Author's response to reviews

Title: Under-treatment of elderly patients with ovarian cancer: A population-based study

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Author's response to reviews: see over
Montpellier, 22 July 2015

Re: MS: 3668629641689952
TITLE: “Under-treatment of elderly patients with ovarian cancer: a population based study”
AUTHORS: Elisabeth Fourcadier, Brigitte Trétarre, Claudine Gras-Aygon, Jean-Pierre Daurès, Faïza Bessaoud

Dear Editor in Chief,

Please find enclosed a revised version of our article entitled “Under-treatment of elderly patients with ovarian cancer: a population based study” which we would like to re-submit for publication in BMC cancer.

We would like to thank the reviewers and the editor for the constructive critique. We have studied the reviewer’s suggestions in detail, and have made the appropriate changes in the revised manuscript (modifications shown in red). We believe that these suggestions have helped to substantially improve the quality of our paper.

You will find enclosed in a separate file our point-by-point responses to each comment, detailing the relevant modifications made.

We hope that this paper will now be considered suitable for publication, and we look forward to hearing from you again in due course.

Yours sincerely,

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Title: “Under-treatment of elderly patients with ovarian cancer: a population based study”

Authors: Elisabeth Fourcadier, Brigitte Trétarre, Claudine Gras-Aygon, Jean-Pierre Daurès, Faïza Bessaoud

Responses to Referees’ Comments

Referee 1 (Elona Juosaityte)

1. The data were obtained from tumor registry and all cases of ovarian cancer were validated through systematic verification across original medical records. The incomplete clinical information with regards the study population is the major limitation of this study. For example: no information about comorbidities, not full patient’s survival data (survival analysis focuses on 389 death and 206 censored from 1151 cases), big amount of unknown histology and tumor grade. Are the possibility to upgrade the information from medical records? It would be very helpful in order to know clear situation.

We agree with the reviewer that the missing comorbidities information is a major limitation of this study. However, this population-based study included all cases recorded in the Department over many years (1997-2011). Unfortunately, data regarding comorbidities, functional status or performance status are not systematically recorded in the registry. These data are sometimes recorded for the purposes of specific studies performed over a short time period (generally, one to two years from diagnosis). The more longitudinal study we present here does not fall within this category, and therefore, does not record this type of data in the permanent cancer registry.

Regarding the vital status, given the huge amount of data recorded, follow-up of vital status is only completed in an exhaustive manner every 5 years. At the time that this analysis was performed, the survival data was only available for the years 1997-2004, with a cut-off date (date of last news) in 2008. The data have been updated in the meantime, with survival data available for the period 1997-2010, with a cut-off date at 30 June 2013. We have therefore updated the results of the survival analysis with these new data. The results have been modified accordingly, as well as the relevant figure.

The new results show that there is a significant difference in survival between groups (p<0.0001 by the log rank test). Survival in elderly patients who did not receive guidelines-recommended therapy did not differ significantly from that of younger patients who did not receive guidelines-recommended therapy, when survival was ≤10 years (p=0.20). When survival exceeds 10 years, the difference between these two groups is significant (p=0.02).
Regarding tumour stage and grade, we indeed noted a high proportion of advanced stage or unknown grade cancers, despite having verified the medical records. However, the rate of missing data in our study is similar to that of other reports in the literature. The same is also valid for the histology, where our rate of 6.7% unknown histology compares favourably with other similar studies published in the literature, and which reports rates varying from 4 to 19% (1-3). The overall percentage of cases with unknown stage was <5%. In other reports in the literature, this rate varies from 4 to 29% (5% (4), 25% (5), 3% (2), 29% (3)). As regards the grade, the rate of unknown grade is admittedly higher in our study, although in the literature, when reported, the rate varies from 25 to 51% (1,5,6). However, it should be underlined that in our study, the rate of missing data decreased over time, which probably reflects improved data collection and histopathological reporting in recent years. Indeed, the proportion of unknown grade decreased from 66% in 1997 to 40% in 2011, although the rate remains higher among patients aged over 70 years (70% in 1997 and 46% in 2011 in those aged >70 years, vs 62% in 1997 and 36% in 2011 for patients aged <70).


2. Abstract- in general is acceptable.
Thank you.

3. Background- acceptable. In my opinion- additional file (table 1 „Consensus treatment guideline of ovarian cancer”) is very primitive and also needs grammatical correction -„treatment, guideline.” I would recommend to remove this additional file (table 1) and make the disease management more clear in the text.

We agree with the reviewer. Table 1 of the additional file has been removed, and the information has been included in the revised manuscript as follows:
Treatment strategy depends on the tumour stage and grade. Surgery is generally the first line treatment, with a view to full tumour resection. Surgery alone may be sufficient to treat early grade cancers (stages IA/IB and grade 1). For intermediate stage cancers (stages IC, II, III and grades 1-3), surgery is followed by chemotherapy with a view to eliminating any residual cancer cells and reducing the risk of relapse. When the tumour is diagnosed at an advanced stage (stage IV), chemotherapy may be performed before surgery to reduce the size of the tumour before resection, or may be used as a stand-alone approach.

4. Methods. Explanatory variables- this section is too long. In my opinion, it is not necessary to explain in details TNM classification, pathological classification, staging of ovarian cancer, because the readers of „BMC Cancer” are educated in this field.

We agree with the reviewer. The relevant paragraph has thus been shortened as follows:

“Tumor stage was recorded and classified into four groups according to the TNM classification system and International Federation of Gynecology and Obstetrics (FiGO) staging system (UICC 6th edition). In our study, tumour histology was classified according the World Health Organization (WHO) classification and grouped into epithelial type; other; or “unknown histology”, when there was no microscopic confirmation or no histological testing.

5. Results. It is not clear whether the analyses were sufficiently powered. Presented Kaplan Meier curves showing the survival results of study population do not include p – values from long –rank tests (fig. 1). Median survival of 595 women
was 34.4 months. Survival of the patients by stage of the disease would be very helpful to understand the quality of ovarian cancer care. This study highlight the incomplete diagnostic and complex management for ovarian cancer patients. For example – among operated patients – no histology for 1 and unknown grade of tumor for 469 patients (71.1%), unknown stage of the disease-32 patients, etc. (table 2). No standard treatment availability for 30.2% of young and for 47.9% of elderly patients.(table 5).

We agree with the reviewer, and have added the p-values from the log rank tests. They show that there was a significant difference between groups by age and by adherence to guidelines-recommended therapy. The reviewer raises an interesting point in suggesting a survival analysis by cancer stage. However, the main objective of the study was to investigate whether management practices varied according to age, with all other factors being equal (i.e. adjusted for other factors). Therefore, we did not perform survival analyses per stage. However, we do agree with the reviewer that the survival analysis is an important aspect that would merit further investigation, in particular with analysis by cancer stage, and analysis of relative survival for ovarian cancer.

Our working hypothesis was that management practices differ among elderly vs younger patients. Based on our data, we show that diagnostic tests (grade, stage, histology) are more often overlooked in elderly patients vs their younger counterparts (Table 1). Indeed, the fact that there are many patients with unknown histology or unknown grade is precisely the reflection of this phenomenon, as this indicates that the diagnosis is not pursued in detail to obtain this information in elderly patients. This could also be explained by the fact that the group of patients who underwent surgery comprises patients who had surgery after having chemotherapy, which may render analysis of the surgical specimens more difficult, or even impossible, thus leading to more missing data.
1. Discussion. The findings of the study highlight the pure situation in complex diagnosis and management of ovarian cancer patients. Please make it more clear in the discussion.

We have emphasised this point more in the discussion, adding some arguments regarding the missing information from the diagnostic tests. We hope that this is now clearer. We would welcome any further suggestions from the reviewer for points to include.

**Minor Essential Revisions**

1. Several grammatical errors that need to be corrected throughout the manuscript.

3. The article needs more language correction than these few points. The manuscript has been thoroughly revised by a native English-speaking medical writer. We would be happy to correct any grammatical errors that the reviewer would care to point out.

2. Table 1 „Age - 70 years“, please correct „> 70 years“.

Thank you for pointing out this mistake. This has now been corrected.
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**Referee 2 (Sigita Liutkauskiene)**

1. The questions posed by the authors in this article are not clearly defined and incorrect. Based on the results that are presented, one may assume that the authors posed the question about the influence of age on ovarian cancer treatment modality. This issue not important and key. The key issue according presented inconsistent and confusing data must be treatment modality’s influence on clinical outcomes of elderly patients. This question must be more analyzed in introduction, results and discussion sections.

The main objective of this study was to show that (1) elderly patients less favourable cancer characteristics, with more advanced stage at diagnosis, and fewer diagnostic tests; and (2) that treatment is sub-optimal insofar as the therapeutic strategy is often less aggressive, and guidelines-recommended therapies are less often applied. We believe that our findings illustrate both these points. There are several factors that could explain these results, such as refusal of the patient to receive treatment, physician choice of treatment strategy, or the presence of risk factors and/or comorbidities. Clearly, our study cannot investigate all these points, and this is one of the limitations of this analysis. However, we do believe that our study highlights the disparities in diagnosis and treatment among elderly patients that has often been observed in recently years. This is important, since elderly patients represent around 60% of all cancer patients, but yet are often excluded from clinical trials.

2. The data presented in the abstract, results and discussion parts, tables, graph are inconsistent and confusing.

Thanks to the suggestions from both reviewers, the manuscript has now been revised, and we hope that the data are now presented more clearly.

3. The data was obtained from the tumor registry in the Hérault department. Inclusion criteria must be clearly and exactly described. It would be helpful to know what methods were used to identify the patients that were treated with surgery, chemotherapy or surgery and chemotherapy. A consort diagram showing the flow of the cases used for analysis would be helpful in justifying the case selection.

As with all exhaustive cancer registries, there were no selection criteria for this study, as there may be for a clinical trial, for which CONSORT diagrams are usually used. The reviewer is correct in indicating that the CONSORT flow-chart is useful for analysing inclusion and exclusion criteria, and actual treatment and/or adherence to randomization groups. However, we report here findings from the cancer registry of the Herault Department, which by definition includes systematic and exhaustive recording of ALL cancer cases diagnosed in the Department from 01 January 1997 to
31 December 2011. The objective is to show that treatment strategies vary according to age. This is therefore a population-based registry study, with no sampling or selection bias. Information about the treatment strategies for each patient were obtained from the medical files of each patient in the relevant hospital unit where the patient was treated.

4. While the authors attempt to state that elderly women with ovarian cancer were undertreated, it is not clear the influence of undertreatment of elderly patients on overall survival. First of all, presented Kaplan Meier curves (Figure 1) showing these results are misleading as the graphs do not include p-values from log-rank tests.

We agree with the reviewer, and the p-values from the log-rank test have now been included on the Kaplan-Meier curves. Furthermore, and in response to a similar comment from another referee, the survival data have now been updated to include a longer time period. Indeed, at the time that this analysis was performed, the survival data was only available for the years 1997-2004, with a cut-off date (date of last news) in 2008. Follow-up of vital status is completed in an exhaustive manner every 5 years in this registry, and the registry data have now been updated for the next 5-year period, with survival data available for the period 1997-2010, with a cut-off date at 30 June 2013. We have therefore updated the results of our survival analysis with these new data. The results have been modified accordingly, as well as the relevant figure. The new data, and p-values from the log-rank tests show that there is a significant difference between groups by age, and by adherence to guidelines-recommended treatment strategies.

Secondly, including comorbidities, age, performance status and other prognostic factors in univariate and multivariate analysis is needed to establish the reason of possible less overall survival of undertreated elderly patients. Consequently, the statement that ,,the elderly patients in whom guidelines-recommended treatment was not applied had poorer likelihood of survival as compared to elderly patients who received guidelines-recommended therapy, and as compared to younger women“ was not statistically proven.

We agree with the reviewer that the lack of information regarding comorbidities is clearly a major drawback of this analysis. However, this population-based study was performed on an exhaustive registry of all cancer cases in the Herault Department over a long period of time. Unfortunately, data regarding comorbidities, functional status or performance status are not systematically recorded in the registry. These data are sometimes recorded for the purposes of specific studies performed over a short time period (generally, one to two years from diagnosis). The more longitudinal study we present here does not fall within this category, and therefore, does not record this type of data in the permanent cancer registry.

5. The manuscript do not adhere to the relevant standards for reporting and data deposition, presented data in the tables 2 and 3 do not represent the content of the article and the questions posted by authors
We agree with the reviewer that the main factor of interest in this study was treatment differences according to age. However, as other authors have done in previous reports (Hershman, Jordan), we chose to display the data regarding certain adjustment variables in order to illustrate the potential confounders. We can clearly see that the variable “Surgery” is intricately linked to the histology, the grade, and stage, but also the place where the patient was treated. These factors are also linked to age. By displaying all these factors and taking them into account in the multivariate analysis, we can see that the impact of age on the choice of treatment strategy is independent of all these factors.