Author's response to reviews

Title: Hospital factors and patient characteristics in the treatment of colorectal cancer: a population based study.

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Author's response to reviews: see over
Response to the referees’ comments.

Title: Hospital factors and patient characteristics in the treatment of colorectal cancer: a population based study.

Version: 2 Date: 16 April 2012
Reviewer: Dianne O'Connell

REFEEER 1
Major Compulsory Revisions

Abstract
1. The abstract should include a section on methods

Authors’ reply:

We have introduced the suggested section.

Results and Discussion
2. Para 3. Table 1 refers to the use of preoperative radiotherapy (RT) for patients with rectal cancer who underwent an elective intervention. However the use of preoperative RT is not indicated for all rectal cancer cases (only stage II/III) according to the Background. Therefore the proportion of patients receiving preoperative RT may be underestimated, and some of the differences in patients who did and did not receive this may be confounded by cancer stage. If stage, other than whether or not metastases are present, cannot be obtained in these data, then this is a major limitation of the study.

An accurate staging of cancer is not available from the HDR database. This is a limitation of all researches based on ICD9-CM coded diagnoses. However, the information on presence of metastases is captured by ICD9-CM codes and has been validated using the "high resolution sample" of clinical records as a gold standard. We think that this validation sample of 605 patients (390 rectal cancer) randomly selected from the cohort for whom we analyzed in detail all the clinical records represents a strength of our study. The percentage of rectal cancer patients in stage II and III in the validation sample is 72% (age 50-69 years). We can assume that in older patients the percentage of stages >I could be even higher. Furthermore in this sample none of the patients with stage<II received radiotherapy. According to these data we can assume that stage is not a likely confounder of the reported results.

Anyway, this important point has been clarified in the discussion as a limitation of the study.

Methods
Study population
3. A main concern is the use of the Hospital Discharge Record system for identifying colorectal cancer cases. Is this truly population-based? Does this system really include all hospitals in the region? Are there private hospitals that are not included?

The Italian National Health Service covers the entire population and private funding is residual, particularly for life-threatening diseases like cancer. Providers, both public and private, including hospitals outside the region, to be reimbursed by the NHS need to deliver a Hospital Discharge Record. As a consequence, all the in-patient and day-care activities are included in the database for administrative purpose.

According to our previous experiences in the use of routinely-collected data for quality of care evaluations
4. Were the colorectal cancer cases histopathologically confirmed?

The histopathological confirmation cannot be directly obtained from the HD database, but the inclusion of surgical cases only is an indirect assurance of a histopathological confirmation of the diagnosis. Anyway looking at the data of the “high-resolution sample” we could verify that 96% of the colorectal cancers were histologically confirmed. We have introduced this information in the validation section.

5. Information from the Piedmont Cancer Registry was used in a validation study. Why was it not linked to the clinical information in the HDR for this study?

The Piedmont Cancer Registry, covers the population of the City of Turin (910,504 inhabitants) which represents one fifth of the whole Piedmont population (about 4.3 millions of inhabitants).

Statistical analysis

6. Para 1. The usual indicator of quality of care is 30-day mortality (ie the proportion who died up to 30 days after surgery). This requires information on vital status possibly after discharge which would be obtained by active follow-up of patients or passive follow-up via linkage with death records. The in-hospital mortality analysed in this study is a time-dependent variable with censoring when the patient is discharged alive. Therefore it should be analysed using statistical methods for time-to event data (often referred to as “survival analysis”).

We agree that the 30-day mortality is considered a slightly better indicator of quality of care than the postoperative in-hospital mortality. However, the in-hospital mortality is an extensively validated and more easily available indicator of in-hospital quality of care for selected surgical procedures. It is also one of the few in-hospital quality indicator recommended by the US Agency for Healthcare Research and Quality (AHRQ) (“The Inpatient Quality Indicators (IQIs) are a set of measures that provide a perspective on hospital quality of care using hospital administrative data. These indicators reflect quality of care inside hospitals and include inpatient mortality for certain procedures and medical conditions”) (accessed at http://www.qualityindicators.ahrq.gov/Modules/iqi_overview.aspx, 3 July 2012). Even if in theory a survival approach could be an appropriate method to analyze mortality of a cohort of subjects with different lengths of follow-up, we think that the very short time frame of observation doesn’t allow to appreciate any meaningful difference in survival times.

Validation

colorectal cancer cases in the HDR compared with the Piedmont Cancer Registry was 89.9%. This means that 10% of cases included in the analysis of the HDR were not found in the Cancer Registry. Who are these cases? Also what is the false negative rate? That is, how many cases in the Cancer Registry were not identified in the HDR?

8. Para 3. The “high resolution sample” used to validate the information in the HDR is restricted in age to 50-69 years. Why did this occur? The cohort included in the wider study is all ages with 49% aged over 70. Given that the data may be less accurate for older patients this casts some doubt on the validity of the HDR data for this cohort.

The high resolution study has been restricted to the screening age (50-69 years). The Piedmont region is covered by a colorectal screening program and the “high resolution” study had also the objective to evaluate the quality of care in screened and not screened patients. Due to the administrative aim of the HDRs, we think there is no reason to suspect a lower accuracy of the data in the whole cohort. In addition, a general decrease of data accuracy is an unlikely explanation of the reported associations.

**Minor Essential Revisions**

**Abstract**

9. Para 1 of results. N=24,187 patients were included in the analysis, not 25,302. Also there was no association between being less educated and post-operative mortality.

10. Para 2 of results. This is a repeat of the last sentence in the previous paragraph.

We agree with the reviewer. We have introduced the suggested correction.

**Abstract and Background (para 4)**

11. The authors indicate in the first sentence that the focus of the study is on “non-clinical” factors that can lead to disparities in the management and outcome of care. However the next sentence indicates that “social, clinical and hospital determinants” were investigated. This is inconsistent.

We have amended the text and made uniform in all the article the definition of the analyzed determinants: social, clinical and hospital determinants.

**Results and Discussion**

12. Para 2. The numbers of patients with colon and rectal cancers in Figure 1 add to 22,431 not 22,289. Did some patients with a first diagnosis before 1995. Few cases had an incorrect place of residence in HDR (the cancer registry cover only the population of the city of Turin) and a provisional diagnosis of malignant cancer instead of benign or in situ cancer. Among the false negatives, the majority of cases of colorectal cancer were present in hospital discharge abstracts, but did not meet the inclusion criteria for the present analysis (restricted to surgical cases). A minority of cases are missing because they were ascertained in the RTI from death certificate only.

142 patients with a double lesion in colon and rectum were originally included in Figure 1. To be more clear we changed Figure 1 and amended the text to account only for number of patients and not for site of lesions.
have tumours in both their colon and rectum? If so, how were these classified in Table 3 where 15,256 colon and 7,033 rectal cancer patients (which add to 22,289) are reported on?

13. Para 3, last sentence. The odds ratio does not vary with distance, rather the odds of receiving neoadjuvant RT vary. Was a test for trend conducted? This would be required to draw a conclusion of decreasing odds with increasing distance.

14. Para 4. Is the difference in odds of AP resection for patients with and without an emergency admission statistically significant? The upper 95% confidence limit is 1.01. What is the corresponding p-value?

15. Para 4, last sentence. This is poorly expressed. It should say something like: "There was no independent association between disease stage, Charlson index or year of admission and having an AP resection for rectal cancer.”

16. Para 5. As odds ratios are calculated, not relative risks, it is incorrect to say that mortality is “two to three times higher ...” based on the magnitude of the odds ratio. It is the odds of dying that are two to three times higher.

17. Para 5. For education level, the only odds ratio that is significantly different from 1 is for the “unknown” group, not the less educated groups.

18. Para 6, second sentence. This is speculation but you could (and should) examine this in the data. Did older patients have more comorbidities (a cutpoint of 1 or more may be too insensitive) or live further from RT facilities? Also,
this could be confounded by older patients being diagnosed with later stage disease.

19. Para 6, last sentence. Did older patients have “a higher burden of comorbidities”? This should be examined in the data, not speculated on. The sentence has been revised according to the reviewer’s comment.

20. Para 7. Again, the likelihood of having preoperative RT may be confounded by cancer stage. We have highlighted in the limitation section the problem of missing stage.

21. Para 9. The association between education level and mortality was confined to the group with “unknown” education level (Table 3). We agree with the reviewer. We have introduced the suggested correction.

22. Para 10. Do not know what “comparing row percentages” means in this context. Please describe the proportions that are being compared. The sentence has been revised according to the reviewer’s comment. It is unclear what is meant by “non-clinical” factors. Are the authors distinguishing between individual patient characteristics and health system variables? The sentence has been revised and the term non-clinical has been deleted.

Conclusion
23. Para 2. The discussion of the limitations of the study should be moved to the discussion, not included in the conclusions. We have introduced the suggested correction.

24. Para 3. This conclusion cannot be drawn from this study. The conclusions should refer to what was found in the study about the management of people with colorectal cancer. The conclusions have been completely revised.

Methods
25. The methods section should be moved to between the Introduction and Results sections. We have introduced the suggested correction.

Patient characteristics
26. Para 1. More information is required about the patient records in the HDR system. What is Patient’s HDRs are identified by means of an encrypted unique identification code based on the tax identification number.
actually meant by the "data set is de-identified at source"? How are different patient episodes linked? Do individual patients have an encrypted or some other form of identification so multiple records can be linked?

Multiple records relative to each patient are linked by means of such encrypted code. We have better clarified such aspect in Methods.

27. Para 5. What is the basis for the cutpoints for annual hospital caseloads? Are they based on the distribution in the data (e.g. tertiles) or are they based on categories used in the literature previously?

They are based on categories used in the literature and used as recommendations of the regional guidelines (Regione, Piemonte: Tumori del Colon-Retto. Linee guida clinico organizzative per la Regione Piemonte. In Edited by Commissione Oncologica Regionale. Turin, Italy: Assessorato Sanità; 2001).

**Statistical analysis**

28. Para 1. The first sentence describing the outcomes of interest should be moved to a new section "Outcomes" following the section on patient characteristics. Also “rates” of preoperative RT etc were not analysed. It is the proportion of patients receiving RT etc that are analysed and reported. Suggested wording: "... the proportions of rectal cancer patients who received preoperative RT or abdominoperineal (AP) resection, and the proportion who died post-operatively in hospital."

The paragraph has been revised according to the referee’s comment.

**Tables**

29. Overall p-values for each factor should be included in the tables. These will indicate whether overall, there is a significant association between each variable and the outcome, adjusting for the other variables in the model.

We included the p values in the tables.

30. Table 1. Hospital volume is not included in the logistic model due to its strong association with presence of an RT service. As a sensitivity analysis, the model should be refitted including hospital volume and omitting RT service and the results reported in the text.

We performed the sensitivity analysis and we have included the results in the text.
31. Table 3. The APR-DRG risk-of-mortality score also includes age and age is included in the logistic model. Is there multicollinearity?

Even if age is included in the definition of the APR-DRG risk of mortality score, the independent effect of age per se on the outcomes analyzed is quite important and justify its inclusion in the models also to better control for residual confounding. No problem of collinearity between age and APR-DRG score was detected.

32. Table 3. Title should indicate that these are colorectal cancer patients who had curative surgery. Also the number of patients with colon cancer (15,256) differs from that in Figure 1 (where, as previously indicated, some patients are double counted). This requires explanation.

There were 142 patients with a double lesion in colon and rectum that were originally included in the fig 1. To be more clear we corrected the figure 1 and the text to account only for number of patients and not for site of lesions.

33. Table 4. The labels on the rows and columns are misleading. The patients are the same in the two “samples”. Should they refer to the data sources “HDR” for the rows and “Medical records” for the columns.

It is a 2X2 table in which the same patient is analyzed in the HDR database and in the “gold standard” DB. The title of table 4 has been revised.

34. Table 4. There are inconsistencies in the numbers of patients. There were 390 rectal cancer patients but data for only 277 patients are shown for type of resection. If patients were classified as not having a resection in either data source then this category needs to be included.

We included in the validation table (table 4) the “missing” category and some new information from clinical records.

35. Why are only 575 patients included in the comparison of presence of metastasis? If this is not recorded in either data source then a category for “unknown” is required. Minor issues to be corrected (but not for publication)

We included in the validation table (table 4) the “missing” category and some new information from clinical records.

Results and Discussion
36. I suggest splitting the results and discussion into two sections. The discussion would start at the current para 6 of the combined section (“In our population ....”).

We have introduced the suggested correction.

37. Para 3. Suggest minor changes to wording: “The
probability of undergoing RT was also reduced in females versus males for patients with at least one comorbidity in the Charlson Index (OR 0.73).” “Furthermore....had a higher probability of receiving ...”

38. Para 6. Suggest changes to wording of first sentence: “In our population, older people with rectal cancer were less frequently treated with preoperative RT, were more likely to undergo AP ...”

Study population
39. Para 2, first sentence. Change to: “... or malignant neoplasm of the rectum or rectosigmoid junction ...”

Patient characteristics
40. Para 1. Move the first sentence to the end of the first paragraph in the section on study population. Start second sentence with “The HDR includes ...”

41. Para 2, last sentence. Suggested word change: “Cases were classified as having concomitant obstruction ...; perforation ..., or an emergency admission (OPE) or not.”

42. Para 4. The labels for the APR-DRG classification system shown in Table 3 (low, medium, high, extreme) need to be mentioned.

43. Para 6. Suggested changing to wording of first sentence: “For each patient, accessibility to preoperative RT was measured as the distance between their residence and the nearest city with a RT service, by car and under normal traffic conditions [43].”

44. Para 6. The second and third categories are not mutually exclusive. Should they be: same city or less than 15 minutes; 15 to
less than 30 minutes; 30 minutes or more?

**Ethical issues**

45. What does CPO stand for?  
Centro di Riferimento per l'Epidemiologia e la Prevenzione Oncologica in Piemonte.

46. I believe that the authors are arguing that this study was considered to be a clinical audit to monitor the quality of treatment, which is considered to be an essential activity rather than research and therefore was exempt from ethical review.  
This is correct. The paragraph has been revised according to the reviewer’s suggestion.

**Abbreviations**

47. Delete “surgical” from the definition of DRG.  
We have introduced the suggested correction.

**Tables**

48. Delete all vertical lines in tables (bottom of Table 1 and right-hand edge of Table 2).  
We have introduced the suggested correction.

49. Table 1. Label for middle category of distance to RT should be 15’ to <30’  
We have introduced the suggested correction.

50. Table 2. What does the second superscript in the title refer to? Also the relevant superscript should be added to the line for OPE in the body of the table.  
In footnote line one there are the explanation for “*” and “†”.  
We have introduced the superscript for OPE.

51. Why are the numbers of rectal cancer patients in Table 1 (5437) and Table 2 without OPE (5382) different?  
Because we have few missing values in the variable OPE.

*We would like to thank the reviewer for the very helpful comments that improved the manuscript substantially.*