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Title: Best available evidence related to clinical benefit of surgical resection in multimodality treatment of metastatic colorectal cancer indicates that a randomised controlled trial is warranted. (Letter in response to De Ridder et al 2016)

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Dear Editors

This letter is in response to the article (de Ridder *et al.*, 2016)

Tom Treasure

Reference List

de Ridder JA, van der Stok EP, Mekenkamp LJ, Wiering B, Koopman M, Punt CJ, Verhoef C, de Wilt JH (2016) Management of liver metastases in colorectal cancer patients: A retrospective case-control study of systemic therapy versus liver resection. *Eur J Cancer* **59** 13-21, doi:S0959-8049(16)00078-2 [pii];10.1016/j.ejca.2016.02.003 [doi]

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Meta-analysis of colorectal cancer follow-up after potentially curative resection

Contribution

Author(s)

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Data acquisition:	<i>"</i>
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"I confirm that all the authors have made a significant contribution to this manuscript, have seen and approved the final manuscript, and have agreed to its submission to the *European Journal of Cancer*".

Signed (corresponding author): *Tom Treasure*

Date: *4/8/2016*
4th August 2016

Letter in response to De Ridder et al(1)

Title: Best available evidence related to clinical benefit of surgical resection in multimodality treatment of metastatic colorectal cancer indicates that a randomised controlled trial is warranted.

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We applaud Dr De Ridder and colleagues for a formidable piece of work in search of ‘second best alternative’ evidence in the absence of controlled trials. From randomised trials of chemotherapy, they have matched 36 of 480 patients with 36 of 632 patients who underwent liver surgery. Their five-year survivals, estimated by Kaplan Meier analysis, are of the order of 20% and 40% respectively. The findings are in favour of inclusion of surgical resection in treatment. We write to comment on the applicability of the method and provide our perception of the limitations of the analysis. We conclude that the findings fall short of sufficient and robust evidence in themselves, but are a valuable published source for a sample size calculation for a randomised controlled trial (RCT) which would be fully justified by their findings.(2)

We have concerns about the applicability of the method in this instance. Matching studies open the opportunity to working on large existing data sets with completed follow up. For treatment comparisons they work best when, due to a difference in policy or availability of a treatment, some patients arbitrarily receive one, and some another, of two available treatments. The two treated groups can be considered as two circles of a Venn diagram. In the overlap are those who were treated in one way, but could have had the other. It is not as trustworthy evidence as blind randomisation but it is a route to exploratory analyses. In this instance all patients were carefully and expertly considered for one rather than the other treatment. Only recognised and documented features are on the available record. This was compiled in the full knowledge of whether the patients were selected for, and had a resection, or did not.(3) Randomisation avoids this shortcoming inherent in matching studies because it balances both known and unknown factors.

We also have concerns about the analysis. In full knowledge of the two treatment options, a decision was made to include or not include resection in the management in each of 1112 patients. Largely due to limitations on available data this number shrank to 458 who were ‘potentially eligible for matching’. (Fig.1a&b) Figure 2 shows the votes of three surgeons on resectability among 56 patients. In an RCT risk of bias is diminished and it is tested for in a meta-analysis.(4) It may not have been in this study. Were the ‘dedicated’ surgeons blinded to outcomes and was the whole analysis independently scrutinised? There was disagreement on resectability in 20 and lack of concordance about the resection strategy in a further 19. Whether one expects the more rigorous use of only 17 patients where a treatment decision was unanimous, or accepts the authors selected 36 patients on 2/3 majority votes, it is still a small and highly selected sample. These would be inadequate numbers for an RCT.

The researchers provide methods and hard-won results but there is a compelling argument for independent readers to be allowed to interpret and draw their own conclusions.(5) Our conclusion is that an RCT appears to be mandatory for this burdensome treatment. In 27 of the patients at least one or more of the surgeons would now use staged procedures including portal vein embolization or combination with radio-frequency ablation. RFA has been shown in a published RCT to confer no survival advantage: “The study shows that local tumor ablation by RFA in combination with systemic therapy results in an excellent survival, which however was also achieved in the control arm.”(6) There have been *no* RCTs of liver resection but there *have been* 16 randomised comparisons of more versus less intensive monitoring with the express purpose of earlier detection of metastases.(7) The findings are consistent and exemplified in the largest (N=1202 and 1228) most recently published (2014,

2016) and best conducted RCTs.(8, 9) Diagnosis of metastases is brought forward by 1-2 years, providing more opportunities for liver resection but no survival benefit was evident.

In 1992, among patient who had liver resection for colorectal metastases, five-year survival was of the order of 25%. Contemporary estimates were that five-year survival was near zero with best alternative treatments.(10) A published power calculation from the Mayo Clinic suggested that if control survival were to be set, for example, at 1% or 5%, the patient numbers required for an RCT would have been 36 or 74 patients respectively. (11) Scheele and colleagues dismissed the notion of a trial, opining that follow-up and registry studies made “any future demands for prospective trials on the general effectiveness of hepatic resection for metastatic colorectal cancer not only obsolete but unethical.”(12) In their discussion De Ridder and colleagues echo that statement, concluding “On ethical grounds, a true randomised clinical trial comparing both treatment strategies in patients with resectable CRLM has not been, and will not be performed.”(1) It should be noted that no formal or independent ethical consideration is referred to in support of the statements in either paper. In addition, since this is their practice, De Ridder and colleagues are prone to confirmation bias.(13) The evidence they have worked so hard to obtain remains a ‘second best alternative’ gained after the passage of twenty years. Even then it is a flawed version of its kind. What we need is an RCT in the zone of uncertainty.(2) We owe future patients resolution of that uncertainty. “Call randomised trials difficult, very difficult, or nearly impossible to do—but please do not call them unethical. It is the uncontrolled experiments that perpetuate unproven and potentially harmful treatments.”(14)

Reference List

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***Conflict of Interest statement**

No conflict of interest