PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Time from diagnosis to treatment of colorectal cancer in a South Australian clinical registry cohort: how it varies and relates to survival
AUTHORS	Roder, David; Karapetis, Christos; Olver, Ian; Keefe, Dorothy; Padbury, Robert; Moore, James; Joshi, Rohit; Wattchow, David; Worthley, Dan; Miller, Caroline; Holden, Carol; Buckley, Elizabeth; Powell, Kate; Buranyi-Trevarton, Dianne; Fusco, Kellie; Price, Timothy

VERSION 1 – REVIEW

REVIEWER	Hla Hla Thein University of Toronto, Canada
REVIEW RETURNED	15-May-2019

GENERAL COMMENTS	Time from diagnosis to treatment of colorectal cancer in an Australian cohort: how it varies and relates to survival The authors investigated time to treatment at four major public hospitals for benchmarking and to explore associations with survival. Times to treatment were analysed employing rank-order tests and multiple logistic regression. Disease-specific survival was analysed by time to treatment using unadjusted Kaplan-Meier estimates and adjusted Cox proportional hazards regression. Major comments: 1. According to authors using South Australian clinical cancer registry data, regarding title, it might be better to add as “Time from diagnosis to treatment of colorectal cancer in South Australian cohort: how it varies and relates to survival”. Introduction 2. Page 3 line 55-57: Please add definition of 5-FU as Fluorouracil. FOLFOX is a combination of leucovorin calcium, 5-FU and oxaliplatin, which may be used in the treatment of advanced-stage and metastatic colorectal cancer. Regarding “colonic”, it means “colon cleansing”. Colon is related to cancer. So, please make changes related to 4 “colonic” in the text as “colon”. Methods 3. Regarding Methods, it would be better to add for example: Study design and study population; Ethics approval; Data sources; Data linkage Study variables; Outcome measures; Statistical analysis.

	4. Page 5 line 29-30 and Tables: Regarding "Systemic therapy', chemotherapy is usually a systemic therapy. This means that the drugs travel through the bloodstream to reach and destroy cancer cells all over the body, including those that may have broken away from the primary tumour in the colon or rectum. The most common chemotherapy drugs used to treat colorectal cancer are: 5-fluorouracil (Adrucil, 5-FU) given intravenously, capecitabine (Xeloda) given as a pill, oxaliplatin (Eloxatin) given intravenously, irinotecan (Camptosar) given intravenously, and raltitrexed (Tomudex) given intravenously (https://www.cancer.ca/en/cancer-information/cancer-type/colorectal/treatment/chemotherapy/?region=on). Additionally, "any of these treatments among surgical cases or any treatment (surgical cases)", please add treatment titles. 5. Page 5 line 33-38: is this "geographic access to specialist radiotherapy and other specialist metropolitan services based on postcode address (coded as high, medium or low)" related to in the tables and text "Accessibility: High, Med-High, Poor"? Please add as the same information. Also, what do these "country south and country north" mean? Northern metropolitan, central metropolitan and southern metropolitan are fine. Additionally, Sub-site: colon, rectum and Australian Clinico-Pathological Staging (ACPS) stage: A, B, C, D, unknown (UK) have to add here. 6. Table 1: Please add "unadjusted analysis". Tables 2 & 3 to add "adjusted analysis". Table 4 to add "unadjusted analysis" and Table 5 "adjusted analysis". 7. Page 12 B and Table S1. Time from diagnosis to treatment start by sub-site (colon): Predictors of time to treatment start >30 days in adjusted analysis included: (d) For any treatment (surgical cases): northern metropolitan compared with central metropolitan and southern metropolitan areas; stage A compared with stages B and D (stage C not significant); and diagnosis in 2006-2010. Please check. 8. Page 13: Rectum (Supplementary Tables S3 & S4) Page 13 and Table S3: Predictors of time to treatment start of >30 days in adjusted analysis included: (d) For any treatment (surgical cases): northern metropolitan compared with southern metropolitan; and diagnosis in 2006-2010. Please check. 9. Conclusions Page 18 line 43: Is MDT mean "multidisciplinary team"? Please define. Minor comments: 1. Tables 1-3 and S1-S4 sizes to change: Layout – AutoFit – AutoFit Window. 2. MRI to define as "Magnetic resonance imaging".

REVIEWER	L Hess Eli Lilly and Co, USA
REVIEW RETURNED	22-May-2019

GENERAL COMMENTS	How does the inclusion of such a broad range of registry data (starting from 1980) potentially impact the results? I see that it was

	adjusted for but it was a dichotomous variable. Why not use continuous as year of diagnosis? Merging the adjuvant with metastatic treatments by only adjusting for stage may blur the findings. Why not consider adjuvant therapy and advanced therapy in separate analyses? These are certainly different strategies, and the timing of what may happen when may differ. The results in the abstract are unclear. From what I read, the main idea was to evaluate time to treatment and survival, and the result was negative, that there is no association. This should be clearly stated. Although the finding may not be negative if limited to a more homogenous cohort, such as metastatic disease. Predictors of treatment start make up a large part of the results. This does not appear in the methods or objectives of the study. Please clarify the role of these analyses with regard to your primary research question. How was 'treatment start' defined? How was multimodality therapy handled? Was the start date the first start date or potentially the third in case of surgery and radiotherapy? If patients were included with different start dates and different cohorts, this could also cause bias. Please clarify the groups and if estimates were made for the same patients across groups. the conclusions should clearly state the finding of the primary research question. the conclusion bullets are very wordy and could be made more succinct with the appropriate and balanced interpretation of the data. Again, as I read it the conclusion is no relationship. It is unclear how a conclusion was made related to patient anxiety as this was not part of the study. Given the overlap of cohorts and bias introduced by multiple start dates for the same individual, the limitations section could be elaborated. What about limitations of the dataset in itself? Missing data? It would be nice to look at time to treatment by subgroup, where there is less heterogeneity. And then perhaps for specific homogeneous groups look at the relationship. I have a feeling any potential relationship was blurred by the methods applied.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1 feedback:

Comment 1: According to authors using South Australian clinical cancer registry data, regarding title, it might be better to add as “Time from diagnosis to treatment of colorectal cancer in South Australian cohort: how it varies and relates to survival”.
Response:
We have changed the title as suggested to: “Time from diagnosis to treatment of colorectal cancer in a South Australian clinical registry cohort: how it varies and relates to survival”

Comment 2: Please add definition of 5-FU as Fluorouracil. FOLFOX is a combination of leucovorin calcium, 5-FU and oxaliplatin, which may be used in the treatment of advanced-stage and metastatic colorectal cancer. Regarding “colonic”, it means “colon cleansing”. Colon is related to cancer. So, please make changes related to 4 “colonic” in the text as “colon”.
Response:
That section has been changed as follows: “Chemotherapies evolved from common use of single-agent 5-FU (5-Fluorouracil) to 5-FU and leucovorin. FOLFOX (leucovorin calcium, 5-FU and oxaliplatin) + bevacizumab and capecitabine (+ oxaliplatin) also became more common, along with protracted infusion of 5-FU for colon cancer, and with radiotherapy for rectal cancers.”(page 3, paragraph 4).

Comment 3: Regarding Methods, it would be better to add for example: Study design and study population; Ethics approval; Data sources; Data linkage Study variables; Outcome measures; Statistical analysis.
Response:
We have now included in the Methods these sections:
“Study design: A historic cohort design was used, including colorectal cancer patients diagnosed in 2000-2010 at four major public hospitals in South Australia. Ethics approval was obtained from the South Australian Human Research Ethics Committee (HREC/14/SAH/145) and University of South Australia Research Ethics Committee. Data sources and linkage: Our data source was the South Australian clinical cancer registry, which is authorised under Section 64, Part 7 of the South Australian Health Care Act (2008) to support service monitoring and quality assurance.5 Dates and causes of death were obtained by linkage with official death records using full names, dates of birth, and sex, and for additional guidance, postcode of residence, for linkage purposes. Outcome measures: These were time in days from diagnosis to treatment start, and survival from diagnosis to death from colorectal cancer.) (page 4, paragraph 5) Also included (page 5, paragraph 3) is: “Time from diagnosis to treatments start was categorised in days for cross-tabulations with clinical and sociodemographic variables. Statistical analysis: The Spearman rank test was used to analyse ordinal clinical and sociodemographic predictors; Kruskal-Wallis ANOVA for multinomial predictors, and Mann-Whitney U test for predictors measured on a binary scale.23, 24 For multiple logistic regression analyses of time as the outcome variable, time was reduced to a binary outcome of “>30 or <30 days” and “>60 or <60 days” respectively.23, 24 The results were expressed as relative odds (i.e., odds ratios) with 95% confidence ranges. Disease-specific survival was analysed by time to treatment using Kaplan-Meier product-limit estimates (unadjusted) and Cox proportional hazards regression (adjusted for co-variables shown in Tables 2 and 3).23,24”

Comment 4: Regarding “Systemic therapy’, chemotherapy is usually a systemic therapy. This means that the drugs travel through the bloodstream to reach and destroy cancer cells all over the body, including those that may have broken away from the primary tumour in the colon or rectum. The most common chemotherapy drugs used to treat colorectal cancer are: 5-fluorouracil (Adrucil, 5-FU) given intravenously, capecitabine (Xeloda) given as a pill, oxaliplatin (Eloxatin) given intravenously, irinotecan (Camptosar) given intravenously, and raltitrexed (Tomudex) given intravenously (https://www.cancer.ca/en/cancer-information/cancer-type/colorectal/treatment/chemotherapy/?region=on).
Additionally, “any of these treatments among surgical cases or any treatment (surgical cases)”, please add treatment titles.
Response:
The revised document is more specific, referring to chemotherapy rather than systemic therapy throughout. The treatment titles for chemotherapy types are included.

Comment 5: is this “geographic access to specialist radiotherapy and other specialist metropolitan services based on postcode address (coded as high, medium or low)” related to in the tables and text “Accessibility: High, Med-High, Poor”? Please add as the same information.
Also, what do these “country south and country north” mean? Northern metropolitan, central metropolitan and southern metropolitan are fine. Additionally, Sub-site: colon, rectum and Australian Clinico-Pathological Staging (ACPS) stage: A, B, C, D, unknown (UK) have to add here.
Response:
Accessibility has now been classified as High, Med-High or Poor throughout.
Country south and country north are defined, namely: “…local health network of residence, as applying during the study period (i.e., northern metropolitan, central metropolitan, southern metropolitan, and for non-metropolitan areas to the south, country south, and for non-metropolitan areas to the north, country north)” (page 5, paragraph 2) ACPS staging has been defined, i.e., “Australian Clinico-Pathological Staging (ACPS) as A, B, C, D or unknown (UK)…” (page 5, paragraph 2). Also, cases were classified by sub-site (colon or rectum). (page 5, paragraph 2)
Comment 6: Table 1: Please add “unadjusted analysis”. Tables 2 & 3 to add “adjusted analysis”. Table 4 to add “unadjusted analysis” and Table 5 “adjusted analysis”.
Response:
These changes have been made.

Comment 7: Time from diagnosis to treatment start by sub-site (colon): Predictors of time to treatment start >30 days in adjusted analysis included: (d) For any treatment (surgical cases): northern metropolitan compared with central metropolitan and southern metropolitan areas; stage A compared with stages B and D (stage C not significant); and diagnosis in 2006-2010.
Response:
This now reads: (d) For any treatment (surgical cases): northern metropolitan compared with central metropolitan and southern metropolitan areas; stage A compared with stages B and D; and diagnosis in 2006-2010 (page 13, paragraph 2).
Comment 8: Page 13: Rectum (Supplementary Tables S3 & S4)
Predictors of time to treatment start of >30 days in adjusted analysis included: (d) For any treatment (surgical cases): northern metropolitan compared with southern metropolitan; and diagnosis in 2006-2010.
Response:
This now reads for time to treatment start >30 days: (d) For any treatment (surgical cases): northern metropolitan compared with southern metropolitan; and diagnosis in 2006-2010 (page 13, paragraph 4). This now reads for time to treatment start >60 days: (d) For any treatment (surgical cases): low compared with higher grade lesions; and diagnosis in 2006-2010 (page 13, paragraph 5).

Comment 9: Conclusions Page 18 line 43: Is MDT mean “multidisciplinary team”? Please define.
Response:
MDT has been changed to multidisciplinary teams.

Comment 10: MRI definition
Response:
MRI has been changed to magnetic resonance imaging.

Minor comments:
1. Tables 1-3 and S1-S4 sizes to change: Layout – AutoFit – AutoFit Window.
AutoFit has been used for the tables.

Reviewer 2 feedback:

Comment 1: How does the inclusion of such a broad range of registry data (starting from 1980) potentially impact the results? I see that it was adjusted for but it was a dichotomous variable. Why not use continuous as year of diagnosis?
Response:
The range was 2000-2010 diagnoses. The earlier data back to the 1980s were in the literature review only. We considered a priori that two epochs within 2000-2010 would provide numbers of cases in each for reasonably precise estimates. When year was entered as a continuous variable, the results for other predictors were essentially unchanged, but in our view, data for year would be less readily interpretable than data for the two epochs by local health administrations.

Comment 2: Merging the adjuvant with metastatic treatments by only adjusting for stage may blur the findings. Why not consider adjuvant therapy and advanced therapy in separate analyses? These are certainly different strategies, and the timing of what may happen when may differ.
Response:
As you know, we did supplementary analyses of time to treatments (surgery, radiotherapy, chemotherapy, and any treatment separately) with tumour stage classified by stage as D (distant metastasis) compared with earlier stages in aggregate to provide more specific output for metastatic as opposed to earlier stage cancers (page 11, paragraph 5). That said, we agree that providing more granularity would be desirable. We intend to broaden the range of hospitals included in a new study, using data linkage to build larger case numbers for statistical precision. We are uncertain at this time, however, whether the quality of data available through data linkage will be good enough.

Comments 3: The results in the abstract are unclear. From what I read, the main idea was to evaluate time to treatment and survival, and the result was negative, that there is no association. This should be clearly stated. Although the finding may not be negative if limited to a more homogenous cohort, such as metastatic disease.
Response:
The results indicated that survival was lower in the first two years from diagnosis when treatment occurred within 30 days of diagnosis. We have highlighted that this was a negative association, although consistent with other study findings, namely: Lower survival <2 years from diagnosis for cancers treated <30 days from diagnosis (i.e., a negative association of survival with shorter duration to treatment) is consistent with other study results attributed to preferencing more complicated cases for earlier care. (Abstract, Conclusions).

Comment 4: Predictors of treatment start make up a large part of the results. This does not appear in the methods or objectives of the study. Please clarify the role of these analyses, with regard to your primary research question.
Response:
We have now made it clear in the revised Abstract that Time to treatment of colorectal cancer and associations with survival were investigated. (Abstract, Objectives) The outcome measures were specified to be: Time to treatment and survival from colorectal cancer. (Abstract, Outcome measures).

Comment 5: How was 'treatment start' defined? How was multimodality therapy handled? Was the start date the first start date or potentially the third in case of surgery and radiotherapy? If patients were included with different start dates and different cohorts, this could also cause bias. Please clarify the groups and if estimates were made for the same patients across groups.
Response:
The clinical registry had access to data from electronic medical records which specified treatment start times for surgery, radiotherapy and chemotherapy, respectively, and for surgical cases, the first of any of these three treatments. The treatment recorded for individual patients was the first occurring in each stream. Individual patients could therefore present in two or more streams depending on their

care. For surgical cases, only the first treatment applied, irrespective of treatment type. This has been clarified in Tables 1-5 and associated text descriptions.

Comment 6: The conclusions should clearly state the finding of the primary research question. the conclusion bullets are very wordy and could be made more succinct with the appropriate and balanced interpretation of the data. Again, as I read it the conclusion is no relationship. It is unclear how a conclusion was made related to patient anxiety as this was not part of the study.
Response
We have shortened the conclusions and excluded material not covered in the study. References to patient anxiety have been deleted.

Comment 7: Given the overlap of cohorts and bias introduced by multiple start dates for the same individual, the limitations section could be elaborated. What about limitations of the dataset in itself? Missing data?
Response:
We have elaborated the limitations section, pointing out that: The present study has limitations. An opportunistic approach was taken in selecting cases where a gap presented between recorded diagnosis date and start of treatment. (page 17, paragraph 2) Also: (a) precise diagnostic and treatment data were limited to 65% of cases, which could have led to bias; (b) the study was observational and vulnerable to bias from practitioner choice and self-selection by patients into comparison groups; and (c) the ability to adjust for potential confounding influences was limited by the range of data available (page 3, paragraph 3).

Comment 8:
It would be nice to look at time to treatment by subgroup, where there is less heterogeneity. And then perhaps for specific homogeneous groups look at the relationship. I have a feeling any potential relationship was blurred by the methods applied.
Response:
Yes, there is more research to be done. We shall be exploring other opportunities with broader linked data when numbers of patients available will be larger, which is expected to enable finer subgroup analysis (page 17, paragraph 4).

VERSION 2 – REVIEW

REVIEWER	Hla-Hla Thein Dalla Lana School of Public Health, University of Toronto, Toronto, ON, Canada
REVIEW RETURNED	25-Jul-2019

GENERAL COMMENTS	Time from diagnosis to treatment of colorectal cancer in a South Australian clinical registry cohort: how it varies and relates to survival The authors have done an important revision on the Title, Abstract, Strengths and limitations of this study, Introduction, Methods, Results, Discussion, Conclusions, and Tables. Currently, a few comments below and better to change manuscript according to BMJ Open published articles. ABSTRACT 1. Better to add: Setting and participants; Clinical registry data for a cohort of colorectal cancer cases diagnosed in 2000-2010 at four major public hospitals in South Australia and treated by surgery

	(n=1675), radiotherapy (n=616) and/or systemic therapy (n=1556); and Design: Rank-order tests were used to analyse ordinal clinical and sociodemographic predictors. Multiple logistic regression methods were used to analyse relative odds (odds ratios) of time from diagnosis to treatment, age, sex, stage, and socioeconomic factors for colorectal cancer. Unadjusted Kaplan-Meier estimates and adjusted Cox proportional hazards regression methods were used to evaluate disease-specific survival by time from diagnosis to treatment. Please check if ok. Under Outcome measures, better to change as "Time from colorectal cancer diagnosis to treatment and survival from diagnosis to death from colorectal cancer". INTRODUCTION 2. Page 3 line 28: Change "age-standardized" to "age-standardised".

REVIEWER	LM Hess Eli Lilly and Company USA
REVIEW RETURNED	06-Aug-2019

GENERAL COMMENTS	While real-world data are inherently limited, the authors have noted these limitations and reframed the revision to better fit the scope of work presented. I believe the revision adequately addresses my earlier concerns and the reader is now able to better determine the value of the findings given the improved clarity of the content.

VERSION 2 – AUTHOR RESPONSE

Reviewer 1 feedback:

Comment 1: The reviewer has indicated that it would be better to add the cited section now added to the Abstract.

Response:

We have added the following and edited to contain the word count, namely:

We investigated time to treatment of colorectal cancer and associations with survival.

Setting and participants

Clinical registry data for colorectal cancer cases diagnosed in 2000-2010 at four major public hospitals in South Australia and treated by surgery (n=1675), radiotherapy (n=616) and/or systemic therapy (n=1556).

Design

A historic cohort design, with rank-order tests for ordinal clinical and sociodemographic predictors and multiple logistic regression for comparing time from diagnosis to treatment. Unadjusted Kaplan-Meier estimates and adjusted Cox proportional hazards regression were used to investigate disease-specific survival by time to treatment.

Outcome measures

Time to treatment and survival from diagnosis to death from colorectal cancer.

Comment 2: Change “age-standardized” to “age-standardised”.

Response:

Introduction (page 3, 1st paragraph of Introduction) now reads:

By comparison, the age-standardised colorectal cancer mortality rate approximately halved between these periods.

Reviewer 2 feedback:

No changes required.