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CHEST

Chest X-ray in suspected lung cancer is harmful

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Abstract

Objectives The aim of this study was to analyse the use of the chest radiograph (CXR) as the first-line investigation in primary care patients with suspected lung cancer.

Methods Of 16,945 primary care referral CXRs (June 2018 to May 2019), 1,488 were referred for suspected lung cancer. CXRs were coded as follows: CX1, normal but a CT scan is recommended to exclude malignancy; CX2, alternative diagnosis; or CX3, suspicious for cancer. Kaplan-Meier survival analysis was undertaken by stratifying patients according to their CX code.

Results In the study period, there were 101 lung cancer diagnoses via a primary care CXR pathway. Only 10% of patients with a normal CXR (CX1) underwent subsequent CT and there was a significant delay in lung cancer diagnosis in these patients ($p < 0.001$). Lung cancer was diagnosed at an advanced stage in 50% of CX1 patients, 38% of CX2 patients and 57% of CX3 patients ($p = 0.26$). There was no survival difference between CX codes ($p = 0.42$).

Conclusion Chest radiography in the investigation of patients with suspected lung cancer may be harmful. This strategy may falsely reassure in the case of a normal CXR and prioritises resources to advanced disease.

Key Points

- *Half of all lung cancer diagnoses in a 1-year period are first investigated with a chest X-ray.*
- *A normal chest X-ray report leads to a significant delay in the diagnosis of lung cancer.*
- *The majority of patients with a normal or abnormal chest X-ray have advanced disease at diagnosis and there is no difference in survival outcomes based on the chest X-ray findings.*

Keywords Lung cancer · Diagnosis · Survival · Chest X-ray · Computed tomography

Abbreviations

ANOVA	Analysis of variance
CT	Computed tomography
CX1	Normal chest radiograph
CX2	Alternative diagnosis on chest radiograph
CX3	Suspicion for malignancy on chest radiograph
CXR	Chest radiograph
NICE	National Institute for Health and Care Excellence
TNM	Tumour, node, metastasis

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Introduction

Lung cancer is the third most common cancer and is the most common cause of cancer mortality in the UK [1]. Lung cancer mortality in the UK ranks highest amongst comparable countries worldwide [2]. Hence, the National Optimal Lung Cancer Pathway was introduced in 2017 following development by the Lung Clinical Expert Group on behalf of the National Health Service. The goals of this pathway were earlier diagnosis, prompt treatment and improved survival in patients with lung cancer. This pathway exists in tandem with the NICE guidelines, which recommend an urgent chest radiograph (CXR) for patients with suspected lung cancer based on the presence of suspicious clinical history or examination findings [3].

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We hypothesise that using CXR as the first-line investigation to triage primary care patients with suspected lung cancer is potentially harmful.

Methods

Patient population

Following local audit committee approval, a retrospective review of 16,945 CXRs between June 1, 2018, and May 31, 2019, was performed (Fig. 1). One thousand four hundred eighty-eight patients referred from primary care for suspected lung cancer were included. Subsequent thoracic computed tomography (CT) and multidisciplinary team consensus diagnosis of lung cancer were recorded. This constituted 101 lung cancer diagnoses from primary care (out of a total of 180 lung cancer diagnoses in the study period consisting of $n = 12$ with initial investigations at another institution, $n = 7$ from active nodule surveillance, $n = 20$ without CXR as the initial investigation, $n = 40$ not referred from primary care).

Radiograph interpretation

In our institution, there is a same-day walk-in CXR service for primary care referrals for suspected lung cancer. Each CXR is assigned a 'CX' code by the reporting Consultant Radiologist with a reporting target of within 24 h. CX1 CXRs are normal and are accompanied by the following text; 'please note that a normal CXR *does not exclude* malignancy. If there is still a strong suspicion of malignancy (weight loss/unresolved cough/significant or unresolved haemoptysis) referral for *a CT scan is advised*'. CX2 CXRs are those with an alternative diagnosis or indeterminate findings not sufficient to warrant further urgent investigation. CX3 CXRs are those suspicious for malignancy and are referred for urgent CT. In our study period, $n = 13$ GP-referred CXRs with proven lung cancer were excluded because of lack of CX code, leaving a total

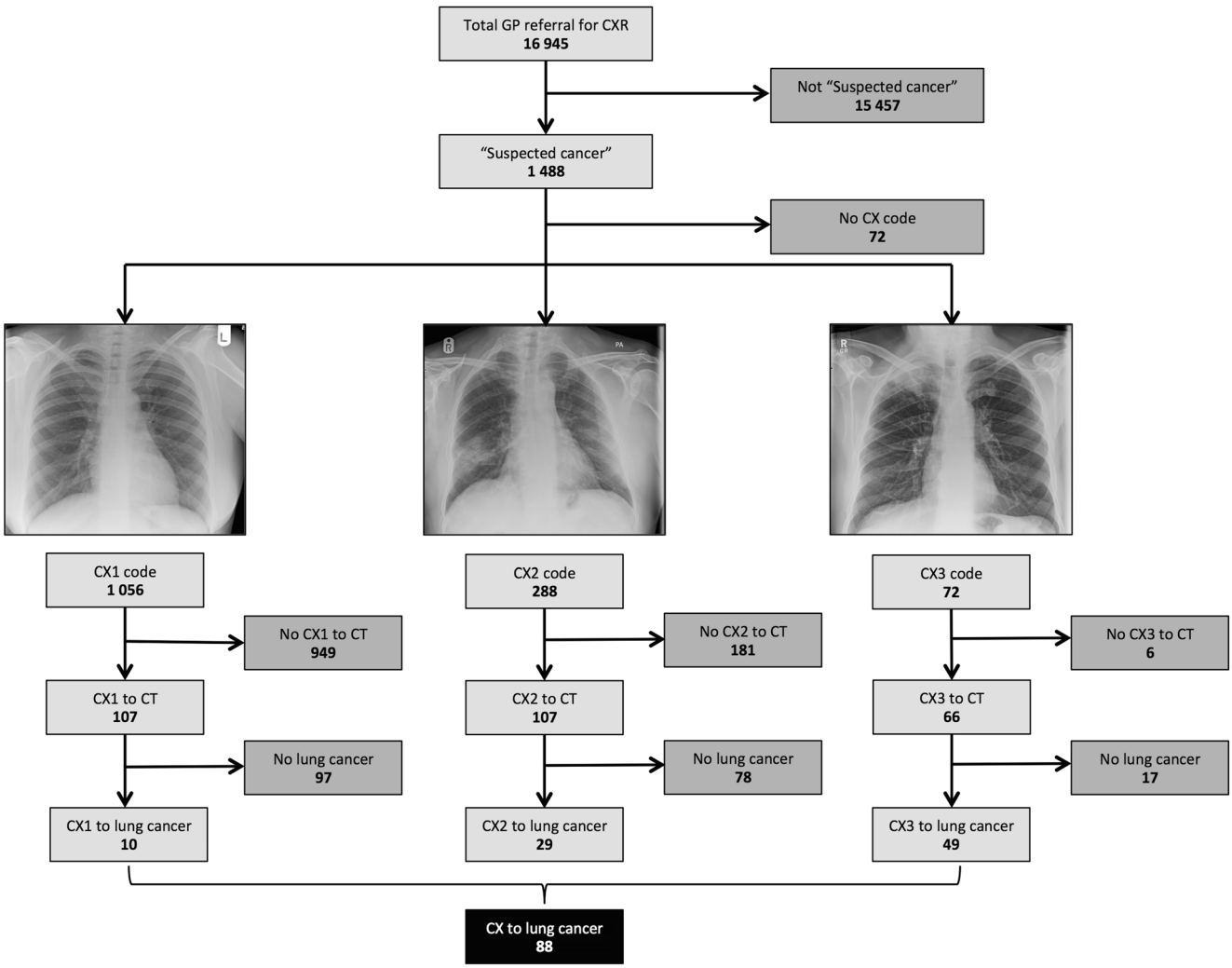

Fig. 1 Flow diagram illustrating the patient cohort and study design. Chest radiographs are as either CX1 (normal), CX2 (alternative diagnosis) or CX3 (suspicious for malignancy)

study size of 88. Tumour, node, metastasis (TNM) staging was performed according to the American Joint Committee on Cancer 8th edition Lung Cancer Staging [4].

Statistical analysis

Categorical variables are summarised as proportions and continuous variables as mean ± standard deviation. Comparison of variables took place via the chi-square for categorical variables and the one-way analysis of variance (ANOVA) test for continuous variables. The D'Agostino-Pearson test was used to assess normality in continuous variables. The log-rank test was used for the comparison of Kaplan-Meier survival curves. Data was censored at 489 days (16 months) with a minimum follow-up period of 132 days (4.5 months). Statistical significance was defined at two-tailed $p < 0.05$. Statistical analysis was carried out using MedCalc version 19.2.0 (MedCalc Software).

Results

The characteristics of the study cohort are demonstrated in Table 1. The mean age of the study cohort was 73 years, 73 years and 70 years in the CX1, CX2 and CX3 subgroups respectively ($p = 0.49$). The proportion of males in each CX categories was significantly different, representing 70%, 31% and 59% of patients respectively ($p = 0.02$). There were a similar proportion of ever-smokers in each group, representing 90%, 92% and 90% of patients, respectively ($p = 0.94$), and the most common presenting complaint in each subgroup was cough.

Diagnosis Of 1,488 GP-referred CXRs for suspected cancer, 88 went onto a lung cancer diagnosis, accounting for 49% of total lung cancer diagnoses in our Institution over the study period, with overall 6% cancer diagnosis rate. Of CX3 CXRs, 92% (66/72) had a CT and a total of 68% (49/72) were diagnosed with lung cancer. Of CX2 CXRs, 37% (107/288) had a CT and a total of 10% (29/288) were diagnosed with lung cancer. Of CX1 CXRs, 10% (107/1056) had a CT and a total of 1% (10/1056) were diagnosed with lung cancer.

Time to diagnosis The number of days between initial chest radiograph and the subsequent CT scan was significantly longer in the CX1 patients. There were 34.6 days from radiograph to CT in the CX1 subgroup, compared to 19.6 in the CX2 subgroup and 1.9 in the CX3 subgroup ($p < 0.001$). There was no difference in the time from CT request to CT scan between CX codes ($p = 0.16$). However, there was a significantly longer time to diagnosis in the CX1 subgroup, with an average of 89.7 days in the CX1 patients, 65.3 days in the CX2 group and 30.2 days in the CX3 patients ($p < 0.001$).

Staging and treatment T staging was significantly higher in the CX3 subgroup, with 53% of patients harbouring T4 disease, compared to 7% of CX2 patients and 40% of CX1 patients ($p = 0.001$). The proportion of patients with positive nodal disease was significantly higher in the CX3 group (76%) compared to 55% and 40% of patients in the CX2 and CX1 subgroups ($p = 0.04$). Metastases were present in 50% of CX1 patients, 41% of CX2 patients and 55% of CX3 patients ($p = 0.50$). Advanced lung cancer (stage IIIC/IV) was diagnosed in 50% (5/10) of CX1 patients, 38% (11/29) of CX2 patients and 57% (28/49) of CX3 patients ($p = 0.26$).

Table 1 Characteristics of patients with lung cancer in the study cohort, stratified by CX code

	CX1	CX2	CX3	*p* value
Patients	10	29	49	
Mean age ± SD	73.3 ± 5.8	72.6 ± 11.8	70.0 ± 9.8	0.49*
Male	7 (70%)	9 (31%)	29 (59%)	0.02¥
Smoking (current and past)	9 (90%)	26 (90%)	45 (92%)	0.94¥
Symptoms				
Cough	4 (40%)	16 (55%)	24 (49%)	
Dyspnoea	2 (20%)	11 (38%)	10 (20%)	
Haemoptysis	2 (20%)	4 (14%)	9 (18%)	
Chest pain	4 (40%)	4 (14%)	14 (29%)	
Weight loss	3 (30%)	1 (3%)	13 (27%)	
Recurrent infection	1 (10%)	0	2 (4%)	
Hoarse voice	0	0	1 (2%)	

CX1, normal; *CX2*, alternative diagnosis; *CX3*, suspicious for cancer; *SD*, standard deviation

*ANOVA

¥ Chi-squared test

With regard to management strategy, treatment with curative intent was undertaken in 40% (4/10) of CX1 patients, 48% (14/29) of CX2 patients and 27% (13/49) of CX3 patients ($p = 0.14$). In those patients undergoing treatment with curative intent, a primary surgical strategy, as opposed to a primary oncological strategy with chemotherapy ± radiotherapy, was undertaken in 100% (4/4) of CX1 patients, 57% (8/14) of CX2 patients and 77% (10/13) of CX3 patients ($p = 0.21$).

Mortality There was an average follow-up period of 322 days in the total cohort, with a minimum follow-up of 132 days. In the CX 1 subgroup, there were 5 deaths in the follow-up period (50%), there were 10 deaths in the CX2 subgroup (34.5%) and 27 deaths in the CX3 subgroup (55.1%). Survival analysis was undertaken by stratifying patients according to their CX code. Kaplan-Meier analysis demonstrated that there was no significant difference in mortality between these 3 groups (Fig. 2 ($p = 0.42$)).

Discussion

In the present study, we have examined the use of chest radiography in patients referred from general practice with suspected lung cancer. The vast majority of patients with a suspicious CXR (CX3) underwent subsequent CT. The majority of patients with a normal CXR (CX1) did not undergo subsequent CT, despite a caveat in the report, and this led to a significant delay in diagnosis. The CX3 subgroup was more likely to have a higher T and N stage; however, there was no difference in the likelihood of metastasis or in overall TNM staging. There was also no difference in survival between these groups.

The identification of patients with early-stage disease is critical to improve survival, with 5-year survival varying from 92% for patients with stage IA disease to 0% for stage IVB disease [5]. Approximately 20–25% of lung cancers are missed on chest radiography [6, 7], and CT is certainly more sensitive for the diagnosis of lung cancer [8]. Of the 1,488 suspected cancer cases in this study, only a small percentage of cases that were coded as CX1 underwent a CT scan and so there may be patients with potentially treatable lung cancers who are not being adequately imaged. Examples of false-negative CXR findings and the subsequent CT scan are illustrated in Fig. 3.

The National Optimal Lung Cancer Pathway recommends urgent CT (same-day or within 72 h) in patients with a normal radiograph if there is high clinical suspicion [9]. In the present study, only 10% of 1,056 patients with a CX1 code received a subsequent CT scan. Primary care physicians may be falsely reassured by the results of chest radiography, despite a specific stipulation in the report that CT is required if there is clinical suspicion of lung cancer. It is possible, therefore, that we are missing large numbers of lung cancers that are also potentially lower stage and therefore treatable, through this strategy of CXR for the triage of patients with a suspected lung cancer diagnosis.

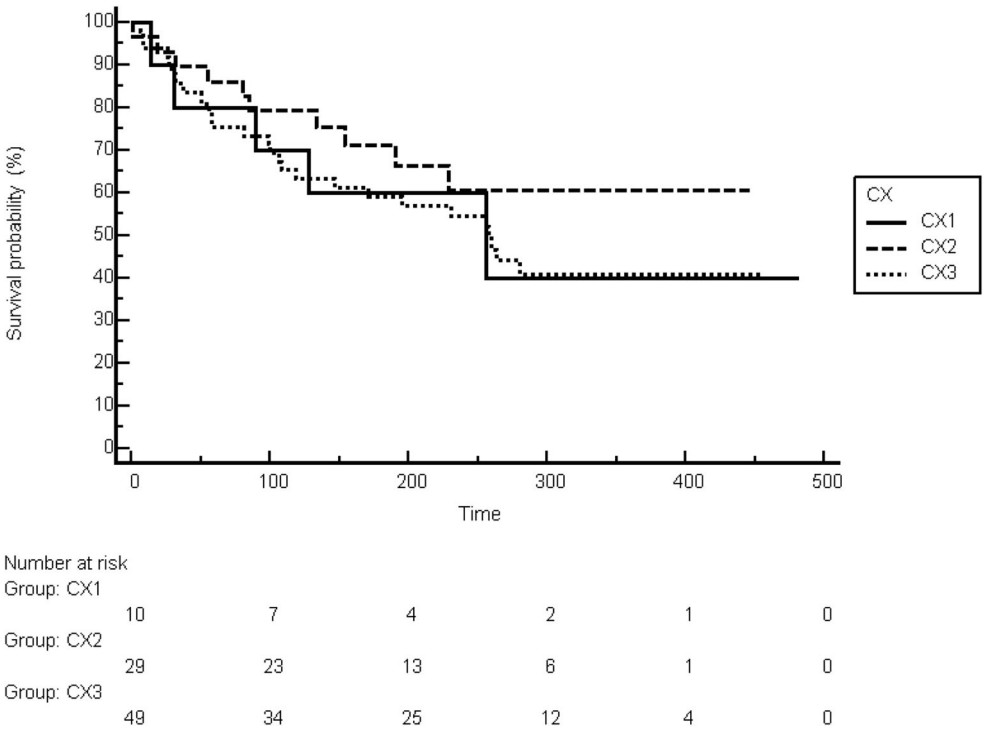

Fig. 2 Survival analysis with Kaplan-Meier curves stratified according to CX code. There is no difference in survival between the CX1, CX2 and CX3 subgroups ($p = 0.42$)

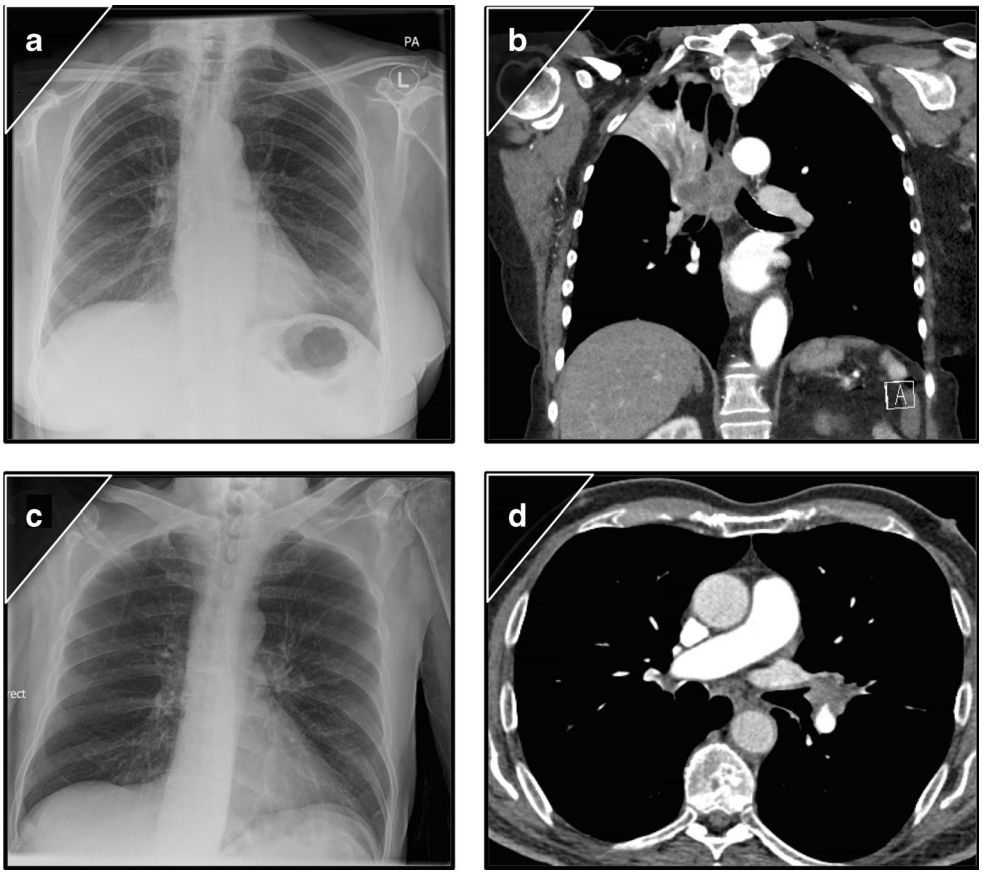

Fig. 3 False-negative chest radiographs reported as 'CX1' are illustrated. A 65-year-old woman with a CX1 chest radiograph (**a**) and a right upper lobe primary lung cancer on subsequent CT chest (**b**) 3 months following the index chest radiograph. A 70-year-old man with a CX1 chest radiograph (**c**) and a left hilar primary lung cancer on CT (**d**) 7 days following the index chest radiograph

The results of the present study highlight the need for direct access to CT in patients with suspected lung cancer. This CXR-focused pathway may prioritise resources to CX3 patients, most of whom will have advanced stage disease so whilst important for the patient will not stage shift. Lung cancer screening with CT has demonstrated benefit in asymptomatic high-risk patients [10] and lung cancer screening pilots are underway in the UK [11]. In the largest study of lung cancer screening, the use of a CT screening approach was originally thought to be associated with a higher cost than a CXR screening approach [12]; however, more recent analysis has demonstrated that there is little cost difference between the two strategies [13]. However, importantly, the use of CT screening is associated with a reduction in lung cancer-specific mortality and all-cause mortality, and so is a superior strategy to that of CXR screening. The use of chest radiography in the present study led to significant delays in diagnosis for patients with a normal result (CX1). As was demonstrated by Henschke and colleagues [14], a CT first pathway can 'get it right first time' and offers the opportunity to identify early-stage disease.

We acknowledge some limitations to the present study. This study was retrospective and performed in a single centre. A detailed analysis of all chest radiographs was not performed, and so, there may have been cases that were incorrectly coded. However, this reflects clinical practice in a real-world setting. Furthermore, we did not assess the strategy of CT as a first-line investigation, and further research is required to examine whether this would lead to a downstaging of disease and improved patient outcomes.

Conclusion

Chest radiography in the investigation of patients with suspected lung cancer may be harmful. This strategy may prioritise resources to advanced disease and may falsely reassure in cases of a normal radiograph. In an attempt to improve the diagnosis of early-stage disease and hence improve outcomes, consideration should be given to the use of CT as the first-line investigation for primary care patients with suspected lung cancer.

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Declarations

Guarantor The scientific guarantor of this publication is Benjamin J Hudson.

Conflict of interest The authors of this manuscript declare no relationships with any companies whose products or services may be related to the subject matter of the article.

Statistics and biometry No complex statistical methods were necessary for this paper.

Informed consent Written informed consent was waived by the Institutional Audit Committee.

Ethical approval Institutional Review Board approval was not required because approval was obtained from our Institutional Audit Committee.

Methodology
- Retrospective
- Observational
- Performed at one institution

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