Increased use of diagnostic CT imaging increases the detection of stage IA lung cancer: mechanisms and implications.

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Introduction

In 2019, 4,890 new cases of lung cancer were diagnosed in Denmark.(1) For both men and women, lung cancer is the most frequent cause of cancer-related death and accounts for 23% of cancer deaths.(2) The most important prognostic factor is the stage of the cancer at the time of diagnosis with a more than 10-fold higher mortality rate for stage IV compared to stage I.(3) It has been estimated that more than 25% of lung cancers may have a preclinical phase of more than 10 years, suggesting a potential for early detection.(4) One of the ways to achieve early diagnosis is access to sensitive diagnostic methods. The most sensitive method for diagnosing lung cancer is contrast-enhanced computed tomography (CECT) of the chest. CECT is the recommended diagnostic method when there is a clinical suspicion of lung cancer. An alternative is CT without contrast enhancement and performed with reduced radiation dosage (low-dose CT, LDCT). This is used in organised screening programs for lung cancer, because of concern about radiation exposure. The reduced radiation and the lack of contrast has a cost in sensitivity for detection of lung cancer.(5-7) The sensitivity of LDCT is much higher than conventional chest X-ray.(6, 8) Two alternatives may be considered to achieve timely diagnosis: organised screening for lung cancer in a defined population at risk, or extended access to CT imaging at a low threshold of suspicion of lung cancer. The first alternative has been shown to reduce lung cancer mortality in the screened population,(9-11) but the clinical effectiveness of increased access to referral to CT examination is uncertain.(12) For both alternatives, overdiagnosis may be a concern.(13)

Changed practice at Silkeborg Regional Hospital and preliminary observations.

From 2016, Silkeborg Regional Hospital in Denmark has used LDCT as an alternative to conventional X-ray of the chest. LDCT of thorax was used upon direct referral from primary care, and it was also available as a supplement to chest X-ray for patients referred from primary care, and for in-patients and out-patients at the hospital.

The annual report for 2018 from the Danish Lung Cancer Registry (14) and subsequent analyses of data from the registry showed an increase in the frequency of early stage lung cancers at Silkeborg Regional Hospital in 2016-2018, compared to previous years (Table 1). This small hospital diagnosed on average 101 lung cancers per year in 2016-2018 of which 38 (37.6%) were stage I. In the period from 2016 to 2018, increased use of thoracic CT imaging and a corresponding decrease in chest X-rays was observed (Figure 1). The increase in use of CT was approximately 2000 persons examined with CT each year, and about 40% of the volume of chest X-rays were replaced with CT examinations in this period.

The present study was designed to analyse the mechanisms by which the increased use of CT imaging led to the larger numbers of low-stage lung cancers at Silkeborg Regional Hospital, and to infer the possible implications of this diagnostic intervention for early detection and diagnosis of lung cancer.

Methods

Study population

We included all patients diagnosed with lung cancer between January 2013 and December 2018, who underwent investigation at the Departments of Radiology or Internal Medicine at Silkeborg Regional Hospital, Denmark.

Data sources

The Danish Lung Cancer Registry (DLCR) (15) was used to identify patients with a first diagnosis of lung cancer. Patients are included in the DLCR based on the first occurrence in the Danish National Patient Registry (DNPR)(16) of cancer of the trachea or lung (ICD10 C33 and C34). Information of procedures and treatments in the DNPR are combined with information from the Danish Pathology Register.(17) Data in the DLCR are verified by clinicians. The inclusion of incident cases in the DLCR is above 95%.(18)

The Charlson comorbidity index was derived from hospital discharge diagnoses at Danish hospitals in the 10 years before the lung cancer diagnosis. (19)

Clinical data were obtained from the regional electronic clinical information system (Columna Clinical Information System (CCIS), Systematic), which contains all data regarding admissions and outpatient contacts at the hospitals in the Central Denmark Region. Radiological referral and booking information were retrieved from four regional electronic archiving systems: Carestream RIS (Version 10.1.10), AGFA IMPAX 6.5.5.1608 "Enterprise unlimited", the CCIS imaging component, and the Regional Picture Archiving and Communication system. Radiology reports were retrieved manually from the radiology systems and regional electronic patient records.

Index image

We defined the index image as the first image with an abnormal finding in the imaging cascade resulting in the lung cancer diagnosis, e.g., if an abnormal chest X-ray preceded a LDCT or CECT, then the X-ray was considered the index image. If a normal or non-suspicious chest X-ray preceded a LDCT or CECT, then the CT was considered the index image.

We assigned index image "None of the above" for CT scans with a clinical purpose other than lung cancer detection, e.g., cardiac CT, CT angiography of the pulmonary arteries, CT angiography of the aorta, CT urography, abdominal CT, and high-resolution CT of the lungs. When other imaging modalities showed signs of metastatic disease and raised the first suspicion of lung cancer, these were also included in the “None of the above” category, e.g., MRI of the brain or spine, or ultrasound of the neck.

Clinical pathways

The examination date and type of all imaging procedures were registered until a CECT was performed, either isolated or as part of an ^{18}FDG-PET/CT. The following clinical pathways were then assigned based on manual curation of all available data:

Lung cancer referral pathway: This pathway was assigned when patients received CECT of the chest and upper abdomen on suspicion of lung cancer after GP referral, or from a hospital-based outpatient clinic or hospital ward. All CECTs were evaluated by a radiologist and reviewed in collaboration with a pulmonologist at multidisciplinary lung cancer team meetings. Based on the CT findings, further medical examinations were initiated or a follow-up LDCT was scheduled as needed.

LDCT pathway: This was assigned when the index image was a LDCT or ultra-low dose CT of the chest, which was not part of the urgent referral pathway for patients with non-specific serious symptoms. It included referrals directly from the GP and referrals from hospital. Furthermore, the pathway included patients above 40 years of age referred to an X-ray not raising suspicion of lung cancer and who, due to their smoking history (>15 pack-years), also had a supplementary LDCT or ultra-low dose CT on the same day.

Urgent referral pathway for non-specific serious symptoms: During the study period, this pathway consisted of a standardised blood test panel, a chest X-ray and an abdominal ultrasound as the basic investigations. Since November 2017, chest X-ray was replaced by an ultra-low dose CT. Patients received supplementary CECT of the chest, abdomen and pelvis when the radiologist considered it relevant or if the abdominal ultrasound provided insufficient information.

Not a defined clinical pathway: We assigned patients to this group if they did not fulfil the criteria for one of the three pathways mentioned above.

After completion of the chart review and establishment of the main imaging routes, we linked the clinical data to lung cancer stage, Charlson comorbidity index, (19) and histology in the DLCR, using the person identification number in the Danish civil registration system.(20)

Symptoms of lung cancer were gathered from referral information prior to diagnosis and classified according to Hamilton *et al.* (none, cough, fatigue, dyspnoea, chest pain, loss of weight, loss of appetite, abnormal spirometry, thrombocytosis, and haemoptysis).(21) Each patient was assigned the highest positive predictive value corresponding to either one symptom or a combination of two symptoms.

Data analysis

The data for the present study is on the lung cancer patients that were diagnosed at Silkeborg Regional Hospital in 2013-2018. The information consists of information about the person and the subtype of the cancer, the referral pathway, the radiological examinations and conclusions, and the time interval from initiation of the diagnostic process to the diagnosis with lung cancer. The outcome variable was the clinical stage of the cancer.

We aimed at characterising the stage IA lung cancers (tumour size 3cm or less and no lymph node involvement and no metastasis) that occurred in 2016-2018, after the change towards more CT examinations at the hospital. The change over time was predominantly in the frequency of stage IA

cancers (Table 1) and we therefore did a logistic regression analysis of the proportion of stage IA cancers out of the total.

Secondly, we used the entire dataset to give estimates in absolute numbers of the change in frequency of early stage cancers that could be attributed to the explanatory variables. We used three-way tabulated data in the form of *period*stage*covariate* for these estimations, and the results were visualised as mosaic plots for selected variables.

The study was approved by the regional hospital authorities of the Central Denmark Region (Record number 1-45-70-37-20).

Results

The starting point was 554 lung cancer patients identified in the Danish Lung Cancer Registry as diagnosed at Silkeborg Regional Hospital. Initial data cleaning identified seven patients who did not have their primary diagnostic work-up at Silkeborg Regional Hospital. Four of these were diagnosed in 2013-2015 (two stage IA patients) and three were diagnosed in 2016-2018 (one stage IA patient).

Table 2 shows the variables in the dataset for the entire period 2013-2018 and for the two three-year periods 2013-2015 and 2016-2018. We observed 34 stage IA cancers (13.8%) in 2013-2015 and 85 stage IA cancers (28.3%) in 2016-2018, corresponding to an absolute increase of 51 stage IA cancers over time. This increase was of the same magnitude as the overall increase from 247 to 300 cases. In the more advanced stage groups, overall numbers were constant but there was an increase in numbers of stage IB-III cancers and a decrease in stage IV cancers. The use of the CECT imaging cascade increased from 11.3% to 19.7%; the use of the LDCT imaging cascade increased from 3.6% to 20.7%; while the use of the X-ray then CECT imaging cascade decreased from 52.2% to 26.0% (Table 1, Diagnostics). The use of the lung cancer referral pathway increased from 6.5% to 8.0%; the use of LDCT pathway increased from 4.5% to 20.7%, and the use of the urgent referral pathway for patients with non-specific serious symptoms declined from 19.0% to 15.7% (Table 1, Clinical pathway).

Stage IA vs. IB+ comparison in 2016-2018

Table 3 shows the comparison between stage IA and more advanced cancers in 2016-2018. Six lung cancer patients had no record of stage and were excluded from these analyses. The age-distribution of stage IA patients was narrower than for more advanced cancers, and the stage IA proportion was

highest (36.5%) in patients in their 70s. The median age was higher in IA patients (72.0 years) than in other patients (69.9 years).

Stage IA patients had lower prevalence of smoking, with high odds-ratios for stage IA cancer in persons with less than 20 pack-years, and especially so with less than 10 pack-years (OR: 3.87; 95% CI: 1.41-10.63)

Stage IA patients had more comorbidity than patients with more advanced cancer (e.g. OR: 2.95; 95% CI: 1.41-6.18 in those with a comorbidity score of 2), and the proportion of stage IA cancers was lower in patients referred from their general practitioner than those referred from the hospital (OR: 0.52; 95% CI: 0.31-0.87).

The stage IA cancers were mostly adenocarcinoma: 57 cases, corresponding to 67% of all IA cancers.

The presence of red-flag symptoms (21) was negatively associated with stage IA cancer, with ORs of 1.36; 1.00; and 0.63 for PPV% groups 0; 0.1-0.9; and 1+. The trend over the three red flag symptom groups was statistically significant: Chi2(1)=4.0; p=0.04 (data not shown).

The initial imaging conclusion was more often not-suspicious (OR: 4.40; 95% CI: 1.64-11.79) or requiring a follow-up investigation (OR: 6.60; 95% CI: 3.55-12.27) in stage IA patients. The time from initial imaging to lung cancer diagnosis was higher in stage IA patients, e.g. more often exceeding six months (OR: 9.86; 95% CI: 4.36-22.27).

The detection and diagnosis of stage IA cancer was associated with the LDCT imaging cascade (OR: 1.44; 95% CI: 0.66-3.14), and especially so when an initial X-ray examination was followed by LDCT (Imaging cascade X-ray then LDCT: OR: 1.97; 95% CI: 0.88-4.41), both compared with imaging cascade CECT direct. These results are consistent with the detection of stage IA cancer being highest in patients where LDCT and not CECT was the index image (OR: 1.64; 95% CI: 0.78-3.42) and in the LDCT pathway compared with the lung cancer referral pathway (OR: 2.57; 95% CI: 0.85-7.78). The detection of stage IA cancer in the LDCT imaging cascade was strongest in patients referred from their GP (OR: 4.03; 1.21-13.42; data not shown).

Of the 85 stage IA patients in Table 3, 58 had a surgical resection, 22 had primary radiotherapy and five had no record of treatment.

Absolute differences contributing to the change in number of stage IA cancers.

Figure 3 shows the absolute numbers of stage IA patients and higher tumor stage patients in the two time-periods 2013-2015 and 2016-2018, in subgroups defined by comorbidity (Figure 3A), morphology (Figure 3B), origin of referral (Figure 3C), and imaging cascade (Figure 3D).

For comorbidity, the proportion of CCI 2+ patients was higher in stage IA patients than in other patients in 2016-2018, and the increase in numbers of IA patients in these comorbid patients was 24 cases corresponding to 47% of the overall increase of 51 stage IA patients.

The increase in adenocarcinoma was 73% of the total increase in stage IA cancers.

In 2013-2015 stage IA patients were most often referred by their GP, but this changed in 2016-2018 where these patients were mostly referred from the hospital. The majority of the increase in the number of IA cancers (35 cases or 69% of the total increase) came from hospital referrals.

Most of the imaging procedures contributed to the overall increase in IA numbers from 2013-2015 to 2016-2018: CECT (22%), LDCT (35%), X-ray followed by LDCT (25%), and other imaging (25%). Results for LDCT were similar to this in analyses of index image (39%) and clinical pathway (39%) (data not shown).

Stage IA patients had longer duration from first imaging to diagnosis, and more so in 2016-2018 where the increase in stage IA numbers came from patients where this duration exceeded one month (28 cases; 55% of total increase), and especially where the duration from first examination to diagnosis was longer than six months (23 cases; 45% of the total) (data not shown).

During the period 2016-2018 age, morphology and follow-up time was comparable between GP- and hospital referred patients, but comorbidity measured by the CCI tended to be higher among hospital referred patients (p=0.056) (data not shown).

Patients who were referred by their general practitioner and initially examined with LDCT (16 patients) had odds-ratio of 0.73 (0.37-1.46) for stage IA cancer, compared with those referred from the hospital (47 patients). The highest proportion of IA cancer was in patients referred by the general practitioner and examined first with X-ray and then with LDCT (14 patients) (OR: 1.53; 95% CI: 0.68-3.40) (data not shown).

Discussion

We identified *a priori* several possible and not mutually exclusive mechanisms that could contribute to the association between CT use in the hospital and the incidence of early-stage lung cancer. The following discussion is structured according to those possible mechanisms*. The role of LDCT in the detection of stage IA lung cancer in 2016-2018.*

It is evident from these data that many diagnoses of early-stage lung cancer at Silkeborg Regional Hospital in 2016-2018 involved the use of LDCT in the diagnostic process. Of the 85 stage IA cases, 26% (22/85) involved the direct use of LDCT (Table 3, Imaging cascade), and contributed to 35% (18/51) of the increase in the number of stage IA cases from 2013-2015 to 2016-2018 (Figure 3D). The supplementation with LDCT based on patient risk profile was unique to Silkeborg, but it is not known if a setting without access to LDCT would result in CECT or an X-ray follow-up potentially resulting in the same diagnosis. Overall, direct LDCT or LDCT following an X-ray was seen in 51% of patients with a stage IA cancer.

The contribution of the general practitioner's referral choice

The diagnostic centre at Silkeborg offered several referral options to the GPs in the area. This included the introduction of a referral route directly to LDCT aimed at *low risk but not no risk* patients (22) who were considered not to fulfil the criteria for the principal CECT referral for patients with symptoms of lung cancer, and in whom a referral to X-ray would be considered sub-optimal.

Patients who were referred by their general practitioner and diagnosed with stage IA cancer (38 patients) were initially examined with X-ray and LDCT in similar numbers (16 and 17, respectively). The GP referred patients with the highest yield of stage IA cancer was those initially investigated by X-ray and then by LDCT. This illustrates that the *low risk but not no risk* category is difficult to identify, even when a specific referral option exists for such patients. A controlled trial has earlier been reported from Denmark, where an option of direct GP referral to LDCT was compared with a standard scenario without this added option.(23) The study population yielded 331 incident cases of lung cancer but found no effect of the added LDCT option on the stage distribution. This may illustrate that stage IA lung cancer most often is non-symptomatic, which renders it likely that other mechanisms than GP referral choice led to the increase in stage IA cancer at Silkeborg Regional Hospital.

The origin and contribution of incidental findings

This investigation started with the observation of a large and highly statistically significant increase in the incidence of stage IA cancers from 2013-2015 to 2016-2018. When the data were stratified by referral origin, it became evident that this increase was much stronger for hospital referrals where the proportion of stage IA increased 3-fold from 12% to 35% ($p<0.001$), than for GP referrals where the increase was 1.5-fold from 15% to 23% ($p=0.10$).

In 2016-2018, the largest proportion of stage IA patients (55%) came from within-hospital referrals (Figure 3) explaining 69% of the increase between the two periods. The majority of these lung cancers were detected due to imaging procedures with other indications than suspected lung cancer. A wide range of imaging procedures contributed, mainly as part of investigation for abdominal or urological disease, non-malignant pulmonary disease and heart disease. The observed statistically significant associations between comorbidity and stage IA and between hospital referral and stage IA both point strongly towards the contribution of incidental findings to the incidence of stage IA cancer. Hospital-referred stage IA patients tended to score higher on the 10-year comorbidity index than the GP referred stage IA patients ($p=0.056$) (data not shown).

Evidence suggestive of possible overdiagnosis

Overdiagnosis in cancer is the detection of a tumour that would not otherwise have become clinically apparent in the life-time of the individual. Overdiagnosis is often an intrinsic feature of screening, which by its nature seeks to detect occult disease in asymptomatic individuals. Overdiagnosis causes anxiety, and the treatment may cause unnecessary physical harm.

In the absence of lung cancer screening, the identification of most stage IA lung cancer is incidental. In the present study, the tendency of a higher median age among patients with stage IA compared with higher stages may suggest an extent of overdiagnosis, although the difference is not statistically significant. The increase in the number of small, slow-growing tumours needing long follow-up before a diagnosis was made, may also point towards this. These characteristics (age, adenocarcinoma morphology and time-to-diagnosis) were similarly distributed in the hospital and GP referrals (data not shown).

There is substantial heterogeneity in growth rates of LDCT screening detected lung cancers, indicating that a reservoir of slowly or non-growing lung cancer exists.(24) LDCT scans have a much higher resolution than chest radiography, thus increasing its ability to detect the reservoir of indolent and slow-growing pathology.

The conclusive appraisal of overdiagnosis requires observation on the lung cancer mortality rate in the catchment area of Silkeborg Regional Hospital in future years.

Further information needed.

The present analysis was restricted to the lung cancer patients that were diagnosed at Silkeborg Regional Hospital. The numbers are small, and it was possible to manually retrieve the detailed clinical information. A further study is in preparation in which the starting point will be the much larger cohort of patients who were investigated with CT imaging at Silkeborg Regional Hospital. This will be based on electronically available data and should enable the calculation of lung cancer detection rates in different diagnostic pathways and hereby contribute to the understanding of the screening-like clinical process (the high use of CT) and the screening-like outcome (the rapid increase in early-stage cancer) that we have described here.

Practical implications of these results.

A full evaluation of the Silkeborg protocol requires attention to the broad range of patients and outcomes of thousands of CT examinations, not just the lung cancers that were detected. The high use of CT may contribute to the management of a wide range of other conditions, but the benefits should be balanced with the possibility of incidental findings and overdiagnosis that may cause unnecessary or harmful interventions.

It is evident from these data that the practice change at Silkeborg Regional Hospital has had the effect of increasing the rate of detection of stage IA lung cancers, and that half of this detection has involved the use of LDCT imaging. The results show that a large proportion of the increase in these early-stage cancers are in the form of incidental findings. The incidental finding of serious disease may certainly be of benefit to the patient, indeed life-saving, but clinical diagnostic processes are not designed for the primary purpose of increasing the yield of incidental cancers. A clinical practice set up primarily to make incidental findings is similar to a screening programme, and its design and implementation should follow the principles of analysis of benefits and costs that apply to an organised screening programme.

A limitation of this study is that it had to be conducted as an observational epidemiological study, relying on data that could be retrieved by chart review from clinical data in the hospital. An intervention and practice change on the scale of the transition from X-ray to CT imaging at Silkeborg Regional Hospital should preferably be designed with prospective collection of data on the indications and the results of the investigations, hereby making the evaluation a protocolled part of the intervention.

List of tables and figures, and legends to figures.

References

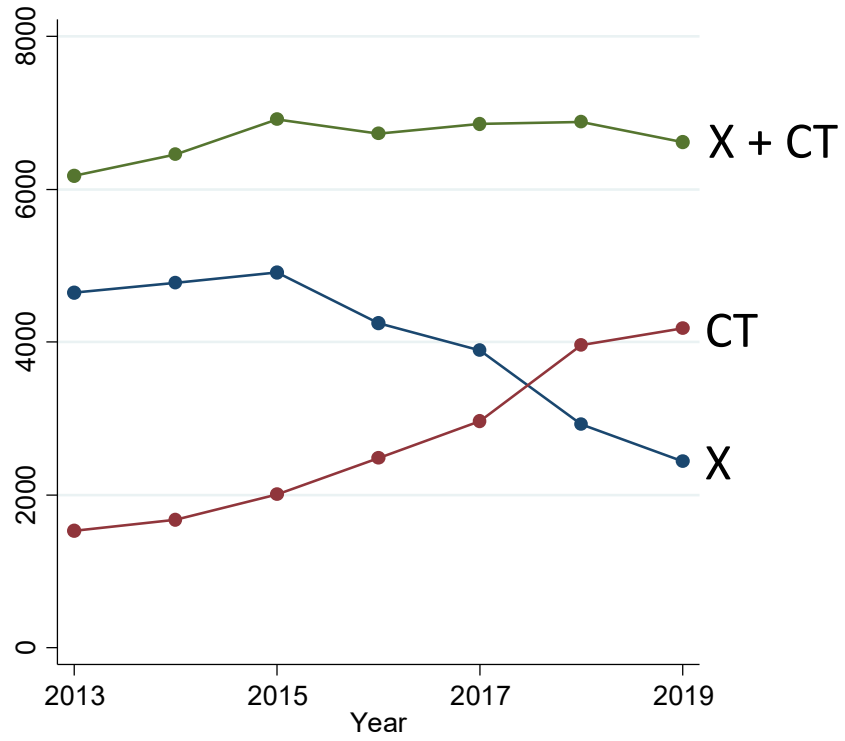
1. https://sundhedsdatastyrelsen.dk/da/tal-og-analyser/analyser-og-rapporter/sygdomme/kraeft-_-nyetilfaelde. 2019 [
2. NORDCAN. https://www-dep.iarc.fr/NORDCAN/English/frame.asp [
3. Jakobsen E, Rasmussen TR, Green A. Mortality and survival of lung cancer in Denmark: Results from the Danish Lung Cancer Group 2000-2012. Acta Oncol. 2016;55 Suppl 2:2-9.
4. González Maldonado S, Motsch E, Trotter A, Kauczor HU, Heussel CP, Hermann S, et al. Overdiagnosis in lung cancer screening: Estimates from the German Lung Cancer Screening Intervention Trial. Int J Cancer. 2021;148(5):1097-105.
5. Toyoda Y, Nakayama T, Kusunoki Y, Iso H, Suzuki T. Sensitivity and specificity of lung cancer screening using chest low-dose computed tomography. Br J Cancer. 2008;98(10):1602-7.
6. Church TR, Black WC, Aberle DR, Berg CD, Clingan KL, Duan F, et al. Results of initial low-dose computed tomographic screening for lung cancer. N Engl J Med. 2013;368(21):1980-91.
7. Veronesi G, Maisonneuve P, Spaggiari L, Rampinelli C, Pardolesi A, Bertolotti R, et al. Diagnostic performance of low-dose computed tomography screening for lung cancer over five years. J Thorac Oncol. 2014;9(7):935-9.
8. 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.
9. de Koning HJ, van der Aalst CM, de Jong PA, Scholten ET, Nackaerts K, Heuvelmans MA, et al. Reduced Lung-Cancer Mortality with Volume CT Screening in a Randomized Trial. N Engl J Med. 2020;382(6):503-13.
10. Team NLSTR. Lung Cancer Incidence and Mortality with Extended Follow-up in the National Lung Screening Trial. J Thorac Oncol. 2019;14(10):1732-42.
11. Pastorino U, Silva M, Sestini S, Sabia F, Boeri M, Cantarutti A, et al. Prolonged lung cancer screening reduced 10-year mortality in the MILD trial: new confirmation of lung cancer screening efficacy. Ann Oncol. 2019;30(10):1672.
12. Orrason AW, Sigurdsson MI, Baldvinsson K, Thorsteinsson H, Jonsson S, Gudbjartsson T. Incidental detection by computed tomography is an independent prognostic factor for survival in patients operated for nonsmall cell lung carcinoma. ERJ Open Res. 2017;3(2).
13. Brodersen J, Voss T, Martiny F, Siersma V, Barratt A, Heleno B. Overdiagnosis of lung cancer with low-dose computed tomography screening: meta-analysis of the randomised clinical trials. Breathe (Sheff). 2020;16(1):200013.
14. https://www.lungecancer.dk/wp-content/uploads/2019/11/%C3%85rsrapport-2018_netudgave_rev.pdf [
15. Jakobsen E, Rasmussen TR. The Danish Lung Cancer Registry. Clin Epidemiol. 2016;8:537-41.
16. Schmidt M, Schmidt SA, Sandegaard JL, Ehrenstein V, Pedersen L, Sørensen HT. The Danish National Patient Registry: a review of content, data quality, and research potential. Clin Epidemiol. 2015;7:449-90.
17. Bjerregaard B, Larsen OB. The Danish Pathology Register. Scand J Public Health. 2011;39(7 Suppl):72-4.
18. Christensen J, Kejs AMT, Schmidt LKH, Søgaard J, Rasted MC, Andersen O, et al. Agreement between the Danish Cancer Registry and the Danish Lung Cancer Registry. Dan Med J. 2020;67(8).
19. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40(5):373-83.
20. Schmidt M, Pedersen L, Sørensen HT. The Danish Civil Registration System as a tool in epidemiology. Eur J Epidemiol. 2014;29(8):541-9.

21. Hamilton W, Peters TJ, Round A, Sharp D. What are the clinical features of lung cancer before the diagnosis is made? A population based case-control study. Thorax. 2005;60(12):1059-65.
22. Harrison CJ, Spencer RG, Shackley DC. Transforming cancer outcomes in England: earlier and faster diagnoses, pathways to success, and empowering alliances. J Healthc Leadersh. 2019;11:1-11.
23. Guldbrandt LM, Fenger-Grøn M, Rasmussen TR, Rasmussen F, Meldgaard P, Vedsted P. The effect of direct access to CT scan in early lung cancer detection: an unblinded, cluster-randomised trial. BMC Cancer. 2015;15:934.
24. Wilson DO, Ryan A, Fuhrman C, Schuchert M, Shapiro S, Siegfried JM, et al. Doubling times and CT screen–detected lung cancers in the Pittsburgh Lung Screening Study. Am J Respir Crit Care Med. 2012;185(1):85-9

Table 1. Frequencies of lung cancer in each stage-group, 2013-2015 and 2016-2018, with statistical comparison of the rate of change in each stage-group between geographical areas.

	Silkeborg						Region Midtjylland, except Silkeborg					Denmark, except Region Midtjylland			
Clinical stage	Frequency 2013-2015	Frequency 2016-2018	Absolute change	Relative change	p-value vs. Region M.	p-value vs. Denmark	Frequency 2013-2015	Frequency 2016-2018	Absolute change	Relative change	p-value vs. Denmark	Frequency 2013-2015	Frequency 2016-2018	Absolute change	Relative change
IA	36	86	50	2.39	*0.004*	*0.001*	359	473	114	1.32	*0.23*	1,205	1,441	236	1.20
IB	13	29	16	2.23	*0.01*	*0.06*	182	171	-11	0.94	*0.07*	672	788	116	1.17
II	16	26	10	1.63	*0.26*	*0.43*	206	225	19	1.09	*0.39*	789	946	157	1.20
III	49	62	13	1.27	*0.69*	*0.34*	445	516	71	1.16	*0.18*	2,125	2,232	107	1.05
IV	117	93	-24	0.79	*0.09*	*0.14*	1,262	1,297	35	1.03	*0.32*	5,415	5,326	-89	0.98
NA	20	7	-13	0.35	*0.30*	*0.11*	190	116	-74	0.61	*0.14*	857	635	-222	0.74
Total	251	303	52	1.21	*0.15*	*0.06*	2,644	2,798	154	1.06	*0.33*	11,063	11,368	305	1.03

Silkeborg



Region Midtjylland, except Silkeborg

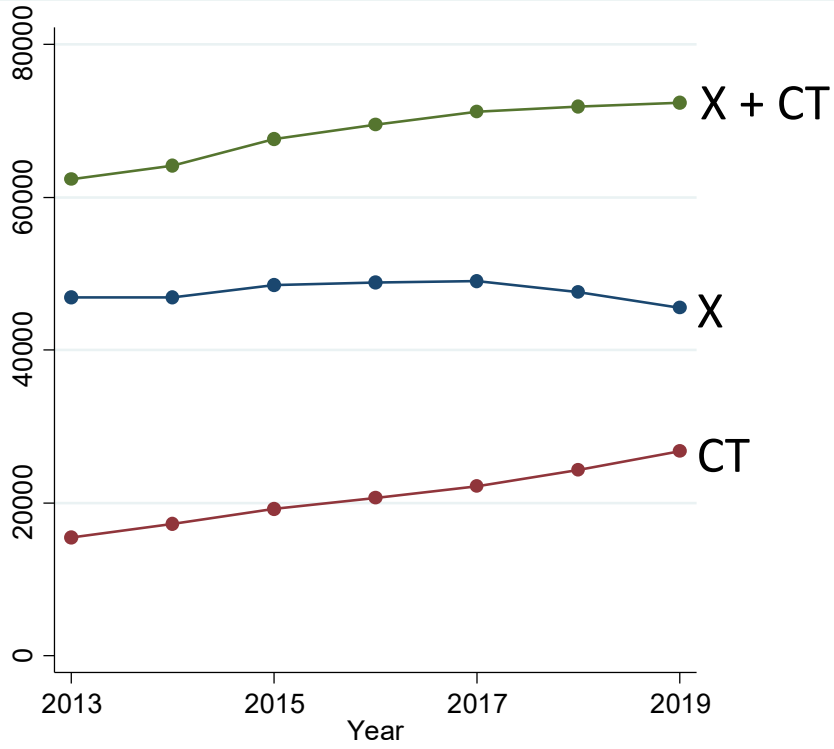


Table 2. Description of 547 lung cancer patients, Silkeborg Regional Hospital 2013-2018, and comparison of distributions in two periods 2013-2015 (247) and 2016-2018 (300)

	2013-2018 (547)		2013-2015 (247)		2016-2018 (300)	
	N	%	N	%	N	%
Outcome						
Clinical TNM stage						
IA	119	21.8	34	13.8	85	28.3
IB	42	7.7	13	5.3	29	9.7
II	42	7.7	16	6.5	26	8.7
IIIA	54	9.9	22	8.9	32	10.7
IIIB-IIIC	57	10.4	27	10.9	30	10.0
IV	208	38.0	116	47.0	92	30.7
NA	25	4.6	19	7.7	6	2.0
			Chi2(6)=37.1; p<0.001			
			Chi2(5)=27.2; p<0.001 (ex. NA)			
Person characteristics and constitution						
Age at diagnosis						
			Median		*Median*	
			70.7		*70.8*	
-59	66	12.1	27	10.9	39	13.0
60-69	192	35.1	89	36.0	103	34.3
70-79	216	39.5	97	39.3	119	39.7
80+	73	13.3	34	13.8	39	13.0
			Chi2(3)=0.66; p=0.88			
Sex						
Male	293	53.6	132	53.4	161	53.7
Female	254	46.4	115	46.6	139	46.3
			Chi2(1)=0.003; p=0.96			
Charlson comorbidity score						
0	235	43.0	106	42.9	129	43.0
1	130	23.8	60	24.3	70	23.3
2	83	15.2	41	16.6	42	14.0
3+	99	18.1	40	16.2	59	19.7
			Chi2(3)=1.6; p=0.67			
Pack-years						
40+	252	46.1	116	47.0	136	45.3
20-39	187	34.2	78	31.6	109	36.3
10-19	41	7.5	18	7.3	23	7.7
0-9	43	7.9	24	9.7	19	6.3
NA	24	4.4	11	4.5	13	4.3
			Chi2(4)=3.0; p=0.56			
			Chi2(3)=3.0; p=0.40 (ex. NA)			
Morphology						
Small cell carcinoma	71	13.0	40	16.2	31	10.3
Adenocarcinoma	269	49.2	110	44.5	159	53.0
Squamous cell carcinoma	96	17.6	47	19.0	49	16.3
NSCLC unspecified	67	12.2	33	13.4	34	11.3
Other and NA	44	8.0	17	6.9	27	9.0
			Chi2(4)=7.3; p=0.12			

Continues …

Table 2. Continued.

Referral						
Initiation of referral						
General practice	310	56.7	143	57.9	167	55.7
Hospital	237	43.3	104	42.1	133	44.3
			Chi2(1)=0.27; p=0.60			
Red flag symptoms (PPV, %)						
0.0	169	30.9	70	28.3	99	33.0
0.1-0.9	247	45.2	109	44.1	138	46.0
1+	131	23.9	68	27.5	63	21.0
			Chi2(2)=3.5; p=0.18			
Diagnostics						
Initial imaging conclusion						
Suspicious for cancer	414	75.7	194	78.5	220	73.3
Referral for follow-up	93	17.0	33	13.4	60	20.0
Not suspicious	40	7.3	20	8.1	20	6.7
			Chi2(2)=4.4; p=0.11			
Index image						
CECT	105	19.2	37	15.0	68	22.7
LDCT	73	13.3	11	4.5	62	20.7
Xray	260	47.5	149	60.3	111	37.0
None of the above	109	19.9	50	20.2	59	19.7
			Chi2(3)=46.4; p<0.001			
Imaging cascade						
CECT direct (includes 7 with PET)	87	15.9	28	11.3	59	19.7
LDCT or ULDCT	71	13.0	9	3.6	62	20.7
Xray then CECT	207	37.8	129	52.2	78	26.0
Xray then LDCT	82	15.0	33	13.4	49	16.3
Other	100	18.3	48	19.4	52	17.3
			Chi2(4)=61.9; p<0.001			
Clinical pathway						
Pathway						
Lung cancer referral pathway	40	7.3	16	6.5	24	8.0
LDCT pathway	73	13.3	11	4.5	62	20.7
Urgent referral pathway for non-specific serious symptoms	94	17.2	47	19.0	47	15.7
Not a defined clinical pathway	340	62.2	173	70.0	167	55.7
			Chi2(3)=35.5; p<0.001			
Timing of investigation and diagnosis						
Days from investigation to diagnosis						
Less than 31	431	78.8	205	83.0	226	75.3
31-60	33	6.0	12	4.9	21	7.0
61-179	29	5.3	9	3.6	20	6.7
180+	53	9.7	20	8.1	33	11.0
NA	1	0.2	1	0.4	0	0.0
			Chi2(4)=6.8; p=0.15			
			Chi2(3)=5.6; p=0.14 (ex. NA)			

Table 3. Logistic regression analysis of 294 lung cancer patients, Silkeborg Regional Hospital 2016-2018.
Outcome is cTNM stage IA.

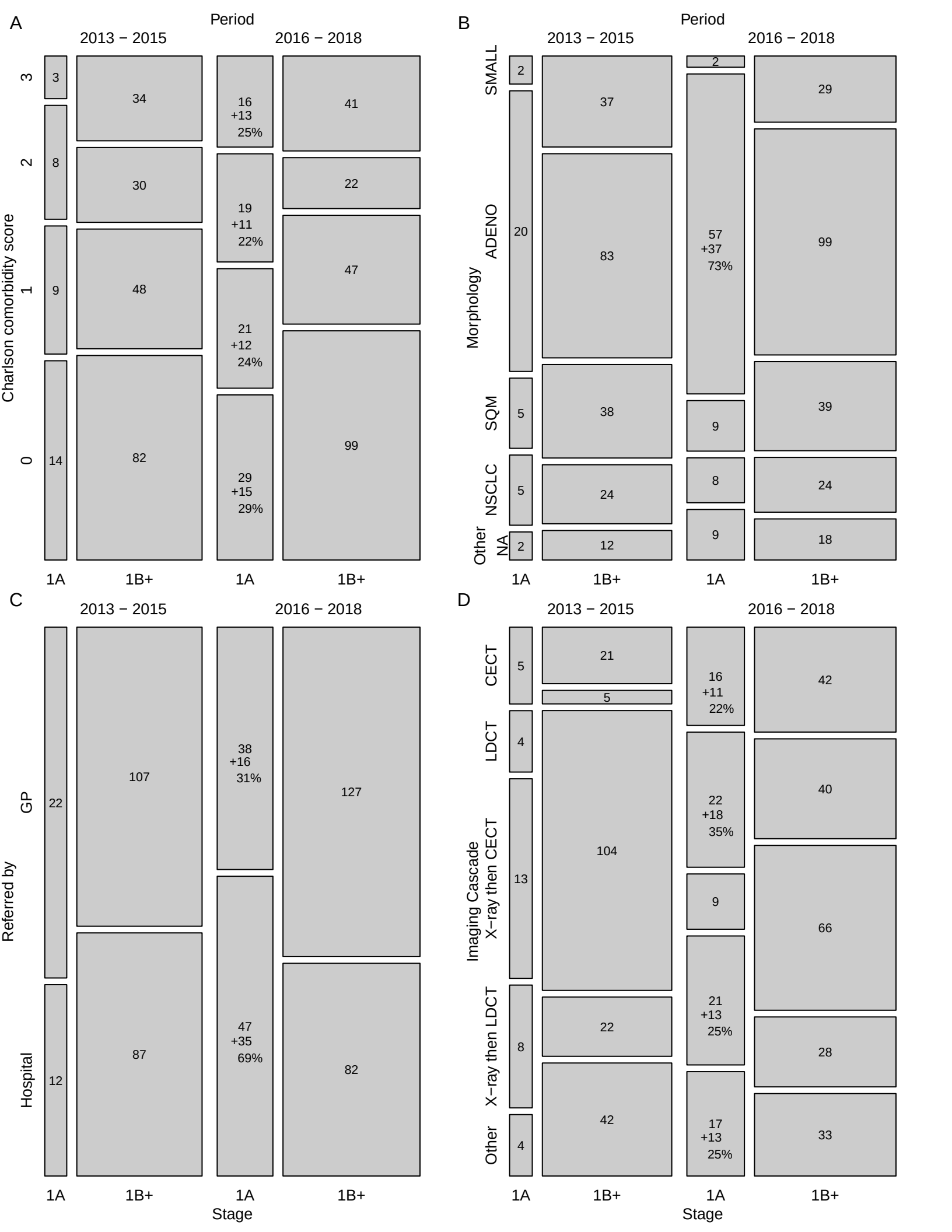
	cTNM					
	IA (85)	Higher (209)	%IA	OR	95% CI	
Patient characteristics and constitution						
Age at diagnosis						
	Median 72.0	*Median 69.9*				
-59	10	29	25.6	0.60	0.27	1.35
60-69	26	76	25.5	0.59	0.33	1.07
70-79	42	73	36.5	1.00		
80+	7	31	18.4	0.39	0.16	0.97
				Chi2(3)=5.9; p=0.11		
Sex						
Male	40	120	25.0	1.00		
Female	45	89	33.6	1.52	0.91	2.52
				Chi2(1)=2.6; p=0.11		
Charlson comorbidity score						
0	29	99	22.7	1.00		
1	21	47	30.9	1.53	0.79	2.95
2	19	22	46.3	2.95	1.41	6.18
3+	16	41	28.1	1.33	0.65	2.71
				Chi2(3)=8.3; p=0.04		
Pack-years						
40+	32	99	24.4	1.00		
20-39	33	76	30.3	1.34	0.76	2.38
10-19	9	14	39.1	1.99	0.79	5.03
0-9	10	8	55.6	3.87	1.41	10.63
NA	1	12	7.7	0.26	0.03	2.06
				Chi2(3)=7.9; p=0.048 (ex. NA)		
Morphology						
Small cell carcinoma	2	29	6.5	0.12	0.03	0.52
Adenocarcinoma	57	99	36.5	1.00		
Squamous cell carcinoma	9	39	18.8	0.40	0.18	0.89
NSCLC unspecified	8	24	25.0	0.58	0.24	1.37
Other and NA	9	18	33.3	0.87	0.37	2.06
				Chi2(4)=12.6; p=0.01		
Referral						
Initiation of referral						
General practice	38	127	23.0	0.52	0.31	0.87
Hospital	47	82	36.4	1.00		
				Chi2(1)=6.2; p=0.01		
Red flag symptoms (PPV, %)						
0.0	34	63	35.1	1.36	0.78	2.37
0.1-0.9	39	98	28.5	1.00		
1+	12	48	20.0	0.63	0.30	1.31
				Chi2(2)=4.0; p=0.13		

Continues …

Table 3. Continued.

Diagnostics						
Initial imaging conclusion						
Suspicious for cancer	40	176	18.5	1.00		
Referral for follow-up	36	24	60.0	6.60	3.55	12.27
Non-suspicious	9	9	50.0	4.40	1.64	11.79
				Chi2(2)=38.9; p<0.001		
Index image						
CECT	19	46	29.2	1.00		
LDCT	25	37	40.3	1.64	0.78	3.42
Xray	23	87	20.9	0.64	0.32	1.30
None of the above	18	39	31.6	1.12	0.52	2.42
				Chi2(3)=7.4; p=0.06		
Imaging cascade						
CECT direct	16	42	27.6	1.00		
LDCT or ULDCT	22	40	35.5	1.44	0.66	3.14
Xray then CECT	9	66	12.0	0.36	0.15	0.88
Xray then LDCT	21	28	42.9	1.97	0.88	4.41
Other	17	33	34.0	1.35	0.60	3.07
				Chi2(4)=15.5; p=0.004		
Clinical pathway						
Pathway						
Lung cancer referral pathway	5	19	20.8	1.00		
LDCT pathway	25	37	40.3	2.57	0.85	7.78
Urgent referral pathway for non-specific serious symptoms	12	33	26.7	1.38	0.42	4.52
Not a defined clinical pathway	43	120	26.4	1.36	0.48	3.87
				Chi2(3)=5.2; p=0.16		
Timing of investigation and diagnosis						
Days from investigation to diagnosis						
Less than 31	42	180	18.9	1.00		
31-60	8	11	42.1	3.12	1.18	8.23
61-179	12	8	60.0	6.43	2.47	16.72
180+	23	10	69.7	9.86	4.36	22.27
				Chi2(3)=41.1; p<0.001		

Six patients with missing value for clinical stage are not included.


A
Period
2013 − 2015
2016 − 2018
Charlson comorbidity score
3
2
1
0
3
8
9
14
34
30
48
82
16
+13
25%
19
+11
22%
21
+12
24%
29
+15
29%
41
22
47
99
1A
1B+
1A
1B+
B
Period
2013 − 2015
2016 − 2018
Morphology
SMALL
ADENO
SQM
NSCLC
Other
NA
2
20
5
5
2
2
37
83
38
24
12
2
57
+37
73%
9
8
9
29
99
39
24
18
1A
1B+
1A
1B+
C
2013 − 2015
2016 − 2018
Referred by
GP
Hospital
22
12
107
87
38
+16
31%
47
+35
69%
127
82
1A
1B+
1A
1B+
Stage
D
2013 − 2015
2016 − 2018
Imaging Cascade
CECT
LDCT
X−ray then CECT
X−ray then LDCT
Other
5
4
13
8
4
21
5
104
22
42
16
+11
22%
22
+18
35%
9
21
+13
25%
17
+13
25%
42
40
66
28
33
1A
1B+
1A
1B+
Stage