

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Is palliative care support associated with better quality end of life care indicators for patients with advanced cancer? A retrospective cohort study
AUTHORS	Ziegler, Lucy; Craigs, Cheryl; West, Robert; Carder, Paul; Hurlow, Adam; Millares Martin, Pablo; Hall, Geoff; Bennett, Mike

VERSION 1 – REVIEW

REVIEWER	Bruno Gagnon Laval University Canada
REVIEW RETURNED	07-Jul-2017

GENERAL COMMENTS	<p>The authors aimed to estimate the association between timing and contact with Palliative care services and quality of end-of-life care indicators.</p> <p>Title: The title is misleading as this is not a longitudinal cohort but a database retrospective case series. The use of 'Quality of End-of-Life Palliative Care indicators' would be preferable to 'better quality outcomes'.</p> <p>General comments;</p> <p>It will be better to use 'Quality of End-of-Life Palliative Care (QEoLPC) indicators, decedents instead of patients, use contact with PC health care providers (which need in fact to be defined, physicians only? Nurses?, social workers? Etc. If it is only physicians, this has to be clearly stated and discuss in the limitations) instead of event, timing of first contact with PC t before death instead of duration (as clearly found in the study a great number of decedents had only one contact. (Hard to define this as 'duration'), throughout the manuscript.</p> <p>Abstract:</p> <p>Objectives:</p> <p>Replace by ' This study aimed to estimate the association between timing and provision of palliative care and quality of end-of-life care indicators in a population of patients dying of cancer.</p> <p>Results:</p> <p>The last sentence on duration of PC and indicators should be rephrased as it is confusing. Maybe More than 4 weeks of involvement of PC before death was associated avoiding emergency hospital admissions, more than 33 weeks with access to an opioid, and more than 2 weeks with avoiding death in hospital.</p>
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	<p>Conclusion:</p> <p>Remove 'these findings provide evidence to support... models'. Reason will be given when commenting the manuscript.</p> <p>Manuscript:</p> <p>Methods:</p> <p>Study population: this study used databases that are 5 years old. This fact needs to be addressed in the limitations. Are they still valid?</p> <p>Data collection: SystemOne is 'used by approximately 75% of primary care providers'. This reality needs to be commented in the limitation in more details: the missing data is random? Risk of Bias?, Would it change the results significantly?</p> <p>Is Methadone not an opioid available in the UK?</p> <p>Statistical analysis : well described</p> <p>Results:</p> <p>Rewrite the description of Table 1 as follow starting from 'Palliative care was more likely to be received by decedents who were younger ($p<0.001$), etc.</p> <p>Please define Hospice. In my understanding, Hospice is equivalent to PC. Is it not true? Why then not 100% contact with PC?</p> <p>Discussion:</p> <p>Reference that can help with opioid prescription (Gagnon et al. JPSM, 2014) where prescription of opioid in the community is a late in the great majority of decedents, and for age and female (Gagnon et al. JPSM 2016) are also found to be associated with better QEqLPC indicators. You may use the later ref to discuss differences of the influence with cancer type.</p> <p>Data does not support earlier integration of PC within oncology service delivery models but earlier referral to PC services that could take place in the community. In fact this study supports more the necessity for early identification of patients likely to benefice from PC wherever they are receiving their care.</p> <p>Conclusion</p> <p>With a median of 2 events, I don't think we can use the term 'intensity'...</p>
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REVIEWER	Hilde Buiting Netherlands Cancer Institute, the Netherlands
REVIEW RETURNED	31-Aug-2017

GENERAL COMMENTS	<p>Is palliative care support associated with better quality outcomes at end of life for patients with advanced cancer? A longitudinal population cohort study</p> <p>General</p> <p>This study explores whether palliative care is associated with better quality outcomes at the end of life. Specific attention was paid to duration of palliative care involvement in relation to patient's quality of care. The study is well-written, with illustrative tables. Some results replicate previous findings with respect to (early) palliative care provision. The authors further conclude that duration of palliative care is indeed related to indicators of quality end-of-life care, which is an interesting finding.</p>
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	<p>I however have some questions with respect to the results/conclusions of this study.</p> <p>Abstract In the results section it is stated: 'Duration of PC is associated with avoiding late chemotherapy/death in the hospital'. I suggest to rephrase this sentence a bit, like: Patients receiving PC for more than ... were less likely to receive ... or die in a hospital.</p> <p>In my opinion, the finding that PC and chemotherapy provision (in an earlier stage of the disease trajectory) go hand in hand warrants further attention too. I would suggest to add these results too. This could be considered as a strong finding in that palliative care is a continuum where chemotherapy is provided where appropriate and ceased when it is not appropriate anymore.</p> <p>Introduction Page 5, line 27/28; Could the authors explain more specifically why shorter duration of palliative care go together with negative effects on end-of-life outcomes.</p> <p>Page 5, line 40/41; In my view, it is impossible to predict the time period cancer patients need palliative care since all patients may suddenly die. Could the authors explain this more specifically, e.g. do they refer to specific cancer patients / a common cancer disease trajectory, et cetera.</p> <p>Methods Page 6, line 43; Record of a palliative care event. - What exactly embraces a 'palliative care event', e.g. how is palliative care defined in this study. Is this similar to contact with a palliative care physician/team; how often; et cetera. - Will 'the content' of palliative care change throughout the disease trajectory, and how is this defined with respect to 'palliative care events'? The authors mention a first and second stage but this is not altogether clear to me. - When is decided to start a new palliative care event?</p> <p>Page 7, line 19; - I agree with the authors that access to strong opioids is proxy for adequate access to end-of-life care. I also agree with the authors that in the very last phase of life, you would like to prevent hospital admissions, et cetera. You however need to measure this, retrospectively. Thus, sometimes starting palliative care and a last hospital admission may easily follow; this cannot be considered inappropriate care. Could the authors please reflect a bit more on this (in the methods / discussion section)?</p> <p>Page 8, Line 12 and further I think the statistical analysis is appropriate, I however have insufficient expertise.</p> <p>Page 7, line 49; I wonder how patients are involved in the design of the study.</p>
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	<p>Results</p> <p>Page 9, line 23; See my comments in the Methods section; to me, it is not altogether clear what is the difference between different palliative care events.</p> <p>Page 10, line 10; I wonder how opioids in the last phase of life are described. Is this the prescription of opioids in the last 4 weeks of life? In the Table they speak about 12 months. I suggest to define this more specifically in the Methods section.</p> <p>Page 10, line 33; Do the authors have any ideas why palliative care is associated with chemotherapy provision in an earlier stage of the disease trajectory? I think this is an interesting finding. This would indeed suggest that chemotherapy is given when it is considered appropriate and stopped when it is not appropriate anymore. I would suggest to address this in the Discussion section too (and in the Abstract).</p> <p>Page 10, line 47; The significant association between hospital admissions and receiving palliative care is interesting. I can imagine that it is sometimes adequate care to send people to the hospital. See my previous remarks, I would suggest to address this more specifically in the Discussion-section.</p> <p>Discussion</p> <p>Page 11, line 41; I'm not sure whether this is a language problem, but I would think it is not 'access' to palliative care, but 'receiving' palliative care.</p> <p>Page 12, line 18; I wonder whether these differences are related to the way palliative care is provided. E.g. I can imagine that everyone defines the provision of palliative care differently. Could the authors please explain?</p> <p>Page 12, line 35; What do the authors mean with the direction of the relationship is unclear?</p> <p>Page 13, line 3 or 4; In general, this study has the starting point that palliative care (and its duration) will probably improve quality of life outcomes. While reading the whole paper, I sometimes noted results that showed the opposite (such as last hospital admissions). I agree with the authors that emergency hospital admissions might trigger palliative care involvement. It however also could be that these hospital admissions were necessary. I suggest to incorporate this perspective too. E.g. although most people prefer home as their place of death, sometimes hospital is better / a hospital admission can be considered appropriate. So a general perspective in what can be considered appropriate (end-of-life)care.</p>
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REVIEWER	Debbie Cavers University of Edinburgh, Scotland, UK
REVIEW RETURNED	05-Sep-2017

GENERAL COMMENTS	<p>I think this study has been clearly reported and contributes to what is known about the role of palliative care in improving experience at the end of life. The study design has been explicitly justified and quality outcomes are evidence-based. I think the only limitation to the study I identified would be to acknowledge the potential shortcomings of a narrow definition of quality outcomes but I feel the authors have addressed this. I think this study would be complemented well with some qualitative work to explore in-depth people's experiences of good quality care at the end of the life with potential bereavement interviews with carers, professionals in addition to patient record reviews to more fully understand the concept of quality of life at the end of life. A couple of other points:</p> <ul style="list-style-type: none"> - PC is used in the abstract. Please spell out in full the first time you use this. - You mention in the strengths and limitations section what you have based your quality outcomes on. I think it is worth repeating this in the methods section more explicitly although you do justify and explain your choice of measures. - I would like to see a more detailed definition in the introduction of what you mean by quality at the end of life. Quality of life, of death, or quality of care? All have different implications for the study measures and should therefore be addressed. - Again, you do state that your measures are based on assumptions about what constitutes good quality care at the end of life. I think in the discussion you could acknowledge how further exploration of concepts of quality (complemented by qualitative work) could add to understand on the topic.
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REVIEWER	<p>Melissa Garrido Department of Veterans Affairs & Icahn School of Medicine at Mount Sinai USA</p>
REVIEW RETURNED	21-Sep-2017

GENERAL COMMENTS	<p>In this study, data on 2479 decedents with advanced cancer were examined to understand relationships among palliative care access and duration and health care use at the end of life. Understanding relationships between palliative care receipt and patient outcomes is important to optimizing timing of provision of palliative care to seriously ill individuals. However, I have several concerns about the analytic methods used in this paper.</p> <ol style="list-style-type: none"> 1. There is a high likelihood of selection bias in these analyses. Patients who receive palliative care for fewer days before death may be more acutely ill than patients who receive palliative care for several weeks. In addition, illness severity may be associated with both timing of palliative care receipt and with outcomes. It's unclear whether the observed results are due to palliative care duration or underlying illness severity. 2. It was not clear to me why the sample was chosen based on decedent status. Was there an opportunity to identify patients who met a set of inclusion criteria at an index date who could then be followed prospectively? 3. In the analysis of optimal palliative care duration, palliative care duration was the only explanatory variable. Optimal palliative care
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	<p>duration will vary with patient characteristics and cannot be determined in isolation, especially in an observational study design.</p> <p>4. Analyses did not control for several potential confounders of the relationship between palliative care duration and outcomes, including comorbidities, earlier receipt of chemotherapy, stage of cancer diagnosis, and symptom burden.</p> <p>5. Community-based and hospital-based palliative care were grouped into one treatment variable. Given the different needs of hospitalized and community-based patients, it's not clear that these two types of palliative care should be grouped together in analyses.</p>
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VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Bruno Gagnon

Institution and Country: Laval University, Canada Competing Interests: none declared

3. Title: The title is misleading as this is not a longitudinal cohort but a database retrospective case series. The use of 'Quality of End-of-Life Palliative Care indicators' would be preferable to 'better quality outcomes'.

3. Response: The title has been changed to 'Is palliative care support associated with better quality end of life care indicators for patients with advanced cancer? A retrospective cohort study'

General comments;

4. It will be better to use 'Quality of End-of-Life Palliative Care (QEoLPC) indicators,

4. Response: We have changed the wording throughout the manuscript to refer to Quality of End-of-life Care Indicators.

5. Use decedents instead of patients

5. Response: We have changed patient to decedent throughout the manuscript

6. Instead of event, use contact with PC health care providers (which need in fact to be defined, physicians only? Nurses? Social workers? Etc. If it is only physicians, this has to be clearly stated and discuss in the limitations).

6. Response: We have expanded the assessment of palliative care provision section within the methods on page 6 to explain in more detail how we have defined a palliative care 'event' and have included a list of read codes as a supplementary file.

7. Timing of first contact with PC t before death instead of duration (as clearly found in the study a great number of decedents had only one contact. (Hard to define this as 'duration'), throughout the manuscript.

7. Response where we previously used the term duration we have replaced it with 'timing of first contact with palliative care before death'

8. Objectives: Replace by 'This study aimed to estimate the association between timing and provision of palliative care and quality of end-of-life care indicators in a population of patients dying of cancer.

8. Response: we have changed the objectives to the wording suggested above

7. The last sentence on duration of PC and indicators should be rephrased as it is confusing. Maybe More than 4 weeks of involvement of PC before death was associated avoiding emergency hospital

admissions, more than 33 weeks with access to an opioid, and more than 2 weeks with avoiding death in hospital.

Conclusion: Remove 'these findings provide evidence to support... models'. Reason will be given when commenting the manuscript.

7. Response: The suggested changes to the abstract have been made.

Methods:

Study population: this study used databases that are 5 years old. This fact needs to be addressed in the limitations. Are they still valid?

8. Response: This study used a complex data linkage process to explore outcomes in relation to access to palliative care and we used the most up to date linked data available. We are reassured that the data is representative of current practice having undertaken a relatively recent national survey on timing of referral to palliative care in 31,000 cancer patients who died in 2015. Although this is a survey and does not explore access to palliative care in relation to outcomes it did find the median time between first contact with palliative care and death is consistent with the timing identified in the study reported here.

9. Data collection: SystmOne is 'used by approximately 75% of primary care providers'. This reality needs to be commented in the limitation in more details: the missing data is random? Risk of Bias? Would it change the results significantly?

9. Response: The data linkage process we used intentionally restricted data linkage to practices that used the SystmOne electronic medical record system. The reason for this is two fold; it is the most commonly used electronic record system in the UK and the one that interfaces with community palliative care services (hospices). We worked closely with a SystmOne data manager to identify and pilot test and refine codes for data extraction that are unique to that system. The general practices that use SystmOne in our region do not differ in terms of the patient populations they serve therefore limiting linkage to SystmOne practices was unlikely to introduce bias and we believe optimised the quality of the data linkage. If it was possible to extract and link data from alternative electronic systems we anticipate the findings would be unchanged. We have added information to the discussion (highlighted) on page 13 to make this clearer.

10. Is Methadone not an opioid available in the UK?

10. Response: Methadone is used in the UK mainly as a replacement in heroin addiction. It is not an analgesic typically used in palliative care

Statistical analysis: well described

Results:

11. Rewrite the description of Table 1 as follow starting from 'Palliative care was more likely to be received by decedents who were younger ($p < 0.001$), etc.

11. Response: The text associated with table 1 has been amended as suggested (highlighted in yellow).

Discussion:

12. Reference that can help with opioid prescription (Gagnon et al. JPSM, 2014) where prescription of opioid in the community is a late in the great majority of decedents, and for age and female (Gagnon et al. JPSM 2016) are also found to be associated with better QeOLPC indicators. You may use the later ref to discuss differences of the influence with cancer type.

12. Thank you for these suggestions the 2014 reference in particular was very useful and has been added page 12- highlighted.

13. With a median of 2 events, I don't think we can use the term 'intensity'...

13. We agree and have removed the word intensity

Reviewer: 2

Reviewer Name: Hilde Buiting

Institution and Country: Netherlands Cancer Institute, the Netherlands Competing Interests: None declared

General

This study explores whether palliative care is associated with better quality outcomes at the end of life. Specific attention was paid to duration of palliative care involvement in relation to patient's quality of care. The study is well-written, with illustrative tables. Some results replicate previous findings with respect to (early) palliative care provision. The authors further conclude that duration of palliative care is indeed related to indicators of quality end-of-life care, which is an interesting finding. I however have some questions with respect to the results/conclusions of this study.

Abstract

14. In the results section it is stated: 'Duration of PC is associated with avoiding late chemotherapy/death in the hospital'. I suggest to rephrase this sentence a bit, like: Patients receiving PC for more than ... were less likely to receive ... or die in a hospital.

14. Thank you we have rephrased this section in the abstract – highlighted

15. In my opinion, the finding that PC and chemotherapy provision (in an earlier stage of the disease trajectory) go hand in hand warrants further attention too. I would suggest to add these results too. This could be considered as a strong finding in that palliative care is a continuum where chemotherapy is provided where appropriate and ceased when it is not appropriate anymore.

15. Although this is an interesting discussion point and we have expanded our discussion about chemotherapy and palliative care on page 13 it was not a key objective of the study to explore outcomes earlier in the disease trajectory therefore we feel it would be a departure from our original objectives to focus on it in the results.

Introduction

Page 5, line 27/28;

16. Could the authors explain more specifically why shorter duration of palliative care go together with negative effects on end-of-life outcomes.

16. Response: We hypothesise that the shorter duration of palliative care limits the opportunity for identification of needs and subsequent provision of effective support and symptom management. We have added this to page 5 – highlighted.

17. Page 5, line 40/41;

In my view, it is impossible to predict the time period cancer patients need palliative care since all patients may suddenly die. Could the authors explain this more specifically, e.g. do they refer to specific cancer patients / a common cancer disease trajectory, etcetera.

17. Response: We agree that it is not possible to predict the optimum time period patients need palliative care at an individual patient level. In this study we are exploring associations with timing of palliative care and quality of end of life indicators at a population level.

Methods

18. Page 6, line 43;

Record of a palliative care event.

- What exactly embraces a 'palliative care event', e.g. how is palliative care defined in this study. Is this similar to contact with a palliative care physician/team; how often; et cetera. Will 'the content' of palliative care change throughout the disease trajectory, and how is this defined with respect to 'palliative care events'? The authors mention a first and second stage but this is not altogether clear to me. When is decided to start a new palliative care event?

18. The sub-section 'Assessment of palliative care provision' within the methods section has been expanded to provide further details of how palliative care events were identified (Changes/additions highlighted in yellow). A supplementary appendix (Appendix 1), which details the read codes which were used to indicate palliative care provision, has also been added.

19. Page 7, line 19;

- I agree with the authors that access to strong opioids is proxy for adequate access to end-of-life care. I also agree with the authors that in the very last phase of life, you would like to prevent hospital admissions, et cetera. You however need to measure this, retrospectively. Thus, sometimes starting palliative care and a last hospital admission may easily follow; this cannot be considered inappropriate care. Could the authors please reflect a bit more on this (in the methods / discussion section)?

19. Response: Thank you for this helpful suggestion we have now included a sentence in the discussion (highlighted) to explain that it is important to acknowledge that for some patients dying in hospital represents appropriate end of life care.

20. Page 7, line 49;

I wonder how patients are involved in the design of the study.

20. Response: Jean Gallagher is a co-investigator on the study and a cancer patient. She helped refine the research question and was involved in the decision about which quality of life indicators to adopt from national policy documents.

Results

21. age 10, line 10;

I wonder how opioids in the last phase of life are described. Is this the prescription of opioids in the last 4 weeks of life? In the Table they speak about 12 months. I suggest to define this more specifically in the Methods section.

21. Response: The outcome of interest was if patients had access to a strong opioid in the last year of life. If SystmOne had one or more prescriptions for a strong opioid recorded within the last twelve months of life for a patient then that patient was identified as having had access to an opioid in the last year of life.

A more detailed description of the opioid outcome measure is included in the methods section, first sentence in the Outcomes sub-section (highlighted in yellow).

22. Page 10, line 33;

Do the authors have any ideas why palliative care is associated with chemotherapy provision in an earlier stage of the disease trajectory? I think this is an interesting finding. This would indeed suggest that chemotherapy is given when it is considered appropriate and stopped when it is not appropriate anymore. I would suggest to address this in the Discussion section too (and in the Abstract).

22. Response: Please see response 15 above.

23. Page 10, line 47;

The significant association between hospital admissions and receiving palliative care is interesting. I can imagine that it is sometimes adequate care to send people to the hospital. See my previous remarks, I would suggest to address this more specifically in the Discussion-section.

23. Thank you for this point, we have referenced a study in the discussion which explains that 77% of admissions are avoidable therefore as you correctly point out a quarter are entirely appropriate. This paragraph is highlighted. We hope this provides the necessary clarification.

Discussion

24. Page 11, line 41; I'm not sure whether this is a language problem, but I would think it is not 'access' to palliative care, but 'receiving' palliative care.

24. Thank you we have changed 'access' to the 'level of palliative care involvement'

25. Page 12, line 18; I wonder whether these differences are related to the way palliative care is provided. E.g. I can imagine that everyone defines the provision of palliative care differently. Could the authors please explain?

25. We have included the following sentence which we hope addresses this issue: These differences may reflect differences in the availability of hospice or palliative care services, or bias in the selection of suitable patients for palliative care.

26. Page 12, line 35; What do the authors mean with the direction of the relationship is unclear?

26. We have included a sentence in the discussion (highlighted) to explain that it is unclear whether the referral to palliative care drives the opioid prescription or the opioid prescription triggered the palliative care referral

27. Page 13, line 3 or 4; In general, this study has the starting point that palliative care (and its duration) will probably improve quality of life outcomes. While reading the whole paper, I sometimes noted results that showed the opposite (such as last hospital admissions). I agree with the authors that emergency hospital admissions might trigger palliative care involvement. It however also could be that these hospital admissions were necessary. I suggest to incorporate this perspective too. E.g. although most people prefer home as their place of death, sometimes hospital is better / a hospital admission can be considered appropriate. So a general perspective in what can be considered appropriate (end-of-life)care.

27. Please see responses 9 and 23 above.

Reviewer: 3

Reviewer Name: Debbie Cavers

Institution and Country: University of Edinburgh, Scotland, UK Competing Interests: None declared

28. I think this study has been clearly reported and contributes to what is known about the role of palliative care in improving experience at the end of life. The study design has been explicitly justified and quality outcomes are evidence-based. I think the only limitation to the study I identified would be to acknowledge the potential shortcomings of a narrow definition of quality outcomes but I feel the authors have addressed this. I think this study would be complemented well with some qualitative work to explore in-depth people's experiences of good quality care at the end of the life with potential bereavement interviews with carers, professionals in addition to patient record reviews to more fully understand the concept of quality of life at the end of life. A couple of other points:

28. Thank you for this suggestion. We agree and recognise that while our study provides population level data it does not advance understanding of what constitutes a good quality end of life care at an individual patient level and the role palliative care has to play in achieving that. We have recently secured UK National Institute for health research funding for a study which builds on this project and will undertake qualitative interviews with patients with cancer and their healthcare professionals to provide this more in depth understanding.

29. PC is used in the abstract. Please spell out in full the first time you use this.

29. Response – we have now written Palliative Care in full in the abstract.

29 You mention in the strengths and limitations section what you have based your quality outcomes on. I think it is worth repeating this in the methods section more explicitly although you do justify and explain your choice of measures.

29. We have added more detail within the methods section under the heading 'outcomes' to explain more clearly how the outcomes were determined. This text is highlighted.

30. I would like to see a more detailed definition in the introduction of what you mean by quality at the end of life. Quality of life, of death, or quality of care? All have different implications for the study measures and should therefore be addressed.

30. Please see responses 3,4, 6 and 7 which I think all relate to this issue and we hope we have adequately addressed the point raised by defining the outcomes more clearly as end of life care quality indicators.

31. Again, you do state that your measures are based on assumptions about what constitutes good quality care at the end of life. I think in the discussion you could acknowledge how further exploration of concepts of quality (complemented by qualitative work) could add to understand on the topic.

31. Please see response 28

Reviewer: 4

Reviewer Name: Melissa Garrido

Institution and Country: Department of Veterans Affairs & Icahn School of Medicine at Mount Sinai, USA

Competing Interests: None declared

In this study, data on 2479 decedents with advanced cancer were examined to understand relationships among palliative care access and duration and health care use at the end of life. Understanding relationships between palliative care receipt and patient outcomes is important to optimizing timing of provision of palliative care to seriously ill individuals. However, I have several concerns about the analytic methods used in this paper.

32. There is a high likelihood of selection bias in these analyses. Patients who receive palliative care for fewer days before death may be more acutely ill than patients who receive palliative care for several weeks. In addition, illness severity may be associated with both timing of palliative care receipt and with outcomes. It's unclear whether the observed results are due to palliative care duration or underlying illness severity.

32. In this paper we are reporting associations rather than trying to establish a causal relationship between late palliative care and poor outcomes. The associations between timing of palliative care involvement and quality of life indicators we have identified have many influences and we agree with the reviewer that it seems logical that illness severity is likely to be associated with timing of palliative care involvement but as we are not seeking to establish a causal relationship we feel these are not issues of selection bias.

33. It was not clear to me why the sample was chosen based on decedent status. Was there an opportunity to identify patients who met a set of inclusion criteria at an index date who could then be followed prospectively?

33. This study was designed to respond to the need for population level data on timing of palliative care involvement and its association with quality of life indicators to help inform future research direction in this field. This design was advantageous in that it allowed us to identify a large cohort of patients who we could confirm had died from cancer (rather than with cancer).

A prospective study from an index date for example at diagnosis with advanced cancer would need to be conducted over many years given that some cancer patients such as those with prostate or breast cancer live for 10 years or more with advanced disease.

34. In the analysis of optimal palliative care duration, palliative care duration was the only explanatory variable. Optimal palliative care duration will vary with patient characteristics and cannot be determined in isolation, especially in an observational study design.

34. Response: We chose to include palliative care duration as the only variable within the classification trees as our aim was to partition palliative care duration into the most homogeneous

groups across the whole dataset for each of the outcomes. We then controlled for other extraneous variables in the regression models.

35. Analyses did not control for several potential confounders of the relationship between palliative care duration and outcomes, including comorbidities, earlier receipt of chemotherapy, stage of cancer diagnosis, and symptom burden.

35. Response: A range of potential confounding factors were included in the analysis covering age, gender, area deprivation, cancer site, and duration of illness. Limitations in the routine clinical data available meant that other potential confounders, such as comorbidities, earlier receipt of chemotherapy and symptom burden were not available to use. Stage at diagnosis was included in the dataset but could not be included in the analysis because of the large percentage of missing data. We have included the sentence (also highlighted in manuscript):

‘Though we included a range of potential confounders in the regression models we acknowledge that our choice of confounders was guided and limited by the availability and reliability of information in the datasets in the limitations section within the discussion.

36. Community-based and hospital-based palliative care were grouped into one treatment variable. Given the different needs of hospitalized and community-based patients, it’s not clear that these two types of palliative care should be grouped together in analyses.

36. Approximately 25% of patients who receive specialist palliative care accessed both community and hospital palliative care services. Given that both services may have provided care to the same patients we decided to consider both together to enable us to accurately capture the first contact with specialist palliative care. In a future paper we will report analysis where we separate community palliative care contacts with hospital based palliative care.

VERSION 2 – REVIEW

REVIEWER	Hilde Buiting Netherlands Cancer Institute
REVIEW RETURNED	17-Nov-2017

GENERAL COMMENTS	<p>In this new version, the authors carefully addressed all comments of the reviewers.</p> <p>While reading this paper, I only have one question/suggestion. In this paper, with palliative care, palliative care as provided by general practitioners as well as healthcare professionals in the hospital is meant. I think it is useful to address that this multi-disciplinary approach apparently is a right approach.</p> <p>It would be interesting to know how often PC was delivered by GPs/healthcare professionals in the hospital/both. But this may be interesting for another paper also.</p>
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REVIEWER	Debbie Cavers, CSO Research Fellow University of Edinburgh, Scotland
REVIEW RETURNED	01-Nov-2017

GENERAL COMMENTS	<p>Thank you for addressing my concerns outlined in my initial review of your manuscript. I think that you have addressed these adequately and that, together with your response to the other reviewers, have significantly improved the manuscript. I would now recommend this for publication in BMJ Open to contribute to the</p>
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	evidence base on early provision of palliative care.
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REVIEWER	Melissa Garrido Department of Veterans Affairs Icahn School of Medicine at Mount Sinai
REVIEW RETURNED	15-Nov-2017

GENERAL COMMENTS	<p>I continue to have serious concerns about the analytic methods used in this paper.</p> <p>1. I continue to have concerns about both unobserved confounding and about the fact that underlying factors are likely simultaneously associated with timing of palliative care and outcomes. I appreciate the authors' clarification that they are more interested in associations than causal relationships, but without further information about the potential impact of confounding, it is difficult to draw meaningful inferences from these associations.</p> <p>For instance, the authors state that the multivariable regression models "showed overall greater odds ratios for better outcomes at the end of life with longer time between first contact with palliative care and death". This could be due to underlying differences in people with earlier vs later PC and have nothing to do with PC.</p> <p>The authors also state that "For some outcomes such as place of death at home, there appears to be a minimum interval between first contact with palliative care and death that is associated with higher odds of home death." Again, a large part of this relationship is likely due to underlying illness severity/acuity, but the data set used does not allow the authors to determine whether this is the case.</p> <p>When referencing other literature on the inconsistent relationship between palliative care and home death, the authors state: "Our data suggest that the interval between first contact with palliative care and death may account for this inconsistent relationship". For the reasons provided above, this conclusion cannot be drawn from the analyses presented.</p> <p>In the conclusion, the authors state: "Characterising the impact of palliative care services based on interval between first contact and death provides new evidence which will aid policymakers when modelling palliative care service provision." It's unclear how these descriptive results will do this. Differences in patient characteristics across earlier and later PC receipt are not adequately addressed in the analysis or in the text. From these analyses, there is not enough evidence to support provision of earlier PC or to inform targeting of appropriately timed PC to different groups of patients.</p> <p>2. The rationale for selecting the sample based on decedent status should be provided in the text.</p> <p>3. The lack of available data on several potential confounders of the relationship between palliative care duration and outcomes, including comorbidities, earlier receipt of chemotherapy, stage of cancer diagnosis, and symptom burden, is a serious limitation.</p>
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VERSION 2 – AUTHOR RESPONSE

We want to thank the reviewers for helping us to strengthen our manuscript and we recognise the arguments presented by Reviewer 4. However, we believe that these limitations do not detract from important conclusions arising from our analysis of these data and that our manuscript still merits publication, as supported by reviewers 1-3.

The key objections appear to be:

- (a) the lack of an objective clinical measure about whether palliative care should be provided (e.g. based on clinical guidelines)
- (b) whether our claims of associations attributed to palliative care are more appropriately attributed to other clinical indicators.

We were unable to include data on prevalence and severity of specific symptoms and underlying disease (especially at time of any referral to palliative care) as these are not routinely coded in UK health data. However, since 2002, eligibility criteria for palliative care have been adopted throughout the city of Leeds (http://nww.lhp.leedsth.nhs.uk/referral_info/detail.aspx?ID=55) and which are based on this peer review publication: <http://pmj.sagepub.com/content/14/2/157>.

These criteria enable us to say with confidence that the 65% of patients in our cohort referred to palliative care had active, progressive advanced disease and a high symptom burden. Patients with stable inactive disease were not eligible. For the 35% of patients that did not receive a palliative care referral, two conclusions are possible: these patients either had less severe underlying disease and symptoms OR they had similar severity underlying disease and symptoms but declined/were not offered a palliative care referral.

Reviewer 4 suggests that the association between improved outcomes and access to palliative care can be explained by 'a lower underlying illness severity/acuity' in the population who received palliative care. This logic is not plausible given the eligibility criteria described above. The most plausible assumption is that patients who received palliative care had greater or at least similar illness severity to those not referred, yet still experienced better outcomes.

A similar argument holds true for early versus late palliative care; patients referred earlier to palliative care would have reached referral eligibility threshold sooner because of greater illness severity than those referred later, yet still experienced better outcomes. Access to palliative care and timing of access is linked to illness severity by rigorously applied clinical guidance. This is not unique to our study population or even the UK. We note a recently published study by Reviewer 4 in the USA of 3,096 advanced cancer patients (<https://www.ncbi.nlm.nih.gov/pubmed/28628352>) which found exactly this; that 'advanced cancer patients were more likely to be referred to the palliative care consultation team if they had high symptom burden.'

The scientific challenge here is to identify the most plausible explanation for the associations in the data that we have identified. We argue that despite the high likelihood of greater illness severity triggering referral to palliative care, these patients still experienced better outcomes. We have made it very clear in our manuscript that causality cannot be assumed; we are simply reporting significant associations observed within the limitations of routinely collected data. Furthermore our interpretations are consistent with evidence from randomised controlled trials of early palliative care. Our finding of similar associations within routine data is therefore not surprising, but it is original in terms of being the first study to examine associations between duration of palliative care and outcomes.

Previous work from our group published in BMJ Open in 2016

<https://www.ncbi.nlm.nih.gov/pubmed/27940628>) examined a large cohort of patients that all received palliative care. We determined associations between patient characteristics and early or late referral. We were similarly careful to avoid assumptions of causality in that paper which was based on very similar quality routinely collected data. We believe our revised manuscript builds on this work and is of a similar high quality to merit publication in BMJ Open.

We sincerely hope that we have addressed the key objections:

- (a) palliative care was provided on the basis of clinical guidelines and these reflect a threshold of greater illness severity
- (b) associations attributed to palliative care are not more plausibly attributed to other clinical indicators

We have substantially revised our discussion (pgs 15 and 16) as requested by reviewer 4 and the editorial board member to include explanation of the above issues in substantially more detail.