Author's response to reviews

Title: The role of general practice in routes to diagnosis of lung cancer in Denmark A population-based study of GP involvement, diagnostic activity and diagnostic intervals

Authors:

Louise M Guldbrandt (louise.mahncke@alm.au.dk)
Morten Fenger-Grøn (MFGR@alm.au.dk)
Torben R Rasmussen (torbrasm@rm.dk)
Henry Jensen (henry.jensen@alm.au.dk)
Peter Vedsted (p.vedsted@alm.au.dk)

Version: 2
Date: 19 March 2014

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

We hereby resubmit the revised manuscript entitled “The role of general practice in routes to diagnosis of lung cancer in Denmark - a population-based study of GP involvement, diagnostic activity and diagnostic intervals”, to be considered for publication in BMC Health Services Research.

The manuscript has previously been submitted (Number: 9263871141019894). Thank you for giving us the opportunity to resubmit after revision. We have in details, addressed all suggestions and concerns given by the three reviewers. Further, we have gained additional data on the pre-diagnostic activity in primary care, making the study much more complete. The revision has been delayed as we waited for additional register data.

Below, please find our detailed response. Major changes to the manuscript are; the text has been shortened and made clearer. Results and figures are more easily read and we have made additional analyses as suggested by the reviewers.

The results are still clear. Only one fourth of all lung cancer patients followed the fast-track route. At the same time, general practice was involved in the diagnosis of 68% of all cases. We found increased likelihood of a long diagnostic interval if the GP interpreted the patient’s symptoms as “not alarming” and if fast-track was not used. Overall 1/3 had two or more X-rays performed during the 90 days before diagnosis. There was an increased risk of having many X-rays performed if the GP interpreted the symptoms as “symptoms of serious disease” compared to patients with “alarm symptoms”.

These results demonstrate that the health care system must offer different routes for lung cancer diagnosis. Further, the proportion of patients with two or more X-rays prior the diagnosis, and in particular those without alarm symptoms, calls for better diagnostic tests in primary care. We find these results important in health care planning and we hope that you will reconsider the manuscript for publication in the Journal.

None of the authors have any competing interests.

Kind regards,

On behalf of the authors

Research fellow Louise Mahncke Guldbrandt and Professor Peter Vedsted
Research Unit for General Practice
Aarhus University, Denmark
Reviewer 1

1. The article has good potential and present like a well-designed study; however too much data that is contradictory and confusing. The paper should be assessed by a statistician and should be presented more clearly.

Comment: Thank you for rating the article as one with good potential and a well-designed study. The paper is now revised based on the review rapport and we have shortened it to make it more precise and less confusing.

Reviewer 2

2. The methods adopted are appropriate for the research question and the data appear sound. The authors acknowledge the limitations of GP questionnaires to ascertain primary care intervals and they address these limitations in the discussion. The discussion is balanced and draws appropriate conclusions.

Comparison with other studies is extensive and informative and the limitations of the study are clearly stated.

Comment: Thank you very much for the fine words.

3. ‘a false negative x-ray may risk to increase the diagnostic interval’ – remove ‘risk’ from this sentence?

Comment: The ‘risk’ is now removed.

4. ‘and pre diagnostic activities in specific’ suggested change to ‘...activities in particular’

Comment: Yes, it is much clearer and is now changed.

5. “Conclusions and Implications – LC patients follow different routes to diagnosis” – change ‘different’ to ‘various’?

Comment: It is changed.

DISCRETIONARY REVISIONS:

6. The authors state that lung cancer mortality is largely determined by disease stage. We know that lung cancer mortality is at least partly determined by stage at diagnosis, but also by treatment? – see :

Answer: We fully agree. What we meant was that stage determines type of treatment and therefore it is an important prognostic marker. These sentences have been changed and the article refers to the suggested study.

7. In the discussion the authors conclude – ‘we found that one in five patients had at least two x-rays performed within the 90 days prior to the diagnosis implying that this group of patients could have had a false negative test’. Alternatively this might indicate that these patients appeared to have a chest infection on 1st CXR, indicating a repeat CXR a few weeks later to rule out infection as a cause of abnormal CXR? Were those having 2 CXRs more likely to have COPD/higher comorbidity score? However, this interpretation would probably lead to a similar conclusion – that alternative diagnostic tests are required.

Comment: We absolutely agree! Some of the repeated x-rays may be rooted in rational clinical work. But, like you, we guess that the conclusion would be the same. We have conducted the analyses on X-rays and comorbidity and included it in the result section; Further, a higher proportion of patients with co-morbidity (CCI > 0) had two or more X-rays performed (41.6%, 95% CI: 37.0-46.3) compared to patients with no co-morbidity (CCI=0) (26.8%, 95% CI: 23.2-30.8) giving RD: 14.7, 95% CI: 8.8-20.6 (p=0.001).

8. In the analyses, GP interpretation of symptoms was adjusted for a comorbidity score and other covariates. There might be an interaction between co-morbidity and GPs interpretation of symptoms – did you investigate this? You also say that there is no difference in PI according to disease stage. Was this analysis adjusted (for other covariates including GP interpretation of symptoms), or unadjusted? If recall bias led to an underestimation of the relationship between time intervals and non-alarm symptoms, as suggested in your discussion, this might account for the lack of difference according to disease stage?

Comment: We agree that patients with comorbidity (especially lung disease) may have a longer primary care interval as the symptoms “might already be there”. We tested that and found that there was no statistical difference between PI and comorbidity.

9. It is suggested that GP questionnaires result in under-estimation of primary care intervals; would this underestimation indicate a need for further research to inform the optimisation of the ‘non-fast track’ diagnostic pathways? The abstract concludes that ‘We need studies investigating the low diagnostic activity prior to diagnosis’. Perhaps a more in-depth discussion could be provided in the article, of the further evidence/ type of studies needed.
Comment: It should be more explicitly stated what studies we would recommend. First, we would recommend a RCT on better access to a technologically upgraded investigation for lung cancer i.e. low-dose CT scan. Second, there could be some clinical algorithms for patients in high risk of having a lung cancer. That is, e.g. studies on positive predictive values for specific combinations of symptoms and clinical signs and decision support in general practice.

Minor essential revisions:

10. I found the first paragraph of ‘descriptive data’ difficult to follow. For example, if there were 124 patients registered before the 1st May why would they be included, and if they were not included, why are they being described? I was also unclear how the authors arrived at 971 (included).

Comment: We are sorry that the paragraph was confusing, it has now been revised.

Reviewer 3

11. Introduction. What is now the 4th sentence of Introduction contains some often quoted non-sequitur logic, i.e. it may be possible that stage at diagnosis is more advanced in Danish patients (first half of the sentence), but the ‘proof’ of this cannot be had by simply looking at short-term relative survival differences (second half of sentence, after ‘e.g.’). Apart from stage at diagnosis, short-term survival is known to be also influenced by quality (or aggressiveness) of treatment, host factors such as co-morbidity or frailty, and also route to diagnosis per se and independently of stage (see papers by Brewster BJC 2011 http://www.ncbi.nlm.nih.gov/pubmed/21206498 and also McPhail et al BJC 2013 http://www.ncbi.nlm.nih.gov/pubmed/24045658 – incidentally the last recent reference would be useful to quote in addition to Elliss-Brookes BJC 2012 which the authors do usefully cite). I am not saying that Danish patients do not present at comparatively later stage, this cannot be demonstrated by referring to short-term survival statistics.

Comments: The reviewer is absolutely right. The stage at diagnosis is only one contribution to the prognosis. The sentences are now revised and shortened. The reference suggested by the reviewer is used in discussion in addition to Elliss-Brookes.

12. Methods. Please stipulate what was the source of staging information (was it the decision of the treating multi-disciplinary team or the decision of a trained medical coder / registrar) and was it based on pathological, radiological or clinical information, or any of above. Often studies do not indicate the method
used for assigning stage at diagnosis, and this poses problems of comparability and interpretation between studies.

Comments: It is very important to know the source and type of staging in order to interpret the results and compare with other studies. The methods section about staging is elaborated. “Information about tumour stage at diagnosis in DCR is provided by a multi-disciplinary team decision based on pathological (pTNM) information with few exceptions”.

13. If information on stage relates to ‘stage at diagnosis’, please use this term instead of simply ‘stage’.

Comments: ‘Stage’ is now ‘stage at diagnosis’ throughout the article.

14. Results. Routes to diagnosis. Information here is very difficult to follow – I do not think I could understand. This is likely to fox other readers too – it is important information that will interest international readers in particular. Please re-write and use a new bar chart figure dedicated to this issue.

Comments: Routes to diagnosis. We are sorry that the information is difficult to understand. The section is re-written and the chart figure is made clearer.

15. Primary care interval and diagnostic interval acronymisation. The authors are using (if I understood well) the acronym PI to denote ‘primary care interval’. This is very unfortunate as PI would typically denote ‘patient interval’ – not ‘primary care interval’. I would personally avoid acronymising of ‘primary care interval’ in any case, but if you feel you must acronymise please opt for an unequivocal and intuitive acronym. Please implement de-acronymising (preferably) or intuitive choice of initial for acronymising through the paper (e.g. also in discussion).

Comments: Thank you for pointing out this important issue. We do not wish to cause any confusion about acronymisations and the section is changed so the intervals are de-acronymised.

16. On both intervals: Please present information on overall median intervals (for either primary care or diagnostic interval) in Results / main text, not only PRs etc.

Comment: This is very important information and of course the overall median intervals are now included in the result section.
17. Discussion. In comparisons with other studies please consider reflecting on two additional items of reflection.

A. Overall primary care interval. In the English Audit of Cancer Diagnosis in Primary Care the median primary care interval for lung cancer was 14 days, compared with 7 days in this study – could you reflect on the difference (see Table 1 of Lyratzopoulos, Abel, McPhail, Neal, Rubin http://www.ncbi.nlm.nih.gov/pubmed/24045658 ).

Comment: That is now cited as well.

B. Number of pre-referral consultations. Also, the same table of the same paper, and also http://www.ncbi.nlm.nih.gov/pubmed/22365494 indicate that > 30% of all lung cancer patients whose diagnosis involved first presenting to a general practitioner required 3 or more pre-referral consultations. Are there any similar statistics in Demark that can be quoted, or could the measure of pre-referral consultations in the Danish context be reflected upon?

Comment: The aim of this paper was not to measure the number of pre-referral consultations. The use of that is very difficult and may be misleading as 1) it should be a relative measure compared to others presenting to the GP, 2) it is arbitrary to use three consultations as some patients would need three contacts to be proper examined (e.g. three in a week) and it would be worse to have only two in a year, 3) it should be within a specific time interval and 4) it should be related to the cancer and not other diseases. Therefore, that would be another interesting paper..

18. Could the authors in limitations consider the potential influences / biases from missing data? Can it be for example that the proportion of patients who had seen a GP is higher / lower than that observed in complete case analysis – what are the authors’ thoughts on the potential directionality of any potential bias?

Comment: Thank you for this comment, missing data is a problem in this study and we can only guess in which direction it will go. “It might be that GPs who did not respond more often were not involved in the diagnostic pathway. For these patients the diagnostic intervals may be shorter because those patients are diagnosed in hospitals in connection with another disease thus making us overestimate the overall intervals”.

Minor Essential revisions:

None.
Discretionary revisions:

19. Introduction. First two sentences add no new information to any biomedical reader (or even to lay readers) – the article can easily start from what is now the 3rd sentence with no loss of clarity or argument. I flag up as an example of possible shortening of the presentation of the whole article, throughout. Aiming for word count of 2500-3000 words would be beneficial, even if not strictly required by the journal house-style.

Comment: The reviewer is right. We have removed the two sentences and throughout the article we tried to shorten it.

20. The use of the term ‘waiting time’ (e.g. in the first paragraph of introduction) is open to misinterpretation, often there is no ‘waiting’ as such, just misinterpretation of the importance of symptoms either by patients or doctors. ‘Waiting’ as such can only happen if the correct diagnosis has been suspected but there are bottlenecks in the system or other practical obstacles to timely presentation or referring action. I think the authors simply mean ‘prolonged intervals to diagnosis’ or similar terminology with which I am sure are very familiar (given the Aarhus statement).

Comment: The sentence is removed, thank you for pointing it out for us.

21. The figure 3 legend appears chopped and I cannot make full sense of it.

Comment: The legend is elaborated.

22. Lastly, it would be useful if the authors knew / can present information about the proportion of all patients who are referred ‘fast track’ for investigation for lung cancer that are found to have lung cancer (not only what proportion of lung cancer patients are fast-track referrals).

Comment: Yes, indeed this information would be very useful and interesting. Unfortunately, this information is not available in Denmark.