Outcome of molecular targeted agent plus chemotherapy for second-line therapy of metastatic colorectal cancer: a meta-analysis of randomized trials.

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Microabscract:

The efficacy and toxicity of molecular targeted agent in second-line therapy for patients with metastatic colorectal cancer was evaluated by 11 randomized trials. Among the targeted agents, the addition of VEGF inhibitor to chemotherapy had a significant advantage in PFS, OS and ORR over chemotherapy alone except adverse events, and showed a better result for patients than other inhibitors.

Abstract

The aim of this study is to evaluate the efficacy and toxicity of molecular targeted agent plus chemotherapy compared with chemotherapy alone as second-line therapy for patients with metastatic colorectal cancer (mCRC). We identified randomized controlled trials (RCTs) compared molecular targeted agent plus chemotherapy with chemotherapy alone by using Pubmed and Embase database ranging from January 2000 to September 2015. The outcome measures were made up of progression-free survival (PFS), overall survival (OS), objective response rate (ORR), and adverse events. Two investigators independently performed information retrieval, screening and data extraction. Stata 10.0 software was used to statistically analyze the extracted data. In accordance with inclusion criteria, eleven trials, a total of 7440 patients, were included in this meta-analysis through rounds of selection. Based on the type of biologics, we divided these biologics into three subgroups—vascular endothelial growth factor (VEGF) inhibitor, other pathway inhibitors and epidermal growth factor receptor (EGFR) inhibitor. Our results suggested the regimen of molecular targeted agent plus chemotherapy had a significant advantage in PFS, OS and ORR over chemotherapy alone (hazard ratio (HR) =0.74, 95% confidence interval (CI): 0.70-0.78; HR=0.88, 95% CI: 0.83-0.93; risk ratio (RR) =2.24, 95% CI: 1.58-3.17, respectively). However, the rate of grade ≥ 3 adverse events was also higher in the combination therapy arm (RR=1.25, 95% CI: 1.17-1.33). Subgroup analysis showed combination VEGF inhibitor with chemotherapy had a significant advantage in PFS, OS and ORR over chemotherapy alone, but there was also a higher RR in adverse events compared with control group. In conclusion, molecular targeted agent plus chemotherapy is worth for patients with metastatic colorectal cancer (mCRC) as second-line therapy, especially

VEGF inhibitor. However, more RCTs on a larger scale are needed for evaluating the value of EGFR and other pathway inhibitors.
Key words: metastatic colorectal cancer; molecular targeted drug; second-line; meta-analysis

Introduction

Colorectal cancer (CRC) is a serious public health problem and metastatic CRC (mCRC) also poses more threats to human life in many countries. The American Cancer Society estimates that there will be 132,700 people diagnosed with colon or rectum cancer, and 49,700 patients will succumb to this disease in 2015 [1]. Since the mid-1980s, the incidence rate of colorectal cancer was continuously declining on the whole. The reason is mainly prevalent in risk factors and introduction of colorectal cancer screening[2]. Incessant improvement in therapy regimens and the implementation of personalized cancer medicine have also made more patients see the hope of survival. In past decade, the median overall survival was approximately 2 years with the advances in chemotherapy[3]. In addition, the median overall survival was improved in patients with failure to first treatment to 13.5 months[4].

The current approach to treat mCRC with first-line therapy favors the combination cytotoxic chemotherapy [5-7] or addition of targeted drugs. In the recent two decades, introduction and development of targeted drugs, mainly including vascular endothelial growth factor (VEGF) inhibitor, the epidermal growth factor receptor (EGFR) inhibitor and other signaling pathway inhibitors, have markedly improved clinical outcomes and brought great benefit to patients [8-10]. Different from VEGF inhibitor, an EGFR inhibitor is usually efficient in a subset of patients characterized with *RAS* wild-type disease[10,11].

However, many patients would suffer more pain after first-line treatment failure or unacceptable toxicity. Therefore, the second-line therapies are necessary. Indeed, great work has been done to improve survival of the patients failed to standard therapies through varied clinical trials, of which many schedules were molecular targeted agent in conjunction with chemotherapy[12-14]. Evidence from previous studies indicated that VEGF, EGFR or other small molecule play important roles in tumor progression, growth and invasion[15-17]. In theory, the efficacy of combination treatment should be superior to chemotherapy alone. But some trials showed the combination therapy did not increase survival, and just the opposite, mCRC patients experienced more toxicity profiles. As a result, we conducted this meta-analysis to evaluate and further understanding the efficacy and safety of molecular targeted agent in combination with chemotherapy for second-line therapy in patients with mCRC.

Materials and methods

Search strategy

According to inclusion criteria, we searched Pubmed and Embase fron January 2000 to September 2015. The searching keywords mainly included the following words: “metastatic colorectal cancer”, “mCRC”, “advanced colorectal cancer”, “therapy”, “treatment” and “random”. The language was limited as English.

Selection criteria

We would include a study when it met the following criteria: (a) histologically or pathologically confirmed colorectal cancer; (b) 0-2 points on the basis of Eastern Cooperative Oncology Group Performance Status (ECOG PS); (c) randomized controlled trials (RCTs); (d) second-line treatment; (e) experimental group treated by addition of one targeted drug to chemotherapy-based regimen. If there was more than one study from the same population, we selected it equipped with relatively intact research data.

Data extraction and quality assessment

Two investigators (Pei and Liu) independently performed information retrieval, screening and date extraction. If there were divergences over one article between the two investigators, the third investigator (Sun) would further analysis and discussion. The following data were extracted from the included studies: first author, year, phase, regimen, number of patients, Jadad score. We used Jadad Scale, ranging from 0-5 points, to assess the methodological quality for the 11 RCTs[18]. This standard for evaluation is composed of randomization (0-2 points), blinding (0-2 points), as well as dropouts and withdrawals (0-1 point). A study mentioning one of the three criteria would gain one score. The second score would obtain if the method of randomization or blinding had an appropriate description. High-quality trials scored more than 2 points, and low-quality trials are those scoring less than or equal to 2 points[19].

Statistical analysis

In this meta-analysis, STATA software (version 10.0, Stata Corporation, College Station, USA) was utilized to analyze all of the data. Progression-free survival (PFS) and overall survival (OS) were assessed by hazard ratios (HRs) with 95% confidence intervals (CIs), while objective response rate (ORR) and the rate of grade ≥ 3 adverse effects were evaluated by risk ratios (RRs) with 95% CIs. I^2 was performed to assess heterogeneity between included trials. The random-effects model is used when I^2 ≥50%, otherwise a fixed-effects model is employed if I^2 ≤50%. The Begg's test and Egger's test were conducted to evaluate the publication bias.

Results

Literature search

The electronic database search identified 3,591 relevant records, and finally, 11 articles were met all of the inclusion criteria through rounds of selection[4,12-14,20-26]. The specific screening process of the studies is shown in Figure 1. Characteristics of 11 RCTs are exhibited in Table 1. Among them, the types of molecular targeted agents conclude anti-VEGF agent [4,12,21,22,25,26], EGFR inhibitor[13,20,24], DR5 inhibitor[14], IGF1R inhibitor[14] and Ang-Tie2 inhibitor[23]. 7,440 eligible patients were included with 3,740 cases in the chemotherapy plus one targeted agent group and 3,700 cases in the chemotherapy alone group. In addition, the study conducted by Cohn *et al* [14] compared conatumumab/FOLFIRI and ganitumab/ FOLFIRI with placebo/FOLFIRI, respectively. As a result, the study was regarded as two independent trials (Cohn (a) and Cohn (b)).

PFS

All eleven RCTs reported PFS[4,12-14,20-26]. No significant heterogeneity between trials was detected (I^2=39.3%, p=0.079). Thus the pooled HR for PFS was conducted using a fixed-effects model. The pooled data showed that targeted agent plus chemotherapy significantly improved PFS (HR=0.74, 95% CI: 0.70-0.78) than chemotherapy alone in second-line treatment (Figure 2). In accordance with the type of molecular targeted agents, we divided the 11 trials into three subgroups:

1 (VEGF inhibitor), 2 (other pathway inhibitor) and 3 (EGFR inhibitor). The addition of VEGF or EGFR inhibitor evidently prolonged PFS (HR=0.74, 95% CI: 0.69-0.79; HR=0.72, 95% CI: 0.65-0.78, respectively) compared with monotherapy. However, the regimen of other pathway inhibitor plus chemotherapy did not significantly improve PFS (HR=0.99, 95% CI: 0.75-1.29). There was no significant publication bias (Begg's test, Z=0.75, p=0.451 and Egger's test, Z=1.27, p=0.233).

OS

Eleven RCTs were involved in the analysis of OS data[4,12-14,20-26]. A fixed-effects model was used to pool the data, since the heterogeneity across the eleven studies was not significant (I^2=30.4%, p=0.149). The result indicated that combination therapy significantly prolonged OS compared with monotherapy (HR=0.88, 95% CI: 0.83-0.93) (Figure 3). However, in the subgroup analysis we can notice that EGFR or other pathway inhibitor combined with chemotherapy did not significantly improve OS of mCRC patients (HR=0.95, 95% CI: 0.86-1.05; HR=1.01, 95% CI: 0.75-1.36, respectively). The addition of VEGF inhibitor provided significant OS benefit for patients (HR=0.84, 95% CI: 0.79-0.90). And then, no significant publication bias existed (Begg's test, Z=0.21, p=0.837 and Egger's test, Z=0.28, p=0.787).

ORR

Objective response rate relevant data were provided by ten RCTs[4,12-14,20-25]. The pooled analysis showed that there was a high heterogeneity among the ten trials (I^2=79.0%, p=0.000). Therefore, a random-effects model was conducted. As the Figure 4 suggested, the patients with mCRC treated with combined therapy had a higher RR than those treated with chemotherapy alone (RR=2.24, 95% CI: 1.58-3.17). Subgroup analysis revealed there was a significant difference in each subgroup comparing combination arm with chemotherapy alone arm (Figure 4).

Adverse events

Treatment related toxicity was analyzed through grade ≥ 3 adverse events data which were provided by ten studies [4,12-14,20-23,25,26]. A moderate heterogeneity was detected (I^2=61.9%, p=0.003),

then the random-effects model was used to analyze. A higher RR was observed in the arm of chemotherapy plus targeted agents compared to control arm (RR=1.25, 95% CI: 1.17-1.33) (Figure 5). The following subgroup analysis suggested addition of EGFR inhibitor and VEGF inhibitor to chemotherapy induced a higher RR (Figure 5).

Discussion

In this meta-analysis, our results suggested that patients with mCRC benefited substantially from targeted agent plus chemotherapy as second-line therapy in terms of DFS, OS and ORR (HR=0.74, 95% CI: 0.70-0.78; HR=0.88, 95% CI: 0.83-0.93; RR=2.24, 95% CI: 1.58-3.17, respectively), especially VEGF inhibitor.

Molecular targeted agents were frequently used in the second-line therapy of mCRC. At present, VEGF inhibitors and EGFR inhibitors, such as bevacizumab, panitumumab and cetuximab were extensively applied in cancer treatment. Besides, Van Cutsem *et al.* conducted a study to compare aflibercept (a novel antiangiogenic agent) with placebo in combination with FOLFIRI in patients with mCRC previously treated with an oxaliplatin-based regimen [4]. Their results indicated that aflibercept is an alternative agent to bevacizumab in combination with FOLFIRI in second-line therapy of mCRC. Previous studies have proved that VEGF perform as a key regulator in pathological angiogenesis of colon cancer, and its expression was essential for vessel count, further resulting in distant recurrence [27]. The antitumor activity of VEGF monoclonal antibody or VEGF receptors inhibitors relies on the blocking on VEGF signaling axis. On the other hand, anti-EGFR agent, another key way in second-line therapy of mCRC was limited to subpopulation with *RAS* wild-type disease, whose response rate to EGFR inhibitors was generally below 30% [28,29]. However, it is still necessary to assess the condition of *KRAS* and more other accurate biomarkers before anti-EGFR therapy. Our results were similar to the study of E. Segelov et.al[30], although we added two studies which have relevant and detailed data. For example, VEGF inhibitor in second-line therapy of metastatic colorectal cancer improved PFS, OS and ORR. Besides, EGFR inhibitor prolonged PFS and increased ORR compared with control group, but it had no improvement in OS. Compared with E. Segelov et.al[30], our study showed the following new findings: I. The toxicity of different types of molecular targeted agents was assessed in this meta-analysis. The rate of grade ≥ 3

adverse events brought by EGFR and VEGF inhibitors was higher in the combination therapy arm. Thus the result would catch our more attention in clinical practices. II. The efficacy and toxicity of other pathway inhibitors were evaluated in our study. However, these inhibitors did not improve PFS and OS in patients with metastatic colorectal cancer. In this way, VEGF inhibitor in combination with chemotherapy would bring more clinical benefit for mCRC patients as second-line therapy on the premise of detecting gene. On the contrary, Hecht *et al.* demonstrated that panitumumab with FOLFIRI and bevacizumab with FOLFIRI as second-line treatment had similar PFS and OS [31].

Other pathway inhibitors, such as DR5, IGF1R and Ang-Tie2, increased ORR and had no significant difference in toxicities compared with control group. Currently, these inhibitors were in the stage of preliminary clinical trials. In consideration of the few studies, our results were limited in a large part. Thus, it still needs more RCTs and further study to investigate.

However, some potential limitations in the study should be taken into account. First, study design between the trials was widely differed. For example, method of blind design was scientific and logical, but the open-label study might influence the accuracy of our results. Second, in the experimental group of eleven trials, the administration and dosage of different targeted drugs cannot be unified. Third, our results showed a significant heterogeneity among the studies, which may cause by the difference of follow-up, characteristics of populations and the former two reasons.

In conclusion, our meta-analysis showed that available molecular targeted agent plus chemotherapy improved progression-free survival, overall survival and overall response rate as second-line therapy for mCRC, compared with chemotherapy alone group. But what should we take attention is the drug related toxicities also increase. Otherwise, further subgroup analyses indicated VEGF inhibitor in combination with chemotherapy was the most valid treatment option than others on the whole as second-line therapy for these patients. However, more RCTs on a larger scale are needed for EGFR and other pathway inhibitors.

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Table 1: Characteristics of the included 11 RCTs in the meta-analysis

Figure 1: Flow chart for the included literatures in the meta-analysis

Figure 2: The forest plot of PFS compared chemotherapy plus molecular targeted agent with chemotherapy alone. Subgroup 1: anti-VEGF agents; 2: other pathway inhibitors; 3: EGFR inhibitors.

Figure 3: The forest plot of OS compared chemotherapy plus molecular targeted agent with chemotherapy alone. Subgroup 1: anti-VEGF agents; 2: other pathway inhibitors; 3: EGFR inhibitors.

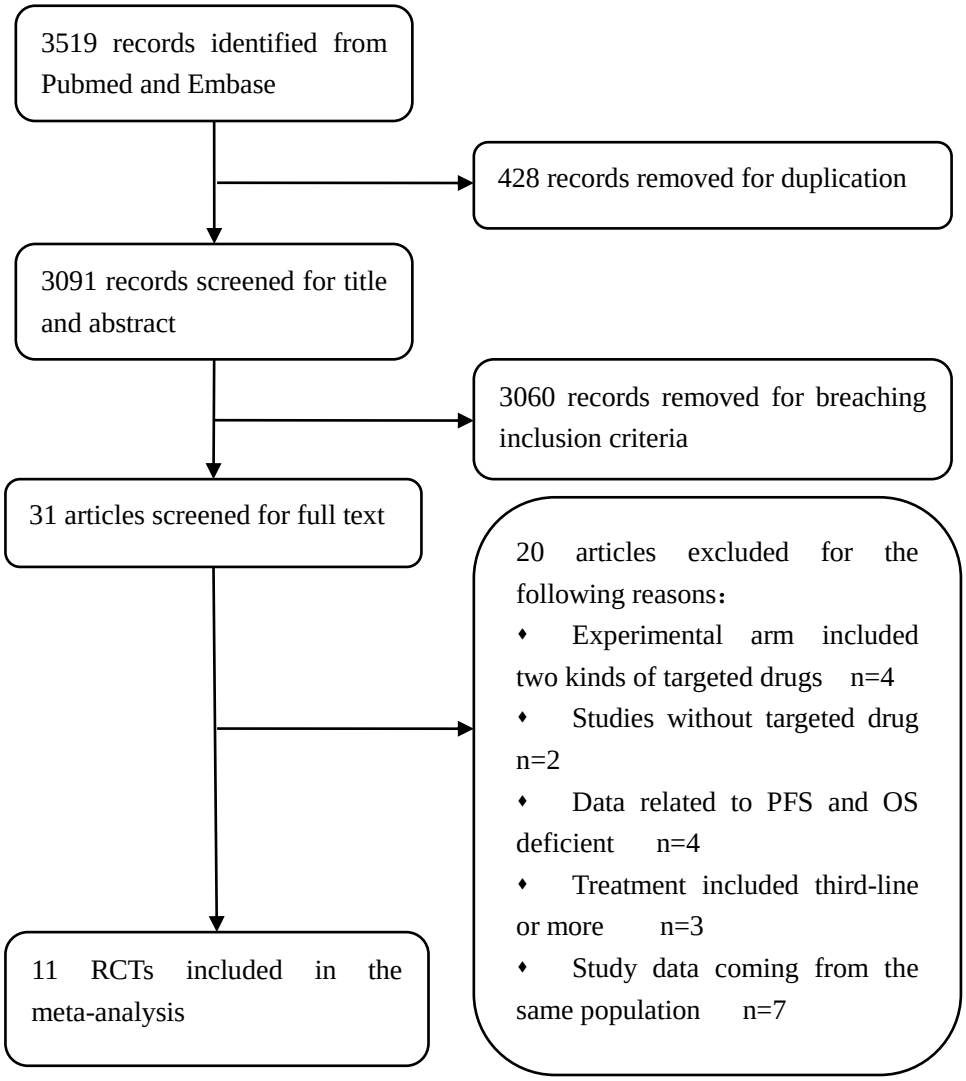
Figure 4: The forest plot of ORR compared chemotherapy plus molecular targeted agent with chemotherapy alone. Subgroup 1: anti-VEGF agents; 2: other pathway inhibitors; 3: EGFR inhibitors.

Figure 5: The forest plot of grade $\geq$ 3 adverse events compared chemotherapy plus molecular targeted agent with chemotherapy alone. Subgroup 1: anti-VEGF agents; 2: other pathway inhibitors; 3: EGFR inhibitors.

First Author	Year	Phase	Median age (Experiment/ Control arm)	Regimen(E/C)	Number of Patients (E/C)	Jadad score
Tabernero [25]	2015	III	62(21–83)/ 62(33–87)	FOLFIRI + ramucirumab FOLFIRI + placebo	536/536	5
Masi [22]	2015	III	62(38–75)/ 66.5(38–75)	FOLFIRI/mFOLFOX-6+ bevacizumab FOLFIRI/mFOLFOX-6	92/92	3
Bennouna [12]	2013	III	63(27–84)/ 63(21–84)	CT + bevacizumab CT	409/411	3
Cohn(a) [14]	2013	II	59(37–79)/ 59(32–80)	FOLFIRI + conatumumab FOLFIRI + placebo	51/52	5
Cohn(b) [14]	2013	II	58(28–81)/ 59(32–80)	FOLFIRI + ganitumab FOLFIRI + placebo	52/52	5
Peeters [23]	2013	II	56(23–79)/ 55(29–79)	FOLFIRI +trebananib FOLFIRI + placebo	95/49	4
Seymour [24]	2013	NR	64(57–70)/ 63(56–69)	Irinotecan + panitumumab Irinotecan	230/230	3
Van Cutsem [4]	2012	III	61(21–82)/ 61(19–86)	FOLFIRI + aflibercept FOLFIRI + placebo	612/614	5
Van Cutsem [26]	2011	III	60.5(21–85)/ 59.2(18–81)	FOLFOX4 + PTK/ZK FOLFOX4 + placebo	426/429	5
Peeters [13]	2010	III	60(28–84)/ 61(29–86)	FOLFIRI + panitumumab FOLFIRI	303/294	3
Sobrero [20]	2008	III	61(23-85)/ 62(21-90)	Irinotecan + cetuximab Irinotecan	648/650	3
Giantonio [21]	2007	III	62.0(21-85)/ 60.8(25-84)	FOLFOX4 + bevacizumab FOLFOX4	286/291	3

E: Experiment arm; C: Control arm; FOLFIRI: 5-fluorouracil, leucovorin and irinotecan; FOLFOX: infusional fluorouracil, leucovorin and oxaliplatin; CT: chemotherapy; NR: Not Reported.

Cohn (a) and Cohn (b) came from the same article.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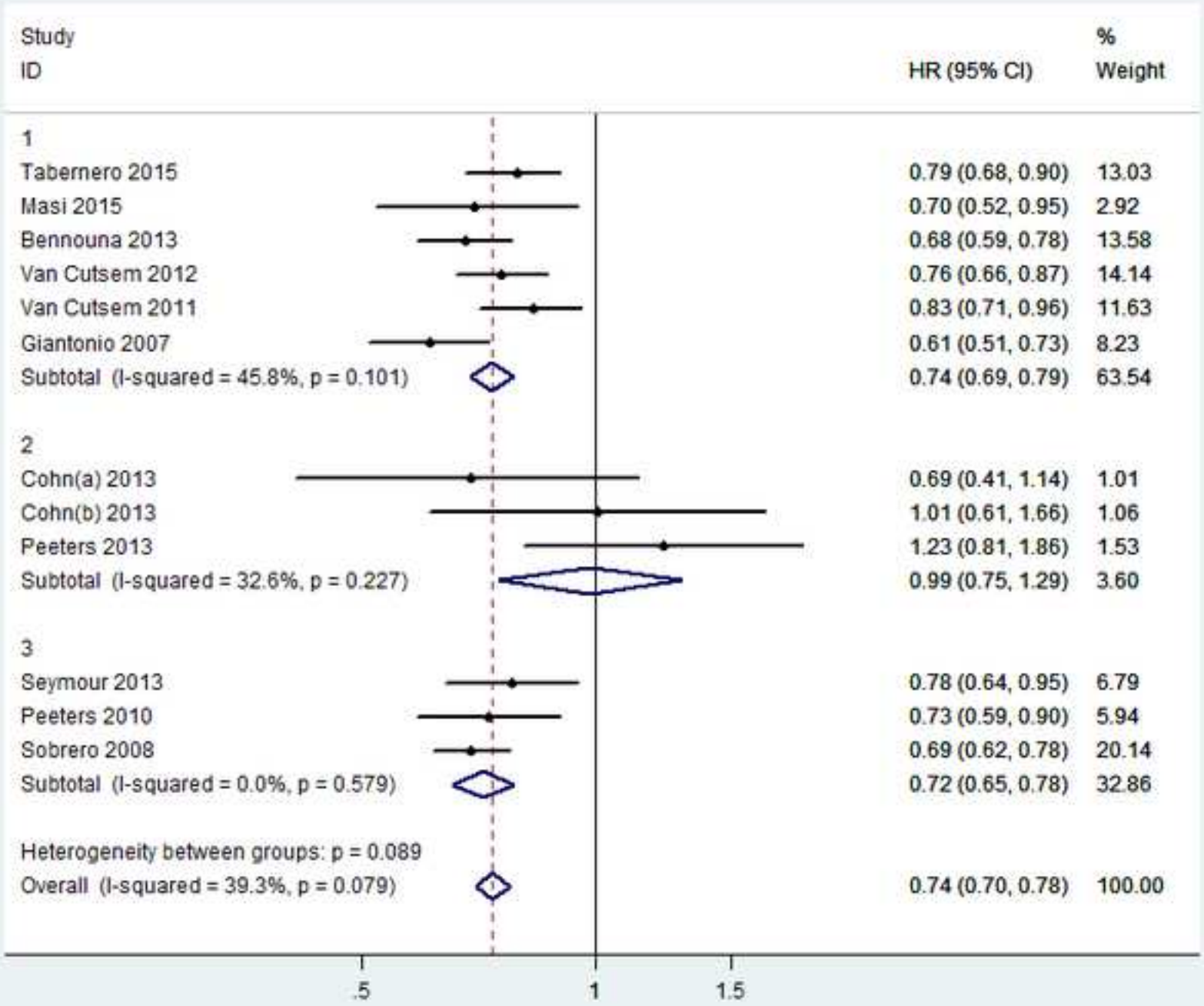
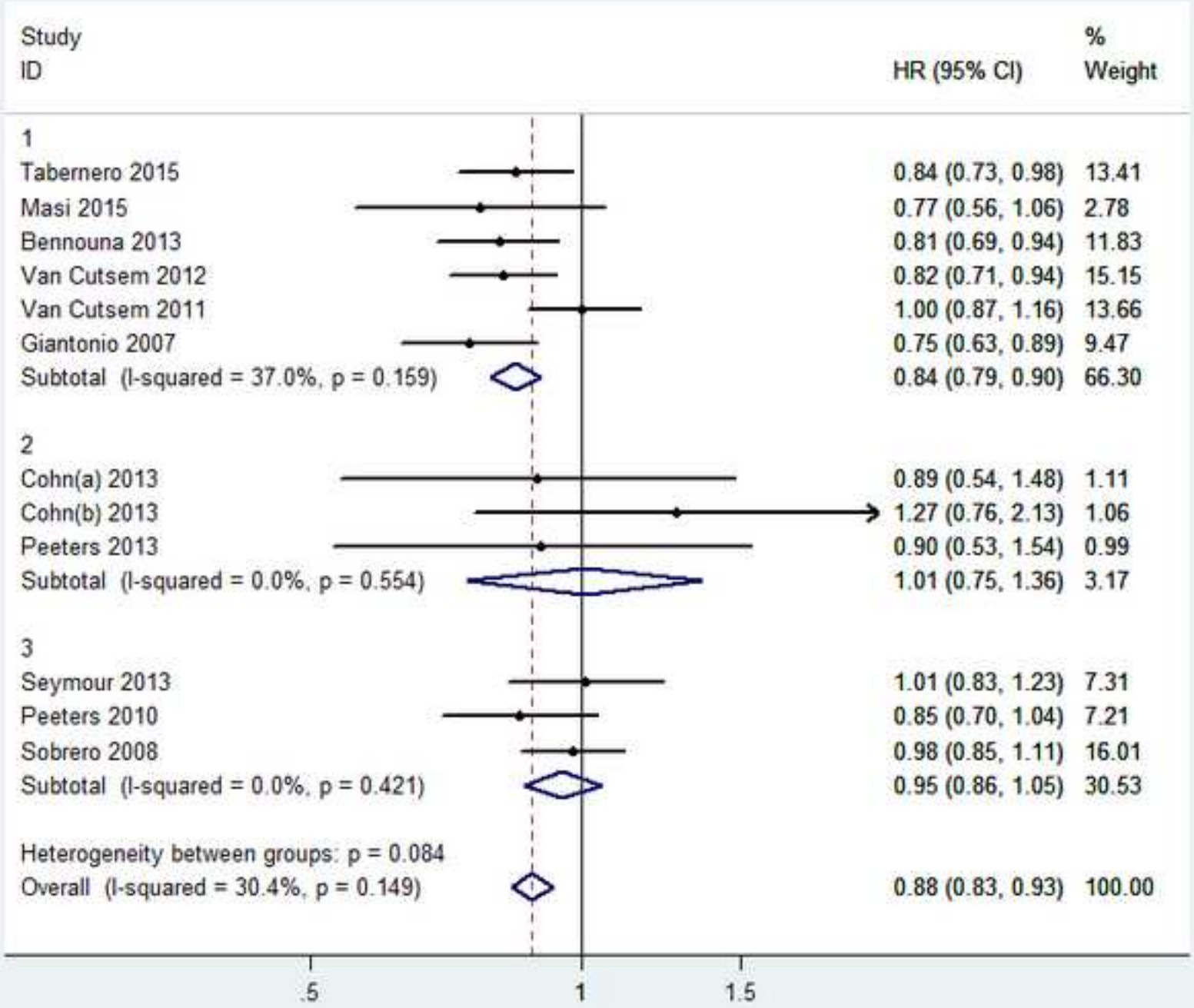
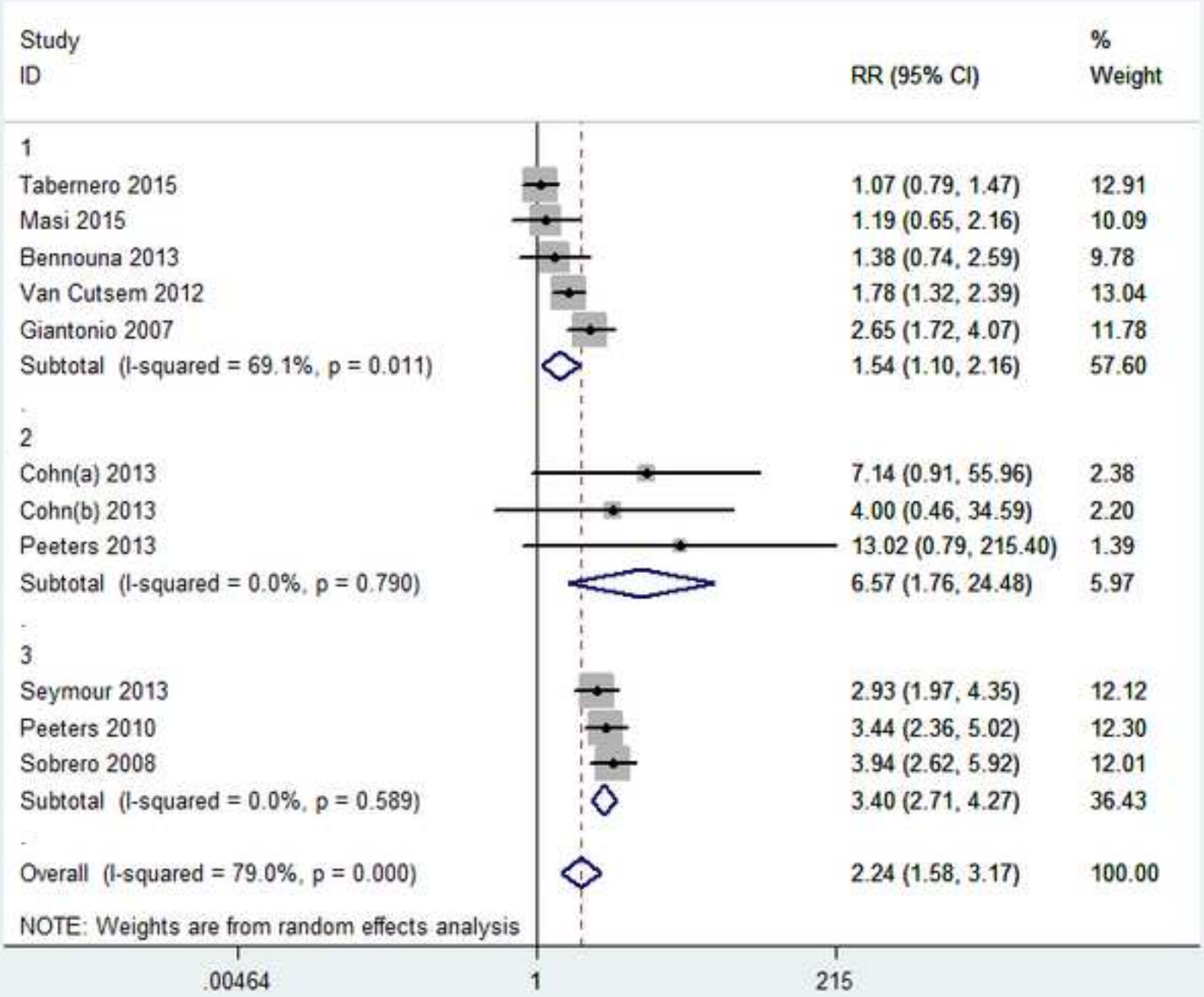
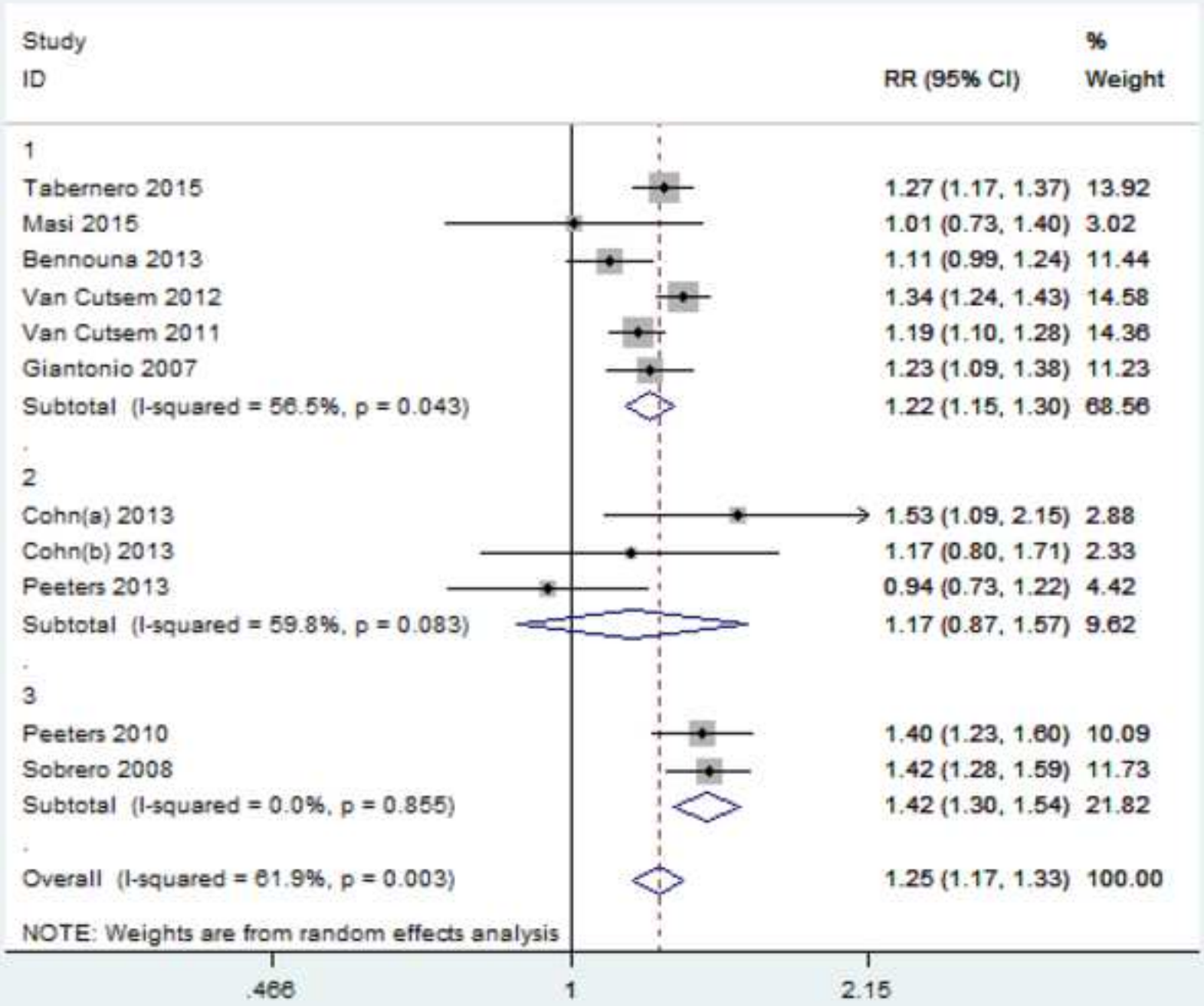
428 records removed for duplication
3091 records screened for title and abstract
3060 records removed for breaching inclusion criteria
31 articles screened for full text
20 articles excluded for the following reasons：
♦ Experimental arm included two kinds of targeted drugs n=4
♦ Studies without targeted drug n=2
♦ Data related to PFS and OS deficient n=4
♦ Treatment included third-line or more n=3
♦ Study data coming from the same population n=7
11 RCTs included in the meta-analysis


Study
ID
HR (95% CI)
% Weight
1
Tabernero 2015
0.79 (0.68, 0.90)
13.03
Masi 2015
0.70 (0.52, 0.95)
2.92
Bennouna 2013
0.68 (0.59, 0.78)
13.58
Van Cutsem 2012
0.76 (0.66, 0.87)
14.14
Van Cutsem 2011
0.83 (0.71, 0.96)
11.63
Giantonio 2007
0.61 (0.51, 0.73)
8.23
Subtotal (I-squared = 45.8%, p = 0.101)
0.74 (0.69, 0.79)
63.54
2
Cohn(a) 2013
0.69 (0.41, 1.14)
1.01
Cohn(b) 2013
1.01 (0.61, 1.66)
1.06
Peeters 2013
1.23 (0.81, 1.86)
1.53
Subtotal (I-squared = 32.6%, p = 0.227)
0.99 (0.75, 1.29)
3.60
3
Seymour 2013
0.78 (0.64, 0.95)
6.79
Peeters 2010
0.73 (0.59, 0.90)
5.94
Sobrero 2008
0.69 (0.62, 0.78)
20.14
Subtotal (I-squared = 0.0%, p = 0.579)
0.72 (0.65, 0.78)
32.86
Heterogeneity between groups: p = 0.089
Overall (I-squared = 39.3%, p = 0.079)
0.74 (0.70, 0.78)
100.00
.5
1
1.5


Study
ID
HR (95% CI)
% Weight
1
Tabernero 2015
0.84 (0.73, 0.98) 13.41
Masi 2015
0.77 (0.56, 1.06) 2.78
Bennouna 2013
0.81 (0.69, 0.94) 11.83
Van Cutsem 2012
0.82 (0.71, 0.94) 15.15
Van Cutsem 2011
1.00 (0.87, 1.16) 13.66
Giantonio 2007
0.75 (0.63, 0.89) 9.47
Subtotal (I-squared = 37.0%, p = 0.159)
0.84 (0.79, 0.90) 66.30
2
Cohn(a) 2013
0.89 (0.54, 1.48) 1.11
Cohn(b) 2013
1.27 (0.76, 2.13) 1.06
Peeters 2013
0.90 (0.53, 1.54) 0.99
Subtotal (I-squared = 0.0%, p = 0.554)
1.01 (0.75, 1.36) 3.17
3
Seymour 2013
1.01 (0.83, 1.23) 7.31
Peeters 2010
0.85 (0.70, 1.04) 7.21
Sobrero 2008
0.98 (0.85, 1.11) 16.01
Subtotal (I-squared = 0.0%, p = 0.421)
0.95 (0.86, 1.05) 30.53
Heterogeneity between groups: p = 0.084
Overall (I-squared = 30.4%, p = 0.149)
0.88 (0.83, 0.93) 100.00
.5
1
1.5


Study
ID
RR (95% CI)
% Weight
1
Tabernero 2015
1.07 (0.79, 1.47)
12.91
Masi 2015
1.19 (0.65, 2.16)
10.09
Bennouna 2013
1.38 (0.74, 2.59)
9.78
Van Cutsem 2012
1.78 (1.32, 2.39)
13.04
Giantonio 2007
2.65 (1.72, 4.07)
11.78
Subtotal (I-squared = 69.1%, p = 0.011)
1.54 (1.10, 2.16)
57.60
2
Cohn(a) 2013
7.14 (0.91, 55.96)
2.38
Cohn(b) 2013
4.00 (0.46, 34.59)
2.20
Peeters 2013
13.02 (0.79, 215.40)
1.39
Subtotal (I-squared = 0.0%, p = 0.790)
6.57 (1.76, 24.48)
5.97
3
Seymour 2013
2.93 (1.97, 4.35)
12.12
Peeters 2010
3.44 (2.36, 5.02)
12.30
Sobrero 2008
3.94 (2.62, 5.92)
12.01
Subtotal (I-squared = 0.0%, p = 0.589)
3.40 (2.71, 4.27)
36.43
Overall (I-squared = 79.0%, p = 0.000)
2.24 (1.58, 3.17)
100.00
NOTE: Weights are from random effects analysis
.00464
1
215


Study
ID
RR (95% CI)
%
Weight
1
Tabernero 2015
1.27 (1.17, 1.37) 13.92
Masi 2015
1.01 (0.73, 1.40) 3.02
Bennouna 2013
1.11 (0.99, 1.24) 11.44
Van Cutsem 2012
1.34 (1.24, 1.43) 14.58
Van Cutsem 2011
1.19 (1.10, 1.28) 14.36
Giantonio 2007
1.23 (1.09, 1.38) 11.23
Subtotal (I-squared = 56.5%, p = 0.043)
1.22 (1.15, 1.30) 68.56
2
Cohn(a) 2013
1.53 (1.09, 2.15) 2.88
Cohn(b) 2013
1.17 (0.80, 1.71) 2.33
Peeters 2013
0.94 (0.73, 1.22) 4.42
Subtotal (I-squared = 59.8%, p = 0.083)
1.17 (0.87, 1.57) 9.62
3
Peeters 2010
1.40 (1.23, 1.60) 10.09
Sobrero 2008
1.42 (1.28, 1.59) 11.73
Subtotal (I-squared = 0.0%, p = 0.855)
1.42 (1.30, 1.54) 21.82
Overall (I-squared = 61.9%, p = 0.003)
1.25 (1.17, 1.33) 100.00
NOTE: Weights are from random effects analysis
.466
1
2.15