Therefore, we do not believe that the omission of these studies poses a significant risk to the validity of this meta-analysis.

In regards to the similarities between our study and the study conducted by Mass et al. [6], we do acknowledge that all six of their cited radical prostatectomy studies were also included in our analysis. However, in contrast to Mass et al., the goal of our study was to compare the differential effect of statins on biochemical recurrence by primary treatment modality (radical prostatectomy as opposed to radiotherapy).

There was also concern that the study by Zaorsky et al. [7] may have heavily influenced the results of the meta-analysis due to their use of multiple logistic regression analysis. However, hazard ratios from survival analysis obtained from direct e-mail correspondence with the authors were used in our meta-analysis instead of odds ratios (Figure 2). In addition, we carried out an inference analysis demonstrating that omission of the data from this individual study, or any other one study, did not significantly influence our overall estimate of effect.

The inclusion of abstracts, in addition to full-text articles, was listed as acceptable in our Methods section. The use of the term 'full-text analysis' in Figure 1 was meant to indicate that we analyzed the full text of the 25 eligible articles if available, not that we limited our analysis to only full-text articles.

We wholeheartedly agree that this meta-analysis is not the final word on this subject, and should be updated frequently to include new articles in this rapidly evolving body of literature. We hope to inspire further research by generating new hypotheses that can explored in greater depth in the future, preferably in a prospective manner.

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references


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Not only chemotherapy in the second-line treatment of metastatic gastric cancer

We read with great interest the meta-analysis carried out by Kim et al. [1] focusing on second-line chemotherapy versus supportive care in advanced gastric cancer.

Being gastric cancer one of the major cause of cancer-related deaths, further improvement in the treatment of the disease is needed. Many patients with metastatic gastric cancer receive a first-line chemotherapy that usually consent a disease control for <6 months; the majority of patients after progression maintains a good performance status due to the improvements in supportive care and chemotherapy, and can be therefore candidates to further treatments.

Kim et al. [1] pooled together three trials evaluating chemotherapy versus best supportive care (BSC) as second-line treatment of patients with advanced gastric cancer enrolling a total of 410 patients: Thuss-patience trial using irinotecan; Kang trial with docetaxel or irinotecan; and Cook trial with docetaxel and Ramucirumab (Lilly Oncology, USA). A significant reduction of the risk of death was detected in the meta-analysis [hazard ratio (HR) 0.64; 95% confidence interval (CI) 0.52–0.79 P < 0.0001]; still a significant reduction of the risk of death was confirmed considering both docetaxel and irinotecan alone [1].

In addition to chemotherapy, new biologic agents have also been recently tested in pretreated metastatic gastric cancer patients; in particular, anti-VEGFR agents seem to be worthy of interest. Two randomized studies evaluating antiangiogenic agents in pretreated metastatic gastric cancer patients are available. In the first study by Li et al. [2] enrolling 144 patients, patients have been randomized to placebo (group A), or a VEGFR tyrosine kinase inhibitor, apatinib, at the dose of 850 mg daily (group B) or 425 mg twice daily (group C). The HR for overall survival for group B versus placebo was 0.37 (95% CI 0.22–0.62, P = 0.0001) and for group C versus placebo 0.41 (95% CI 0.24–0.72, P = 0.0017).

The second study by Fuchs et al. [3] enrolled 355 patients assigned 2:1 to receive ramucirumab (Lilly Oncology, USA) (n = 238), an anti-VEGFR-2 monoclonal antibody, or placebo (n = 117). The estimated HR for overall survival with ramucirumab was 0.776 (95% CI 0.603–0.988, P = 0.047). The combined HR for VEGFR inhibitors versus BSC is 0.51 (95% CI 0.3–0.87, P = 0.00001).

Putting together these results with those related to chemotherapy in a global meta-analysis, an interesting HR for the use of second-line treatment (chemotherapy or anti-VEGFR) emerges: HR 0.64 (95% CI 0.56–0.74, P < 0.00001) (Figure 1).
With these results, the role of further treatments after first-line chemotherapy in metastatic gastric cancer is reinforced. Two different options, chemotherapy and anti-VEGFR therapy, are available and confirmed efficacy in this setting. The combination of the two strategies as used in other cancers is promising and could become a new standard for second-line treatment of metastatic gastric cancer. The results of the RAINBOW trial, a phase III study evaluating ramucirumab in combination with paclitaxel versus paclitaxel alone, will add new information on this topic considering that the primary end point of the study of improved overall survival was met [4].

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Can tumor location predict effectiveness of bevacizumab conducted in the first-line setting for metastatic colorectal cancer
Bevacizumab has been confirmed to improve progression-free survival (PFS) when combined with chemotherapy for metastatic colorectal cancer (MCRC). Although some molecular markers were investigated to predict effectiveness of bevacizumab, none was clearly proved in clinical practice [1]. Boisen et al. [2] published an interesting paper, which suggested that tumor site could be a marker for the use of bevacizumab.

Boisen et al. [2] explained that vascular endothelial growth factor (VEGF-A), target of bevacizumab, was present in higher levels in left-sided colon and rectal cancers than in right-sided colon cancers, thus leading to higher effectiveness of bevacizumab in treating the former tumor than the latter. However, published study indicated that expression level of VEGF-A could not predict effectiveness of bevacizumab [1]. Thereby, the explanation by Boisen et al. for tumor location as a marker for use of bevacizumab may not be tenable.

The study method of Boisen et al. [2] may not be appropriate. They selected two cohorts of patients, one was treated with capicitabine and oxaliplatin (CAPEOX) from 2003 to 2006 and the other CAPEOX plus bevacizumab from 2006 to 2011. Results showed that tumor location was a significant predictor of oncologic outcome in the CAPEOX plus bevacizumab group, while no association was found between tumor location and survival in CAPEOX group. Could that prove tumor location predicted effectiveness of bevacizumab, though which differed in the two cohorts? In our opinions, their evidence was not convincible. To achieve their study goal, they may need to compare survival between patients who received bevacizumab combined with chemotherapy and those who received chemotherapy alone in subgroups of cecum and ascending colon cancer, right flexure and transverse colon cancer, left flexure and descending colon cancer, sigmoid colon, and rectal cancer. Or, they may just divided all the patients into two large groups, one group was with cancer of sigmoid colon and rectum and the other with tumor originating from cecum to descending colon. It is more suitable for them to compare baseline characteristics between patients who did and did

Figure 1. Meta-analysis of overall survival of second-line treatment versus best supportive care.

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Log(Hazard ratio)</th>
<th>SE</th>
<th>Weight</th>
<th>Hazard ratio</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thuss-Patience</td>
<td>−0.734</td>
<td>0.3324</td>
<td>4.7%</td>
<td>0.48 (0.25, 0.92)</td>
<td>2011</td>
</tr>
<tr>
<td>Kang, Docetaxel Arm</td>
<td>−0.2744</td>
<td>0.1813</td>
<td>15.8%</td>
<td>0.76 (0.53, 1.08)</td>
<td>2012</td>
</tr>
<tr>
<td>Kang, Irinotecan Arm</td>
<td>−0.543</td>
<td>0.193</td>
<td>13.9%</td>
<td>0.58 (0.40, 0.85)</td>
<td>2012</td>
</tr>
<tr>
<td>Cook</td>
<td>−0.4005</td>
<td>0.1607</td>
<td>20.1%</td>
<td>0.67 (0.49, 0.92)</td>
<td>2013</td>
</tr>
<tr>
<td>Fuchs</td>
<td>−0.2536</td>
<td>0.1285</td>
<td>31.4%</td>
<td>0.78 (0.60, 1.00)</td>
<td>2013</td>
</tr>
<tr>
<td>Li, Arm B</td>
<td>−0.9943</td>
<td>0.2643</td>
<td>7.4%</td>
<td>0.37 (0.22, 0.62)</td>
<td>2013</td>
</tr>
<tr>
<td>Li, Arm C</td>
<td>−0.8916</td>
<td>0.2803</td>
<td>6.6%</td>
<td>0.41 (0.24, 0.71)</td>
<td>2013</td>
</tr>
</tbody>
</table>

Total (95% CI) 100.0% 0.64 (0.56, 0.74)

Heterogeneity: $\chi^2 = 11.05$, df = 6 ($P = 0.09$); $I^2 = 46$

Test for overall effect; $Z = 6.20$ ($P < 0.00001$)