Title: In patients with unresectable colorectal cancer metastases, do chemotherapy with biologic agents result in a higher proportion of patients undergoing resection? A systematic review and meta-analysis.

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1. Need for a review: Problem to be addressed and background

Colorectal cancer is one of the most frequent malignancies in the western world with an overall 5-year survival rate over 60% but less than 5% in patients with metastatic disease. (1, 2) The most common site of distant metastases is the liver, with almost 50% of patients with colorectal cancer developing liver metastases. (3) Only 20% of patients with colorectal cancer liver metastases are able to undergo resection. These patients with metastatic disease who undergo resection have a 5-year survival of approximately 50%. (4) The other 80% of patients are not candidates for resection due to the extent of disease in the liver or due to extrahepatic disease and have a limited 5-year survival rate (0-5%). (2) Recently, newer chemotherapeutic agents using biologic agents have increased the survival for these patients while at the same time allowed patients who were previously considered to be not resectable, to undergo resection. (5, 6) The majority of these patients have liver-only disease, but there are some that have limited extrahepatic disease (lung, nodes, local recurrence) that also benefit from resection. (7)

It has been shown that first line chemotherapy for patients who are initially considered to be unresectable can achieve good results, leading to resection rates ranging from 5-20% depending on the population studied (i.e., liver-only disease vs. extrahepatic disease). (8) The variation in the proportion of patients who undergo resection lies in the different definitions of resectability across different institutions and countries and the type of chemotherapeutic regimens utilized. Most patients who are considered to be unresectable at presentation undergo chemotherapy with biologic agents as they have been shown to increase progression free and overall survival in this patient population. (6) A recent population based study showed that bevacizumab, the most widely used biologic agent in colorectal cancer is safe and efficacious in patients undergoing secondary resection (resection following chemotherapy); (9) however, the extent of its influence in resection rates is not well summarized as there have not been prior meta-analysis on the subject; therefore we embarked with this systematic
review to assess the added value of biologic agents to standard chemotherapeutic regimens as it relates to resection rates.

2. **Study Objectives**

*Primary objective:* To evaluate the proportion of patients with unresectable colorectal cancer metastases undergoing resection following chemotherapy with and without biologic agents.

*Secondary objectives:* 1) To evaluate the overall survival of patients with unresectable colorectal cancer who undergo chemotherapy with and without biologic agents. 2) To evaluate the progression free survival of patients with unresectable colorectal cancer metastases undergoing chemotherapy with or without biologic agents. 3) To evaluate the overall survival of patients with unresectable colorectal cancer who undergo chemotherapy with and without biologic agents who undergo resection. 4) To evaluate the proportion of patients with unresectable liver-only colorectal cancer metastases undergoing surgical resection following chemotherapy with or without biologic agents.

3. **Eligibility criteria / Study sample population:**

Patients over 18 years old with histologically confirmed metastatic colorectal cancer, with one or more measurable lesions, who are not resectable by local institutional criteria, ECOG status of 0 or 1, and no prior chemotherapy for metastatic colorectal cancer. Patients with prior surgery for colorectal cancer are eligible for the study.

4. **Intervention:**

Cytotoxic chemotherapy including but not limited to any combination of: fluoruracil, leucovorin, capecitabine, oxaliplatin, irinotecan or S1, with simultaneous use of one of the following biological agents divided into the following categories: antiangiogenics (bevacizumab, aflibercept and ramucirumab), antiepithelial growth factor receptors (EGFR) (cetuximab and panitumumab), multitargeted agents (regorafenib) and immunotherapy (pembrolizumab).

5. **Comparator:**

Patients receiving cytotoxic chemotherapy without the simultaneous use of any biological agents.
6. Outcomes:

*Primary outcome:* Proportion of patients with unresectable colorectal cancer metastases undergoing surgical resection following chemotherapy with or without biologic agents.

*Secondary outcomes:* Overall survival, progression free survival and the proportion of patients with liver-only metastatic disease undergoing resection.

7. Study questions:

a. What is the proportion of patients with unresectable colorectal cancer metastases undergoing surgical resection following chemotherapy with or without biologic agents?

b. What is the overall survival of patients with unresectable colorectal cancer metastases undergoing chemotherapy with or without biologic agents?

c. What is the progression free survival of patients with unresectable colorectal cancer metastases undergoing chemotherapy with or without biologic agents?

d. What is the overall survival of patients undergoing surgical resection for unresectable colorectal cancer metastases following chemotherapy with or without biologic agents?

e. What is the proportion of patients with unresectable liver-only colorectal cancer metastases undergoing surgical resection following chemotherapy with or without biologic agents?

8. Design: Only randomized controlled trials will be included.

9. Exclusion criteria:

Major surgery within 28 days of initiation of study intervention, radiation therapy within 14 days of initiation of intervention, patients on full dose anticoagulation, or patients with inadequate haematological, renal or hepatic function making them unfit to undergo chemotherapy or surgery.

10. Selected databases:

The following databases will be included in our review: Medline, Embase, Cochrane Central Register of Controlled Trials (CENTRAL) and PubMed. All languages will be searched. The pre-tested SIGN
filters (http://www.sign.ac.uk) will be used for randomized controlled trials for the MEDLINE and EMBASE searches (Appendix 1 and 2).

11. Grey literature:
The grey literature will be reviewed as follows: 1) Hand search of abstracts published by the American Society of Clinical Oncology in their journal: Journal of Clinical Oncology for the following meetings: ASCO-GI, ASCO and ASTRO. Abstracts published in the Annals of Surgical Oncology, as part of the Society of Surgical Oncology (SSO) meeting will also be searched. As well as a hand search of abstracts for the following meetings: European Society of Surgical Oncology (ESSO), European Society of Medical Oncology (ESMO), Japanese Society of Medical Oncology (JSMO), the European Society of Medical Oncology – Asia meeting (ESMO-Asia), the Chinese Society of Clinical Oncology (CSCO) meeting and the Federation of Asian Clinical Oncology (FACO) meeting. 2) Review clinical trials registries for relevant unpublished studies: clinicaltrials.gov, the International Standard Randomized Controlled Trial Number (ISRCTN) Register, and the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP). 3) The references of included studies in the meta-analysis will be reviewed to evaluate for potential studies to be included. 4) Experts in the field will be contacted to determine what studies they are aware of that meet the inclusion criteria.

12. Methods to ensure agreement:
There will be two independent researchers involved in selecting and reading abstracts and full papers to determine if they meet eligibility criteria for inclusion in the meta-analysis (P. Serrano and L. Ruo). Data from different sources, including Medline, Embase, Cochrane and Pubmed will be exported to a software called “endnote” in order to perform a duplicate screening of retrieved references’ titles and abstracts. Once the final list has been obtained, it will be distributed to the reviewers via a web-base software called “Distiller SR” (http://www.distillercom) in order to start the process of inclusion / exclusion of studies. For excluded references, a justification for the most important reason for exclusion will be documented. The full text of all references that are relevant will be obtained. For
those with discrepancies between reviewers, an in depth analysis will take place to see why one person thought it should or should not be included. After discussion we expect there will be agreement. If there is not, a third party reviewer will be consulted. We will use weighted kappa to assess agreement between reviewers on the selection of articles for inclusion, assessment of the certainty of effect and data abstraction. We will consider a Kappa statistic of >0.60 to be good.

13. **Risk of Bias**: For each selected study and outcome, the risk of bias will be assessed by two independent reviewers using the modified Cochrane tool. This is included in the Cochrane handbook Chapter 8. Risk of bias section 8.6. We will use the three point scale (low, unclear or high) for each outcome from each study selected. We will assess six domains for each outcome: sequence generation, concealment of allocation, blinding, incomplete outcome data, selective reporting, other biases (i.e. definition of resectability or definition of progression free survival). The results will be analyzed in RevMan.

14. **Heterogeneity**: Heterogeneity will be calculated using a statistical program (P value for Chi-squared for heterogeneity) and will also be informed using the $I^2$ statistic, following the recommendations of The Cochrane Collaboration, where a result between 0 to 40% indicates not important heterogeneity, 30 to 60% moderate, 50 to 90% substantial and 75 to 100% high heterogeneity.

15. **A priori hypothesis to explain possible heterogeneity**: This meta-analysis will pool widely, including different types of chemotherapy agents and biological agents, all with different effect sizes, although limited to a certain degree by including only chemotherapeutic agents that are currently known to be effective and are considered to be standard of care. Also the population may be different between studies (liver-only metastatic disease vs. extrahepatic disease). We expect to have high heterogeneity between studies due to the effect of pooling.

**A priori hypothesis to explain clinical sources of heterogeneity:**
• Diversity of interventions: patients treated with combination chemotherapy with FOLFOX (the combination of 5-FU, leucovorin and oxaliplatin) or FOLFIRI (the combination of 5-FU, leucovorin and irinotecan) will have a better resection rate and survival compared to those treated with single agents (5-FU, S1, capecitabine),

• Different patient population (liver-only metastatic disease vs. widespread metastatic disease, single focus of metastases vs. various foci, degree of involvement of the liver): we expect that studies who include liver-only metastatic disease patients will have a higher rate of resection compared to other studies that include patients with extrahepatic metastatic disease. We will perform a sensitivity analysis exploring the effect of adding biologic agents to chemotherapy in patients with liver-only metastatic disease excluding those studies that include all patients with metastatic disease.

• Different definitions of resectability across centers and studies: resection rates will be higher in high volume centers that specialize in hepatobiliary diseases compared to low-volume centers. We will perform subgroup analysis of studies that were performed in high volume centers and in low volume centers.

• Duration of follow-up: less than 2 years vs. more than 2 years: we expect that studies with longer follow up will have a higher resection rate. We will perform sensitivity analysis excluding studies with shorter follow up (less than 2 years).

A priori hypothesis to explain methodological sources of heterogeneity:

• Risk of bias: we will perform sensitivity analysis with studies with high vs. low risk of bias. We expect that studies with a higher risk of bias will show higher resectability rate.

• Missing data: sensitivity analysis will be performed comparing studies with missing data for the primary outcome vs. studies with complete data: we expect studies with missing data will show a lower proportion of patients undergoing resection.
16. **Data collection and missing data:**

Two independent reviewers will collect data using pre-defined data collection forms. The corresponding author will be contacted for relevant missing data. If after 2 weeks the corresponding author does not answer by email, we will contact the last author of the paper. If after 2 weeks there is no answer, we will call the first author and then the last author. If they fail to give an answer after two weeks of our last contact, we will acknowledge the missing data.

17. **Plans to summarize results (time-points for pooling data):**

We will use the statistical program Review Manager (RevMan) to calculate the effect sizes as the Cochrane Collaboration has endorsed this program. Data will be analyzed at the aggregate level. A quantitative synthesis is planned. The effect size will be stated along with a 95% confidence interval and presented as well in a graphical representation (i.e., forest plots). The pool estimates of effect will be calculated using random-effects model with Mantel-Haenszel statistics. The results will be presented as relative risk with 95% confidence interval for dichotomous variables and as mean difference or standardized mean difference when appropriate with 95% confidence interval for continuous outcomes. Potential publication bias will be analyzed using Funnel Plot. Subgroup analysis will be performed to assess for clinical and methodological sources of heterogeneity. We expect to finish with the different processes of review as follows: article assessment for eligibility: March 2016, Data analysis: May 2016, Manuscript writing: June 2016, Publication: August 2016.

18. **Assessment of confidence in estimates of effect:**

Two independent reviewers will evaluate the confidence of the estimates of effects using the GRADE approach ([http://gdt.guidelinedevelopment.org/central_prod/_design/client/index.html](http://gdt.guidelinedevelopment.org/central_prod/_design/client/index.html)).

19. **Reporting:**

This protocol will be published in PROSPERO ([http://www.crd.york.ac.uk/PROSPERO/index.asp](http://www.crd.york.ac.uk/PROSPERO/index.asp)). The final meta-analysis will be published in a peer-reviewed journal.
References


