

Accepted Manuscript

British Journal of General Practice

Chest x-ray sensitivity and lung cancer outcomes: A retrospective observational study

Bradley, Stephen; Bhartia, Bobby; Callister, Matthew; Hamilton, William;
Hatton, Luke; Kennedy, Martyn; Mounce, Luke; Shinkins, Bethany;
Wheatstone, Pete; Neal, Richard

DOI: <https://doi.org/10.3399/BJGP.2020.1099>

To access the most recent version of this article, please click the DOI URL in the line above.

Received 10 December 2020

Revised 31 March 2021

Accepted 07 April 2021

© 2021 The Author(s). This is an Open Access article distributed under the terms of the Creative Commons Attribution 4.0 License (<http://creativecommons.org/licenses/by/4.0/>). Published by British Journal of General Practice. For editorial process and policies, see: <https://bjgp.org/authors/bjgp-editorial-process-and-policies>

When citing this article please include the DOI provided above.

Author Accepted Manuscript

This is an 'author accepted manuscript': a manuscript that has been accepted for publication in British Journal of General Practice, but which has not yet undergone subediting, typesetting, or correction. Errors discovered and corrected during this process may materially alter the content of this manuscript, and the latest published version (the Version of Record) should be used in preference to any preceding versions

Chest x-ray sensitivity and lung cancer outcomes: A retrospective observational study

Stephen H Bradley¹, Bobby SK Bhartia², Matthew EJ Callister³, William T Hamilton⁴, Nathaniel Luke Fielding Hatton⁵, Martyn PT Kennedy⁶, Luke TA Mounce⁷, Bethany Shinkins⁸, Pete Wheatstone⁹, Richard D Neal¹⁰

1 Clinical research fellow, Leeds Institute of Health Sciences, University of Leeds
MRCP

Address for correspondence: Academic Unit of Primary Care, Leeds Institute of Health Sciences, Rm 10.39, Worsley Building, University of Leeds, LS2 9JT
medsbra@leeds.ac.uk

2 Consultant thoracic radiologist, Leeds Teaching Hospitals NHS Trust, Leeds
MRCP, FRCR

3 Consultant respiratory physician, Leeds Teaching Hospitals NHS Trust, Leeds
FRCP, PhD

4 Professor of primary care diagnostics, University of Exeter, Exeter
FRCP, FRCGP, CBE

5 Academic Clinical Fellow, Leeds Teaching Hospitals NHS Trust
MBChB

6 Consultant respiratory physician, Leeds Teaching Hospitals NHS Trust, Leeds
MRCP

7 Research fellow, College of Medicine & Health, University of Exeter
PhD

8 Associate professor, Test Evaluation Group, Leeds Institute of Health Sciences, University of Leeds
DPhil

9 Patient and Public Representative, CanTest Collaborative, c/o Academic Unit of Primary Care, University of Leeds, Leeds

10 Professor of primary care oncology, Academic Unit of Primary Care, University of Leeds, Leeds
PhD, FRCGP

Abstract

Background: Chest x-ray (CXR) is the first line investigation for lung cancer in many healthcare systems. Understanding of the consequences of false negative CXRs on time to diagnosis, stage and survival is limited.

Aims: To determine the sensitivity of CXR for lung cancer and to compare stage at diagnosis, time to diagnosis and survival between those with CXR which detected, or did not detect, lung cancer

Design & Setting: Retrospective observational study using routinely collected healthcare data.

Methods: All patients diagnosed with lung cancer in a teaching hospital trust during 2008 – 2015 who had a GP requested CXR in the year before diagnosis were categorised based on the result of the earliest CXR performed in that period. We calculated sensitivity of CXR and performed analyses with respect to time to diagnosis, survival and stage at diagnosis.

Results: CXR was negative for 18% of patients (n=376/2129). Median time from initial CXR to diagnosis was 43 days (IQR: 27-78) for those with positive CXR and 204 days (105-287) for those with negative CXR. Of those with positive CXR, 29% (95% CIs 27-31%) were diagnosed at either stage I/II, compared to 34% (95% CIs 29-39%) of those with a negative CXR.

Conclusion: GPs should consider lung cancer in patients with persistent symptoms even when CXR is negative. Despite longer duration to diagnosis for those with 'false negative' CXRs, there was no evidence of an adverse impact on stage at diagnosis or survival; however this comparison is likely to be affected by confounding variables.

Keywords (no more than 6)

chest x-ray, lung cancer, radiograph, early diagnosis, general practice, test accuracy

How this fits in

The understanding of the accuracy of chest x-ray for diagnosing lung cancer in people with symptoms is limited, and little is known about adverse consequences when the investigation does not identify cancer. Analysing chest x-ray results for over 2,000 patients, this study demonstrated the sensitivity of chest x-ray was 82%. Aside from a longer time to diagnosis, no adverse consequences in terms of survival or stage of disease were observed for patients who had a chest x-ray that did not detect lung cancer; however, these results could be explained by confounding factors. GPs should be aware that chest x-ray may initially miss lung cancer in around a fifth of cases and consider further investigation if symptoms persist.

Introduction

Lung cancer is the world's leading cause of cancer mortality.(1) Since those who are diagnosed at an earlier stage of disease have improved outcomes, there has been a heavy emphasis in cancer policy on streamlining diagnosis.(2) For example, England's National Health Service (NHS) aims to achieve diagnosis at stage 1 or 2 in three quarters of all patients who have cancer by 2028.(3) Given the central

role of chest x-ray (CXR) in lung cancer diagnosis in countries like the UK, it is important to understand both its ability to detect lung cancer and the possible adverse implications on outcomes when lung cancer is not detected.(4) There is currently insufficient high quality evidence to address these questions.

Studies identified in a systematic review and a subsequently published study have estimated that CXR does not identify lung cancer in approximately 20-25% of cases.(5, 6) The pooled number of individuals with lung cancer from these studies is relatively small (n=494) and definitions of positive and negative results was not entirely consistent between studies. Evidence regarding the consequences of false negative CXR results in terms of time to diagnosis, stage at diagnosis and survival is even more limited. A case series and two diagnostic audits suggest that those with false negative chest x-rays may experience a greater time to diagnosis.(7-9) A retrospective review of 24 patients found no adverse association between survival and 'missed' lung cancer on CXR.(10)

Using routinely collected data, this study had the following aims:

- To calculate the sensitivity of GP-initiated CXR for lung cancer in the year before diagnosis
- To compare time to diagnosis from CXR, stage at diagnosis and survival between patients who had positive and negative CXR results for lung cancer in the year before diagnosis.

Method

Leeds Teaching Hospital NHS Trust (LTHT) is a regional centre for lung cancer diagnosis and treatment, serving a population of approximately 750,000. (11) LTHT's lung cancer database is a comprehensive record of multi-disciplinary team confirmed lung cancer diagnoses which has previously been described.(12) From this, we created a database containing de-identified data on all patients diagnosed with a primary lung cancer between 1st January 2008 and 31st December 2015 within LTHT. We included lung cancer cases which conformed to the international classification of diseases diagnostic code C34; therefore other intrathoracic malignancies such as mesothelioma were excluded. (13) Patients who did not have a CXR requested by their GP in the year before they were diagnosed with lung cancer were excluded. All radiology reports for GP-requested CXRs in the year before diagnosis were coded according to criteria adapted from a national audit. (14) The CXR report codes were as follows:

- 1) Suspicion of lung cancer identified/urgent investigation indicated
- 2) Abnormality identified/non-urgent investigation indicated, including diagnoses of pneumonia or consolidation even if repeat imaging was not explicitly suggested
- 3) Abnormality identified but no further investigation/assessment indicated
- 4) Normal CXR. No abnormalities identified.

We considered codes 1 and 2 to be 'positive' results while codes 3 and 4 were 'negative'. A sample of 100 chest x-ray reports were independently categorised by SHB and NLH. This yielded Cohen's kappa scores of 0.80 and 0.92 on comparing agreement across all four codes (1-4) and into the positive (1-2) versus negative (3-4) categories, respectively. Coding was subsequently performed by SHB with advice obtained from MEJC on categorisation of results which were ambiguous.

We categorized patients according to the code of the earliest GP requested CXR in the year prior to diagnosis (initial CXR) into four groups. This period was chosen as it is likely that cancer would be present during this interval before diagnosis. (15) The date of diagnosis was the date of biopsy confirmation or of the multi disciplinary team meeting's decision to accept a radiological diagnosis, which occurs in instances when biopsy is not obtained, for example if a patient is too ill to tolerate the procedure.

The study population included 113 (5%) patients who attended a service which allowed them to request their own CXR. The characteristics of that subpopulation have been previously described (addendum S1). (6)

Statistical Analysis

We calculated sensitivity as the proportion of patients who had an initial CXR coded as either 1 or 2. We used Pearson's chi-squared test to determine if a statistically significant association was present between early stage (I and II) and late stage (III and IV) disease and positive and negative CXR results.

We generated Kaplan-Meier survival curves to compare 'true positive' and 'false negative' groups in terms of survival from initial CXR and duration from initial CXR to lung cancer diagnosis. We used the log rank test to test the null hypothesis that there was no difference in survival between these two groups. We fitted a Cox proportional hazards model to allow adjustment for age, sex, deprivation, performance status and lung cancer stage. We tested the assumption of proportional hazards by including interaction terms between time and each explanatory variable; significant effects for these interactions indicate violation of the assumption. Where this occurred, the interaction terms were adjusted for in the final model. (16) Since detectability of lesions may be associated with size and stage, which would be expected to progress over time, we conducted an additional analysis comparing stage at diagnosis and survival between cases diagnosed earlier and later than six weeks following initial CXR. This was intended to facilitate comparison of cancers that were diagnosed within six weeks despite a negative CXR result with those which were diagnosed at later than 6 weeks.

Results

A total of 4,698 patients were diagnosed with lung cancer, including 2,129 (45%) with at least one GP requested CXR in the year before diagnosis. Sensitivity of chest x-ray, based on initial CXR (code 1 or 2), was 82% (95% CI 81-84%). 370 (17%) patients had an initial CXR result which advised non-urgent further review or investigation (code 2). Of these, 191 (52%) patients had a second GP requested CXR. The median duration to second CXR was 42 days (29, 28-57) and the result was negative in 10% of cases (95% CIs 6% to 14%).

324 patients (15%) had two or more CXRs prior to diagnosis (code 1-4), with sensitivity of these follow up CXRs increasing only slightly from 82% (95% CI 81-84) on initial CXR to 84% (95% CI 79-88) on the subsequent CXR. 98 patients (26%) out of 376 who had an initial CXR which was negative had at a second CXR (Table 2).

Median time from initial CXR to diagnosis for those with a 'positive' result was 43 days (interquartile range = 51 days, 27-78) compared to 204 days (IQR=182, 105-287) for those who had a 'negative' CXR. Further detail on CXR results, median durations to diagnosis and stage at diagnosis by group are displayed in Table 1. Kaplan Meier and Cox regression survival analyses for duration to diagnosis and chest x-ray result are presented in Figures S1 to S3.

Stage at diagnosis was similar across groups, with 634 (30%) patients diagnosed at stage I or II, including 508 (29%) who had a 'positive' initial CXR and 126 (34%) who had a negative initial CXR. There was no evidence of a statistically significant association between chest x-ray result and stage at diagnosis, $\chi^2 (1, N=2124) = 2.92, p = 0.09$.

Patients who were diagnosed within six weeks of initial CXR regardless of CXR result were more likely to have stage III or IV disease ($n=775/880, 82\%$ vs $n=715/1244, 58\%$, $p<0.001$) and small cell histology

(n=115/884, 18% vs n=109/1245, 9%, $p<0.001$) (Tables 3 and S1). This suggests that late stage disease and histology associated with rapidly progressive disease is more likely to be diagnosed rapidly, which could be due to severity of presenting symptoms and/or more clear-cut radiological evidence of cancer. Among patients diagnosed six weeks (42 days) or more after initial chest x-ray, there was evidence that those for whom the initial CXR was negative were more likely to have stage III or IV disease than those for whom the initial CXR was positive (n=225/350, 64%, vs n=490/894, 55%, $p = 0.002$) (Table 4). Few patients with negative initial CXRs received a diagnosis of lung cancer within six weeks of initial chest x-ray (n=26/376, 7%) (Table 5). Of those who did have negative initial CXRs and were diagnosed within six weeks, almost all had stage III or IV disease (n=25/26, 96%) (Table 6).

Survival analysis demonstrated no adverse effect on survival for those with a negative CXR result compared to those with a positive CXR. Adjustment for co-variables using Cox proportional hazards regression found those with positive CXR results had poorer survival relative to the negative CXR group (hazard ratio 1.35, 95% CI 1.19 to 1.52, $p<0.000$) (Figure S1).

Discussion

Summary

This study estimates that the sensitivity of CXR for lung cancer diagnosed within one year amongst patients presenting to primary care is 82% (95% CI 81-84%). The study builds on evidence from smaller studies that 'false negative' CXR results are associated with additional delay to lung cancer diagnosis, compared to 'true positive' results.^(7, 17) We found that, of the patients who have had a CXR in the year prior to their diagnosis with lung cancer, those with positive results had a median duration to diagnosis of 43 days compared to 204 days for those with a negative initial CXR.

We did not find evidence of a direct association between failure to detect lung cancer on CXR and adverse stage at diagnosis or survival. It is possible that such associations do exist but are obscured by confounding due to the retrospective observational study design or that the study lacked the statistical power to detect such associations.

Strengths and limitations

The study is the first to analyse CXR results systematically with respect to time to diagnosis, stage at diagnosis and survival. It also draws on by far the largest published population in estimating the sensitivity chest x-ray for lung cancer in symptomatic patients, exceeding by more than five-fold the total population of three studies identified in a recent systematic review (n=380).⁽⁵⁾ The classification of positive and negative results is poorly defined in many of the studies that have previously reported sensitivity of CXR. We employed a systematic approach to classifying CXR results, which was validated and refined using a sample of CXR results prior to commencement of the study.

Smoking status, co-morbidities and the symptoms that prompted investigation with chest x-ray were not available. It is not possible to know whether CXRs were requested because of respiratory symptoms or symptoms stipulated in guidance from the National Institute of Health and Care Excellence.⁽¹⁸⁾ However, this reflects real world clinical practice, and investigations that lead to a lung cancer detection may be initiated without malignancy having been initially considered as a likely diagnosis.

The study population was drawn from a single city; therefore it is possible that local patterns of demography or clinical practice may mean the findings are less applicable to other settings. However, Leeds is broadly representative of the wider English population in terms of age, ethnicity and deprivation. (19)

We chose a period of one year from CXR to diagnosis to determine sensitivity, reflecting much of the existing literature.(5) One year was chosen as a period in which it would be likely that a macroscopic lesion would be present. The choice of time period has important consequences for sensitivity as choosing a longer period; for example two years would likely result in lower sensitivity, while a shorter period, for example six months, would probably lead to higher sensitivity. Estimates derived from screening studies suggest that, in a large proportion of cases, lung cancer develops over years prior to detection, although a small proportion of cancers develop more rapidly. (15, 20-22) It is possible that, in some cases, the lung cancer did not constitute a macroscopic lesion at the time at which the initial CXR was performed.

Due to the retrospective observational design of this study no definitive conclusions can be drawn from the lack of observed association between detection of lung cancer and stage at diagnosis or survival. It is likely that the detectability of lung cancers has an independent relationship with stage and survival. Larger tumours may have been more detectable and could also have been more likely to represent late stage disease. Lesions which were initially not detected could, however, have been more likely to be faster growing tumours, with poorer prognoses, akin to 'interval cancers' described in screening studies.(23) Exploratory analyses in this study suggest that late stage disease is associated with diagnosis within six weeks. Since we did not find evidence that this effect is mediated by CXR result, it is possible that patients with more advanced disease are more likely to be diagnosed early. While this may support the so called 'sick quick' theory, it is important to acknowledge that such observations in this context are speculative.(24)

Comparison with existing literature

A recent systematic review for the sensitivity of CXR for lung cancer in symptomatic patients identified three studies with estimates of 79% (95% CIs 68 to 91), 77%; 95% CIs 65 to 84%) and 80% (95% CI = 73 to 87%).(5) Sensitivity in this study (82%) was consistent with previous estimates, though the larger sample size has yielded tighter confidence intervals (81 to 84%) than previous investigations. The sensitivity of a subset of patients who were represented in this study population has previously been published (75%, 95% CIs 68-83).(6) Sensitivity is affected by the prevalence of the disease and differences in the spectrum of disease, which might have contributed to the higher sensitivity in this study, since all of the patients in the present study had a diagnosis of lung cancer.(25)

In a Danish study, 12 patients with lung cancer who had a negative chest x-ray result had a median duration from presentation to GP to diagnosis of 161 days to diagnosis compared to 27 days for those with a positive CXR.(7) In another retrospective study diagnosis was 'missed' on the CXRs of 14 patients who had experienced an additional median delay of 101 (48-339) days.

The association between duration to diagnosis and survival is known to be complex. Tørring et al. and Redaniel *et al.* found increasing mortality with longer diagnostic intervals; however they also observed higher mortality with short diagnostic intervals.(26, 27) A systematic review which examined time to diagnosis and outcomes for lung cancer presented 'mixed findings' with similar numbers of studies demonstrating positive, negative and no associations. Such observations are likely to be related to the

clinical heterogeneity of cancer presentations. While cancers which are undetected will progress unchecked by treatment, rapidly progressive cancers which confer poor outcomes may also have shorter diagnostic intervals both through their more florid clinical presentation and shorter overall survival.(28) In this study it is possible that any adverse consequences of failure to detect cancer have been obscured by comparison with cancers which were more advanced and therefore more likely to be detected on CXR.

We found that 44.9% of patients diagnosed with lung cancer had a GP requested chest x-ray in the year prior to diagnosis which is broadly similar to that found in a larger study,(29, 30) but less than that found in an older cohort of 247 patients (66%).(17) In England, it is estimated that 48% of lung cancer diagnoses result from GP referrals, although it is not known how many of these referrals occurred following a GP requested chest x-ray. (31)

Implications for research and practice

This study suggests that CXR fails to identify lung cancer in around 18% of patients with the disease in the year before diagnosis. Therefore GPs should be mindful that a negative CXR does not necessarily exclude lung cancer. It is also important for GPs to recognise that although the risk of lung cancer with a negative CXR for most symptoms is low, the risk for patients with unexplained haemoptysis is almost 3% and urgent referral for suspected cancer is often warranted for this symptom, regardless of CXR result.(6, 18)

Compared to many similar countries, the United Kingdom has less capacity for more advanced imaging modalities like computed tomography (CT).(32) Within the UK several local initiatives have expanded access to CT for GPs in recent years in order to help expedite cancer diagnoses, while improving radiology capacity nationwide has been recognised as a policy priority.(33,34) Given both the deficit in two week referrals for suspected lung cancer and the backlog in CT imaging due to the coronavirus pandemic, making effective use of CXR capacity is likely to remain crucial in optimising lung cancer diagnosis in coming years.(35-37) For GPs, recognising those patients who may warrant additional investigation or referral despite unremarkable CXR will remain a challenge. In this context, a prospective study that compares CXR with CT in symptomatic patients with careful consideration of benefits, harms and health-economic implications may be required to understand whether transitioning to CT as the first line investigation would be justified.

We found that for the 15% of patients who had a further CXR in the year before diagnosis sensitivity increased only slightly from 82% on the initial CXR to 84% on the repeat CXR. Meanwhile in 10% of those who had another CXR following a result which indicated non-urgent follow up, this result was negative. Therefore even for patients who have a repeat CXR which is negative GPs should not dismiss the possibility of lung cancer if symptoms persist. In such circumstances further actions could include reassessment after a suitable interval, requesting imaging with another modality such as computed tomography (CT) or asking for advice from colleagues in respiratory medicine.

The finding that patients who had a positive CXR with a recommendation for non-urgent follow up had a median duration to diagnosis almost three times longer than those who have a positive CXR and a recommendation for urgent further investigation suggests that efforts to expedite diagnosis for this group of patients may be warranted. It is also striking that only about a half of those who had a CXR recommending non-urgent follow up actually had a further GP requested CXR in the year prior to diagnosis. As this study recorded only GP requested CXRs it is possible that appropriate management was instituted, for example through referral to secondary care, but further audit or quality

improvement work would be required to understand if the diagnosis for these patients could have been expedited.

Additional information

Funding

This research arises from the CanTest Collaborative, which is funded by Cancer Research UK [C8640/A23385], of which SB is a Clinical Research Fellow, BS is Postdoctoral Researchers, WH is director and RN is associate director.

Ethical approval

The study was approved following review from the University of Leeds School of Medicine ethics committee (SoMREC 18-035) and Leeds Teaching Hospitals NHS Trust Data Oversight Committee (LTH19034).

Competing Interests

MEJC and RDN are co-investigators for the Yorkshire Enhanced Stop Smoking Study. MEJC is the chief investigator and RND is a co-investigator of the Yorkshire Lung Screening Trial. Both studies are funded by Yorkshire Cancer Research.

Acknowledgements

We wish to thank Mr Atif Rabani, Data Analyst for preparing the de-identified datasets and Gary Abel, University of Exeter and Matthew Barclay, University of Cambridge for advice they provided on this study.

References

1. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer*. 2015;136(5):E359-E86.
2. NCLA annual report 2017: Royal College of Physicians; 2018 [Available from: <https://www.rcplondon.ac.uk/projects/outputs/nlca-annual-report-2017>].
3. NHS Long Term Plan. Chapter 3 Further progress on care quality and outcomes: Cancer: National Health Service; 2019 [Available from: <https://www.longtermplan.nhs.uk/online-version/chapter-3-further-progress-on-care-quality-and-outcomes/better-care-for-major-health-conditions/cancer/>].
4. Eurostat. Healthcare resource statistics-technical resources and medical technology: eurostat; 2019 [Available from: https://ec.europa.eu/eurostat/statistics-explained/index.php/Healthcare_resource_statistics_-_technical_resources_and_medical_technology#Availability_of_technical_resources_in_hospitals].

5. Bradley SH, Abraham S, Callister ME, Grice A, Hamilton WT, Lopez RR, et al. Sensitivity of chest X-ray for detecting lung cancer in people presenting with symptoms: a systematic review. *Br J Gen Pract.* 2019;69(689):e827-e35.
6. Bradley SH, Hatton NLF, Aslam R, Bhartia B, Callister ME, Kennedy MP, et al. Estimating lung cancer risk from chest X-ray and symptoms: a prospective cohort study. *Br J Gen Pract* 2020;bjgp20X713993.
7. Bjerager M, Palshof T, Dahl R, Vedsted P, Olesen F. Delay in diagnosis of lung cancer in general practice. *Br J Gen Pract.* 2006;56(532):863-8.
8. Neal RD, Robbé IJ, Lewis M, Williamson I, Hanson J. The complexity and difficulty of diagnosing lung cancer: findings from a national primary-care study in Wales. *Primary Health Care Research & Development.* 2014;16(5):436-49.
9. Mitchell ED, Rubin G, Macleod U. Understanding diagnosis of lung cancer in primary care: qualitative synthesis of significant event audit reports. *Br J Gen Pract.* 2013;63(606):e37-e46.
10. Turkington PM, Kennan N, Greenstone MA. Misinterpretation of the chest X-ray as a factor in the delayed diagnosis of lung cancer. *Postgrad Med J.* 2002;78(917):158-60.
11. Provider: Leeds Teaching Hospitals NHS Trust: Care Quality Commission; 2019 [Available from: <https://www.cqc.org.uk/provider/RR8/reports>].
12. Kennedy MPT, Cheyne L, Darby M, Plant P, Milton R, Robson JM, et al. Lung cancer stage-shift following a symptom awareness campaign. *Thorax.* 2018.
13. World Health Organisation, International Classification of Diseases (ICD) 2016 [Available from: <http://apps.who.int/classifications/icd10/browse/2016/en>].
14. Missed lung cancers on chest radiographs: Royal College of Radiologists; [updated 24th October 2016. Available from: <https://www.rcr.ac.uk/audit/missed-lung-cancers-chest-radiographs>].
15. Detterbeck FC, Gibson CJ. Turning Gray: The Natural History of Lung Cancer Over Time. *J Thorac Oncol.* 2008;3(7):781-92.
16. Tabachnick BG, Fidell LS. *Using Multivariate Statistics.* Boston: Pearson; 2013.
17. Stapley S, Sharp D, Hamilton W. Negative chest X-rays in primary care patients with lung cancer. *Br J Gen Pract.* 2006;56(529):570-3.
18. NICE. NICE Guideline [NG12]. Suspected cancer: recognition and referral: National Institute of Health and Care Excellence; 2015 [updated June 2015. Updated July 2017. Available from: <https://www.nice.org.uk/guidance/ng12>].
19. Leeds Observatory. [Available from: <https://observatory.leeds.gov.uk/>] Accessed 25 March 2021.
20. Ades AE, Biswas M, Welton NJ, Hamilton W. Symptom lead time distribution in lung cancer: natural history and prospects for early diagnosis. *Int J Epidemiol.* 2014;43(6):1865-73.
21. ten Haaf K, van Rosmalen J, de Koning HJ. Lung Cancer Detectability by Test, Histology, Stage, and Gender: Estimates from the NLST and the PLCO Trials. *Cancer Epidemiology Biomarkers & Prevention.* 2015;24(1):154-61.
22. Wu D, Erwin D, Rosner GL. Sojourn time and lead time projection in lung cancer screening. *Lung Cancer.* 2010;72(3):322-6.
23. Kvale PA, Johnson CC, Tammemägi M, Marcus PM, Zylak CJ, Spizarny DL, et al. Interval lung cancers not detected on screening chest X-rays: How are they different? *Lung cancer (Amsterdam, Netherlands).* 2014;86(1):41-6.
24. Rogers TK. Minimising diagnostic delay in lung cancer. *Thorax.* 2019;74(4):319-20.
25. Usher-Smith JA, Sharp, Stephen J, Griffin SJ. The spectrum effect in tests for risk prediction, screening, and diagnosis. *BMJ.* 2016;353:i3139.
26. Tørring ML, Frydenberg M, Hansen RP, Olesen F, Vedsted P. Evidence of increasing mortality with longer diagnostic intervals for five common cancers: A cohort study in primary care. *Eur J Cancer.* 2013;49(9):2187-98.
27. Redaniel MT, Martin RM, Ridd MJ, Wade J, Jeffreys M. Diagnostic Intervals and Its Association with Breast, Prostate, Lung and Colorectal Cancer Survival in England: Historical Cohort Study Using the Clinical Practice Research Datalink. *PLoS One.* 2015;10(5):e0126608.

28. Neal RD, Tharmanathan P, France B, Din NU, Cotton S, Fallon-Ferguson J, et al. Is increased time to diagnosis and treatment in symptomatic cancer associated with poorer outcomes? Systematic review. *Br J Cancer*. 2015;112 Suppl 1(Suppl 1):S92-107.
29. O'Dowd EL, McKeever TM, Baldwin DR, Anwar S, Powell HA, Gibson JE, et al. What characteristics of primary care and patients are associated with early death in patients with lung cancer in the UK? *Thorax*. 2014.
30. Rogers TK, Hamilton W, Tod A, Neal R. Response to: What characteristics of primary care and patients are associated with early death in patients with lung cancer in the UK? *Thorax*. 2015;70(2):184-.
31. Routes to diagnosis National Cancer Registration and Analysis Service; 2021 [Available from: http://www.ncin.org.uk/publications/routes_to_diagnosis.] Accessed 25 March 2021.
32. OECD Data. Computed Tomography (CT) Scanners. [Available from: <https://data.oecd.org/healthqt/computed-tomography-ct-scanners.htm>] Accessed 29 March 2021
33. Tsiakkis D, Graham Y, Cox J. Early diagnosis of lung cancer: is rapid access CT scanning the answer? *Br J Gen Pract* 2019; 69 (679): 90-91. DOI: <https://doi.org/10.3399/bjgp19X701189>
34. Diagnostics: Recovery & Renewal. Report of the Independent Review of Diagnostic Services for NHS England. [Available from: <https://www.england.nhs.uk/wp-content/uploads/2020/11/diagnostics-recovery-and-renewal-independent-review-of-diagnostic-services-for-nhs-england-2.pdf>] Accessed 29 March 2021
35. Cancer Research UK. Lung cancer and Covid 19. [Available from https://www.cancerresearchuk.org/health-professional/diagnosis/hp-covid-19-and-cancer-hub#HP_COVID-191] Accessed 29 March 2021
36. BBC News. Covid: Cancer scan backlog raises late detection fears. [Available from <https://www.bbc.co.uk/news/uk-55234280>]. Accessed 29 March 2021
37. Cancer Research UK. Queues build for GP appointments and cancer tests. [Available from <https://www.cancerresearchuk.org/about-us/cancer-news/press-release/2020-12-16-queues-build-for-gp-appointments-and-cancer-tests>]. Accessed 29 March 2021

	Initial CXR code 1	Initial CXR code 2	Initial CXR code 3	Initial CXR code 4	'Positive' (code 1 or 2)	'Negative' (code 3 or 4)	Total
Number (%)^a	1383 (65.0)	370 (17.4)	230 (10.8)	146 (6.9)	1753 (82.3)	376 (17.6)	2129
Age (mean)	71	72	75	70	71	73	72
Male (n, %)	753 (54.4)	189 (51.1)	121 (52.6)	72 (49.3)	942 (53.7)	193 (51.3)	1135 (53.3)
CXR to diagnosis (days) Median (Interquartile Range, Q1-Q3)	36.0 (40, 23.0-63.0)	93.0 (98.8, 55.0-153.8)	210.5 (114.0, 180.8- 295.8)	192.5 (191.8, 87.0-278.8)	43.0 (51.0, 27.0-78.0)	203.5 (182.3, 104.75-285.0)	51.0 (78.0, 29.0-107.0)
Survival from CXR (days) Median (Interquartile range, Q1-Q3)	313.0 (750.5, 126.0-876.5))	400.0 (801.3,163.0-964.3)	408 (719.5, 238.3-957.8)	419.5 (903.3, 213.5-1116.8)	328.0 (764.0,135.0-899.0)	412 (785.8,224.8-1010.5)	345 (772,148.0-920.0)
Stage							
I / II n (% , 95% CIs)	397 (28.7, 26.4-31.2)	111(30.0, 25.4 -35.0)	83 (36.1, 30.0-42.7)	43 (29.5, 22.4-37.7)	508 (29.0, 26.9-31.2)	126 (33.5, 28.8-38.6)	634 (29.8, 27.9-31.8)
III / IV n (% , 95% CIs)	981 (70.9, 68.4-73.3)	259 (70.0, 65.0-74.5)	147 (63.9, 57.3-70.1)	103 (70.5, 62.4-77.7)	1240 (70.7, 68.5-72.9)	250 (66.5, 61.4-71.2)	1490 (70.0, 68.0-71.9)
Unknown n (%)	5 (0.4)	0	0	0	5 (0.3)	0	5 (0.2)
Histology							
Small-cell	170 (12.3)	39 (10.5)	30 (13.0)	25 (17.1)	209 (11.9)	55 (14.6)	264 (12.4)
Non small-cell	961 (69.5)	257 (69.5)	123 (53.5)	87 (60.0)	1218 (69.5)	210 (55.9)	1428 (67.1)
Other histologies ^b					12 (0.7)	5 (1.3)	17 (0.8)
Unknown	244 (17.6)	70 (18.9)	76 (33.0)	30 (20.5)	314 (17.9)	106 (28.2)	420 (19.3)

Table 1: Study population by initial chest x-ray group. SCLC

^aPercentages in some cases exceed 100 due to rounding.

^b In order to maintain anonymity numbers not reported for CXR groups 1-4 not reported

Number of CXRs performed	Number of patients	Male (%)	Mean age	Positive CXR (%)	Previous CXR positive (%)	Stage I or II at diagnosis (%)	Median days from previous CXR (IQR)	Median days to diagnosis from initial CXR (IQR)
1	1805	978 (54.2)	72	1527 (84.6)		523 (29.0)		44 (57, 27-84)
2	277	126 (45.5)	72	244 (88.1)	185 (66.8)	83 (30.0)	49 (110, 29-139)	128 (144, 79-223)
3	43	21 (48.8)	70	37 (86.0)	26 (60.5)	13 (30.2%)	74 (97, 44-141)	239 (97, 186-283)
4	4	*	*	4 (100.0)	3 (75.0)	*	96 (132.5, 38.5-170.1)	339.5 (309, 54-363)
1, 2, 3 or 4^a	2129	1135 (53.3)	72	1753 (82.3)		634 (29.8)		51 (78, 29-107)
2, 3 or 4^a	324	156 (48.1)	72	271 (83.6) ^b	226 (69.8) ^c	111 (34.3)	48.5(106, 29-134)	147.5 (167,84-251)
3 or 4^a	47	23 (48.9)	70	40 (85.1)	28 (59.6)	14 (29.8)	67(102, 42-144)	251 (190, 114-304)

Table 2: Number of GP requested chest x-rays in year prior to diagnosis.

IQR=interquartile range, CXR=chest x-ray

* Demographic data has been excluded to maintain patient anonymity

^a CXR Results pertain to the first CXR in each row, not to the total of all CXRs, e.g. for '1,2,3 or 4' indicates that the first CXR was positive for 1753, row '2, 3 or 4' indicates that the second CXR was positive in 271 out of 324 patients who had at least two CXRs.

^b In those who had a negative initial CXR and who had a second CXR (98), the second CXR code was 1 for 52 (53.1%), 2 for 16 (16.3%), 3 for 21 (21.4%) and 4 for 9 (9.2%)

^c Of those who had two or more CXRs in the year prior to diagnosis, the initial CXR code was 1 for 35 patients (10.8%), 2 for 191 (59.0%), 3 for 53 (16.4%) and 4 for 45 (13.9%)

	Diagnosed <i>within</i> six weeks of initial CXR (%)	Diagnosed <i>after</i> six weeks of initial CXR
Stage I/II	105 (11.9)	529 (42.5)
Stage III/IV	775 (85.2)	715 (57.5)
Total	880	1244

Table 3: Lung cancer stage with respect to diagnosis with lung cancer within, or after six weeks (42 days) following initial chest x-ray. Unknown stage excluded to maintain anonymity. Pearson's chi squared demonstrated a statistically significant association between both late stage and diagnosis within six weeks, $X^2 (1, N=2124) 230.36, p<0.001$

	Patients diagnosed after six weeks of initial CXR (%)	Positive initial CXR (%)	Negative initial CXR (%)
Stage I/II	529 (42.5)	404 (45.1)	125 (35.7)
Stage III/IV	715 (57.5)	490 (54.7)	225 (64.3)
Total	1244	494	350

Table 4: Lung cancer stage at diagnosis and initial chest x-ray results for those who were diagnosed after six weeks (42 days) following initial chest x-ray. Those with unknown stage are not included in order to maintain anonymity. Pearson's chi squared test did demonstrate a statistically significant association, X^2 , (1, N=1244) 9.24, $p=0.002$.

	Diagnosed within six weeks of initial CXR (%)	Diagnosed after six weeks of initial CXR (%)
CXR Positive	858 (97.1)	895 (71.9)
CXR Negative	26 (2.9)	350 (28.1)
Totals	8854	1245

Table 5: Result of initial chest x-ray and diagnosis within or after six weeks (42 days). Pearson's chi squared test demonstrated a statistically significant association between positive CXR and diagnosis within 42 days, X^2 (1, N=2129) 225.24, $p < 0.001$.

	Patients diagnosed <i>within</i> six weeks of initial CXR (%)	Positive initial chest x-ray (%)	Negative initial chest x-ray (%)
Stage I/II	105 (11.9)	105 (12.2)	1 (3.8)
Stage III/IV	775 (87.7)	749 (87.3)	25 (96.2)
Totals	884	858	26

Table 6: Stage and initial chest x-ray results for those who were diagnosed within 42 days (six weeks). Pearson's chi squared test did not demonstrated a statistically significant association between stage and chest x-ray result, $X^2 (1, N=880) 1.67, p=0.196$. The result is *not* significant at $p < .05$, 1 degree of freedom.

Accepted Manuscript – BJGP – BJG,