Author's response to reviews

Title: Neoadjuvant chemotherapy or primary surgery for stage III/IV ovarian cancer: contribution of diagnostic laparoscopy.

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Response to the referees’ reports

All changes in the manuscript have been highlighted in yellow.

Referee 1

1. Abstract-29, not 26 patients received neoadjuvant chemotherapy

Response to the comment 1. The number has been corrected.

2. Methods- indicate the management of neoadjuvant chemotherapy treated patients following their cytoreductive surgery. Did they stay on the same chemotherapy or did the chemotherapy change? How many cycles of chemotherapy in total were they to receive compared to those treated in a conventional fashion?

Response to the comment 2. Additional data has been provided on the neoadjuvant and adjuvant chemotherapy.

Methods (Study design, end §2)
Adjuvant chemotherapy always consisted of carboplatin and paclitaxel administered every 3 weeks. Six chemotherapy cycles were planned.

Methods (Study design, end §4)
After debulking, chemotherapy combining carboplatin and paclitaxel was subsequently administered to all patients.

Results (Primary Surgery, end §2)
The adjuvant chemotherapy regimen was carboplatin and paclitaxel in all 26 patients. The median number of adjuvant chemotherapy cycles was 6 (range, 1–9). Five patients died before completing the 6 cycles. Three patients with incomplete response to chemotherapy (abnormal CA 125 levels at the end of the 6 cycles) underwent 3 additional cycles of the same regimen.

Results (Neoadjuvant chemotherapy, last §)
After debulking, chemotherapy combining carboplatin and paclitaxel was administered to 20 patients until 6 cycles. For 5 patients with incomplete response to 6 cycles of carboplatin paclitaxel, a second line chemotherapy with gemcitabin or topotecan was administered. The remaining patient died post-operatively from the evolution of the disease before receiving the first post-operative cycle of chemotherapy. The median number of chemotherapy cycles was 8 (range, 4–16). The median number of post-operative chemotherapy cycles was 4 (range, 2–8).

3. Results- The three patients with significant medical comorbidities all died within one month of the first cycle of chemotherapy. What were the causes of their deaths? Were any deaths due to the chemotherapy?

Response to the comment 3. The causes of death have been clarified in the result section, end §2.

The causes of death were not related to the toxicity of the chemotherapy but to bowel obstruction in two patients and pulmonary embolism in one patient.

4. The authors indicated that in the conventionally treated group, those who underwent surgery by a gynecologic oncologist were 100% cytoreduced to no macroscopic residual disease, while those treated by surgeons not trained in gynecologic oncologic surgery were only able to optimally cytoreduce 33% of their patients. Who operated on the neoadjuvant chemotherapy treated patients? If both groups of surgeons were involved, was there a difference in the success in cytoreduction to no macroscopic disease following neoadjuvant chemotherapy?

Response to the comment 4. These questions have been replied in the results, neoadjuvant chemotherapy section, §3.
The surgeon’s expertise did not influence the probability of complete cytoreduction; cytoreduction was complete in 60% and 81% of cases when debulking surgery was performed by an oncologic gynaecologist and a non-oncologic gynaecologist respectively.

5. Discussion- Page 9. The authors state that half of their patients had Stage III or IV disease and were considered good candidates for primary cytoreductive surgery on the basis of diagnostic laparoscopy, yet according to Table 1 all of the stage IV patients received neoadjuvant chemotherapy. This statement should be clarified.

Response to the comment 5. Indeed, there is a misprint and this error has been corrected (§2).
Half of the patients, all of whom had stage III ovarian cancer, were considered to be good candidates for primary cytoreductive surgery on the basis of diagnostic laparoscopy.

6. The authors refer several times in the Discussion Section to the meta-analysis of Bristow, et al regarding the fact that the patients who underwent optimal primary cytoreductive surgery had a seemly better survival than those who received neoadjuvant chemotherapy followed by surgery, a finding also observed in this study. The authors should indicate that in the meta-analysis, as in this report, almost all of the studies were retrospective and non-randomized. Those who received the neoadjuvant chemotherapy had clinically worse disease than those chosen to undergo conventional therapy and should have been expected to have a worse survival.

Response to the comment 6. We agree that the meta-analysis results are mainly based on retrospective data. This has been clarified in the last § of the discussion. This can be explained by the inclusion of non-randomized studies in this meta-analysis [5]. Moreover, patients receiving the neoadjuvant chemotherapy had clinically worse disease than those chosen to undergo primary surgery and should have been expected to have worse survival.

7. Discretionary Revisions:
It would be nice to see the differences, if any, in the surgical experience of the two groups of patients, i.e. time of surgery, estimated blood loss, intensive care unit stays and the duration of hospitalizations.

Response to the comment 7. Unfortunately, these data are missing in our database.

8. There are two important messages in this paper. The first is that laparoscopy can identify those patients with advanced stage ovarian cancer who may be surgically cytoreduced to no macroscopic residual disease. The second is the importance of the operation being performed by a surgeon trained in radical cancer surgery. The conventionally treated patients had 100% cytoreduction following surgery by a gynecologic onoclogist while those not so trained only were able to cytoreduce 33% of the patients to no macroscopic disease.

Response to the comment 8. We totally agree with the comment and we re-wrote our conclusion according to the reviewer’s suggestions.
Our results support the use of diagnostic laparoscopy for identifying patients with advanced-stage ovarian cancer who are likely to benefit of primary surgery with complete cytoreduction, and the importance of the primary surgery being performed by an oncologic gynaecologist.

9. I believe this paper would be substantially enhanced if the authors refer to the latest Gynecologic Oncology Group reports that show the importance of the primary surgery cytoreducing the patients to no microscopic residual disease, rather than to 1cm or 2cm residual disease (J Clin Oncol 2007; 25:3621-7 and J
There was a dramatic difference in survival between no macroscopic residual disease and any residual disease for both stage III and Stage IV patients. Diagnostic laparoscopy may now allow us to select those patients who may be cytoreduced to no macroscopic residual disease by a gynecologic oncologist and identify those patients who should receive neoadjuvant chemotherapy.

Response to the comment 9. We totally agree with the reviewer. The recent data of the GOG have been added in §3 of the discussion section.

Although the definition of optimal cytoreduction remains debatable, it should be noted that the cut-off of 1 cm residual disease commonly used does not reflect major differences in terms of prognosis. Indeed, in a retrospective review of 1895 patients with stage III ovarian cancer carried out by the Gynecologic Oncology Group (GOG), patients with 0.1 to 1.0 cm and > 1.0 cm residual disease had a 2 – 2.5 fold increased risk of recurrence and death compared with patients with no macroscopic residual disease [20].

Referee 2

10. The authors report their experience with laparoscopy as a tool to assess the likelihood of complete tumor resection at primary diagnosis of advanced ovarian cancer. The findings of laparoscopy were then used to determine whether the patient was a candidate for primary surgery or neoadjuvant chemotherapy followed by interval debulking surgery. Following laparoscopy complete tumor resection was achievable in 100% and 33% of patients operated on by a gynecologic oncologist or gynecologist, respectively. This implies that the most important factor in determining the likelihood of optimal cytoreduction is the training and operative intent of the primary surgeon and not the laparoscopic findings. Most concerning is that the laparoscopic findings that led to “non-resectability and neoadjuvant chemotherapy” are loosely defined and not quantifiable (page 6 end 1st paragraph; diffuse, extensive).

Response to the comment 10. Effectively, referee 2 pointed out two main issues. Firstly, there are cumulative evidences to support the contribution of laparoscopy in evaluating the resectability of the disease. Fagotti et al. and our team have published data on this topic [Fagotti A et al., Ann Surg Oncol 2006; Brun JL et al., Gynecol Oncol 2008]. Moreover, the prospective study recently reported by Fagotti et al. confirms the usefulness of laparoscopy [Fagotti A., Am J Obstet Gynecol 2008]. But it is clear that further studies comparing new imaging techniques to laparoscopy are required to draw definitive conclusions. Secondly, we totally agree that the experience of surgeons remains the major determinant of prognosis in patients with advanced ovarian cancer. In this way, as the first referee suggested, we added data on the results of the GOG experience (discussion section, §3) and modified the conclusion (conclusion section).

See discussion section, §3. Although the definition of optimal cytoreduction remains debatable, it should be noted that the cut-off of 1 cm residual disease commonly used does not reflect major differences in terms of prognosis. Indeed, in a retrospective review of 1895 patients with stage III ovarian cancer carried out by the Gynecologic Oncology Group (GOG), patients with 0.1 to 1.0 cm and > 1.0 cm residual disease had a 2 – 2.5 fold increased risk of recurrence and death compared with patients with no macroscopic residual disease [20].

See conclusion section. Our results support the use of diagnostic laparoscopy for identifying patients with advanced-stage ovarian cancer who are likely to benefit of primary surgery with complete cytoreduction, and the importance of the primary surgery being performed by an oncologic gynaecologist.

11. As a result they are difficult to validate in another patient population. The fact the a higher mean body mass was seen in the patients chosen for interval cytoreduction implies that
factors other than tumor extent effected the surgeons willingness to perform primary cytoreduction. I find this difference hard to explain.

Response to the comment 11. We agree with the comment of the reviewer but as this difference of BMI is only marginal (P=0.048), it is not therefore possible to draw any conclusion on the influence of obesity in the choice of surgical strategy. Moreover, when we consider the number of patient with obesity (BMI ≥ 30), there is no difference between both groups (2 patients in each group). This has been added in table 1.

12. The follow-up of the patients is too short with 24 month survival reported. Since survival can be altered by secondary treatments progression-free survival would be a more accurate way to assess the effect of primary therapy. The size of the study is small and no power calculation is provided to tell us the likelihood of a significant difference being missed in this patient population.

Response to the comment 12. Effectively, the follow up might appear relatively short but in advanced ovarian cancer, the vast majority of recurrences occur during the two first post-therapeutic years. As suggested, we underlined in our manuscript the short follow-up of this retrospective study explaining why no power calculation is required. See last paragraph of discussion section. Although no significant difference was observed in our study, probably owing to a small sample size and short follow-up, survival tended to be better after primary surgery than after interval surgery among women who had complete cytoreduction. Probably due to the same limits of the study, no such difference was observed between the patients with residual tumours after primary and interval surgery.

13. Surprisingly, only 55 patients were seen by the authors over 5 years suggesting this is a relatively low volume center.

Response to the comment 13. Effectively, the number of patients might be considered as relatively low for a five year period. However, we focused exclusively on advanced stages and epithelial malignant tumours. When we consider all patients referred with ovarian malignancies whatever the stage and the histological type in the same period, 177 were operated on. In addition, in accordance with INCa (National Institute of Cancer in France), the minimum number of ovarian cancer cases per center should be over 15. Finally, since the end of the present study, at least 40 ovarian cancer patients are operated each year in our department, representing one of the most important gynecologic cancer centers in France.

14. Although residual disease has been identified as an important prognostic factor in numerous prospective and retrospective studies the authors state in the last sentence of the results section that the size of the residual disease had no effect again implying that the report is underpowered.

Response to the comment 14. In the last sentences of the result section, we underlined that survival was better after complete cytoreduction in the primary surgery group than in the neoadjuvant chemotherapy group. In contrast, for patients with macroscopic residual disease after primary surgery, no difference was observed between patients treated by first attempt of cytoreductive surgery and those treated by neoadjuvant chemotherapy. These results underlined the strong impact of the surgical effort in ovarian cancer and the requirement to evaluate adequately (maybe by first laparoscopy) those who have a high likelihood of complete cytoreduction. However, we specified in the discussion section that the sample size of the present study could explain the absence of difference in survival between patients with macroscopic residual disease after primary surgery and those treated by neoadjuvant chemotherapy (see last part of the discussion).