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Title	Initial presentation of lung cancer through the emergency department: a complete provincial descriptive analysis
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Reviewer 1	Pooya Dibajnia
Institution	Trillium Health Partners, Queensway Health Centre Oncology, Toronto, Ont.
General comments (author response in bold)	The ED newly diagnosed/suspected lung cancer is an interesting topic, and the authors should be commended for their efforts. The retrospective cohort study using NS provincial registry found over a third of lung CA cases to be initially identified/suspected in the ED, which were more likely to be advanced stage. This descriptive study highlights the importance of studying this route to diagnosis. I wonder if similar proportions are found in other provinces, however. In more populous provinces with large urban centres, I hypothesize that a smaller proportion of cases are found in the ED, as patient may have better access to family physicians (FP) or walk-in clinics who can request out-patient imaging. Unfortunately, we don't have data on this in Canada.

The authors suggest that whether a patient has a FP or not does not affect the rates of ED presentation. They cite that only 7% of patients diagnosed in ED had no family physician, representing a minority of cases. Although this may be true, to strengthen their argument, I think they need to provide what proportion of non-ED diagnosed patients lacked a family physician for comparison. As a reference, it is known that approx 42000 Nova Scotians (as of Dec 2017) were on a waitlist to find a family physician, which represents 4.5% of the population, so certainly 7% is not an unreasonable number.
Thank you for this important comment. For clinical reasons, at the time of ED presentation, registration data entry must include information regarding the family physician. Unfortunately, this information was unavailable for 22% of cases in the non-ED cohort. As this data was deemed less reliable by the research working group initially it was not reported. However, we agree that it is important to provide what data we do have and that these limitations should be included. Changes have been made to the methods, results and interpretation sections. We have also added into the interpretation section, data from statistics Canada regarding the number of patients without a physician in Nova Scotia in 2014.

I think the authors need to clarify what the definition of "Registry date of diagnosis" is. I am guessing that this is based on a pathological diagnosis, but it was not explicitly stated in the paper.
This is a key element of our paper and we thank the reviewer for noting the need for clarification. This was defined in the methods section but may have been confusing. We have modified this section to make this definition less confusing.
The registry follows Canadian Council of Cancer Registries standards for deriving date of diagnosis making use of multiple sources of information, including histology/pathology, cancer clinic visits and death certificates (13). Date of diagnosis for lung cancer cases is prioritized in the following hierarchical manner: cytology, pathology, imaging, clinical, and death certificate. This means that lung cancer cases that are first diagnosed through imaging but are later confirmed through biopsy (cytology) will be registered with a diagnosis date consistent with the biopsy not the imaging.

One intriguing finding in this paper was the time delay from clinical to registry diagnosis, and the discrepancy between ED and non-ED diagnosed cases. It found that ED diagnosed cases had a much shorter delay than non-ED cases. I think this highlights the importance of implementing measures to expediting referral of suspected cases to thoracic specialists outside of the ED, something that is supported by several studies in literature. I think the paper could benefit from a description of the current referral process in place in Nova Scotia, such as the presence of regional thoracic programs to Diagnostic Assessment Units found in other provinces (e.g. Ontario).
At the time of the study there were no specific lung cancer referral programs. We have added detail regarding the referral process at the time of the study:
"Patients may not self-refer for diagnostic imaging, biopsy or specialist consultation in Nova Scotia. Therefore, all patients diagnosed with lung cancer through the non-ED route had a referring physician but not necessarily a primary care provider. In 2014 there were no lung-cancer specific clinics in the province; the diagnostic process could be guided by primary care or by specialist. Referrals for work up or treatment could be sent to internal medicine, respirology (pulmonology), oncology or thoracic surgery."
We agree the delay between clinical diagnosis and registry diagnosis is very interesting. We suspect that the shorter delays in the ED group may reflect more severe symptoms. As discussed above, to our knowledge "date of clinical diagnosis" is a clinically-observed concept that does not have an associated epidemiologic measure. The interval between clinical date of diagnosis and registry date of diagnosis is not synonymous with the diagnostic interval as time zero is not the first suspicious test but the first confident or definitive test. We found a large time discrepancy between highly concerning imaging (not just suspicious) and tissue diagnosis. It is interesting that this time delay did not always reflect wait times or poor access to resources. In many cases, patients saw lung cancer specialists in a timely fashion but tissue diagnosis was not confirmed immediately. This appears to be for one of four reasons: poor patient health at the time of initial work up; imaging consistent with cancer treated initially by "active surveillance"; "positive" CT but work up stops inappropriately or is delayed after false negative PETCT or biopsy, and patient preference. This may reflect the difficulty in obtaining lung biopsies relative to other primary cancer sites including breast, prostate, cervix, and colon cancers. A full analysis of the delay between clinical diagnosis and registry diagnosis is certainly worth pursuing but was not the objective of this study and appears to be beyond reasonable scope given CMAJ open word and paragraph limits. We have reviewed this issue at length and because this is a complex issue and somewhat removed from the objectives of the study, we have decided to remove this issue of "clinical date of diagnosis" and hope the reviewers agree this is the appropriate course of action.

I agree with the authors interpretation that there is a large patient-component - such as socioeconomic status, smoking status, fear and stigma - that affects a patient's presentation to a physician. This paper can lead to discussion of how to improve community detection of lung CA, including surveillance strategies. |
| **Reviewer 2** | Camille Maringe |
| Institution | Cancer Research UK Cancer Survival Group, London School of Hygiene and Tropical Medicine, London, UK |
| General comments (author response in bold) | Initial presentation of lung cancer through the emergency department: a complete provincial cohort review

Thank you for this opportunity to review this manuscript on the extremely topical and important subject of emergency presentation of lung cancer. Since the "route to diagnosis" project happened in the UK, cancer patients are assigned a route to diagnosis routinely following linkage of data sources (screening, hospital episode statistics, ...). The initial results of this work, and follow-up analyses looking at short-term survival by route to diagnosis, have led to a general drive in reducing proportions |

of emergency presentation.

It is encouraging to see a growing interest worldwide in understanding diagnoses happening after visiting the emergency department.

It seems the manuscript presents the first Canadian estimates of diagnosis of lung cancer through the emergency department. The authors have access to a wealth of information on the lung cancer patients and tumour characteristics diagnosed in 2014. There is potential for a very fine and detailed analysis of the patients diagnosed through the ED and non-ED.

I have some major comments as well as some minor points I would like to raise, which I hope could be helpful to the authors.

Major comments:

1. Aims and objectives of the manuscript:
I record two main aims of the paper:
Quantify the proportion of lung cancer patients diagnosed through the ED
Highlight characteristics of patients associated with emergency diagnosis
Both of them are followed through in the results section, and in the interpretation. Nonetheless the second aim could have been better addressed, given the data available. The characteristics highlighted mostly refer to post-diagnosis characteristics: stage and survival. What about what happens before diagnosis: who the patients are.
We have included a table (Table 1) comparing the two groups in terms of age, sex and indication for testing. We have added data comparing the 2 groups with respect to the presence of a family physician.

These characteristics are not properly assessed or reported: presence of a family practitioner is only assessed in ED patients, what about the proportions without a practitioner in non-ED patients?
RESPONSE: As discussed above:
For clinical reasons, at the time of ED presentation, registration data entry must include information regarding the family physician. Unfortunately, this information was unavailable for 22% of cases in the non-ED cohort. As this data was deemed less reliable by the research working group initially it was not reported. However, we agree that it is important to provide what data we do have and that these limitations should be included. Changes have been made to the methods, results and discussion sections. We have also added into the discussion section, data from statistics Canada regarding the number of patients without a physician in Nova Scotia in 2014.

"Indication for testing" is not compared between ED and non-ED routes in the results section.
Thank you for this note. It is included in table 1 and a note regarding the table has been added to the results section.

Time variations between clinical and registry dates of diagnosis are not explained or looked into further.
RESPONSE: As discussed above:
"The interval between clinical date of diagnosis and registry date of diagnosis is not synonymous with the diagnostic interval as time zero is not the first suspicious test but the first confident or definitive test. We found a large time discrepancy between highly concerning imaging (not just suspicious) and tissue diagnosis. It is interesting that this time delay did not always reflect wait times or poor access to resources. In many cases, patients saw lung cancer specialists in a timely fashion but tissue diagnosis was not confirmed immediately. This appears to be for one of four reasons: poor patient health at the time of initial work up; imaging consistent with cancer treated initially by "active surveillance"; "positive" CT but work up stops inappropriately or is delayed after false negative PETCT or biopsy, and patient preference. This may reflect the difficulty in obtaining lung biopsies relative to other primary cancer sites including breast, prostate, cervix, and colon cancers. A full analysis of the delay between clinical diagnosis and registry diagnosis is certainly worth pursuing but was not the objective of this study and appears to be beyond reasonable scope given CMAJ open word and paragraph limits. We have reviewed this issue at length and because this is a complex issue and somewhat removed from the objectives of the study, we have decided to remove this issue of "clinical date of diagnosis" and hope the reviewers agree this is the appropriate course of action."

2. Presentation of results:
The presentation of results, in tables and graphs, and in the paper needs some improvement. Table 1 should include the comparison of all variables discussed in the results section. The proportions given the results section (row proportions) are not those presented in Table 1 and bring some confusion. The variable "deaths" should specify the length of time in which deaths were ascertained.
This comment has been partially addressed in the response to the editor. As mentioned previously, the formatting of the graphs has been improved to make them more visually appealing and clear. Table one proportions are vertical and now more consistent. We felt for patient sex it was important to discuss this in the body of the text manuscript with horizontal proportion. We have added a phrase to the text to make this difference more clear. Upon reviewing Table 1 we realized that the proportions in the rows were not clear as to how they were being derived as noted by this reviewer and we have relabeled some of the table entry categories and removed the distracting additional blank rows. The death interval date was described in the methods section. However, this section of the methods has been reworded to more clearly explain that the death interval is based on the interval from the date of diagnosis in 2014 to a death date cutoff of August 31, 2016. We are unsure if the reviewer also wanted this added to the table. We have added it to the table. We understand that we are not to include all data in both the results section and the table.

For both x-axis in Figure 1, the titles are "days from diagnosis". It would be helpful to know which is which, rather than work it out from the values of the x-axis. The number of days is not the most explicit measure of time; months would provide a better indication of time.
We have removed the clinical date of diagnosis graph to add clarity. As for the measure of time, days is the registry standard and in the case of the ED group there were sufficient cases with less than 30 day survival that the first portion of the KM curve would be less illustrative of the trajectory of this patient group if we changed to months as the time unit.

3. Date of diagnosis:
Firstly, although it is specified that the date of diagnosis in the cancer registry data follow the nationwide standards, it would be helpful to know what international rules are followed (SEER, IACR, ENCR?).
Thank you for this comment. We have contacted the Provincial Program for Cancer Care at the Nova Scotia Health

Authority. They have provided some clarification and we have added the details to the methods section.

Secondly, I do not understand why survival time is explored from two "dates of diagnosis". I believe the time between imaging and the cancer registry date of diagnosis may refer to the diagnostic investigation interval – but this is not explicitly stated. There are quite a lot of details in the paper as to how the two dates are defined, but not what the lengths of time would reflect and what the norm should be.

As discussed above:

There are no pre-existing formal criteria for clinical date of diagnosis regarding lung cancer. To our knowledge this is a clinically-observed concept that does not have an associated epidemiologic concept. While there are published standards regarding optimal duration of the diagnostic investigation interval there are no standards regarding delays between clinical date of diagnosis and registry date of diagnosis. The interval between clinical date of diagnosis and registry date of diagnosis is not synonymous with the diagnostic interval as time zero is not the first suspicious test but the first confident or definitive test. We found a large time discrepancy between highly concerning imaging (not just suspicious) and tissue diagnosis. It is interesting that this time delay did not always reflect wait times or poor access to resources. In many cases, patients saw lung cancer specialists in a timely fashion but tissue diagnosis was not confirmed immediately. This appears to be for one of four reasons: poor patient health at the time of initial work up; imaging consistent with cancer treated initially by "active surveillance"; "positive" CT but work up stops inappropriately or is delayed after false negative PETCT or biopsy, and patient preference. This may reflect the difficulty in obtaining lung biopsies relative to other primary cancer sites including breast, prostate, cervix, and colon cancers. A full analysis of the delay between clinical diagnosis and registry diagnosis is certainly worth pursuing but was not the objective of this study and appears to be beyond reasonable scope given CMAJ open word and paragraph limits. We have reviewed this issue at length and because this is a complex issue and somewhat removed from the objectives of the study, we have decided to remove this issue of "clinical date of diagnosis" and hope the reviewers agree this is the appropriate course of action.

Subsequently I am unsure why we would want to study survival time from each of these dates and why it was only done once (in the overall analyses) and not in the stage-specific analyses. I would have thought it would be informative to look/explain the time between the imaging and cancer registry date on one hand, and survival time from diagnosis on the other hand.

Thank you for this comment. We have removed the graph of the imaging date of diagnosis survival time from figure 2.

4. Cox model:

The results from the Cox model are omitted: only two HRs are quickly mentioned in the last paragraph of the results. I thought it would have been an opportunity to understand the complex relationship between stage, maybe age, sex, emergency presentation and hazard of death.

Thank you for this observation. This comment was also partially addressed in the overall comments from the editor above. The omission of the Cox regression analysis was an oversight. The Cox model was done to explore the relationship between stage, age, emergency diagnosis and hazard of death.

Minor points:

(1) Introduction: the introduction presents some incidence estimates for 2017 in future tense, which although I understand there is a delay in case reporting, and publication of incidence figures, reads strangely. Could this be reworded?

Thank you for this kind suggestion. We agree. We have updated the reference (new report released June 2018) and reworded the sentence as follows:

Current Canadian estimates include 28,600 new cases of lung cancer annually, accounting for 14% of all new cancer cases and 26% of all cancer-related deaths.

(2) The sentence "A majority (67%) of lung cancer patients present with general respiratory complaints" needs a reference.

Thank you for noting this error. The reference has now been re inserted.

(3) "most of these patients die within one year (7)" page 7 line 42 need to be more specific, with a proportion.

Thank you for this helpful comment. Originally, we had estimated this based on published US SEER data. However, we have been able to find more specific information and have added the new reference. This section has been updated as follows:

In Canada, 68.8% of lung cancer cases are diagnosed at an advanced stage (III or IV) (2), with 56.4% of stage III and 83.2% of stage IV patients dying within one year of diagnosis (3).

The new reference (3) is:

Walters S, Maringe C, Coleman MP et al. Lung cancer survival and stage at diagnosis in Australia, Canada, Denmark, Norway, Sweden and the UK: a population-based study 2004-2007. Thorax.2013;68;551-564.

(4) Ref 10 line 46 page 7 is not adequate for what is said there.

Thank you for identifying this serious error. We agree reference 10 should not be included here. It was meant to be included in the interpretation section.

(5) Line 52 and 53 page 7 need a reference relative to the growing number of patients without a primary care provide.

Thank you for identifying this oversight. We were able to find current data from the Nova Scotia Health Authority and have added the reference.

(6) Line 88-89, page 9: why not check the evidence of primary care physician in non-ED patients?

This is an important comment. Please see responses above regarding the addition of this data and the limitations.

(7) Line 98-99 page 9: are the examples given from the actual notes? I would keep it more general here, and report these examples in the results section.

Thank you for this comment. We have discussed your comment in depth. These examples were identified prior to initiating the study, to give the data extractors guidance. We did not record the actual specific reasons during the study. In addition, in order to not duplicate the data presented in the table, the text of the manuscript does not repeat the percentage of lung cancers found incidentally.

(8) Sentences in lines 116-118 page 10 could be condensed, and the reason why this is done given here or previously.
Thank you for this suggestion. The methods section has been reorganized as suggested by the editor.

(9) Line 199 page 10: stage and route-specific KM curves
Thank you for noticing this omission. It has been corrected.

(10) Line 147 page 11: 79.4% rather than 80%. Also why are the differences in proportions by route to diagnosis not presented here? It would be more informative and in line with the aims of the paper.
This discrepancy has been corrected. The differences in proportions are noted in Table 1. We understand that we should not include all data in the manuscript if it has been included in a table.

(11) Line 157 page 11: 1947 days is (hopefully) an outlier. You should say it or comment on those lengths of time. It may be that interquartile range should be reported here rather than minimum and maximum values (given outliers). What is the impact of the outlier on the average length? Should the median be reported? Did you look at the distributions of times?
The clinical (imaging) date of diagnosis for the non-ED group had a median value of 43 days earlier than the registry date of diagnosis with an interquartile range of 12 to 95 days. This discrepancy was less marked for the patients diagnosed through the ED route (median 9 days, interquartile range 1 to 43 days). Initially we did examine the distribution of times and performed an outlier analysis by the ROUT method. We considered removing outliers from the analysis but this did not seem a valid approach to us and the ROUT method identified approximately equal numbers of outliers in both diagnostic groups. Regardless, the issue of clinical date of diagnosis has been removed as explained above.

(12) Line 179-180 page 12: Would it be an even lower proportion in non-ED?
We agree this is a confusing sentence. Our intended suggestion is that compared to patients with a family physician, patients without a family physician are more likely to present to an acute care facility even if they do not have an emergent health issue. We have reworded this sentence.

(13) Line 183 page 12: are they truly "attributable causes" or simply associated?
Thank you for the comment. We agree that the references did not prove causation (or even association). We have included the word "postulated" to note that we are referencing opinions and we have changed "attributable causes" to "contributors". The authors' opinions go beyond suggesting association.

(14) Line 212-213 page 13: "more than 80%" – this is not supported by your results. The overall value is 79.4%.
Thank you for noticing this error. We have amended this phrase to "nearly 80%".