Author's response to reviews

Title: Cytoreductive surgery followed by chemotherapy versus chemotherapy alone for recurrent platinum-sensitive epithelial ovarian cancer (SOCceR trial): a multicenter randomised controlled study

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Author's response to reviews: see over
Dear Editor,

Thank you for your favourable response on our manuscript entitled “Cytoreductive surgery followed by chemotherapy versus chemotherapy alone for recurrent platinum-sensitive epithelial ovarian cancer (SOCceR trial): a multicenter randomised controlled study”. We highly appreciate that you are willing to review the manuscript after revision.

We are sincerely grateful to the reviewers because the comments have made a very valuable contribution to the improvement of this manuscript. We have revised the manuscript according to the suggestions of the two reviewers. In this letter we will address an itemized, point-to-point response to the comments of the reviewers. We have incorporated these comments into the revised version of the manuscript.

Please find enclosed the clean and marked version of our revised manuscript. Changes in the marked version are highlighted in red as tracked changes.

We hope you will consider our paper suitable for publication in BMC Cancer.

We are looking forward to hear from you. Please do not hesitate to contact us in case of questions.

Yours faithfully,

on behalf of all co-authors,

Rafli van de Laar, MD
Reviewers’ comments:

Referee #1

This is a well-designed, randomized controlled trial to investigate whether secondary cytoreductive surgery is beneficial for platinum-sensitive recurrence in patients with epithelial ovarian, fallopian tubal, and primary peritoneal cancer. Manuscript was well written. The analysis plan seems appropriate. The priority of this study is very high because there have never been a published RCT and the results of this may change the treatment guidelines. I have some questions and comments.

Comment 1: Line 40: Typographical error “Therefor” / Abstract: in Methods section, all “nine” gynecologic oncologic centers in the Netherlands will participate in this study.

Author Response 1: We thank the reviewer for noticing these imperfections. In the Methods section (page 2, line numbers 26 and 40) we performed the recommended corrections.

Comment 2: Line 121: “Platinum sensitive recurrence” should be defined more clearly. Is it the time interval between last chemotherapy and the first documentation of recurrence? In addition, recurrence between 6 and 12 months after completion of chemotherapy is “relatively platinum-sensitive recurrence”. If the patients had follow-up visit at 3 and 6 months after completion of chemotherapy and they showed recurrent disease in imaging study or CA 125 at 6 months after treatment, we cannot confirm that this is a platinum-sensitive recurrence. They might have recurrence between 4-6 months after treatment (It is platinum-refractory or resistant tumor). Therefore, I think that patients with recurrence free interval > 12 months would be included in this study.

Author Response 2: We thank the reviewer for the critical remark. In the Method section (page 6, line numbers 121-123) we added the exact definition of platinum-sensitive recurrence as stated in the SOCceR trial study protocol: “patients, ≥ 18 years, with first recurrence of platinum-sensitive (≥ 6 months after completion of front-line platinum-taxol chemotherapy) epithelial ovarian cancer, primary peritoneal cancer or fallopian tube cancer”. We agree with the reviewer that recurrence between 6 and 12 months after completion of chemotherapy is “relatively platinum-sensitive recurrence. Nevertheless, we decided to include these patients and chose this definition for platinum-sensitive recurrence because it is widely used in large chemotherapy only trials for recurrent ovarian cancer (Lancet 2003,361(9375):2099-2106 and J Clin Oncol 2012, 30(17):2039-2045) and in the GOG213trial (NCT00565851) and DESKTOP III trial (NCT01166737).
We believe that using the same definition and inclusion citerium will allow a better comparison of the outcome of the different trials. In the primary analysis we will also estimate the treatment effect by Cox’s proportional hazard (PH) regression model by adjusting for baseline covariates including disease free interval.

Comment 3: Line 130: The clear criteria for the possibility of complete resection should be presented to avoid possible introduction of selection bias. Or, all consecutive platinum-sensitive recurrent disease should be eligible for this study.

Author Response 3: We agree with the reviewer that we introduce selection bias by not determining specific criteria for complete resection. To overcome selection bias, at least partially, the inclusion criteria of the SOCceR trial are chosen according known prognostic factors for complete secondary cytoreductive surgery (ascites < 500 ml, ECOG performance status 0-1, complete or optimal primary debulking surgery). Moreover, the estimation if complete resection is possible will only be carried out by gynaecologic oncologists, who are certified as specialized gynecologists by the Dutch Society of Gynecological Oncology. In addition, randomisation will be stratified by center to adjust for differences in surgical skills.

In the GOG 213 trial (NCT00565851) and DESKTOP III Trial (NCT01166737) the estimation of complete resection is also left to the discretion of the gynaecologic oncologist.

Comment 4: The primary endpoint is disease-free survival. But, I wonder why the researchers took DFS as primary endpoint. The goal of secondary cytoreduction is to improve the overall survival of patients. The number of study subjects may be the concern. However, because the mortality of this study population is very high, the number of study subjects may not be many even if the overall survival is taken as primary endpoint of this study.

Author Response 4: We agree that the choice for overall survival as the primary outcome measure is the most appropriate for most patients. The main reason for not choosing overall survival as the primary outcome measure is the required sample size. Taking into account an alpha 0.05, power 0.8, median overall survival of 24 months in the control group, median overall survival of 30 months in the experimental group, accrual of 60 months and follow-up of 36 months, we need 395 patients in total. Unfortunately, we had to conclude that a study with this sample size is not feasible in the Dutch situation. On the other hand, progression free survival measures the real effect of adding secondary cytoreductive surgery to chemotherapy, not influenced by differences in treatment of second and subsequent recurrent disease.
Comment 5: Are IP chemotherapy and targeted therapy at primary treatment eligible?

Author Response 5: To maintain the patient group as homogeneous as possible, patients treated with IP chemotherapy and targeted therapy at primary treatment are not eligible.

Comment 6: Eligibility criteria should be defined in detail.

Author Response 6: We thank the reviewer for the suggestion. In the Method section we already mentioned all inclusion criteria of the SOCceR trial. We complemented the exclusion criteria:

Page 7, line numbers 135-140: “Exclusion criteria are non-epithelial or borderline ovarian tumours, platinum-refractory or resistant tumour, secondary or later recurrence, prior or already planned therapy with respect to recurrence, any disease, medical history or medication not allowing surgery and/or platinum based chemotherapy, concurrent treatment for other primary malignancy except for carcinoma in situ and basal or squamous cell carcinoma of the skin or participation in interfering trial”.

Comment 7: Chemotherapeutic regimen (dosage, interval) should be defined.

Author Response 7: Patients in both arms will receive at least six courses of platinum-containing chemotherapy. Chemotherapy dose and schedule, combination with other chemotherapeutic agents and pre-and post-chemotherapy medication and hydration is left to the discretion of the participating center. We expect that most medical oncologists will treat patients in both arms equally and according to our national guidelines [www.oncoline.nl](http://www.oncoline.nl). In the DESKTOP III trial therapy selection and performance is also the responsibility of the treating physician.

Comment 8: Line 229: Baseline QOL evaluation was not included.

Author Response 8: In the Methods section (page 8, line numbers 168-169) we mention the baseline QoL evaluation: “Patients in both treatment arms should be asked to fill out a baseline quality of life questionnaire (EORTC QLQ-C30 version 3.0 and QLQ-OV28, EQ-5D).” Furthermore we mention: “Health-related quality of life (HRQL) is one of the secondary endpoints in this study. It will be assessed with self-reported questionnaires (EORTC QLQ-C30 version 3.0 and QLQ-OV28, EQ-5D) to evaluate the impact of secondary cytoreductive surgery added to platinum based chemotherapy. The questionnaires have to be filled out after the sixth chemotherapy cycle and at 3, 6, 9, 12, 18 and 24 months following treatment” on page 11, line numbers 231-236.

Comment 9: Is there any plan for audit and monitoring of the study?
Author Response 9: We thank the reviewer for the critical remark.
In the Discussion section we added our safety reviews and monitoring plan (page 14-14, line numbers 299-319): “The SOCceR study has established an Independent Data Safety Monitoring Board (DSMB) comprising of independent experts who have no conflict of interest and agree with the outline of the protocol. The committee will meet once a year. Following this meeting, the DSMB will report to the Study Coordinators about (serious) adverse events, whether or not recruitment is on target and the compliance with the QoL assessments is adequate. The committee may recommend changes in the conduct of the trial and exclusion of a single center if excessive rates of morbidity are present. All data presented at this meeting will be considered confidential. During the study, the committee may decide to change the frequency of discussion.
Safety reviews are planned primarily to guard against unfavorable results in the experimental arm. Death and failure rates and SAE reports for both treatment arms will be closely monitored in order to pick up any (unexpected) trends. Safety reviews will be presented confidentially to the DSMB every six months, and/or at request of the DSMB. These biannual reviews will include data on number and causality of deaths, number of treatment failures and serious adverse events. The DSMB can recommend to modify or stop the study prematurely, if number and causality of deaths, number of treatment failures and serious adverse events are significantly greater than was foreseen in the literature. The assessment of the DSMB, will be presented to the principal investigators and will be reported in the annual progress report to the accredited Medical ethics Committee”.

Comment 10: Please discuss about the ongoing GOG’s trial: (GOG 213) “A Phase III Randomized Controlled Clinical Trial of Carboplatin and Paclitaxel (or Gemcitabine) Alone or in Combination With Bevacizumab (NSC #704865, IND #113912) Followed by Bevacizumab and Secondary Cytoreductive Surgery in Platinum-Sensitive, Recurrent Ovarian, Peritoneal Primary and Fallopian Tube Cancer.”

Author Response 10: We thank the reviewer for the suggestion. We added (page 16, line numbers 352-364) the paragraph Other clinical trials: “Currently, there are two other ongoing randomized controlled trials: the DESKTOP III trial (NCT01166737) and the GOG 213 trial (NCT00565851). The DESKTOP III trial will compare overall survival in patients with platinum-sensitive recurrent ovarian cancer with a positive AGO-score randomized to cytoreductive surgery followed by chemotherapy of physician’s choice versus chemotherapy of physician’s choice alone whereas the GOG 213 trial will determine if surgical secondary cytoreduction in addition to adjuvant chemotherapy comprising carboplatin and paclitaxel with or without bevacizumab increases the duration of overall survival of patients with recurrent platinum-sensitive ovarian epithelial cancer, primary peritoneal cavity cancer, or fallopian tube cancer. A better understanding of the real advantages and
disadvantages and patient’s selection criteria for secondary cytoreductive surgery will be achieved after the completion of these three ongoing trials”.

Level of interest:
An article whose findings are important to those with closely related research interests.

Quality of written English:
Acceptable.

Statistical review:
No, the manuscript does not need to be seen by a statistician.

Referee #2

Platinum sensitive recurrence in ovarian cancer patients is a very interesting research setting and that secondary cytoreductive surgery remains a questionable concept in ovarian cancer treatments. Then I think that AGO-SCORE and DESKTOP I and II trials demonstrated the superiority of surgery and chemotherapy alone in platinum sensitive ovarian cancer. Due to the retrospective nature of most studies reporting on secondary reductive surgery, we need to prospective studies for evaluate real effectiveness in term of progression free survival an overall survival in this setting.

The paper is well written and respects the CONSORT statement.

Comment 1: The paper however does not report any result but only describes its background, methodology and main objectives and I believe has not already started.

Author Response 1: Dear reviewer, the SOCceR trial has already started in July 2012 and is registered in the Netherlands trial register with number NTR3337 (www.trialregister.nl). Unfortunately we cannot report any result because accrual will take at least five years with additional three years of follow-up.