PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Treatment patterns and survival outcomes for patients with non-small cell lung cancer in the United Kingdom in the pre-immunology era: a REAL-Oncology database analysis from the I-O Optimise initiative
AUTHORS	Snee, Michael; Cheeseman, Sue; Thompson, Matthew; Riaz, Majid; Sopwith, Will; Lacoin, Laure; Chaib, Carlos; Manley Daumont, Melinda; Penrod, John; Hall, Geoff

VERSION 1 – REVIEW

REVIEWER	Vinod, Shalini Liverpool Hospital, Cancer Therapy Centre
REVIEW RETURNED	29-Nov-2020

GENERAL COMMENTS	This is largely a descriptive study of the NSCLC population from the Leeds trust. The discussion could be strengthened. What is lacking in the discussion is a comparison against other population based studies in the literature. What are the similarities and differences with other publications and what might explain this. Eg The 34% rate of clinically diagnosed cases is high compared on Australian and Canadian data. This needs discussion. What factors contribute to this, given that these patients were diagnosed by MDT? Is it due to lack of or waiting lists for CT guided biopsies, bronchoscopies, EBUS or is it a reflection of patient reluctance for biopsy confirmation?. This deserves further discussion. At present the discussion is largely confined to UK comparisons but could be strengthened with comparisons to international literature. In addition, it would be useful to compare survival in this study to those reported from major international trials for the different treatments ie what is the difference between clinical trial results and real world population results. Minor comments below. Methods, Page 8 Please clarify if the data were retrieved from a database (REAL oncology database?) where data was entered prospectively or was this a retrospective analysis of routine clinical data entered onto the hospital EMR? If there is a prospective database, what are the variables routinely collected and what is the quality assurance, if any, for this. It says data on chemotherapy, pathology and radiology were extracted from EMR. Where were the data for surgery and radiotherapy extracted from? Was this from a separate database? Were patients with a diagnosis of lung cancer (clinical or pathological) who were not seen by the MDT excluded? Ie Were the inclusion criteria all incident diagnoses of NSCLC during the time period or all incident diagnoses of NSCLC diagnosed by the Lung MDT during that period. Or is there no difference between

	the two. What is the lung MDT, are you just referring to a team of clinicians or is this implying diagnosis and discussion at MDT meeting? The end date of the study is only 7m after last incident case, so there is short FU in more recent cases. How many patients were PET staged over the years? Could this impact on the changes in stage distribution? Page 11 Wrt to initial treatment, what is the definition of curative radiotherapy? Is this based on a minimum dose or just intent of treatment? Was SABR available for the whole time period? Can you add some results about the use of SABR in Stage I NSCLC particularly given the large increase in use of RT in clinically undiagnosed patients (Figure 2) – was this increase largely due to SABR? A major limitation of this study is the lack of radiotherapy details given the importance of radiotherapy as a treatment modality for all stages of NSCLC. Table 1 Suggest combining NSCLC NOS and other, and adding p values for comparisons btwn NSQ, SQ, NSCLC NOS/Other and Clinical diagnosis as there are clearly some differences eg clinically diagnosed patients older median age and worse performance status. Given that 3 different staging systems were used in this cohort with evolution over time, I suggest the stages reported in Table 1 be simply Stage I, II, IIIA, IIIB and IV. There isn't much point in dividing the earlier stages. However Stage IIIA/IIIB/IV results are reported separately so needs to be reported as such in this table. Figure 3 I find this difficult to interpret as there are 3 shades of blue used. Suggest use the same colour by pathology type (eg red, blue, green) and use solid line for one time period and dashed line for different time period, and this will make it easier to see the differences and similarities.

REVIEWER	Savage, Philip Brighton and Sussex University Hospital, Brighton; Imperial College Healthcare National Health Service Trust, Oncology
REVIEW RETURNED	27-Dec-2020

GENERAL COMMENTS	Thanks for this revised manuscript Whilst there were no comments to reviewers included it reads well and is a useful addition of real world data to the literature. I have only 3 minor points 1/ The study is for patients 2007-2017 However the results in page 9 compare 2010 to 2017 patient data 2/ Fig 2 The Venn diagrams seem v hard to follow could the date be presented in numerical data 3/ Fig 3 again a lot of data could it be simplified and still get the key message across However, this is an important data set, has involved a lot of work and is a welcome addition

VERSION 1 – AUTHOR RESPONSE

Reviewer #1: Dr. Shalini Vinod, Liverpool Hospital

Major comments:

Comment: This is largely a descriptive study of the NSCLC population from the Leeds trust. The discussion could be strengthened. What is lacking in the discussion is a comparison against other population based studies in the literature. What are the similarities and differences with other publications and what might explain this. Eg The 34% rate of clinically diagnosed cases is high compared on Australian and Canadian data. This needs discussion.

Response: We thank the reviewer for this comment. The discussion has been updated to include comparisons to international population-based studies in the literature. Regarding the high rate of clinical diagnoses in the UK versus Australia and Canada, this pattern has been reported previously, and may relate to concerns around frail elderly patients undergoing surgery [Walters S, et al. Thorax 2013;68:551–564]. Indeed, in our study, patients with a clinical diagnosis of NSCLC were more likely to be older and have a lower PS than those with a pathologically confirmed diagnosis. This has been added to the discussion as follows (p15):

"These patients were either not deemed suitable for treatment or had an early stage peripheral tumour invisible on bronchoscopy and compromised respiratory function; therefore, biopsy confirmation was not justified. Our findings are consistent with an International Cancer Benchmarking Partnership study showing that the rate of clinical diagnosis (i.e., no pathological confirmation) for lung cancer over 2004–2007 was higher in the United Kingdom (26.0%) compared with Australia (14.4%), Canada (18.2%), Denmark (13.5%), Norway (10.1%) and Sweden (5.2%) [Walters S, et al. Thorax 2013;68:551–564]. Although the National Lung Cancer Audit in England set a target of 75% for pathological confirmation, there remains wide variation. For example, Khakwani et al. (2013) found that the rates of pathologically confirmed lung cancer in England varied widely according to age, sex, PS, comorbidity, and the method of referral to a specialist. The two most important patient features were age and PS, with less than 50% of patients aged ≥75 with PS >2 having a pathological confirmation (Khakwani A, et al. Lung Cancer 2013;79:125–131). "

Comment: What factors contribute to this, given that these patients were diagnosed by MDT? Is it due to lack of or waiting lists for CT guided biopsies, bronchoscopies, EBUS or is it a reflection of patient reluctance for biopsy confirmation? This deserves further discussion.

Response: There are two main reasons. First, a high proportion of patients with advanced disease presented with poor PS and were considered to be unfit for treatment; therefore, biopsy confirmation was not justified. Second, high numbers of patients with early stage disease presented with small lesions and were not fit for surgery; we deemed that biopsy was too risky in these cases. These patients were offered SABR as a form of curative treatment on the basis of a clinical diagnosis. The predominant method of clinical diagnosis was via Brock and Herder models. We have added the following text to the manuscript (p15):

"These patients were not deemed suitable for treatment and therefore, biopsy confirmation was not justified."

Comment: At present the discussion is largely confined to UK comparisons but could be strengthened with comparisons to international literature. In addition, it would be useful to compare survival in this study to those reported from major international trials for the different treatments ie what is the difference between clinical trial results and real world population results.

Response: Thank you for your comment. Some comparisons to international literature have been added to the discussion. We have also included some information from a systematic review and meta-analysis on OS data from international RCTs comparing first-line chemotherapy in patients with stage IIIB/IV NSCLC [Pilkington et al. Thorax 70(4):359–367]; see pages 17–18. These findings highlight that outcomes for patients treated in real-world settings do not compare favourably to those treated in RCTs, possible due to patients in the real-world being older and less fit than those in RCTs. The following has been added to the discussion:

"Despite some improvements in patient outcomes over time, real-world estimates of OS among patients with stage IIIB/IV NSCLC are often below those reported in randomized controlled trials (RCTs). In a systematic review of 23 RCTs published over 2001–2010 comparing first-line chemotherapy for patients with stage IIIB/IV NSCLC, median OS was 6.2–11.8 months for those with SQ, 7.5–11.8 months for NSQ, and 21.6–30.9 for EGFR+ NSCLC [Pilkington et al. Thorax 70(4):359–67]. These values are substantially higher than the median OS reported here for patients with advanced disease. Notably, median patient age was lower in the RCTs at 56–67 years (versus 73 years in our analysis), and the majority of patients had a PS of 1 (versus 35.4% of patients with a PS 0–1 in our analysis). Thus, real-world data from patients treated in routine clinical practice are important to supplement clinical trial data, which may over-estimate real-world outcomes [Lakdawalla et al. Value in Health 2017;866–875]."

Minor comments:

Comment: Methods, Page 8

Please clarify if the data were retrieved from a database (REAL oncology database?) where data was entered prospectively or was this a retrospective analysis of routine clinical data entered onto the hospital EMR? If there is a prospective database, what are the variables routinely collected and what is the quality assurance, if any, for this.

It says data on chemotherapy, pathology and radiology were extracted from EMR. Where were the data for surgery and radiotherapy extracted from? Was this from a separate database?

Response: Our data were based on a retrospective analysis of routine clinical data entered onto the hospital EMR. To clarify this, the text on page 6 underneath 'Study design' has been revised as follows:

"This retrospective analysis extracted data on prescribed chemotherapy and pathology and radiology records that were entered into electronic medical records (EMRs) at the Leeds Teaching Hospitals NHS Trust as part of routine clinical practice."

Comment: Were patients with a diagnosis of lung cancer (clinical or pathological) who were not seen by the MDT excluded? Ie Were the inclusion criteria all incident diagnoses of NSCLC during the time period or all incident diagnoses of NSCLC diagnosed by the Lung MDT during that period. Or is there no difference between the two. What is the lung MDT, are you just referring to a team of clinicians or is this implying diagnosis and discussion at MDT meeting?

Response: Thank you for your comment. All cases were included; patients were all assessed (though not necessarily seen in person) by a member of the MDT (the multidisciplinary team of doctors, nurses and clerical support staff etc). The Lung MDT is responsible for confirming diagnosis for the purpose of recommending treatment options, as well as for audit and performance management.

Comment: The end date of the study is only 7m after last incident case, so there is short FU in more recent cases.

Response: We have acknowledged this in the discussion as a limitation as follows (p18):

"It is also acknowledged that the follow-up duration was relatively short, at 7 months, for patients diagnosed at the end of the study period."

Comment: How many patients were PET staged over the years? Could this impact on the changes in stage distribution?

Response: Patients were staged according to BTS and NICE guidelines at the time of the study; therefore, all patients who were candidates for radical treatment underwent PET staging. PET was fully available from 2008 onwards. We believe that the major factor impacting on stage distribution was the introduction of SABR for early stage patients.

Comment: Page 11. Wrt to initial treatment, what is the definition of curative radiotherapy? Is this based on a minimum dose or just intent of treatment? Was SABR available for the whole time period?

Response: The definition for curative radiotherapy is based on treatment intent. In our centre, SABR was available from May 2009.

Comment: Can you add some results about the use of SABR in Stage I NSCLC particularly given the large increase in use of RT in clinically undiagnosed patients (Figure 2) – was this increase largely

due to SABR? A major limitation of this study is the lack of radiotherapy details given the importance of radiotherapy as a treatment modality for all stages of NSCLC.

Response: We thank the reviewer for this comment. Unfortunately, it was not possible to differentiate between conventional RT and SABR with the data available for this analysis. However, experience with SABR between 2009 and 2012 at St James Institute of Oncology at Leeds supported the effectiveness of SABR as a treatment option for medically inoperable patients with peripheral lung disease. In that study, which reported outcomes for the first series of lung cancer patients treated with SABR in the UK, and included a high proportion of patients without confirmed pathology (188/273 [65.3%]), we observed good local control (>95% at 3 years) and low nodal relapse rates (Murray et al. *R Coll Radiol.* 2016; 28:4–12).

We acknowledge that the lack of RT details (type of RT and dose) is a limitation of our current study, and have noted this as such in the discussion, as follows (p18):

"Additionally, limited information was available regarding radiotherapy at the time of this analysis (date of administration, dose, and type of radiotherapy) and it was not therefore possible to formally differentiate palliative radiotherapy from radiotherapy with curative intent, nor to identify the use of stereotactic ablative radiotherapy in early stage patients. However, the increased use of RT over time in early stage patients with clinically diagnosed NSCLC was almost certainly due to SABR. It is hoped that improvements to the algorithm used and the subsequent availability of more detailed data regarding radiotherapy will address this limitation."

Comment: Suggest combining NSCLC NOS and other, and adding p values for comparisons btwn NSQ, SQ, NSCLC NOS/Other and Clinical diagnosis as there are clearly some differences eg clinically diagnosed patients older median age and worse performance status.

Given that 3 different staging systems were used in this cohort with evolution over time, I suggest the stages reported in Table 1 be simply Stage I, II, IIIA, IIIB and IV. There isn't much point in dividing the earlier stages. However Stage IIIA/IIIB/IV results are reported separately so needs to be reported as such in this table.

Response: Thank you for comment and suggestions. We would prefer to keep the classifications of 'NSCLC NOS' and 'Other' separate, as based on the ICD-O-3 morphological codes for NSCLC, these are considered 'other specified NSCLC carcinoma'. The NOS category reflects cases where the pathological subtype was uncertain; understanding patterns in such diagnoses is important for understanding improvements in histological subtyping over time and the impact on patient treatment and prognosis.

As suggested, the values for Stages IA and IB, and for Stages IIA and IIB have been combined in Stage I and Stage II, respectively, in Table 1.

Comment: Figure 3. I find this difficult to interpret as there are 3 shades of blue used.

Suggest use the same colour by pathology type (eg red, blue, green) and use solid line for one time period and dashed line for different time period, and this will make it easier to see the differences and similarities.

Response: Thank you for this suggestion, we have revised the colours used in Figure 3 as noted. We hope that this is now easier to interpret.

Reviewer #2: Dr. Philip Savage, Brighton and Sussex University Hospital

Comments to the Author:

Thanks for this revised manuscript. Whilst there were no comments to reviewers included it reads well and is a useful addition of real-world data to the literature. I have only 3 minor points.

Comment: The study is for patients 2007-2017. However, the results in page 9 compare 2010 to 2017 patient data

Response: We report evolution on the proportion of patients with stage I NSCLC in the period when the same TNM classification (7th edition) was used. The text has been updated, as follows (p9):

"Over the study period, 717 patients (19.2%) were diagnosed with stage I disease, 434 (11.6%) with stage II, and 806 (21.6%) with stage III; almost half of patients (47.7%) were diagnosed with stage IV disease. TNM classification evolved during the study period, which might have contributed to some of the changes observed over time in the stage distribution at diagnosis. However, over the period when the 7th TNM classification was used (2010–2016), the proportion of patients diagnosed with stage I disease increased from 16.4% in 2010 to 24.8% in 2016 (Figure 1), while diagnoses of stage IIIA and IIIB NSCLC remained stable over time. There was an overall reduction in the proportion of patients diagnosed at stage IV, from 57.0% in 2010 to 45.0% in 2016."

Comment: Fig 2 The Venn diagrams seem v hard to follow could the date be presented in numerical data

Response: Thank you for your comment. We have considered this suggestion and would prefer to retain Figure 2 in its current form. We agree that the figure contains a lot of information, but feel these data are easier to interpret when presented visually than numerically in a table, which would be very busy.

Comment: Fig 3 again a lot of data could it be simplified and still get the key message across. However, this is an important data set, has involved a lot of work and is a welcome addition

Response: Thank you for your comment. We have updated the figure to simplify the colour scheme and moved the 1-, 3-, and 5-year OS data to a new supplemental table (online supplementary appendix table S3), retaining the numbers of patients at risk underneath the respective K–M curve.

VERSION 2 – AUTHOR RESPONSE

Comment: As mentioned previously, please revise your Strengths and Limitations section after your abstract to include limitations which relate specifically to the methods in your study. This section should contain five short bullet points, no longer than one sentence each, that relate specifically to the methods.

Response: Thank you for your comment. The Strengths and Limitations section has been revised to include bullets on the specific limitations of our study, with respect to the methodology, as follows:

- *These data reflect outcomes and trends for a single site in the United Kingdom; however, the REAL-Oncology study represents an unselected population, which is relevant to real-world practice and enables long-term (>10 years) analyses across numerous subgroups*
- *This analysis included patients with a clinical diagnosis of NSCLC who, despite representing a large proportion of patients with NSCLC, are often not captured in real-world studies*
- *Limited information on radiotherapy was available at the time of the analysis; thus, it was not possible to formally differentiate radiotherapy with palliative intent from that with curative intent*
- *The follow-up duration was relatively short for patients diagnosed at the end of the study period, at 7 months*
- *Data on co-morbidities that might have explained why a significant proportion of patients with advanced disease did not receive any systemic anticancer therapy, were not available*

Comment: Please make sure you include an award/grant number for your funder/s in the main document file

Response: This work was supported by Bristol Myers Squibb. There is no specific award/grant number.

Comment: Regarding comment: Page 11. Wrt to initial treatment, what is the definition of curative radiotherapy? Is this based on a minimum dose or just intent of treatment? Was SABR available for the whole time period? Response: The definition for curative radiotherapy is based on treatment intent. In our centre, SABR was available from May 2009.

Please make sure you include this information within the main document of your manuscript.

Response: As this is acknowledged as a limitation of our study, we have included the date from which SABR was available in our centre in the limitations section of the discussion, as follows:

Additionally, limited information was available regarding radiotherapy at the time of this analysis (date of administration, dose, and type of radiotherapy) and it was not therefore possible to formally differentiate palliative radiotherapy from radiotherapy with curative intent, nor to identify the use of stereotactic ablative radiotherapy (SABR) in early stage patients. However, the increased use of RT over time in early stage patients with clinically diagnosed NSCLC was almost certainly due to SABR, which was available in our centre from May 2009.