PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Social differences in lung cancer management and survival in South East England -A cohort study
AUTHORS	Anders Berglund, Mats Lambe, Margreet Lüchtenborg, Karen M. Linklater, Michael D. Peake, Lars Holmberg and Henrik Møller

VERSION 1 - REVIEW

REVIEWER	Susanne Oksbjerg Dalton Senior Researcher, Survivorship Danish Cancer Society Research Center Denmark I declare no competing interest
REVIEW RETURNED	14/03/2012

RESULTS & CONCLUSIONS	This is a well written paper which adresses a very relevant research question using high quality data and appropriate methods. I have only few comments and concerns that I think the authors should consider in order to possible improve the paper: Were there no information on FEV1 or Performance status (PS) in the audit data. Inclusion of this information could qualify the comorbidity data used, as the Charlson index used as I understand it is defined based on discharge diagnosis and thus will not distinguish between severe or lighter cases of a disease, ie COPD? I think that clinicians use PS or FEV1 quite rigidly when they i.e. advice surgery or not - even in the presence of COPD or cardiovascular disease? Might not change results substantially but even if these data are not available, I think at least this limitation should be adressed in regard to the use of Charlson Index Also, I find a discussion of potential dis-/advantages in the use of area-based deprivation measures - as opposed to individual measures. I also think that the literature that they discuss their findings in regard to should be more balanced, i.e. in Denmark and in the US (using insurance data) recently social inequality in stage of lung cancer was observed and inclusion of this evidence is warranted. Further did the authors consider including delay within the health system as a possible mediator of any inequality. Absence of high quality data in the databases available on dates might hinder this, but still this should be discussed - in line with absence of information on 2.line treatment.

REVIEWER	Dr S. Michael Crawford

	Consultant Medical Oncologist Honorary Senior Lecturer in Oncology & Clinical Research Airedale General Hospital West Yorkshire BD20 6TD United Kingdom No conflict of interest.
REVIEW RETURNED	23/03/2012

GENERAL COMMENTS	A number of points of clarification are needed. METHODS p6 l2 as written, "stage III non-small cell lung cancer" and "all stages of small cell..." means that stage III SCLC is counted twice, I take this to be a typo. The effect of the introduction of the 7th edition of the TNM classification will have a bearing on the current applicability of their analysis, this should be discussed. These are points of detail; the further evidence that this study provides into the influence of deprivation on early mortality, which is generally taken to be the effect of late diagnosis, whatever the precise meaning of that term, should be a further stimulus to study what affects the timeliness of a patient's diagnosis. Since BMJ Open referees are not anonymous, I will take the opportunity to point out that in Reference 32 we showed not only that deprivation affected access to the centralised service of thoracic surgery when is was situated at a distance from the patient's home but the same phenomenon coulkd be seen in respect of access through a local hospital to any treatment and to histological diagnosis. p6 l37 socioeconomic quintile - it should be made clear that the population distribution of deprivation defines to which quintile a patient belongs; thus there are more cases in Q5 than Q1. Also, the deprivation index fo a post code relates to an area, not an individual - the rich man in his castle and the poor man at his gate reside in the same super output area and therefore have hte same index. This tends to reduce differences between deprivation groups. RESULTS P8 l28 Table 1 (p18) The histologic type "unspecified" will include those where no histology has been obtained as well as those where the diagnosed is not classifiable by the registry; this difference is important and the group should be divided accordingly. Attainment of a tissue diagnosis is an essential step in the active management of lung cancer and the proiportion in whom this is achieved has previously been shown to vary betwen population groups - if the variation has been abolished in the present cohort, that is an important finding.

VERSION 1 – AUTHOR RESPONSE

Comment 1: Were there no information on FEV1 or Performance status (PS) in the audit data. Inclusion of this information could qualify the comorbidity data used, as the Charlson index used as I understand it is defined based on discharge diagnosis and thus will not distinguish between severe or lighter cases of a disease, ie COPD? I think that clinicians use PS or FEV1 quite rigidly when they i.e. advice surgery or not - even in the presence of COPD or cardiovascular disease? Might not change

results substantially but even if these data are not available, I think at least this limitation should be adressed in regard to the use of Charlson Index

Answer 1: Yes, the information underlying the assessment of the Charlson Comorbidity Index (CCI) was based on discharge diagnosis and could not distinguish between milder or severe cases of a specific disease. Unfortunately, in this register-based approach no information was available on other measures of health status such as forced expiratory volume within one second (FEV1) or performance status (PS). We are aware that measures of FEV1 have been associated with the occurrence of postoperative complications and that decisions regarding oncological treatments often are based on the host's PS. Please see an added sentence in the manuscript that clarifies these limitations (page 11, first paragraph).

Comment 2: Also, I find a discussion of potential dis-/advantages in the use of area-based deprivation measures - as opposed to individual measures.

Answer 2: The use of area-based deprivation measures is likely to lead to an underestimation of social differences in survival (Smith et al, 1998, J Epidemiol Community Health). Since the variability in socioeconomic status based on area characteristics will always be smaller than that on the individual level (Smith et al, 1999, Am J Epidemiol). Please see an added sentence in the manuscript (page 11-12, bottom, second paragraph).

Comment 3: I also think that the literature that they discuss their findings in regard to should be more balanced, i.e. in Denmark and in the US (using insurance data) recently social inequality in stage of lung cancer was observed and inclusion of this evidence is warranted.

Answer 3: We agree. We have updated the discussion with the results from the Danish investigators and the study from Unites States (page 12).

Comment 4: Further did the authors consider including delay within the health system as a possible mediator of any inequality. Absence of high quality data in the databases available on dates might hinder this, but still this should be discussed - in line with absence of information on 2.line treatment.

Answer 4: Data at hand for the purpose of the present project did not allow to assessment of delay as a mediator for observed inequalities. A recent Danish population based study documented associations between educational level and time between referral and diagnosis (Dalton et al, 2011, Br J Cancer), findings which corroborate with results from Sweden (Berglund et al, 2010, Thorax). This is now added in the manuscript (page 13).

Reviewer: Dr S. Michael Crawford
Consultant Medical Oncologist
Honorary Senior Lecturer in Oncology & Clinical Research
Airedale General Hospital
West Yorkshire
United Kingdom

No conflict of interest.

A number of points of clarification are needed.

Comment 5: METHODS p6 l2 as written, "stage III non-small cell lung cancer" and "all stages of small cell..." means that stage III SCLC is counted twice, I take this to be a typo. The effect of the introduction of the 7th edition of the TNM classification will have a bearing on the current applicability

of their analysis, this should be discussed.

Answer 5: The study population was subdivided into three categories (where two of them were not mutually exclusive), 1) stage IA-IIB non-small cell lung cancer 2) stage III non-small cell lung cancer, and 3) stage III-IV disease or all stages of small cell lung cancer. These three subgroups were created based on the basis of the most commonly used initial treatment modalities in every separate group. This has now been clarified in the manuscript (page 6).

The introduction of the 7th edition of the TNM classification was not available until the middle of 2009 (Travis W.D, Histopathology, 2009), and our data was based on patients diagnosed between 2006 and 2008. The new TNM classification provides better prognostic differentiation, hence some caution should be taken when a reader generalise the findings to the situation of today. This has now been discussed in the manuscript (page 11).

Comment 6: These are points of detail; the further evidence that this study provides into the influence of deprivation on early mortality, which is generally taken to be the effect of late diagnosis, whatever the precise meaning of that term, should be a further stimulus to study what affects the timeliness of a patient's diagnosis.

Answer 6: Social differences in stage at presentation have been proposed as an explanation for observed differences in survival early in the follow-up. However in the present study, we observed no social differences in stage at diagnosis, but patients with higher socioeconomic status were more likely to receive an active treatment which may partly explain our findings.

Comment 7: Since BMJ Open referees are not anonymous, I will take the opportunity to point out that in Reference 32 we showed not only that deprivation affected access to the centralised service of thoracic surgery when is was situated at a distance from the patient's home but the same phenomenon coulkd be seen in respect of access through a local hospital to any treatment and to histological diagnosis.

Answer 7: Thank you for the comment and an interesting study. This is now added in the manuscript (page 13).

Comment 8: p6 l37 socioeconomic quintile - it should be made clear that the population distribution of deprivation defines to which quintile a patient belongs; thus there are more cases in Q5 than Q1. Also, the deprivation index fo a post code relates to an area, not an individual - the rich man in his castle and the poor man at his gate reside in the same super output area and therefore have the same index. This tends to reduce differences between deprivation groups.

Answer 8: Please see response to comment 2 (Reviewer 1). The use of area-based deprivation measures is likely to lead to an underestimation of social differences in survival (Smith et al, 1998, J Epidemiol Community Health). Since, the variability in socioeconomic status based on area characteristics will always be smaller than that on the individual level (Smith et al, 1999, Am J Epidemiol). Please see an added sentence in the manuscript (page 11-12, bottom, second paragraph).

Comment 9: RESULTS P8 l28 Table 1 (p18) The histologic type "unspecified" will include those where no histology has been obtained as well as those where the diagnosed is not classifiable by the registry; this difference is important and the group should be divided accordingly. Attainment of a tissue diagnosis is an essential step in the active management of lung cancer and the proiportion in whom this is achieved has previously been shown to vary betwen population groups - if the variation has been abolished in the present cohort, that is an important finding.

Answer 9: In our dataset “unclassifiable” does not include patients without histopathology. Thus, unclassifiable still means that a histopathological assessment was done. The proportion of cases categorized as unspecified was somewhat lower in the most affluent group. Among patients with classifiable disease, the proportion of non-small cell lung cancer was higher in the most affluent group (please see Table 1), which is presented in the result section (page 8).

VERSION 2 – REVIEW

REVIEWER	Dr S. Michael Crawford Consultant Medical Oncologist Honorary Senior Lecturer in Oncology & Clinical Research Airedale General Hospital United Kingdom I have no conflicting interests.
REVIEW RETURNED	20/04/2012

The reviewer completed the checklist but made no further comments.