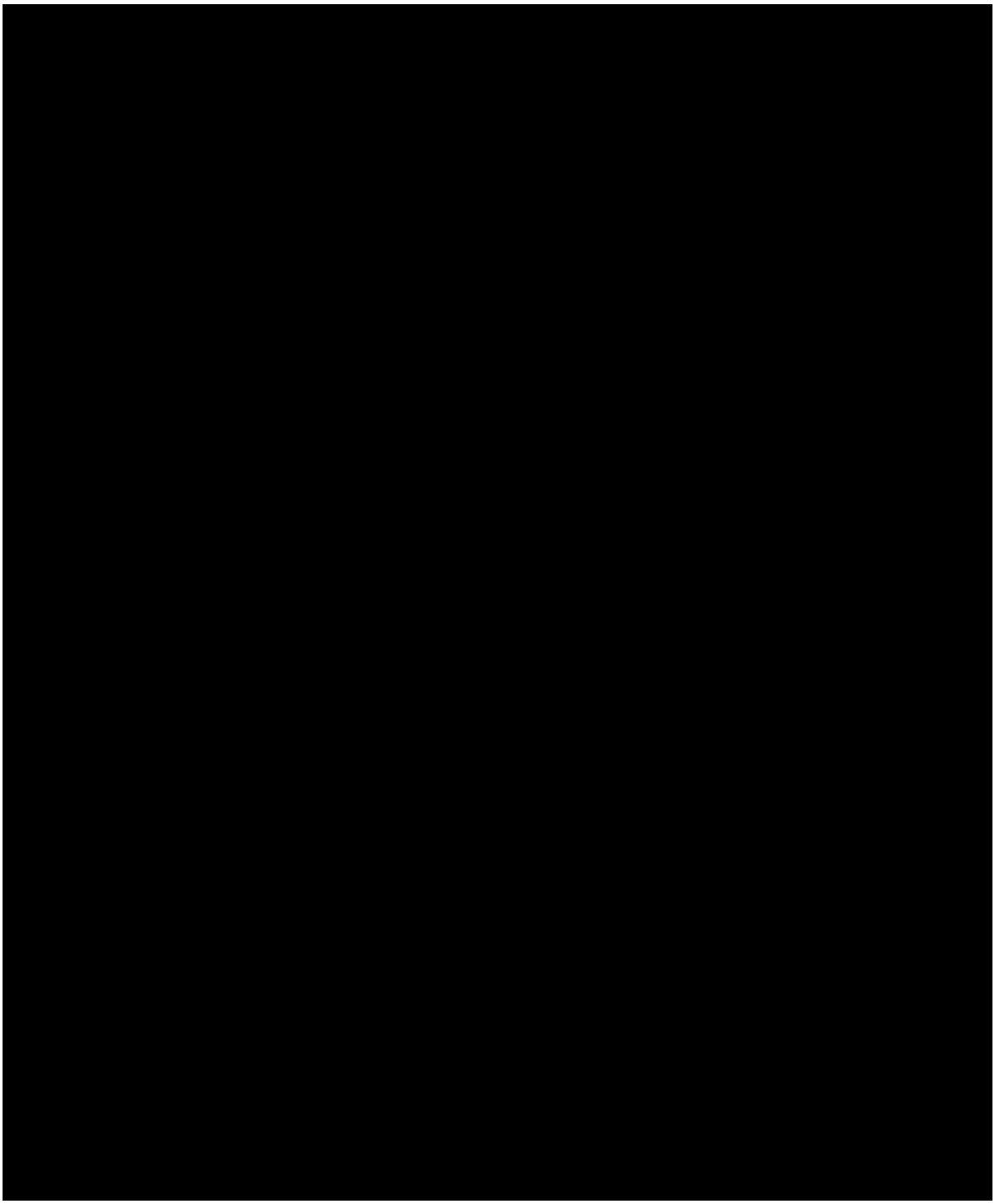

Author Contributions

Conceptualization: II.

Data curation: II MI.

Formal analysis: II.

Investigation: II MI.

Methodology: II MI.

Project administration: II MI.

Supervision: MI.

Validation: II MI.

Visualization: II MI.

Writing – original draft: II MI.

Writing – review & editing: II MI SJ.

References

1. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer. 2015; 136(5): E359–386. doi: 10.1002/ijc.29210 PMID: 25220842
2. Lee YC, Lee YL, Chuang JP, Lee JC. Differences in survival between colon and rectal cancer from SEER data. PLoS One 2013; 8(11):e78709. doi: 10.1371/journal.pone.0078709 PMID: 24265711
3. Lan YT, Yang SH, Chang SC, Liang WY, Li AF, Wang HS, et al. Analysis of the seventh edition of American Joint Committee on colon cancer staging. Int J Colorectal Dis. 2012; 27(5):657–663. doi: 10.1007/s00384-011-1366-6 PMID: 22146786
4. Labianca R, Nordlinger B, Beretta GD, Brouquet A, Cervantes A; ESMO Guidelines Working Group. Primary colon cancer: ESMO Clinical Practice Guidelines for diagnosis, adjuvant treatment and follow-up. Ann Oncol. 2010; 21 Suppl 5:v70–77. doi: 10.1093/annonc/mdq168 PMID: 20555107
5. Hung A, Mullins CD. Relative effectiveness and safety of chemotherapy in elderly and nonelderly patients with stage III colon cancer: a systematic review. Oncologist 2013; 18(1):54–63. doi: 10.1634/theoncologist.2012-0050 PMID: 23299774
6. Van Cutsem E, Lambrechts D, Prenen H, Jain RK, Carmeliet P. Lessons from the adjuvant bevacizumab trial on colon cancer: what next? J Clin Oncol. 2011; 29(1):1–4. doi: 10.1200/JCO.2010.32.2701 PMID: 21115866
7. Vasudev NS, Reynolds AR. Anti-angiogenic therapy for cancer: current progress, unresolved questions and future directions. Angiogenesis 2014; 17(3):471–494. doi: 10.1007/s10456-014-9420-y PMID: 24482243
8. Thornton AD, Ravn P, Winslet M, Chester K. Angiogenesis inhibition with bevacizumab and the surgical management of colorectal cancer. Br J Surg. 2006; 93(12):1456–1463. PMID: 17115389
9. Allegra CJ, Yothers G, O'Connell MJ, Sharif S, Petrelli NJ, Lopa SH, et al. Bevacizumab in stage II-III colon cancer: 5-year update of the National Surgical Adjuvant Breast and Bowel Project C-08 trial. J Clin Oncol. 2013; 31(3):359–364. doi: 10.1200/JCO.2012.44.4711 PMID: 23233715
10. Moher D, Liberati A, Tetzlaff J, Altman DG; The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med. 2009; 6: e1000097 doi: 10.1371/journal.pmed.1000097 PMID: 19621072
11. Higgins JPT, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011; 343:d5928 doi: 10.1136/bmj.d5928 PMID: 22008217
12. National Institutes of Health. Quality Assessment of Controlled Intervention Studies. General Guidance for Determining the Overall Quality Rating of Controlled Intervention Studies. National Heart, Lung, and Blood Institute: Bethesda, MD; 2015.
13. Altman DG, Andersen PK. Calculating the number needed to treat for trials where the outcome is time to an event. BMJ. 1999; 319(7223):1492–495. PMID: 10582940
14. Spitalnic Stuart. "Risk assessment I: Relative risk and absolute risk reduction." Hospital physician 2005; 44:43–46.
15. Review Manager (RevMan) [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.
16. Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org
17. Parmar MK, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. Stat Med. 1998; 17(24):2815–2834. PMID: 9921604

18. Tierney JF, Stewart LA, Ghersi D, Burdett S, Sydes MR. Practical methods for incorporating summary time-to-event data into meta-analysis. Trials. 2007; 8:16. PMID: 17555582
19. Altman DG. Confidence intervals for the number needed to treat. BMJ. 1998; 317(7168):1309–1312. PMID: 9804726
20. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003; 327(7414):557–560. PMID: 12958120
21. Rücker G, Schwarzer G, Carpenter JR, Schumacher M. Undue reliance on I(2) in assessing heterogeneity may mislead. BMC Med Res Methodol. 2008; 8:79. doi: 10.1186/1471-2288-8-79 PMID: 19036172
22. Kabbinavar F, Hurwitz HI, Fehrenbacher L, Meropol NJ, Novotny WF, Lieberman G, et al. Phase II, randomized trial comparing bevacizumab plus fluorouracil (FU)/leucovorin (LV) with FU/LV alone in patients with metastatic colorectal cancer. J Clin Oncol. 2003; 21(1):60–65. PMID: 12506171
23. Moehler M, Sprinzl MF, Abdelfattah M, Schimanski CC, Adami B, Godderz W, et al. Capecitabine and irinotecan with and without bevacizumab for advanced colorectal cancer patients. World J Gastroenterol. 2009; 15(4):449–456. PMID: 19152449
24. Hurwitz HI, Fehrenbacher L, Hainsworth JD, Heim W, Berlin J, Holmgren E, et al. Bevacizumab in combination with fluorouracil and leucovorin: an active regimen for first-line metastatic colorectal cancer. J Clin Oncol. 2005; 23(15):3502–3508. PMID: 15908660
25. Hurwitz H, Fehrenbacher L, Novotny W, Cartwright T, Hainsworth J, Heim W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med 2004; 350(23): 2335–2342. PMID: 15175435
26. Saltz LB, Clarke S, Díaz-Rubio E, Scheithauer W, Figer A, Wong R, et al. Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: a randomized phase III study. J Clin Oncol. 2008; 26(12):2013–2019. doi: 10.1200/JCO.2007.14.9930 PMID: 18421054
27. Stathopoulos GP, Batziou C, Trafalis D, Koutantos J, Batzios S, Stathopoulos J, et al. Treatment of colorectal cancer with and without bevacizumab: a phase III study. Oncology 2010; 78(5–6):376–381. doi: 10.1159/000320520 PMID: 20798560
28. Kabbinavar FF, Schulz J, McCleod M, Patel T, Hamm JT, Hecht JR, et al. Addition of bevacizumab to bolus fluorouracil and leucovorin in first-line metastatic colorectal cancer: results of a randomized phase II trial. J Clin Oncol 2005; 23(16):3697–3705. PMID: 15738537
29. Guan ZZ, Xu JM, Luo RC, Feng FY, Wang LW, Shen L, et al. Efficacy and safety of bevacizumab plus chemotherapy in Chinese patients with metastatic colorectal cancer: a randomized phase III ARTIST trial. Chin J Cancer 2011; 30(10):682–689. doi: 10.5732/cjc.011.10188 PMID: 21959045
30. Giantonio BJ, Catalano PJ, Meropol NJ, O'Dwyer PJ, Mitchell EP, Alberts SR, et al; Eastern Cooperative Oncology Group Study E3200. Bevacizumab in combination with oxaliplatin, fluorouracil, and leucovorin (FOLFOX4) for previously treated metastatic colorectal cancer: results from the Eastern Cooperative Oncology Group Study E3200. J Clin Oncol. 2007; 25(12):1539–1544. PMID: 17442997
31. Tebbutt NC, Wilson K, Gebski VJ, Cummins MM, Zannino D, van Hazel GA, et al. Capecitabine, bevacizumab, and mitomycin in first-line treatment of metastatic colorectal cancer: results of the Australasian Gastrointestinal Trials Group Randomized Phase III MAX Study. J Clin Oncol. 2010; 28 (19):3191–3198. doi: 10.1200/JCO.2009.27.7723 PMID: 20516443
32. Cunningham D, Lang I, Marcuello E, Lorusso V, Ocvirk J, Shin DB, et al; AVEX study investigators. Bevacizumab plus capecitabine versus capecitabine alone in elderly patients with previously untreated metastatic colorectal cancer (AVEX): an open-label, randomised phase 3 trial. Lancet Oncol. 2013; 14 (11):1077–1085. doi: 10.1016/S1470-2045(13)70154-2 PMID: 24028813
33. Passardi A, Nanni O, Tassinari D, Turci D, Cavanna L, Fontana A, et al. Effectiveness of bevacizumab added to standard chemotherapy in metastatic colorectal cancer: final results for first-line treatment from the ITACa randomized clinical trial. Ann Oncol. 2015; 26(6):1201–1207. doi: 10.1093/annonc/mdv130 PMID: 25735317
34. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997; 315(7109):629–634. PMID: 9310563
35. Su Y, Yang WB, Li S, Ye ZJ, Shi HZ, Zhou Q. Effect of angiogenesis inhibitor bevacizumab on survival in patients with cancer: a meta-analysis of the published literature. PLoS One 2012; 7(4):e35629. doi: 10.1371/journal.pone.0035629 PMID: 22539986
36. Amit L, Ben-Aharon I, Vidal L, Leibovici L, Stemmer S. The impact of Bevacizumab (Avastin) on survival in metastatic solid tumors—a meta-analysis and systematic review. PLoS One 2013; 8(1):e51780. doi: 10.1371/journal.pone.0051780 PMID: 23349675

37. Welch S, Spithoff K, Rumble RB, Maroun J; Gastrointestinal Cancer Disease Site Group. Bevacizumab combined with chemotherapy for patients with advanced colorectal cancer: a systematic review. Ann Oncol. 2010; 21(6):1152–1162. doi: 10.1093/annonc/mdp533 PMID: 19942597

38. Zhang G, Zhou X, Lin C. Efficacy of chemotherapy plus bevacizumab as first-line therapy in patients with metastatic colorectal cancer: a meta-analysis and up-date. Int J Clin Exp Med 2015; 8(1):1434–1445. PMID: 25785152

39. Hurwitz HI, Tebbutt NC, Kabbinavar F, Giantonio BJ, Guan ZZ, Mitchell L, et al. Efficacy and safety of bevacizumab in metastatic colorectal cancer: pooled analysis from seven randomized controlled trials. Oncologist 2013; 18(9):1004–1012. doi: 10.1634/theoncologist.2013-0107 PMID: 23881988

40. Macedo LT, da Costa Lima AB, Sasse AD. Addition of bevacizumab to first-line chemotherapy in advanced colorectal cancer: a systematic review and meta-analysis, with emphasis on chemotherapy subgroups. BMC Cancer 2012; 12:89. doi: 10.1186/1471-2407-12-89 PMID: 22414244

41. Chen Y, Yang Q, Kuang J, Chen SY, Wei Y, Jiang ZM, et al. Efficacy of Adding Bevacizumab in the First-Line Chemotherapy of Metastatic Colorectal Cancer: Evidence from Seven Randomized Clinical Trials. Gastroenterol Res Pract. 2014; 2014:594930. doi: 10.1155/2014/594930 PMID: 24971091

42. Lv C, Wu S, Zheng D, Wu Y, Yao D, Yu X. The Efficacy of Additional Bevacizumab to Cytotoxic Chemotherapy Regimens for the Treatment of Colorectal Cancer: An Updated Meta-Analysis for Randomized Trials. Cancer Biother Radiopharm. 2013; 28(7):501–509. doi: 10.1089/cbr.2012.1458 PMID: 23768086