PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	The diagnostic property of direct referral from general practitioners to contrast enhanced thoraco-abdominal CT in patients with serious but non-specific symptoms or signs of cancer: a retrospective cohort study on cancer prevalence after 12 months.
AUTHORS	Møller, Marie; Juvik, Bue; Olesen, Stine Chabert; Sandstrøm, Hanne; Laxafoss, Erling; Reuter, Simon Bertram; Bodtger, Uffe

VERSION 1 – REVIEW

REVIEWER	Penny Allen University of Tasmania, Australia
REVIEW RETURNED	26-Jul-2019

GENERAL COMMENTS	This is a well-written manuscript, with clear study aims, methods and conclusions. However, the methods and study limitations sections require revision and clarification in order to address my concerns below. Introduction Can the authors provide more information on the organ-specific cancer diagnosis pathways, within the Zealand region, for the main cancers identified in the study? Methods Why did the authors select two separate study periods (July-December 2013 and July-December 2015)? The authors comment on the increased number of patients between these periods. However, the authors should explain why these two separate periods were selected. Why did the authors not include continuous study period? Results Can the authors include the cause of mortality for the 21 cases where malignancy was not suspected? Discussion In addition to the prospective UK study (ref 15) cited, have any other studies to-date evaluated the sensitivity, specificity, NPV, PPV, +LR or -LR of ceCT for the diagnosis of cancer? Please state if your study is the first to evaluate ceCT for the diagnosis of cancer. Page 8 appears to be included in error.

REVIEWER	Jason Oke University of Oxford, United Kingdom.
REVIEW RETURNED	29-Aug-2019

GENERAL COMMENTS	Working in this field myself, I find this manuscript of great interest. I think the paper as it stands lacks some clarity on the study

	population and the methods used are not adequately described but both criciticsm should be rectifiable. 1. I would like to see a complete description of the referral criteria used by the GP's. What signs and symptoms qualify as NSSC, what blood tests are done or need to be done before referral, is GP gut feeling considered, etc. What criteria can GP's refer into the pathway. The introduction says "if the initial workup is inconclusive" - but is it possible to describe in more detail what qualifies for inconclusive. Would a patient with normal bloods but unexpected weight loss and GP gut feeling be referred for CT in Denmark? 2. On first reading, table 1 confused me as did the sub-section in the results titled "referral patterns". Initially, I though table 1 was describing the types of referrals into the NSSC pathway so when I read that many were "organ specific" I thought that this was incompatible with NSSC. What table 1 describes (I think) is the actions following the ceCT after referral. Although not everyone will make this mistake I wonder whether it could be made clearer by choosing different phrasing. The term referral patterns should be changed decision following triage ceCT or similar. And make table 1 look less like a baseline table of characteristics and more like a table explaining what happened post ceCT. 3. The sentence "Our primary objective was negative and positive likelihood ratios" doesn't scan well – suggest "Our primary objective was to estimate the negative……" 4. The worst cases scenario analysis is not described in the methods (as it should be) and the first mention of it is in the results. In addition, I am not sure what the rationale is for assuming that anyone who died during follow up, with no know malignancy as a false negative. Is this situation likely, in your opinion? Most of these patients have had a comprehensive investigation and I would have thought the most likely explanation is that they had a serious illness that wasn't cancer. We have found with our own pathway that there is significant amount of serious disease that isn't cancer. 5. In the clinical application section probabilities are given with what looks like confidence intervals but it is not stated or explained in the methods. The methods says "Bayesian statistics were used….." which is not sufficient particularly with respect to the intervals (if, that is what they are). 6. Is staging data available. NSSC patients tend to be late stage cancers and this message is not always conveyed or overlooked. Are you able to provide these data? 7. The term incidence is used throughout but I am not convinced this is appropriate. Incidence is defined as the number of new cases within a defined period divided by the number initially disease free. it describles the risk of something occuring in people withouot the condition. The prevalence represents the probability that any one individual has the disease in question – which I think is what you are describing here. I think use prevelance or use a plain english equivalent.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

This is a well-written manuscript, with clear study aims, methods and conclusions. However, the methods and study limitations sections require revision and clarification in order to address my concerns below.

1.1 Introduction

Can the authors provide more information on the organ-specific cancer diagnosis pathways, within the Zealand region, for the main cancers identified in the study?

REPLY: Thank you for this comment. In the appendix, there is a Background Section describing when and how the organ-specific cancer diagnosis pathway was implemented (including relevant references). Furthermore, we added the paragraph "The first organ specific CPPs was implemented in 2008 including guidelines, descriptions of selected alarm symptoms that may raise specific cancer suspicion, the content of the following workup, which specialist departments to refer to and specific timeframes for all phases in the workup (for instance time from referral to first consult)".

(Changes made on page 12, lines 12-15)

1.2. Methods

Why did the authors select two separate study periods (July-December 2013 and July-December 2015)? The authors comment on the increased number of patients between these periods. However, the authors should explain why these two separate periods were selected. Why did the authors not include continuous study period?

REPLY: We chose these two time periods to explore possible changes in referral patterns over time. On page 4, line 24-25, we have inserted this sentence "(including temporal trends since implementation of NSSC-CPP in 2012))". In Methods, we have inserted the sentence: "By choosing these two separated periods, we aimed at exploring possible temporal trends in reference pattern as a secondary endpoint. (page 5, lines 6-8)"

(Changes made page 4: lines 24-25, 5: lines 6-7)

1.3. Results

Can the authors include the cause of mortality for the 21 cases where malignancy was not suspected?

REPLY: We have inserted the following in Results: "Table 1 shows that 21 patients died in the group with a ceCT classified as "malignancy not suspected" including three patients who were actually diagnosed with malignancy. Six of the 18 patients died in hospital. No post-mortem analyses were made, but none of medical files provided a clinical suspicion of an underlying, missed cancer as cause of death. However, according to the worst-case scenario, all these fatalities were includes as false-negative cases to challenge our estimates:"

In the Discussion, we have added "A limitation of our study is that it we did not have access to cause of death, thus the true number of missed cases of malignancy is unknown. However, it is unlikely that all fatalities were due to missed cancers, so our Worst Case scenario are probably too conservative, as we have included all fatalities as false-negative cases (Table 2)."

(Changes made on page 9, lines 14-19, and page 11, lines 14-17)

1.4 Discussion
In addition to the prospective UK study (ref 15) cited, have any other studies to-date evaluated the sensitivity, specificity, NPV, PPV, +LR or -LR of ceCT for the diagnosis of cancer?
Please state if your study is the first to evaluate ceCT for the diagnosis of cancer.
REPLY: Thank you for this valuable point. To our knowledge, we are the first to include ceCT in a primary cohort population of NSSC. This is already stated in the start of the Discussion session and is now repeated in Conclusion, with the following addition: "Our study is unique in several ways. Most significantly, we have not found other studies that comprehensively describe the use and results of ceCT in a primary care setting. In previous studies of the NSSC-CPP in primary care, patients have had different types of diagnostic imaging and not a consequent use of ceCT (8, 21)."

(Changes made on page 10, lines 23-26)

1.5 Page 8 appears to be included in error.
REPLY: We are sorry that the reviewer has received a version with an erroneous page 8. In our copy of the uploaded article, all pages were relevant. We will ask the editor to solve this point.

Reviewer: 2
Working in this field myself, I find this manuscript of great interest. I think the paper as it stands lacks some clarity on the study population and the methods used are not adequately described but both criticism should be rectifiable.

2.1. I would like to see a complete description of the referral criteria used by the GP's. What signs and symptoms qualify as NSSC, what blood tests are done or need to be done before referral, is GP gut feeling considered, etc. What criteria can GP's refer into the pathway. The introduction says, "if the initial workup is inconclusive" - but is it possible to describe in more detail what qualifies for inconclusive. Would a patient with normal bloods but unexpected weight loss and GP gut feeling be referred for CT in Denmark?
REPLY: Thank you for these questions. We have added the requested data to the background section. In our region, GPs can refer a patient directly to a ceCT on the suspicion of possible malignancy. However, GPs are recommended to initiate the diagnostic workup of NSSC with a history, clinical examination (including urine dipstick, electrocardiogram, fecal occult blood test), supplemented by a predefined set of blood tests (containing hemoglobin, erythrocyte mean cell volume (MCV), mean cell hemoglobin concentration (MCHC), leukocyte differential (L+D), reticulocyte index, thrombocyte count, C-reactive Protein (CRP), sodium, potassium, creatinine, estimated glomerular filtration rate (eGFR), calcium (total), albumin, glucose, bilirubin, alanine Aminotransferase (ALAT), alkaline phosphatase, pancreas specific amylase, lactate dehydrogenase (LDH), Immunoglobulin G-A-M, thyroid-stimulating hormone (TSH), myeloma-protein and prothrombin time INR)).
In cases where the above is inconclusive or without any pathologic findings, a contrast-enhanced thoraco-abdominal CT-scan is performed (step two). The GP then receives the CT-scan rapport with a detailed description of the findings, and on the basis hereof, determines whether to refer the patient to a diagnostic center for further workup. In cases where the workup at the GP is sufficient to indicate an organ-specific cancer diagnosis, the patient is referred via the relevant cancer patient pathway to a

specialized department. If examination, blood test and ceCT is without any pathologic findings, the GP can still refer the patient to a diagnostic center.

(Changes made on page 12 line 26 and page 13 lines 1-11)

2.2 On first reading, table 1 confused me as did the sub-section in the results titled “referral patterns”. Initially, I though table 1 was describing the types of referrals into the NSSC pathway so when I read that many were “organ specific” I thought that this was incompatible with NSSC. What table 1 describes (I think) is the actions following the ceCT after referral. Although not everyone will make this mistake I wonder whether it could be made clearer by choosing different phrasing. The term referral patterns should be changed decision following triage ceCT or similar. And make table 1 look less like a baseline table of characteristics and more like a table explaining what happened post ceCT.

REPLY: Thank you for helping us improve readability. The suggested changes have been incorporated.
In the manuscript, the subtitle “Referral patterns” has been altered to “Actions and referral patterns after ceCT”. In Table 1, we have replaced “filter-CT” with “contrast-enhanced CT (ceCT)”, inserted a row named “Actions after ceCT” above the now changed rows named “Referrals based on ceCT result” (former “Referrals based on CT”) and “Referrals not based on ceCT result” (former Referrals based on other than CT result”).

(Changes made on page 8, line 18, page 17, and in table 1)

2.3 The sentence “Our primary objective was negative and positive likelihood ratios” doesn’t scan well – suggest “Our primary objective was to estimate the negative……”
REPLY: Thank you for helping us to improve readability. We have incorporated the suggested changes.

(Changes made on page 4, line 18)

2.4 The worst cases scenario analysis is not described in the methods (as it should be) and the first mention of it is in the results. In addition, I am not sure what the rationale is for assuming that anyone who died during follow up, with no know malignancy as a false negative. Is this situation likely, in your opinion? Most of these patients have had a comprehensive investigation and I would have thought the most likely explanation is that they had a serious illness that wasn’t cancer. We have found with our own pathway that there is significant amount of serious disease that isn’t cancer.
REPLY: Thank you for finding this error, and we have now inserted a paragraph on worst case scenario analysis in Methods: “In the case of equivocal findings on CT, we choose to apply a worst-case scenario; all indeterminate ceCT results was categorized as being false-negative (in those with a malignancy) or false-positive (in all others).”
Indeed, there are many non-malignant diseases with a poor prognosis. However, we chose to challenge our findings by assuming that all who died actually died due to an undiagnosed malignancy. Please see Reply to Comment 1.3).

(Changes made on page 6, lines 15-17)

2.5 In the clinical application section probabilities are given with what looks like confidence intervals but it is not stated or explained in the methods. The methods says “Bayesian statistics were used…..” which is not sufficient particularly with respect to the intervals (if, that is what they are).
REPLY: Thank you for the clarification. You are correct that we have reported confidence intervals. We have added several paragraphs to the method section.

It now reads “Bayesian statistics were used to calculate the post-test probability of malignancy; according to the Bayesian method, estimates of post-test probability for malignancy is a function of disease prevalence (pretest probability). Using the prevalence of malignancy in the target population, and the LR- and LR+ of ceCT, it is possible to calculate the probability of having a malignancy if the ceCT is without findings suggestive of malignancy respectively suspicious for malignancy (including 95% confidence intervals).”

(Changes made on page 6, lines 25-31)

2.6 Is staging data available. NSSC patients tend to be late stage cancers and this message is not always conveyed or overlooked. Are you able to provide these data?
REPLY: We perfectly agree that NSSC patients tend to be in late stage when diagnosed with cancer. Unfortunately, we do not have access to staging data in the current study. In the Introduction, we have inserted this paragraph: “Patients with non-specific symptoms or signs of cancer (NSSC) have an overall inferior survival *higher disease stage and lower performance* compared with patients referred through organ-specific cancer pathways (2-5)” to address this important perspective.

(Changes made on page 4, line 6)

2.7 The term incidence is used throughout but I am not convinced this is appropriate. Incidence is defined as the number of new cases within a defined period divided by the number initially disease free. It describes the risk of something occurring in people without the condition. The prevalence represents the probability that any one individual has the disease in question – which I think is what you are describing here. I think use prevalence or use a plain English equivalent.
REPLY: Thank you for this point. It might be a game of words: prevalence of cancer, or incidence of a diagnosis of cancer? But you are perfectly right, and we have replaced “incidence” with “prevalence of cancer”.

(Change made on page 4, line 23, page 6 line 19, page 8, line 9, page 9, line 3, 10 and 11, page 10, line 8, 19 and 20, page 11, line 3)

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3.1 Please revise the title of your manuscript to include the research question, study design and setting. This is the preferred format of the journal.
REPLY: We have altered the title to: “Diagnostic properties of direct referral from general practitioners to contrast-enhanced thoraco-abdominal CT in patients with serious but non-specific symptoms or signs of cancer: a retrospective cohort study on the prevalence of cancer after 12 months.”

(Changes made on page 1, lines 3-5)

VERSION 2 – REVIEW

REVIEWER	Jason Oke University of Oxford, UK.
REVIEW RETURNED	16-Oct-2019

GENERAL COMMENTS	Thank you for giving careful consideration to my comments. I have nothing further to add.