Reviewer's report

Title: Histological response of peritoneal carcinomatosis after hyperthermic intraperitoneal chemoperfusion (HIPEC) in experimental investigations.

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Reviewer: Eelco de Bree

Reviewer's report:

In this paper the authors describe their evaluation of different treatment modalities for colonic peritoneal carcinomatosis, including hyperthermic intraperitoneal chemotherapy, in a rat model. This paper concerns a very interesting topic and certainly their study is original and may be of significant importance for clinical practice. In this experimental study, the population to be comparatively study is more homogenous than in any clinical study might be obtained. Although the study design seems adequate, the paper is poorly written and the introduction and discussion are insufficient.

Discretionary revisions = DR
Minor essential revisions = MER
Major compulsory revisions = MCR

It should also be interesting to measure in the histological slices the maximal distance of apoptotic cells from the tumor margin, to evaluate the cytotoxic penetration depth of the different treatment modalities. From the literature it is known that the penetration depth of intraperitoneal administered heat and chemotherapeutics is a few millimeters. Comparison of different treatment modalities in this experimental model seems to me very fascinating. (DR)

In the abstract of a manuscript with a title that promises data on histological response of peritoneal implants after intraperitoneal chemotherapy, histological outcome should be mentioned in the results and in the conclusion. (MER)

For the key words, ‘HIPEC’ has not yet become an established medical term and should be changed in ‘hyperthermic intraperitoneal chemotherapy’. ‘Colon carcinoma’ should be added. (MER)

In the ‘Introduction’ the rationale of (hyperthermic) intraperitoneal chemotherapy for peritoneal carcinomatosis from colorectal origin should be better described (see for example reference 13). To make the link with clinical practice, outcome of various phase II studies should be shortly mentioned. Since there is a recent randomized trial comparing systemic chemotherapy and palliative surgery, if necessary, with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy followed by systemic chemotherapy, results of such a trial should be referred to in detail in this era of evidence based medicine. The last sentence of the introduction should be omitted since the randomized trial already confirmed the results of clinical phase II trials. It seems difficult to confirm results of clinical studies by an experimental animal study. In stead, the authors should emphasize that human populations in clinical trials are always very heterogeneous and that even in a randomized trial the population in the treatment arms may differ significantly. Contrarily, in their experimental rat model potential differences are substantially less. Hence, the effect of treatment modalities can be effectively studied in this model. (MCR)

In the one but last paragraph ‘(Verwaal)’ is probably left in the text by mistake. (MER)

In ‘Methods’, in the first sentence ‘(Martin)’ should be omitted. The first sentences in the paragraph ‘Tumor model’ should be rephrased since the same information is mainly twice mentioned. (MER)

Regarding the treatment groups, the authors should choose for Latin or regular numbers and not use
them mixed. Because the groups are defined in ‘Methods’, they should not be explained again and again in between parentheses through the text. Because is stated that there are five groups if six animals, the number should not be repeated in between parentheses in the abstract, the methods and elsewhere. (MER)

It is unclear when treatment modalities were used. How many days after implantation of the cancer cells? In the abstract is stated that the rats were treated after 10 days of tumor growth. (MER)

The formula for calculation of body surface and its abbreviations should be explained. In the next sentence ‘totally’ should be added before ‘15 mg/m2’ to make the dosage clearer. The ‘sham operation’ could be described in more detail. What was exactly done? The treatment of group 5 should be described in detail. (all MER)

In ‘Results’ is stated that ‘The location and diameter of peritoneal metastasis (should be metastases) did not differ significantly among the five groups at the time of treatment’. However, in group 1 the abdomen was not opened and therefore it is impossible to make such a statement for this group. Probably, the authors meant this was the fact for the groups 2-5. In the next sentence the word ‘disfavorable’ could better be substituted by ‘adverse’. (MCR)

It is unclear to me what ‘port sites’ means in the heading of the second chapter of ‘Results’ and why it is added to ‘total tumor load’. (MCR)

Regarding the cancer index for the different groups it should be made clear that these are the mean values. (MER)

It is incorrect to refer to table 2 before table 1 is mentioned in the next. This is also the point for figures 1 and 2. (MER)

Generally, the text in ‘Results’ should be dramatically reduced since the majority of the data are noticeable in table 2. This duplication of data should be avoided. (MCR)

What is meant by the last sentence of page 9, concerning the fact that ‘tumor morphology did not change with aging of the rats’? Weren’t the rats sacrificed at the same day after treatment? (MCR)

In table 1 the left axis needs a legend. (MER)

Discussion. In the sixth sentence from below on page 11, the German word ‘Gruppe’ should be changed in ‘Group’ and in sentence 12 on page 12 ‘carcinomatosis’ should be added after ‘peritoneal’. (MER)

The same criticism as mentioned for the introduction consists as well for the discussion. (MCR)

The increased tumor load after sham operation in comparison with the control group should be discussed. (MCR)

The references should be written conform the guidelines of the journal and not in various arbitrary ways, omitting even sometimes the year published. (MER)

Finally, the manuscript should be linguistically reviewed.

What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

Level of interest: An article of importance in its field

Quality of written English: Needs some language corrections before being published

Statistical review: No

Declaration of competing interests:

‘I declare that I have no competing interests'