Author's response to reviews

Title: Quality indicators for colorectal cancer surgery and care according to patient-, tumor-, and hospital-related factors

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

Thank you for your comments and review of our manuscript. We have considered all comments and modified the manuscript accordingly, with the addition of some new data. In these revisions we enlisted the help of a representative of the local Cancer Registry (Dr. Gaëlle Coureau), in particular to obtain new data, and we would like to add this person to the list of authors. We hope this will be acceptable.

Please find below point-by-point responses to the reviewers’ concerns. We thank you for your time in considering this revised manuscript.

Best regards,

Prof Simone Mathoulin-Pélissier

Reviewer 1: Ryan Merkow

Reviewer’s report:

Major Issues:
1. I think the primary issue is that based on these data we do not know whether the results were actually related to the implementation of the guidelines, as this report does not evaluate care over time, specifically the time period prior to the implementation of the guidelines. In addition, it is hard to believe that these guidelines impacted treatment decisions drastically in such a short period of time (12 months following there implementation). It would be helpful to see any trends over time, if possible.

Authors:
Indeed, our study design does not allow us to conclude whether there was a direct link between implementation of guidelines and changes in care practices. The main objective of this study was to provide comprehensive data and quality indicators on colorectal cancer care practices and compliance with guidelines just after implementation. A similar study is ongoing (EvaCorr) which should enable us to evaluate trends.

As we are unable to provide trends data from our own research, we propose to provide trends data from an extensive literature search of similar data in comparable French regions. We identified four relevant studies (not previously referenced) that report rates of multidisciplinary discussion, examination of ≥12 lymph nodes, and chemotherapy use in stage II and III patients from data collected between 1990 to
2004. Note that this was the most recent data available, with a recent 2012 article publishing data collected in 2003/2004.

From the revised discussion:

“In terms of interpreting whether the results reported here specifically reflect improvements after implementation of guidelines, with this observational design we cannot infer a definite causality link, although all efforts were undertaken to widely and comprehensively distribute guidelines as described in the methods. To provide an indication of trends in practices across time in France, we collected information from four comparable studies performed between 1900 and 2004 [1-4]. We note that the general trend for chemotherapy use in stage II patients did not change between 1990-1999 (21.8%)[1] to 2000 (20.4%)[4] and 2003/2004 (20.6%) in the present study. For stage III patients, the trend is towards an increase in the use of chemotherapy with usage reported at 46.9% in 1990-1999[1], 61% in 2000 [4] and 71% in our study. Discussion in multidisciplinary meetings also appears to be on the rise. In 2000, between 32.2% [2] and 60.6%[4] of patients’ files were discussed in multidisciplinary meetings, compared to >85% in our series on the whole. We expect that with the creation of the National Institute for Cancer (INCa) in 2005 and standardized national guidelines, this trend has probably continued. Finally, trends in inspection of ≥12 LNs appear to be increasing with 45.2% compliance in 1997-2004 [5] compared to 70.8% in our study.”

We hope that these indications of trends and modified discussion will be acceptable to the reviewer.

2. The authors state that the guidelines were implemented, but it appears all that was done was they were mailed to practitioners. How do the authors know they were implemented? This may need some clarification and further discussion.

Authors: Implementation of the guidelines involved mailing the guidelines to 10 local cancer units, the regional multidisciplinary team and a summary to over 6000 registered physicians, as described on page 5. However, of course, without directly questioning the practitioners, we cannot be sure that these results reflect a causality link with the implementation of guidelines. We have added a sentence covering this in the limitations section:

“In terms of interpreting whether the results reported here specifically reflect improvements after implementation of guidelines with this observational design we cannot infer a definite causality link, although all efforts were undertaken to widely and comprehensively distribute guidelines as described in the methods.”

3. The authors should be careful calling use of adjuvant chemotherapy in stage II patients “overuse.” As they state, it is currently accepted that certain high-risk stage II patients receive adjuvant therapy so this analysis is less relevant. It may be appropriate to leave this analysis out of the manuscript.

Authors: Yes, we agree that perhaps the term ‘overuse’ is too strong and we have replaced with more neutral use of ‘use’ or ‘high use’ as appropriate. However, we feel that while this broad analysis of all stage II patients lacks the complexity of current indications, it is still relevant to explain practices, in particular because it validates the factors included in the current international practice guidelines. For example, our data show that use of chemotherapy in stage II patients is associated with younger age,
greater extension and emergency situations which are all factors included in current guidelines for chemo use for these patients.

Minor Issues:
1. In the introduction the authors state that by performing this study the 27 criteria to assess colorectal cancer care will be validated. This was confusing and perhaps the authors could expand on how these criteria were validated – which usually entails a scientific method such as RAND/UCLA methodology etc.

Authors: In this paper we use the ‘nominal group’ method for group consensus (BMJ 1995;311:376). There were three expert group meetings where experts met to confirm and validate criteria (one meeting for each stage: Diagnosis and preoperative work-up, Surgery and pathological report, and Multidisciplinary team approach). There is an ongoing study that has used the DELPHI consensus method in the same Aquitaine and Midi-Pyrenees regions that has validated and maintained 26 of the 27 criteria.(EvaCCoR)

2. The statistical analysis was nicely described in the methods. Did the authors consider developing a model where the dependent variable was a composite measure of all guideline therapies? This may (or may not) reveal additional important associations.
Authors: No, we chose not to create a composite measure as we did not wish to mix the three different stages of treatment and areas of (non)compliance. We wanted to investigate compliance by stage to reflect the stage-by-stage nature of treatment, rather than a global measure which would be more difficult to interpret in particular for practitioners. This method was chosen because the main objective of the study was to provide useful information for practitioners and to propose focussed interventions in the case of non-compliance.

3. Table 2: For lymph node evaluation, the percentages add up to >100%. This needs some clarification.
Authors: Thank you. This has been corrected, the label values had not been corrected and these actually present the two categories ≥8, and ≥12.

4. Table 3: I would prefer to see point estimates and confidence intervals (with or without p-values) for both univariate and multivariable analyses.
Authors: OK, the 95%CI for univariate analyses have been added to Table 3.

Reviewer 2 : Karen Sherman
Reviewer's report:
Major Compulsory Revisions:
[ 1] In the introduction, the authors state they will validate the use of the 27 criteria to assess quality of colorectal cancer care; however not all 27 factors appear to be included in the model. Please explain.
Authors: As described in the study objectives, 27 criteria were developed and validated to assess the quality of colorectal cancer care. The first section of the results describes % compliant with various criteria. The three statistical models used are not to validate the criteria but to assess associations between practices and three particular factors that have been linked to survival in the literature. These are two separate measures, one of the quality of care and one of the associations between three practices linked with survival and various factors. This was probably not clearly explained in the objectives and we propose a revised text as below:

“In doing so, we will use 27 criteria to describe the quality of colorectal cancer care. We will also propose three statistical models investigating the factors linked to three specific quality indicators identified by the National Quality Forum/American College of Surgeons/Commission on Cancer and National Comprehensive Cancer Network/American Society of Clinical Oncology[6] and potentially linked to better survival: ≥ 12 lymph nodes (LN) examined [7,8] and adjuvant chemotherapy use and non-use for stage II [4] and stage III patients[9]."

We have also modified the description under the data and statistical analysis section:

“Firstly, the quality of care is described using demographic data, tumor characteristics and 27 (11+16) care management criteria presented as percentages. For patient age and management delays, we report medians. Secondly, statistical models are proposed for 3 specific practices: Univariate analyses (χ2 or 2-sided Fisher’s exact tests) were performed to identify associations between the three practice variation factors potentially linked to survival in the literature [7-10]”

[2] The writing style is generally unclear and verbose and organization is lacking. I recommend revisions to improve general clarity, conciseness, and organization.

Authors: We have fully revised the text to simplify and reorganise.

Minor essential revisions:

[1] Table 1, colon, ECOG score >1 should be 11.5
Authors: Thank you, this has been corrected.

[2] List of Abbreviations, page 16, ECOG = Eastern Cooperative Oncology Group or CECOG= Central European Cooperative Oncology Group
Authors: Thank you, this has been corrected to Eastern Cooperative Oncology Group

Authors: This unclear term has been removed and the sentence simplified to: “Compliance was high for resection, pathology report, LN examination, and chemotherapy for stage III.”

[4] Please clarify how hospital volume was determined.
Authors: As mentioned in the methods, hospital volume for CRC procedures was defined as either lower than or greater than or equal to 30 procedures per year (p.7: hospital volume for CRC procedures ($\leq 30$ procedures per year));). This is the threshold as defined by the French Cancer Plan II, under which hospitals are not authorised to perform surgeries (explained in discussion, p15).

Discretionary Revisions:
Adoption of evidence based guidelines is variable, but can many years before practice patterns change. In this study, the authors chose to evaluate treatment patterns during the first year after implementation. How did adherence change in the subsequent years?

Authors: As mentioned previously in response to reviewer 1, we are unable to provide trends data for this study although a follow-up study is underway. We have provided data from four additional studies for four quality indicators that give an indication of patterns across time (from 1990 to 2004, the most recent data available). The only indication of future trends that we have is in one region, from registry data where we see that multidisciplinary discussions increased between 2005 and 2008 from 48% to 63%. This is most probably a direct result of the establishment of the National Cancer Institute (INCa) and development of national guidelines.

Reviewer 3: Michael McGee

Reviewer's report:
Major Compulsory Revisions:
(1) Why did it take 7 years to compile and publish this data? All endpoints are short-term and there are no long-term survival endpoints that would require 7 years to put this data together. A reader may want to know why this older data is still relevant. Is this data is still relevant? Please address this concern in the discussion or methods.

Authors: Indeed, this is a limitation of the data that has been mentioned in the discussion. The reason behind this publication lag is twofold: Firstly, the initial focus was to provide this public health data to the hospitals and inform practitioners on a local level, and secondly, we endeavoured for some time to collect survival data but this was impossible due to limitations imposed in France at the time by the French Comité National de l'informatique et des libertés (CNIL). However, this data is still the most recent data to be published describing practices in France in colorectal care (compare to recent publication Dejardin et al, Dig. Liver Dis. 2012 reporting on data collected in 2003-2004) and the methodology is still particularly relevant for quality assessment, eg. definition of quality criteria, data collection, intervention. All major criteria developed remain valid for practices today that are now monitored and influenced by guidelines from the National Institute for Cancer (INCa, set up in 2005) (apart from MRI use and stage II chemo administration as mentioned in the text).

Minor Essential Revisions:
1. The authors report only 53% of patients of rectal cancer patients were staged locally with ultrasound without mention of MRI. Does this mean that only 53% of rectal cancer patients were locally staged? If so, this is a very low percentage.
Are there a percentage of patients that were staged with MRI? Instead of classifying the percentage of patients who were locally staged with ultrasound, please state the entire percentage of patients who were staged locally with either MRI or ultrasound, and a breakdown of MRI and ultrasound.

Authors: Thank you. Indeed this was not clear in our original manuscript. We have modified the text to clearly indicate the total number of patients staged, and with what methods.

“Three hundred and twenty rectal cancer patients (87%) were locally staged by either a rectal endoscopic ultrasound, a scan or MRI. Specifically, 268 received a scan, 15 received MRI and 195 received transrectal US endoscopy, with some patients receiving more than one examination.”

2. Please clarify the term “curative surgery” (under Results -> Patterns of Care). I interpret that term to mean that surgery was attempted with a goal of cure, but pathology did not necessarily verify a curative (i.e. – R0) resection? Is so, perhaps the term “curative surgery” should be re-labeled as “attempted cure” since pathology did not verify an R0 resection?

Authors: Indeed, this term is unclear and should not have been included. ‘Curative’ has been removed here and from the title of Table 2. In fact, these data refer to all patients receiving surgery.

3. What does the term “general status” (under discussion, paragraph 2, first sentence) refer to?
Authors: This was a mistranslation and should have read specifically: ECOG score. We have corrected this.

4. Please explain the statement “Radiotherapy before surgery explained the lower proportion in rectal cancer patients” (Discussion, second paragraph). Does this refer to the fact that lymph node harvests post-radiotherapy are lower than non-radiated mesorectum? If so, please explain and cite with a supporting study.

Authors: Indeed, this was not well expressed but it refers to the reduced lymph node harvests post radiotherapy for rectal cancer patients. We have added two references to support this idea.

“Pathological findings concerning resection specimens showed that for most CRC cases ≥12 LNs were examined, yet the proportion was slightly lower among rectal cancer patients compared to colon cancer patients. Radiotherapy before surgery may explain the lower proportion in rectal cancer patients due to reduced lymph node harvests post-radiotherapy[11,12].”

5. In the last paragraph of the discussion, there are two “second limitations”.

Authors: Thank you, we have corrected this.

Discretionary Revisions:
1. At least 7 years have transpired since the guidelines were implemented, yet
the authors report on only the first 12 months of effects. Was guideline compliance assessed at later time points (1, 2, or 3 years)? Is there a growing trend of improvement over time? If this data was not collected, please discuss why.

Authors: This is indeed a weakness of the study in that we only provide a description of quality of care at one point in time. However, as previously discussed, we believe that a) the data are still relevant (compare to other papers being published in 2012), b) the methodology used is particularly useful for other assessments of quality of care, and that growing trends for improvement that are indicated by regional data (for ex. 48% to 63% multidisciplinary discussion between 2005 and 2008 respectively) are influenced greatly by the establishment of INCa in 2005 meaning that the effect of focussed regional interventions after this date is difficult to disentangle from larger national patterns in France.

2. Do 5 year actual survival data exist? Rather than compare to surrogates of survival (lymph nodes, chemotherapy for stage III), the authors are in a unique position to look at comparing the effects of guideline compliance with actual survival. Please address in the discussion if future work will assess this.

Authors: As the reviewer rightly points out, reporting survival data would have been ideal. However, at the time of the study, cancer population-based registers did not exist in our area, and, on a national level it was very difficult to obtain information relating to individuals from the French Comité National des Informations et des libertés. The restrictive laws have since changed and a register was established in 2005 meaning that in a subsequent study by our group (EVACCOR study), survival data will be examined. We now mention this in the discussion.

3. The authors report the percentage of R1 resections in pathology reports. Were the percentage of R2 resections tracked?

Authors: Yes, R2 resections were tracked: there were 19 R2 for colon cancer patients (n=767) and 1 R2 for rectal cancer patients (n=340). These figures are given in the notes for Table 2.

4. Was microsatellite instability tracked? This would be a compelling reason to withhold chemotherapy.

Authors: In this study, microsatellite instability was not systematically tracked. No changes to manuscript.

5. Several groups have used permanent colostomy rate as a quality measure with rectal cancer. The authors report that 18% of patients underwent APR. There may be a subset of patients who underwent low Hartmann’s type resections not included. Did you analyze permanent colostomy rate as a quality measure?

Authors: No, we did not analyse permanent colostomy rates as a quality measure. 170 patients (50%) had a colostomy during the initial surgery, but we do not know whether these were permanent or not.

6. Was data collected retrospectively, or in a prospectively maintained database? Please clarify this point within Material and Methods -> Study Population and
Data Colectomy.

Authors:
Yes. Retrospective data collection in prospectively maintained database. This has now been added to the methods section:
“Patients were included prospectively and data collected retrospectively.”