

The effect of direct referral for fast CT scan in early lung cancer detection in general practice. A clinical, cluster-randomised trial.

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THE FOUR ORIGINAL PAPERS ARE

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3. Guldbrandt LM, Rasmussen TR, Rasmussen F, Vedsted P.: Implementing direct access to chest computed tomography in general practice - method, adaption and outcome. PLoS One 2014 Nov 10;9(11):e112162.
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INTRODUCTION

GENERAL INTRODUCTION TO THE THEME

"I followed the patient for almost 12 months because of drastic weight loss. I thought it was due to the patient's serious lung disease (COPD). In hindsight, I should have referred the patient for diagnostic work-up".

These are the words written by a general practitioner (GP).

Another GP writes,

"The patient's spouse has recently been through a long diagnostic process for dementia ... the patient has probably been hiding the symptoms for some time. The patient was arm-twisted to accept referral".

And yet another writes,

"The patient had symptoms from the musculoskeletal system which could not be treated with painkillers or physiotherapy; chest X-ray was normal. The patient's cancer was discovered when he was admitted to hospital for another reason".

These three quotes from Danish GPs participating in one of the studies in the present thesis illustrate some of the difficulties GPs encounter when diagnosing lung cancer in general practice. Most clinicians probably recognise the contents of the case stories above.

The aim of this thesis is to increase our knowledge of the initial stages in the diagnosis of lung cancer in general and the diagnostic activity in primary care and the routes to diagnosis in particular. The thesis will also examine the effect of an additional diagnostic test, low-dose computer tomography (LDCT), performed from general practice. First, however, this chapter gives a brief overview of the epidemiology, treatment and prognosis of lung cancer in Denmark and an introduction to lung cancer diagnostics in primary and secondary care. Finally, the chapter summarises the background and outlines the aims of the study.

LUNG CANCER

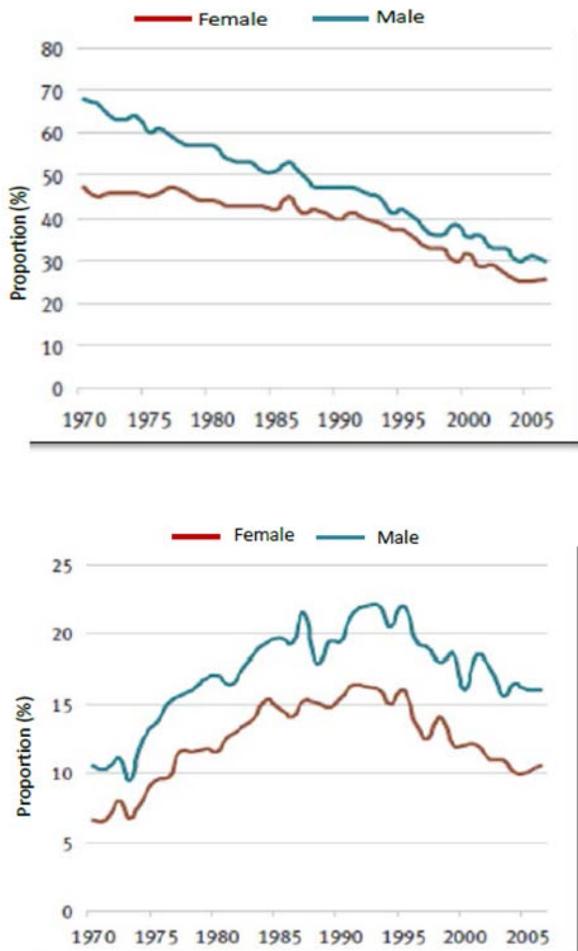
Incidence and aetiology

Lung cancer is the second leading cancer type in both genders in Denmark. Annually, 4350 new cases are diagnosed [1], and the disease accounts for 12% of all cancer diagnoses and 23% of all cancer deaths in Denmark [1]. In Europe, 85-90% of lung cancers are considered to be caused by cigarette smoking, and it is estimated that lung cancer will develop in 15% of lifelong smokers [2]. An increased risk of lung cancer is also seen in people who are exposed to occupational components (e.g. asbestos, tar, soot), residential radiation, indoor/outdoor air pollution and in patients with pulmonary fibrosis [2].

As the overwhelming majority of cases of lung cancer are attributable to cigarette smoking, the change in the incidence of lung cancer reflects a change in smoking habits with a lag phase in the order of 20-30 years (Figure 1). Primary prevention should

accordingly continue to be a major focus. However, primary prevention is likely to only modestly impact mortality in the short term, and initiatives supplementing smoking cessation campaigns are needed to improve health outcomes, also in the growing cohort of ex-smokers.

Figure 1: The First set of curves is the proportion of female and male smokers in Denmark from 1970 to 2005. The second set is the proportion of heavy smokers (≥ 15 cigarettes per day) in Denmark in the same time period. [3]



Histology

Lung cancer can be divided into non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) based on the WHO classification [4]. NSCLC is the dominant type comprising 85-90% of all lung cancers in Denmark.

The simple distinction between SCLC and NSCLC is, however, no longer sufficient. Evidence suggests that NSCLC is a heterogeneous group of diseases requiring different treatment according to the type of NSCLC in question. A group of oncogene driver mutations (e.g. endothelial growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK)) has been discovered, and molecular target drugs have been developed and used since 2002, which has improved patient outcomes [5]. Pathological examination of the cancer before treatment is planned is there-

fore becoming increasingly important, and chest physicians are accordingly faced with mounting pressure to gather sufficient material as are also pathologists to ensure early and correct tissue examination [6].

TNM classification and staging

Treatment options for lung cancer are legion, but the decision which modality to use depends on a detailed and accurate assessment of the disease. In an effort to raise the quality of lung cancer diagnostics, the staging process is centralised at the Danish departments of pulmonary medicine. Investigations performed at these centres are important for answering the following three questions; does the patient have cancer, what are the treatment possibilities and, finally, what is the prognosis?

Patients with NSCLC are staged according to the International System for Staging Lung Cancer which is based on the 7th TNM System Classification [7] (Table 1). The T component describes the extent of the primary tumour in terms of both size and local invasion. The N component describes regional lymph node involvement, and the M component denotes whether distant metastases are present or not.

Table 1: TNM for NSCLC according to the 7th WHO classification. Green boxes are operable stage [8].

T/M	N0	N1	N2	N3
T1a (≤ 2 cm)	IA	IIA	IIIA	IIIB
T1b (> 2 cm)	IA	IIA	IIIA	IIIB
T2a (≤ 5 cm)	IB	IIA	IIIA	IIIB
T2b (> 5 cm)	IIA	IIIB	IIIA	IIIB
T3 (> 7 cm)	IIIB	IIIA	IIIA	IIIB
T3 (invasion)	IIIB	IIIA	IIIA	IIIB
T3 (same lobe nodules)	IIIB	IIIA	IIIA	IIIB
T4 (extension)	IIIA	IIIA	IIIB	IIIB
T4 (pleural effusion)	IV	IV	IV	IV
M1a (ipsilateral lung)	IIIA	IIIA	IIIB	IIIB
M1a (contralateral lung)	IV	IV	IV	IV
M1b (distant)	IV	IV	IV	IV

The TNM stage can be reported as either clinical TNM (cTNM - premised on investigations performed prior to the initiation of therapy) or surgical/pathological TNM (pTNM- based on histological analysis of the resected specimen) [7]. The fact that the prognosis is more accurately predicted by the surgical/pathological stage than by the clinical grading is intuitive. However, all patients can be staged according to cTNM, which facilitates comparison of lung cancer patients across different stages.

The TNM system may be applied to patients with SCLC, but management decisions are not clearly based on the TNM stage. It is therefore more important to identify patients with metastatic disease or patients whose disease is limited to a particular area that may be amenable to radiotherapy, e.g. one hemi-thorax.

One of the key elements in the staging of lung cancer is the contrast-enhanced multi-detector computed tomography (CE-MDCT) of the chest and upper abdomen. CE-MDCT provides information about tumour size and invasion (T), some information about the presence of involved lymph nodes (N) and distant

metastases (M) (e.g. in the liver or in the adrenal glands). The results of the CT are also taken into account when a diagnostic strategy is planned when deciding from which site a biopsy should be obtained in order to establish the final diagnosis.

Central tumours are mostly accessible with a bronchoscope combined with ultrasound endoscopy (either as endobronchial ultrasound (EBUS) (Figure 2) or from the oesophagus (EUS)) and fine needle aspiration. Peripheral tumours are most easily reached by transcutaneous biopsy guided either by CT, ultrasound or X-ray. Biopsies are obtained to confirm the presence of malignant cells, to classify the tumour according to the above histological classification and, for adenocarcinomas, to detect the presence of any oncogene driver mutations. Additional imaging can be used, e.g. positron emission tomography (PET)/CT (primarily for surgery candidates), CT/magnetic resonance (MR) of brain (if suspicion of brain metastases) or bone scintigraphy (if suspicion of bone metastases).

Figure 2: Fine needle biopsy with EBUS. Image courtesy of Olympus Europa SE & Co. KG©.



Each specific stage comes with particular therapeutic and prognostic scenarios; and before the final treatment plan is drawn up, a patient evaluation is needed combining clinical information (extent of comorbidity, lung function and performance status) with the TNM staging and the pathologic typing. In Denmark, the ambition is that all patients should be discussed at a multidisciplinary-team meeting (MDT). Growing evidence supports that these MDT meetings improve patient outcome and adherence to evidence-based guidelines [9,10].

Treatment

Treatment can have a curative or palliative intent depending on the factors mentioned above (stage, histological classification and patient evaluation).

Surgery is the most effective treatment for lung cancer. Patients with localised NSCLC (stage I, II) can be offered surgery if their general health and lung function allow it. Surgery commonly consists of lobectomy (one lobe removed) or pneumectomy (one lung removed). Adjuvant (post operation) chemotherapy increases survival for all patients (except for stage IA and IB) [11].

Chemo-radiotherapy is an alternative treatment with a curative intent for patients who are not fit for surgery or for patients

in stage IIIA. Combination of the two modalities increases the chances of survival compared with radiation alone [12].

Furthermore, stereotactic body radiotherapy (SBR), which is high-dose radiation, or thermal ablation are other modalities that may be used with a curative intent. SBR can be used for patients who are unfit for surgery and with small tumours (≤ 6 cm) and no lymph node involvement [13]. Curative treatment for SCLC (limited disease) consists of combined chemo-radiotherapy [14] and, for a small number of patients, operation.

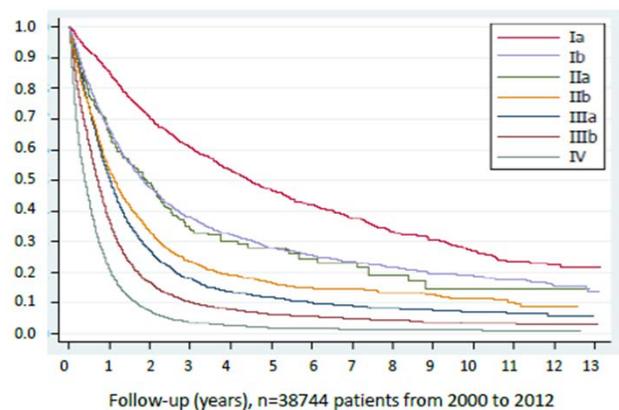
The purpose of palliative treatment is to prolong life and to relieve symptoms by limiting tumour growth and metastasis. For patients with metastatic disease and good general health, the standard palliative treatment is chemotherapy. Patients with one of the before-mentioned oncogene driver mutations constitute an exception to this. In such patients, the first-line treatment is biological treatment targeted at the mutation [15]. Another palliative treatment option is radiation therapy targeted at the primary tumour or any metastases (bone, brain, etc.) [15].

In conclusion, the choice of treatment modality depends on histology, the stage of the disease, the patient's general health and the presence of comorbidity. These factors largely determine the patient's prognosis; and the patient's survival hinges on early diagnosis and a good general health. Furthermore, low-stage treatment is often simple and more likely to be effective.

Prognosis

As mentioned above, the stage of the disease at the time treatment starts is the most significant predictor of survival because an advanced stage reduces the likelihood of curative treatment. Thus, the 1-year survival rate is approximately 80% for stage I lung cancer and 20% for stage VI lung cancer (Figure 3).

Figure 3: Survival curves for Danish lung cancer patients according to stage at diagnosis in the years from 2000-2012 [16].

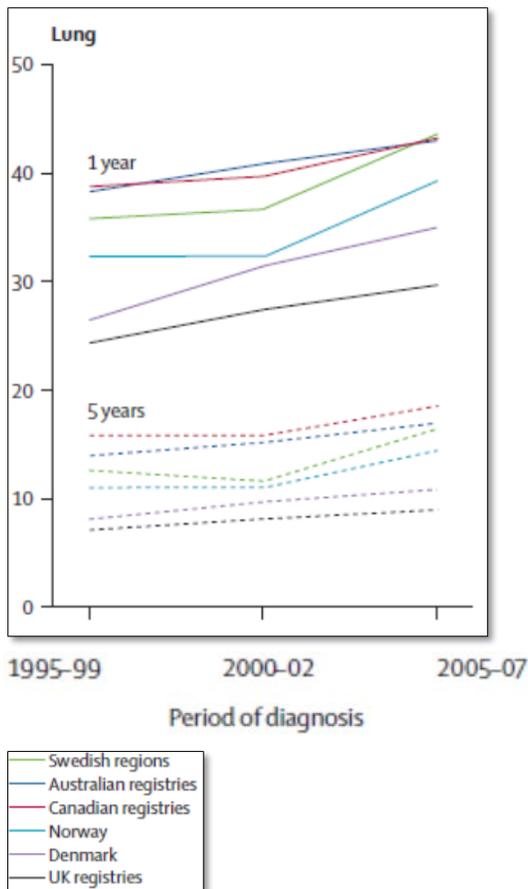


The stage distribution in Danish lung cancer patients has remained constant over the past decades, which implies that approximately 70% of patients with advanced stage lung cancer cannot be offered curative treatment [16].

The overall survival from lung cancer is lower in Denmark than in other comparable European countries. In 2007, the 1-year survival rate was 34.9% in Denmark but 43.6% in Sweden [17] (Figure 4). The low survival in Denmark is partly due to a more advanced stage at diagnosis. A large comparative study of lung cancer in 2004-07 [18] showed that the proportion of early-stage lung cancers (both NSCLC and SCLC) was lower in Denmark (and

the UK) than in Sweden, Norway, Australia and Canada. For NSCLC, the proportion of patients with metastatic disease (TNM stage IV) ranged from 47.8% in Sweden to 55.0% in Denmark. The large proportion of more advanced-stage cancer patients may be due to faster disease progression (possibly related to tumour biology because of the higher incidence of smoking in Denmark than in comparable countries [19]) or it may be due to longer diagnostic time intervals [20].

Figure 4: Age-standardised 1-year and 5-year survival trends 1995-2007, by country [17]



EARLY DIAGNOSIS OF LUNG CANCER

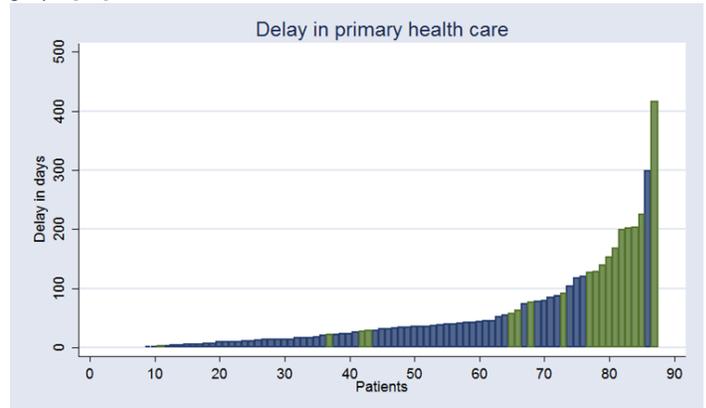
Thus, evidence indicates that one way in which survival from lung cancer may be improved is to ensure that the disease is diagnosed when it is at a low stage. However, it remains rather unclear how this may be achieved. However, studies suggest that avoidable delays in diagnosis do occur and that these delays are attributable to both patient, doctor and system behaviour.

First, patients experiencing a sign or a symptom have to acknowledge this and have to consult their GP. Studies indicate that several factors can delay the patient's presentation of symptoms; for example, underestimating the seriousness of symptoms and signs, the patient may fail to act on changes in his or her health [21-23]. Furthermore, patients may worry wasting the doctor's time and therefore postpone seeking medical advice [24,25].

Second, studies have identified several reasons for a delayed referral from general practice to the secondary healthcare system. Delay may, for example, arise if patients present non-specific symptoms which may cause the GP to misinterpret the symptoms

or not to refer the patient for diagnostic tests [22]. Furthermore, a Danish study from 2006 found that false negative chest radiographs were one of the main reasons for delay in general practice [26] (Figure 5). For lung cancer, the observed median primary healthcare interval (from the patient's first presentation in general practice to referral to secondary healthcare) was 34 days in 2008. The 25% of the patients who waited the longest waited for 64 days or longer [27].

Figure 5: Delay in primary health care for patients with lung cancer. Green columns are patients with a false negative radiograph [28].

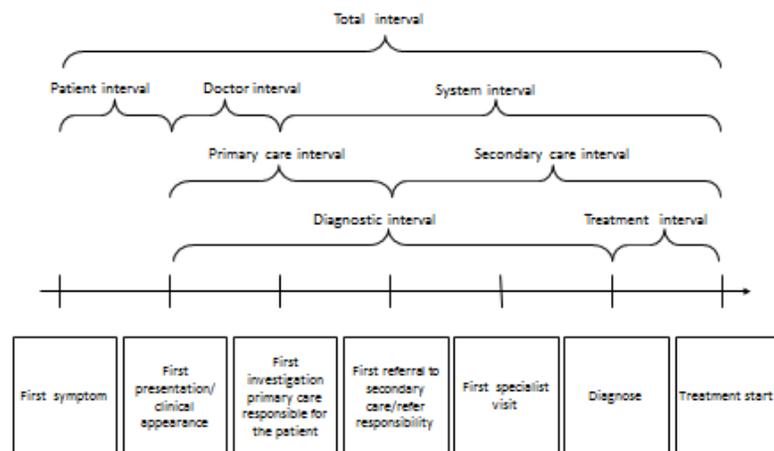


Third, delays can occur in the time interval between referral to the secondary healthcare sector and initiation of treatment. This kind of delay is typically generated through inefficiency or long waiting times for appointments or tests [28]. Three PhD theses from Aarhus University, Denmark document that system delay (from first presentation in general practice to treatment) accounts for a substantial part of the total delay experienced by Danish cancer patients [28-30].

Time intervals

In recognition of the importance of using generally agreed definitions of the different kinds of time intervals and delays in the cancer journey, the present thesis uses the guidelines and definition of the International Consensus Group (Figure 6) [31]. In addition, the term 'time interval' (contrary to 'delay') will be preferred in this thesis when describing time in the diagnostic process.

Figure 6: The diagnostic pathways of the cancer journey [31].



Initiatives to reduce delays in Denmark

The 1990s saw growing general awareness about the existence of long hospital waiting times in the diagnosis of cancer. In response to this, a law was passed in 2001 presenting a 2-week waiting time guarantee from diagnosis to treatment. The years 2006 and 2007 saw the publication of several case stories of cancer patients experiencing delayed diagnosis or delayed treatment with fatal consequences. This, combined with results from the above-mentioned PhD theses from Aarhus University, illustrated that many Danish cancer patients experienced unacceptable clinical pathways. Making it clear that ‘cancer should be seen as an acute disease’, the Danish Cancer Society suggested a new model, and political agreement was reached according to which national cancer patient pathways were prescribed for all cancer types [32]. By the spring of 2009, multidisciplinary groups had outlined fast-track referral pathways for diagnosis and treatment of the most common cancers [33]. In 2012, a fast-track referral for non-specific cancer or serious disease was introduced. Furthermore, in 2011 it was decided to improve continuing medical education (CME) in cancer diagnostic for all GPs. Finally, several awareness campaigns have been launched to reduce patient delay [34].

DIAGNOSING LUNG CANCER IN PRIMARY HEALTHCARE

General practice in Denmark

Denmark’s publicly funded healthcare system provides patients with free access to general practice and to outpatient and hospital care. More than 98% of Danish citizens [35] are registered with a particular GP whom they have to consult for primary healthcare services. The GP functions as a gatekeeper to the rest of the healthcare system with a few exceptions (e.g. emergencies and ear, nose and throat (ENT) diseases).

The GP plays a central role throughout the diagnostic investigation process, from the patient’s first symptom presentation until diagnosis. If a GP suspects lung cancer, (s)he can organise simple investigations like blood tests and chest radiographs (retaining the responsibility for the patient). If diagnosis is difficult or the investigations are abnormal, the GP can refer the patient to a department of pulmonary medicine, either to its normal waiting list or to its fast-track facility. At this point, the patient is no longer the GP’s responsibility. The GPs (in most parts of Denmark) are not allowed to refer patients directly to more specialised test (e.g. CT scan) when they suspect lung cancer.

Symptoms of lung cancer

More than 90% of lung cancer patients are symptomatic at the time of diagnosis at which time patients usually experience two or three symptoms on average [36]. Studies have shown that patients have been symptomatic for several months before they seek medical attention [21,37-39]. Furthermore, most of the patients present initially to their GP [40-42]. Overall, GPs are involved in the diagnosis of 85% of cancer cases [27,43], but we do not know the percentage for Danish lung cancer patients. Furthermore, studies indicate that lung cancer patients have several pre-referral consultations in general practice [44,45]. This could be because many lung cancer patients seem to present with unspecific, vague or low-risk-but-not-no-risk symptoms [46] and because they tend to consult more often for other smoking-related diseases.

Core lung cancer symptoms are indications for the fast-track pathway (Table 2). According to the current guidelines, the GP has to consider lung cancer in people over 40 years who present with new respiratory or general symptoms that have lasted for

more than 4 weeks (or exacerbation of chronic respiratory symptoms). Relevant symptoms include unexplained cough, haemoptysis and constitutional symptoms (e.g. weight loss, fatigue and loss of appetite). The symptom guidelines are based on secondary care research, i.e. the symptoms are those that are experienced by patients in the hospital setting. Symptoms indicating lung cancer are very common in general practice [47]; and even though lung cancer is common, Danish GPs encounter only approx. one new case per year. This implies that the patient’s risk of having the disease when presenting the symptoms is very low.

Much research has been undertaken in recent years in order to characterise lung cancer patients in general practice, mostly by mapping the positive predictive values (PPVs) for symptoms indicating lung cancer [41,46,48]. The PPV of a symptom is the risk of having the disease of interest (here lung cancer) when a certain symptom is reported. Even alarm symptoms have low PPVs (Figure 7) for lung cancer. For haemoptysis, the PPV is 4.5%, meaning that if a GP sees 100 patients (smokers over 40 years) in the clinic with this symptom, 4.5 of the patients will have an underlying lung cancer. For the more vague symptoms such as cough or tiredness, the PPVs are even much lower [48] (Table 2).

Figure 7. Positive predictive values (PPV) (%) for lung cancer for individual risk markers and for pairs of risk makers in combination (against a background risk of 0.16%) for smokers over 40 years.

Cough	Fatigue	Shortness of breath	Chest pain	Loss of weight	Loss of appetite	Raised platelets	Abnormal spirometry	Haemoptysis	
0.86 0.7, 1.1	0.77 0.5, 1.1	1.2 0.9, 1.7	1.3 0.9, 1.8	2.1 1.2, 3.8	1.8 1.0, 3.4	4.2	4.0	4.5	PPV as a single symptom
1.3 0.9, 1.8	1.0 0.6, 1.6	1.4 0.9, 2.0	0.86 0.7, 1.1	2.3 1.1, 4.7	2.8	6.5	3.6	3.9	Cough
	1.2 0.6, 2.3	1.4 0.8, 2.5	1.3 0.6, 2.7	2.0	2.3	2.4	>10	6.1	Fatigue
		1.5 0.9, 2.4	2.2 1.3, 4.1	3.1	5.5	2.4	>10	6.9	Shortness of breath
			1.4 0.7, 2.8	4.4	7.6	>10	>10	4.1	Chest pain
				1.7	5.0	>10	>10		Loss of weight
					2.7				Loss of appetite
								12	Haemoptysis

Notes: The top row (bold) gives the PPV for an individual feature. The cells along the diagonal relate to the PPV when the same feature has been reported twice. Other cells show the PPV when a patient has two different features. The yellow shading indicates a PPV above 1%, the amber shading a PPV above 2% and the red shading a PPV above 5% [48]

Diagnostic strategies in general practice

The GP who deals with patients presenting sign and symptoms that could indicate lung cancer must sort out the minority of patients who need urgent attention from the majority who are likely to have self-limiting or benign disorders. Despite the importance of this complex task, only little research has explored the process from symptom presentation to lung cancer diagnosis in a general practice perspective.

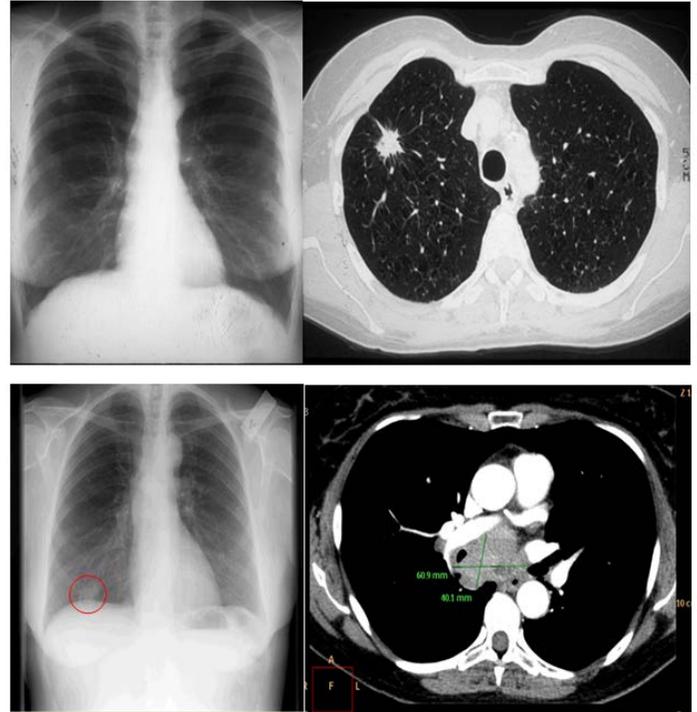
A Danish study from 2010 asked the GPs to interpret the symptoms presented by patients seen in practice before lung cancer was diagnosed [42]. The study found that one third of the patients had alarm symptoms, another one third had symptoms indicating serious disease (not cancer), and the last one third had vague symptoms (not indicating cancer or serious disease). The interpretation of the presented symptoms is important because any further action will depend on this interpretation:

Firstly, the GP can decide on a 'wait and see' approach, especially if the interpretation is that this patient most likely does not have cancer. This, combined with safety netting, follow-up appointments or blood test, etc., could be a reasonable approach in many cases. However, this approach may also be risky if it turns out that the patient did, indeed, have cancer. If the patient has cancer, the 'wait and see' approach could lead to delay with the risk of a stage shift to a more advanced disease.

Secondly, the GP can refer the patient to a chest radiograph which is the main diagnostic test for lung cancer in general practice. Radiographs are cheap and often easily available from general practice; and the radiation dose is low, around 0.1 mSv (Table 3). However, the lung cancer sensitivity is approximately 75% [49], and it is best for tumours in the peripheral lung parenchyma. For small (<2-3 cm) and central tumours, the sensitivity is much lower. Once visualised, the specificity of the chest radiograph is reasonably high (94%), although many chest films show an indistinct abnormality and must therefore be repeated. Studies in lung cancer patients show that negative chest film occur in as much as a quarter of cancers [26,50,51] with lesions being missed by the radiologist [52], and other lesions being not visible [52,53]. This indicates that chest film can be helpful if positive, but that they are not particularly helpful if negative.

Thirdly, the GP can choose to refer the patient for an urgent specialist investigation through the fast-track pathway on the grounds of 'reasonable suspicion' based on an interpretation of the symptoms and/or an abnormal radiograph. This referral pathway includes a standard patient investigation spanning from the point of 'reasonable suspicion' of cancer to treatment initiation. Maximum waiting times between different investigations are specified for the fast-track pathway, and all the standard examinations are pre-booked and pre-planned. Any patient referred to the fast-track pathway must be seen at a department of pulmonary medicine within three days (changed in 2014 to six days). Institution of fast-track treatment in secondary care is decided at the discretion of a chest physician based on an outpatient evaluation. If the suspicion is maintained, the investigations begin with a contrast-enhanced MDCT in most cases. This CT is able to detect changes in the lung parenchyma down to a few mm, compared with 2-3 cm in a plain chest radiograph (Figure 8).

Figure 8: Top: Two imaging modalities. The small tumour can hardly be seen on the radiograph. Bottom: Two imaging modalities from the same patient. A small mass is seen distally in the right lung, but with the CE-MDCT a large central mass was discovered. Courtesy of Finn Rasmussen, Department of Radiology, Aarhus University Hospital, Aarhus, Denmark.



One of the political and administrative requirements to the fast-track program was that a specialist should see the patient before initiation of basic investigations. However, as GPs are already gatekeepers to specialised care, this could be considered a 'double gatekeeping system' which gives rise to inefficiency and delay. A common argument is that a more "straight-to-test" approach would generate unnecessary tests and that the 'double gatekeeping' therefore saves investigations. However, a study of open access to colonoscopy from general practice in the Netherlands in 2011 found only a slight increase in the number of colonoscopies, but a marked decrease in median time to treatment [54].

At this time, we do not know how the fast-track pathway may best be organised. Furthermore, the fast-track pathway does not yet appear to have improved patient outcomes. This may be rooted in the fact that the indications are alarm symptoms or abnormal chest radiographs. Patients without alarm symptoms (or abnormal radiographs) cannot be diagnosed through this pathway; and as only about one third of patients have alarm symptoms, the fast-track option is effectively available only to a fraction of the patients for whom it might be relevant. Studies have shown that only 25% of UK patients are diagnosed through the fast-track (or two-week wait) pathway [55,56], but we do not know the equivalent figures from Denmark.

Other challenges currently facing the fast-track program include the risk of inferring emotional stress on patients when referring them for cancer diagnostics, and the relatively large amount of resources per patient consumed by this program.

In conclusion, based on the interpretation of the presented signs and symptoms, the GP can choose between three different approaches which all have pros and cons. In order to optimise the lung cancer diagnostics in general practice, it is crucial to gain a deeper understanding of the diagnostic process and of the diagnostic pathways. Furthermore, if the most optimal test for lung cancer is not the chest radiograph, how do we ensure that Danish GPs are provided with the best diagnostic options? Could the answer to earlier and faster diagnosis of lung cancer be a technological upgrade that gives GPs direct access to low-dose CT (LDCT)?

THE LOW-DOSE MULTI-DETECTOR COMPUTED TOMOGRAPHY SCAN

The low-dose multi-detector CT (LD-MDCT) utilises a lower dose of radiation than the contrast-enhanced MDCT (Table 2). LD-MDCT may be performed more quickly than a contrast-enhanced MDCT and requires no use of contrast medium. Various screening studies [57] have shown a sensitivity of LD-MDCT of approximately 95%. In screening trials, LDCT is used under the presumptions that 1) lung cancer presents as non-calcified nodules, 2) LDCT accurately detects these nodules, and 3) detection of early-stage disease improves prognosis.

Table 2: Radiation in mSv (milli Sieverts) from different diagnostic modalities [58].

Radiation type	Radiation size
Average annual background radiation (natural background and cosmic radiation) and human made sources (medical equipment)	6.2 mSv
Radiograph, chest	0.1 mSv
Low-dose MDCT, chest	1.5-3 mSv
Contrast enhanced MDCT chest and upper abdomen	5-7 mSv
Cancer risk from exposure to ionising radiation is estimated using cancer risk models: Annual LD-CT examination from 55 to the age of 74: lifetime attributable risk of lung cancer mortality is estimated to 0.07% for males and 0.14% for females.	

Studies have shown that the LDCT outperforms plain chest radiographs for detection of lung cancer. A large US screening trial comparing CT with radiographs found a positive scan in 27% of participants screened with LDCT compared with 6.2% positive chest radiographs [59].

A main challenge in the use of LDCT (and even more so with contrast-enhanced MDCT) is the frequent detection of pulmonary nodules. A lung nodule is defined as a small spherical focus of abnormal soft tissue [60]. The prevalence of such nodules depends on the studied population and the diagnostic modality (LD-MDCT or CE-MDCT). In general, the prevalence is reported to be 8% to 51% in LDCT screening studies [61]. The PPV of lung cancer in a 4-10-mm nodule is 0.2-3.0%. Detecting 233 benign nodules in 1000 healthy screened volunteers, the authors of an UK CT screening study proposed an algorithm for follow-up and investigation of these nodules based on their size [62]. This algorithm was revised in 2013 [63], and it is now part of the standard pro-

cedure in Denmark where it is used to inform the choice of follow-up program for patients with nodules (Table 3).

Table 3: Example of the algorithm for solid nodules: Newly detected indeterminate solid nodule in persons who are 35 years of age or older.

Nodule size ¹	Low-risk patient ²	High-risk patient ³
≤4 mm	No follow-up	Follow-up CE-MDCT at 12 month
4-6 mm	Follow-up CE-MDCT at 12 month, if unchanged size: no further follow-up	Follow-up CE-MDCT at 6-12 and then 18-24 month
6-8 mm	Follow-up CE-MDCT at 6-12 and then at 18-24 month	Follow-up CE-MDCT at 3-6, 9-12 and then at 24 month
>8 mm	Follow-up at 3, 9 and 24 month with CE-MDCT, PET and/or biopsy	Follow-up at 3, 9 and 24 month with CE-MDCT, PET and/or biopsy

¹Average length and width. ²Low risk: minimal or absent history of smoking and of other known risk factors. ³High risk: history of smoking or of other known risk factors [62,63].

LUNG CANCER SCREENING

The main tenant of screening is that early detection improves diagnosis. An evaluation of several decades of screening performed to reduce lung cancer-related deaths concludes that chest radiographs and sputum cytology have done little, if nothing, to reduce mortality [64,65]. Approximately 10 years ago, observational studies found that a chest LD-MDCT may be a more efficacious screening instrument than previously used modalities. In response to this, a large US screening study initiated in 2002 showed a 20% reduction in mortality rates for those screened with LD-MDCT compared with X-rays [59]. At the same time, multiple screening trials in Europe, all using LDCT, were initiated. [66-71].

Although screening with chest LD-MDCT was shown to reduce mortality in lung cancer in a single study [59], several other issues must be addressed before introducing screening as part of standard care. These issues include an evaluation of its cost effectiveness, the radiation risk involved and any adverse events, among others. In Denmark, the decision to implement LDCT awaits the completion of the Danish trial [70] (and a trial combining all European trials). This Danish trial has not yet shown any mortality reduction. The detection rate of lung cancer in the study is 0.8%, which is similar to that of other screening studies.

A final, additional concern about screening is that even with the most optimal screening, the majority of lung cancers are diagnosed outside the program [72]. There would therefore seem to be a need for access to valid investigations for patients who are not covered by the current screening programs. Furthermore, if LDCT screening is going to be implemented in secondary care, one diagnostic strategy could be to give the GPs the same imaging opportunity for case finding in general practice.

INTRODUCING DIRECT ACCESS FROM GENERAL PRACTICE

Earlier and faster diagnosis in general practice may be achieved by granting GPs free, direct access to LDCT; this would provide them with a more sensitive lung cancer test than the chest radiographs, and it would ensure their continued responsibility for the patients as opposed to the present system where patients are referred for specialised tests in the secondary healthcare system.

Concerning early lung cancer diagnosis, only a few studies have examined direct access to tests from general practice. A

study in the UK examined the effect of a campaign encouraging patients with a cough to report to their GP [73]. This was done by posters on billboards and in the local press, and these initiatives were coupled with a liberalisation of the criteria for requesting a chest radiograph. As a result, general practice radiograph referral rates rose by 20%. Moreover, the investigators observed an increase in the number of lung cancers diagnosed. Unfortunately, no significant stage shift (more cancers diagnosed in early stage) was found; the increase in the number of diagnoses was seen at all stages, including the most advanced ones.

In another UK study, patients with respiratory symptoms, who were aged more than 50 years, were granted direct access to a radiograph, thereby bypassing the GP. The study found a 63% increase in community-initiated chest radiographs, but only 0.5% more lung cancers were detected [74].

To the authors' knowledge, no studies on direct access to LDCT from general practice have been published. Therefore, we do not know how many lung cancers will be diagnosed in symptomatic patients presenting to their GP (i.e. LD-CTs cancer PPV in general practice). Furthermore, we have no knowledge of how many extra investigations will be needed. Likewise, we do not know whether the GPs would use a direct access to LD-CT if they had this opportunity or which patients they would refer. Finally, we do not know if direct access to LD-CT would result in earlier diagnosis of lung cancer.

INTRODUCTION IN A GLANCE

- Lung cancer is a common and deadly disease. Its prognosis correlates closely with disease stage when treatment is initiated.
- Lung cancer mortality is higher in Denmark than in most other European countries. This may be due to a more advanced disease stage when treatment is initiated.
- Most lung cancer patients experience symptoms and present these symptoms to the GP. The GP's interpretation of the symptoms shapes any further investigatory activities.
- It is important to provide Danish GPs with the best diagnostic options in order to further early diagnosis of lung cancer. To achieve this, we need knowledge about the routes to diagnosis, the pre-diagnostic activity and the use of fast track in general practice.
- Seeing two specialists before initiation of investigations in the fast-track pathway may not be the most efficient scheme, but we do not know the optimal organisation of the fast-track pathway.
- Chest radiograph is the main diagnostic tool used in general practice diagnosis of lung cancer, but its sensitivity is low and false negative radiographs may introduce delay.
- LD-MDCT has a very high sensitivity for lung cancer, but it mostly deploys a higher radiation dose, and it is a more expensive modality than the chest radiograph. No studies have examined whether GPs will use a direct LD-MDCT access option and what the outcomes of these scans will be.
- No studies have examined whether direct access to LDCT from general practice will reduce the diagnostic intervals or ensure diagnosis of lung cancer at a lower stage.

1.9 Aims:

The aims of this thesis were:

- 1) To describe Danish patients' pathways to the diagnosis of lung cancer in general and the pre-diagnostic activity leading up to diagnosis in particular. An additional aim was to explore the diagnostic intervals for specific patients groups (Paper I).
- 2) In a randomised, controlled trial including all patients referred for the existing fast-track scheme to either direct chest and upper abdomen CE-MDCT or to evaluation by the chest physician, (i) to test: Fast-track performance measured by the number of scans and chest physician specialist time per diagnosis (Paper II).
- 3) In a two-arm, clinical, controlled, cluster-randomised trial where direct referral to CT together with a lung cancer update is compared with usual practice, (i) to test how CT is used in this group of patients and the outcome of CT (Paper III); and (ii) to test the effect of either modality on the time to lung cancer diagnosis, the TNM stage and the use of the fast-track pathway for lung cancer (Paper IV).

MATERIALS AND METHODS

The studies in this thesis differ in design, data sources, study population and outcome measures (Table 1). The methods and materials will therefore be described individually for Paper I, Paper II and Paper III/IV. First, however, this chapter describes the data sources used in one or more of the papers.

Table 1: Characteristics of Papers I-IV

Paper	Study population	Data source	Study design	Outcomes
I	Incident lung cancer patients, Denmark 2010.	GP questionnaire NPR, DCR, HSR	Cohort study	Routes to diagnosis. Time to diagnosis. Diagnostic activity.
II	Patients referred from primary care to fast-track	Patient records Focus group interview. DLCR	RCT	Use of CE-MDCT. Physician time per patient. Physician/nurse satisfaction.
III	Patients referred from primary care to direct CT.	Patient records DLCR, HSR	Cohort study (nested in a RCT)	Characteristics of patients referred. Use of direct LD-MDCT. Outcomes of LD-MDCT Use of fast-track (CE-MDCT).
IV	Incident lung cancer patients, Aarhus 2012-13.	GP questionnaire NPR, DLCR, HSR	Cluster RCT	Time to diagnosis. Stage at diagnosis. Use of fast-track (CE-MDCT).

GP: General practitioner; NPR: The Danish National Patient Registry, DCR: The Danish Cancer Registry, HSR: The Danish National Health Service Registry, DLCR: The Danish Lung Cancer Registry, RCT: Randomised, controlled trial, CE-MDCT: Contrast-enhanced, multi-detector computed tomography, LD-MDCT: Low-dose multi-detection computed tomography.

DATA SOURCES, REGISTRIES

The CPR number and the Danish civil registration system (CRS)

In Denmark (and other Nordic countries), researchers have exceptional opportunities to perform register-based research because every person with a permanent residence in Denmark has a unique personal identification number. At birth or immigration, all citizens in Denmark are allocated a personal 10-digit identification number, the CPR number. This number is registered in the Danish civil registration system (CRS) and allows linkage between all national registries at the individual level. The CRS contains information about vital status (dead or alive) and residence [75].

Statistics Denmark

As a central authority, Statistics Denmark is responsible for collecting, processing and publishing statistical information and for making statistical analyses and prognostics [3]. Researchers can apply for data from Statistics Denmark for further analysis, and we obtained the data on the patients' socioeconomic characteristics (education and marital status) used in Papers I and IV from this institution.

Furthermore, using data from the Integrated Database for Labour Market Research (IDA) [76], which is owned by Statistics Denmark, we were able to calculate a deprivation score for each GP's practice population; these data were used in Paper III and Paper IV. This Danish deprivation index (DADI) has eight variables that are scored individually and sum up to a score between 10 and 100; the higher the number, the greater the extent of deprivation in the practice population. The variables used are: (i) Proportion of adults aged 20-59 with no employment, (ii) proportion of adults aged 25-59 with no professional education, (iii) proportion of adults aged 25-59 with low income, (iv) proportion of adults aged 18-59 receiving public welfare payments (transfer income or social benefits), (v) proportion of children from parents with no education and no professional skills, (vi) proportion of immigrants, (vii) proportion of adults aged 30+ living alone and (viii) proportion of adults aged 70+ with low income (= the lowest national quartile).

The Hospital Discharge Registry

The Patient Administrative System (PAS) stores administrative information on hospital activities for all regions in Denmark. Since 1995, data on outpatients have also been included. These data are collected with the purpose of handling resources and charting activities, service goals and guarantees of treatment. Data include dates of hospital admission and discharge, types of admission (elective or acute) and up to 20 discharge diagnoses classified according to the International Classification of Diseases (ICD-10).

The Danish National Patient Registry (NPR)

Each of the Danish regions runs its own PAS and submits data to the NPR which stores data on 99.4% of all discharges from Danish somatic hospitals. Since 2010, the NPR has served as the basis for the payment of public and private hospitals [77]. Additionally, the NPR is used for medical research, even though this is not its main purpose [78]. In the NPR, we were able to identify lung cancer patients for Papers I and IV. The registry was also used to obtain information about comorbidity and performed chest radiographs (Paper I).

The Danish Cancer Registry (DCR)

The DCR is a national research and surveillance register designed to collect and process data on Danish cancer patients. The files of the DCR hold information on date of diagnosis, cancer type, site morphology and history of cancer, etc. The cancer patients are coded according to the ICD-10. If a patient develops

more than one primary cancer, each cancer is registered in an individual record. In the DCR, information about tumour stage at diagnosis is provided by a multi-disciplinary team decision, it contains both cTNM and pTNM if available. Reporting to the DCR became mandatory in 1987. Due to comprehensive quality control and validation, it is possible to extract data from the DCR only for the previous calendar year [79]. We used the DCR to confirm the diagnoses from the NPR and to obtain information about tumour stage at diagnosis (Paper I).

The Danish National Health Service Registry (HSR)

The HSR holds information about payment of services between the regions in Denmark and all health professionals contracted with the tax-funded primary healthcare system, e.g. GPs. The register is run by the National Board of Health, and its data are based on the health professionals' invoices to the regional health administrations. The purpose of this register is to document activities in primary healthcare for administrative use and to contribute to research in primary care. The registry holds information on GPs' remuneration, whereas no information about diagnoses can be obtained [80]. Information about performed chest radiographs (Paper I) was obtained from the HSR.

The provider number and the Provider Number Registry

Every health professionals contracted with the tax-funded healthcare system has a provider number. The provider number system is used to control the supply of GPs and, to a certain extent, to control expenditures. GPs are allowed to sell or share their provider number and office facilities. GPs can choose to work in solo practices or in group practices (in the latter case, the GPs can share a provider number or have one provider number per GP). Danish citizens are free to choose their own GP unless the GP list is closed (GPs are allowed to close their lists when the number of persons on the list reaches 1600 persons). The list system enables the GP to develop a better knowledge of the individual patient which ensures continuity of care. The Provider Number Registry contains information on the name and addresses of every health professionals with a provider number [81].

The Danish Lung Cancer Registry (DLCR)

The DLCR was established in 2001 as a national database. It contains clinical information about Danish lung cancer patients such as lung function, co-morbidity and stage, which are combined with data on cancer treatment and follow-up. In the DLCR, information about tumour stage at diagnosis is provided by a multi-disciplinary team decision with one TNM stage (which can be either cTNM or pTNM). Since 2003, the DLCR has contained data on more than 90% of all lung cancer cases in Denmark [82]. The registry was used for identification of patients and verification of cancer diagnosis and date of diagnosis in Papers III and IV.

PAPER I

Study design

We conducted a national registry-based cohort study on first-time primary lung cancer patients in Denmark in 2010.

Study participants

The lung cancer patients were sampled to form part of a national cohort of newly diagnosed cancer patients (except non-melanoma skin cancer) aged 18 years or older during a 4-month period from 1 May 2010 to 31 August 2010. During the inclusion period, cancer patients were identified consecutively from the NPR.

The patient inclusion criteria for this study were 1) living in Denmark, 2) ≥ 18 years, 3) registered in the NPR with an ICD-10 code C34.0-9 as the primary diagnosis, 4) diagnosed in the study period and 5) listed with a GP. To identify incident cancer cases,

we excluded patients who had previously been registered with any cancer type (except non-melanoma skin cancer (C44)) in the DCR.

A total of 990 lung cancer patients were identified in the NPR. We excluded 14 patients because the diagnosis could not be validated in the DCR 1 year later. In addition, five patients registered with a lung cancer diagnosis in the DCR before 1 January 2010 were excluded. A questionnaire was sent to the remaining 971 patients' GPs of whom 690 (71.1%) responded.

Data sources

The DCR was used to verify the diagnosis and obtain data on tumour stage. Stage at diagnosis was grouped according to the TNM system (version 6)[83] and was dichotomised into local and advanced disease. A cut-point between stage IIB and IIIA was chosen since a previous study has documented a significant difference in mortality between these two stages [84]. If any of the T, N or M values were missing, we categorised SCLC as limited if the tumour was M0 and as extensive if the tumour was M1 regardless of the values, known or unknown, of other components. We categorised NSCLC as advanced if the TNM stage included values of T4, N3 or M1. This was done regardless of the other components [85].

Since a small number of X-rays are performed outside the hospital in private clinics, we obtained data on radiology procedures from both the NPR and the HSR in the time period from one year before diagnosis until the date of diagnosis.

In order to adjust for confounding by patient characteristics, we obtained data regarding comorbidity from the NPR. This was based on ICD-10 codes for previous hospitalisations until the date of diagnosis. The presence of comorbidity was defined according to the Charlson Comorbidity Index (CCI) [86,87] and categorised as low (CCI=0), medium (CCI=1-2) or high (CCI≥3). Furthermore, education (including basic school) was dichotomised into "≤10 years" and ">10 years" [88]. Marital status was dichotomised into "cohabitating" or "living alone".

GP Questionnaire

A questionnaire was sent to the general practice where the patient was listed. The aims of the questionnaire were to gain knowledge on the extent of GP involvement in the lung cancer diagnosis and dates in the diagnostic process. Furthermore, the GPs were asked to list the symptoms and signs presented by the patients and how they interpreted the patients' symptoms. The questionnaire was developed in 2009 by colleagues at the Research Unit for General Practice, Aarhus University [89]. As no pre-designed questionnaires for the specific purpose were available, ad hoc questions were constructed based on previously used, validated items [26,27,90]. In practices with more than one GP, the GP most familiar with the patient was asked to complete the questionnaire based upon the medical records. There was no reimbursement for participation.

Outcome measures

GP involvement and symptom interpretation

The patients were divided into groups depending on whether or not the GP answered the questionnaire. Patients whose GP answered the questionnaire were divided into groups if the GP was involved in the diagnostic process measured by the yes/no question: "Were you/your general practice involved in the diagnosis of the cancer?". GPs involved in the diagnosis were asked to state whether the patient was referred through a fast-track route. Moreover, GPs were asked to rate their interpretation of the presented symptoms as either 1) Alarm symptoms suggestive of cancer (alarm symptoms), 2) Symptoms suggestive of any serious illness (serious, but unspecific symptoms) or, 3) Vague or ill-

defined symptoms not directly suggestive of cancer or other serious illness (vague symptoms).

The primary care interval and the diagnostic interval

The primary care interval and the diagnostic interval were calculated by combining data from the DCR and the GP questionnaire. The primary care interval was defined as the time from the first presentation in primary care until referral to secondary care (calculated from GP questionnaire). The diagnostic interval was defined as the time from the first presentation until decisive diagnosis (calculated from the GP questionnaire and the DCR data) [31].

Diagnostic activity prior to diagnosis

As a measure of the diagnostic activity in primary care, we assessed the number of chest radiographs performed in the year before diagnosis. In the DCR, the date of diagnosis is the date that matches the day when the patient was admitted to hospital or seen as an outpatient and at which the lung cancer was diagnosed.

Statistical analyses

Patient groups were compared using Wilcoxon's rank-sum test for ordinal or continuous data including time intervals, the Kruskal-Wallis test for differences between groups or Pearson's chi-squared test for nominal or dichotomous data.

Backward cumulative curves for the dates of the latest and the second-latest X-ray before diagnosis and associated 95% confidence bands were drawn by applying a standard Kaplan-Maier procedure and normal approximation on a reversed time scale.

We used generalised linear models for the binomial family to calculate the associations between long intervals and gender, age, marital status, education, comorbidity, GP interpretation and use of fast-track pathways. Long intervals were defined as the 4th quartile for the full study population. This implies a prevalence of the outcome above 20%, in which case interpretation of odds ratios as prevalence ratios can lead to non-negligible bias [91]. Consequently, we chose the logarithm for the link function to facilitate direct estimation of prevalence ratios. Analysis of time intervals was restricted to patients whose GPs were involved in the diagnosis.

PAPER II

Study design

We performed a randomised, two-arm (1:1), controlled study testing contrast-enhanced MDCT scans before evaluation by a chest physician compared with usual practice (patients seen by a chest physician both before and after the CE-MDCT).

Study participants

Cases enrolled in this study were suspected of having lung cancer and referred exclusively from general practice to fast-track evaluation during the period from 1 January to 1 December 2012. Patients referred to fast-track evaluation for lung cancer are coded DZ 031.B (lung cancer observation). We identified patients with this code and the patient's GP, using the practice provider number. There were no exclusion criteria.

Setting

The study was performed at the Department of Pulmonary Medicine, Aarhus University Hospital. The department covers approximately 140 general practices. On average, the department evaluates 650 fast-track referrals from general practice annually, and the Department is highly specialised in lung cancer detection and diagnosis of lung cancer in conformity with the prevailing Danish guidelines [8]. A chest physician triages the patient, referred e.g. from general practice, to an outpatient evaluation. If,

when evaluating the patient, the chest physician shares the referer's suspicion of lung cancer, the patient will usually be referred to a contrast-enhanced MDCT of the chest and upper abdomen.

Randomisation

For practical reasons, we chose to perform the randomisation before the study period as a single procedure in which all potential patients born in even months (February, April, June, August, October and December) were allocated to the intervention group and patients born in odd months were controls. Technically speaking, this could be termed a cluster randomisation. However, as allocation according to birth (odd or even month) must be considered random with respect to the allocation between intervention/control and lung cancer, we consider such a distinction to be appropriate for the present purpose.

Intervention

In the intervention group, the patients were allocated a direct CT scan including information provided by a nurse prior to the CE-MDCT, thus bypassing the chest physician. Control patients were seen by a chest physician, as usual, before the CE-MDCT.

Outcome measures

Numbers of CTs performed

The proportion of patients who had a CE-MDCT scan performed was measured. Data were obtained from the electronic patient records.

Chest physician time

We measured consultation time for a 3-week period (November 2012). All consultations regarding lung cancer were measured by a scientific assistant blinded to the patient's allocation status. The physicians were not aware of the time measurement. Time was measured as minutes from the time where the patient entered the physician's consultation room until the time when the patient left the room again.

Focus group interview

A focus group interview was undertaken to clarify the feasibility of the new organisation. The interview was conducted by LMG and PV after the study had closed. The informants were two consultants (chest physicians) and one pulmonary nurse engaged in the organisation of the fast-track pathway. The interview was recorded with the informant's consent. The interview guide included open-ended questions focusing on the positive/negative characteristics of the traditional organisation in comparison with the new organisation. The informants were encouraged to provide details on changes and to assess the medical quality of the services. The interview lasted 45 minutes, and a summary was compiled at the end to obtain an immediate validation of the presentation of the themes identified by the researchers.

Statistical analyses

Patients groups were compared using Wilcoxon's rank-sum test for ordinal or continuous data and Person's χ^2 -test for unordered or dichotomous categorical data. The proportion of referred patients who did not receive a CT and the difference between the groups were calculated. Associated 95% confidence intervals (CIs) were assessed using a standard normal approximation. Patients were allocated to randomisation groups according to the intention-to-treat principle.

PAPER III AND PAPER IV

Study design

We conducted a clinical cluster-randomised, two-arm (1:1), unblinded study (IV) and a cohort study nested in the trial (III).

Setting and study participants

The study took place in a large catchment area around Aarhus

University Hospital in the Central Denmark Region; the study period was 19 months (November 2011 to June 2013).

A total of 266 GPs organised into 119 general practices, allowed to refer patients to the Department of Pulmonary Medicine, were randomised into two groups. At the patient level (Paper IV), the inclusion criteria were that the patient should be listed with a participating GP in the study period and have a new diagnosis of lung cancer (ICD10 34.0-9). There were no exclusion criteria.

Before November 2011, the GPs in the area had three diagnostic work-up possibilities for patients with respiratory symptoms that could indicate lung cancer. They could either refer patients to 1) a chest radiograph, 2) the Department of Pulmonary Medicine within the normal waiting list, or 3) the lung cancer fast-track pathway with a maximum of 72 hours' waiting time. Indication for fast-track referral was either an abnormal chest radiograph or certain qualifying 'red-flag' symptoms (e.g. coughing (for at least 4 weeks) or haemoptysis). GPs were not allowed to refer patients directly to a CT.

Sampling of lung cancer patients, Paper IV

All cases of lung cancer (ICD10 34.0-9) were identified starting from 1 January 2012 after a 2-month study run-in period. To ensure completeness, cases were obtained from a combined identification in the DLCR and the NPR on a monthly basis. The lung cancer cases were checked against the practice patient lists in order to identify the patients' GPs. From these lists, we also gathered information about practice list size and the age and gender distribution of the patients listed with the practice.

GP questionnaire, Paper IV

A short questionnaire was sent to the lung cancer patient's general practice. In practices with more than one GP, we asked the GP most familiar with the patient to complete the questionnaire. The questionnaire non-responders received a reminder after four weeks. The responding doctors got a reimbursement for their participation (€17, £15). The GPs were told to use their medical records when answering the questions about whether the general practice/GP had been involved in the diagnosis of the lung cancer, the dates in the diagnostic pathway and the use of a fast-track pathway.

A database was created for the purpose of managing questionnaire logistics. The questionnaires were optically scanned using the computer program Teleform Enterprise Version 8 (Cardiff Software Inc., San Marcos, CA, USA). To maximise the completeness and accuracy of the questionnaire data, the optical scanning and the verification of the scanning results was done only by LMG. A coding manual describing the handling of inadequately filled-in items was developed. The verified Teleform questionnaire data were transferred to Stata (StataCorp LP, College Station, Tex, USA).

Randomisation

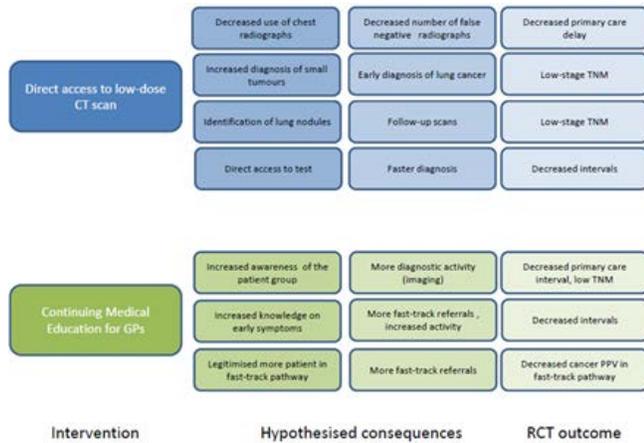
The unit of randomisation was the practice address. The randomisation was performed by a data manager using Stata 12.0. The 119 practices were allocated a random number between zero and one and then listed from the lowest to the highest value. The top 60 practice addresses formed the intervention group.

Intervention

The hypotheses of the intervention

The intervention was allocated at the cluster level. The contents of the intervention, the hypothesised consequences and the measured outcomes are shown in Figure 1.

Figure 1: The intervention, the hypothesised consequences and outcomes. CT: computed tomography, TNM: Tumour, Node, Metastases, GP: General practitioner, PPV: Positive predictive value.



It was hypothesised that direct access to a low-dose MDCT from primary care would result in faster diagnosis of lung cancer. A direct access to LDCT would decrease the use of chest radiographs and thereby decrease the risk of false negative chest films. Combined with the provision of CME, it was further hypothesised that heightened awareness of early lung cancer symptoms would decrease the intervals in the diagnostic process. This effect would be observed notably in the form of a shorter primary care interval; and we hypothesised that if the GPs were more familiar with these patients, more would be referred to the correct department for diagnosis and this would decrease the patients' diagnostic interval as well. Moreover, if the GPs used LD-MDCT directly from general practice instead of chest radiographs, it would be possible to diagnose more patients with small lung tumours. In addition, some of the patients scanned would enter a nodule follow-up program and some of them would eventually be diagnosed with lung cancer, hopefully when the disease was still at a low stage.

Furthermore, it was hypothesised that the provision of CME would imply that more patients would be referred to fast-track diagnostic work-up which would increase the referral rate and hence affect PPV rates in the fast-track route (Figure 1).

The contents of the intervention

Six times within an initial 3-month period, the intervention practices were informed by letter about the possibility of referring patients to direct, low-dose chest CT (Appendix). The letters included information concerning the referral procedures and the specific indications for a CT request. These indications embraced a wide range of concerns; the only exception was patients who already met the indication for a fast-track referral. The idea was to let the GPs substitute the radiograph with a low-dose chest MDCT to rule out lung cancer in patients who did not meet the indications for the fast-track referral.

The GPs were offered participation in a 1-hour small-group-based CME meeting held during the first two months of the study to increase their awareness of early lung cancer and to encourage them to refer more patients to tests (LDCT or fast-track pathway) for lung cancer. During the meeting, the GPs were briefed about the state-of-the-art of early detection of lung cancer based on algorithms for PPVs in primary care [46,48]. The GPs also received

information about the use of LD-MDCT and how to interpret CT reports. The GPs received a pamphlet containing PPVs for lung cancer and indications for LDCT referral. This pamphlet was also sent to intervention GPs who did not participate in the CME meetings.

In the initial 2 months of the project, the patients (approximately 90 patients) were scanned with a contrast-enhanced MDCT of the chest and upper abdomen. Due to a high referral rate of patients and because these scans are more time-consuming than the LDCT without contrast, the project group decided to change to the LDCT. This was done to minimise time spent per patient as well as to minimise the radiation dose.

Chest LD-MDCT, review and lung cancer diagnosis

The Department of Radiology, Aarhus University Hospital, performed the LDCTs. Scans were performed on a Brilliance 64 CT Scanner by Philips with a beam collimation of 64 x 0.625, 2 mm slice thickness, 1 mm increment, 1 pitch and a rotation time of 0.75 s. The effective radiation dose (Monte Carlo simulation program CT-Expo v. 2.1) for the LDCT was 2-3 mSv. Intravenous contrast medium was not administered.

The time limit from referral to performed LDCT was a maximum of two working days. When wanting to refer a patient to direct LDCT, the GP (or the secretary) made a telephone call to the Department of Radiology, and the patient was immediately informed about the time for the scan. In addition, the GP forwarded an electronic referral note to the department.

The CT reports were made by three sub-specialised consultant radiologists. Based on the LD-MDCT report and the patient's medical history, a recommendation was agreed upon at a conference between a consultant chest physician and a consultant radiologist the day after the scan, and this recommendation was forwarded electronically to the GP. The GP had full responsibility for informing the patient about the result and, if necessary, to refer the patient for further diagnostic work-up.

If lung nodules (4-10 mm) that could not be categorised as benign were detected, the GP was responsible for referring the patient to a follow-up program (3, 6, 12 months after the first scan) based on the size and the characteristics of the nodules and according to international standard [62,63]. The follow-up program was decided by the chest physician. Incidental findings on the CT scan outside the lungs judged to be of clinical significance were reported to the GP with recommendations for referral to a relevant department depending on the nature of the suspicion. Pulmonary pathology on the CTs other than lung cancer was also noticed.

If the CT scan gave rise to any suspicion of lung cancer, the GP referred the patients through the fast-track to standard diagnostic work-up at the Department of Pulmonary Medicine. This included contrast-enhanced MDCT (including PET/CT if surgery was an option). Furthermore, a histologic/cytologic diagnosis was obtained by the least invasive method, which was usually either bronchoscopy with biopsy, fine-needle aspiration (FNA) in association with endoscopic ultrasound (EUS) or endobronchial ultrasound (EBUS), or transthoracic FNA. The final staging was decided by a multi-disciplinary team decision based on cTNM information. The lung cancers were staged according to the 7th TNM Classification of Malignant Tumours [83]. Early-stage cancers were defined as stage I-IIb. Early-stage patients were offered surgical resection according to Danish guidelines.

Sample size

It can be assumed that lung cancer patients are randomly distributed among GPs. There could, however, be a higher incidence of cancer in some areas with many smokers and in practices with many elderly patients. To account for an unknown intra-cluster correlation coefficient (ICC), we counted on a design effect of 1.25 [92].

In 2008, half of the Danish lung patients waited 34 days or more (the median) from first presentation to primary care until diagnosis of lung cancer [27]. We hoped to be able to show a decrease in the diagnostic interval to a level where only 25% of the patients had to wait for 34 days or more. Thus, the proportion waiting 34 days or more should be halved. With a one-sided alpha of 5% and a power of 80%, we had to include 54 lung cancer patients in each arm with a 1:1 randomisation. Given the design effect, we had to include a total of $54 \times 2 \times 1.25 = 135$ lung cancer patients with questionnaire data and GP involvement in the diagnosis.

Outcome measures, Paper III

GP/Patients characteristics and LD-MD CT outcome

Based on the GPs' referral notes, we obtained data on the patients' symptoms, known diseases and smoking histories. We obtained the medical records from completed CT scans, including the consensus evaluation between the radiologist and the chest physician. The DLCR was used to obtain information on any subsequent diagnosis of lung cancer (International Classification of Diseases 10: C34.0-9). Furthermore, the DCR was used to obtain information about previous cancer (except non-melanoma skin cancer (C44)). We used DADI to gather information about the deprivation scale in the different GP clinics.

GP variation in use of LDCT and fast-track

The HSR and the Provider Number Registry were used to gather information about GP list size and the age/gender distribution of the patients listed with the GPs. Patients referred to fast-track evaluation for lung cancer are coded DZ 03.1B (lung cancer observation). This code, combined with the unique GP practice number, gave information about referral to the fast-track pathway and on the basis of this information and the information from the DLCR, the lung cancer PPV in the fast-track pathway could be calculated.

Outcome measures, Paper IV

The primary care interval and the diagnostic interval

The primary care interval was defined as the time from the first presentation in primary care until referral to secondary care; the diagnostic interval was defined as the time from the first presentation until decisive diagnosis [31]). Data were obtained from the GP questionnaires and the DLCR (the latter providing the date of diagnosis).

Stage at diagnosis and fast-track referral rate

Stage at diagnosis was stated in a multidisciplinary team decision as cTNM. The cancer stage was re-grouped into stage IA, 1B, IIA, IIB, IIIA, IIIB and IV according to the TNM (version 7). The stage was then dichotomised into local and advanced using a cut-point between stage IIB and IIIA. This was done as there is a significant difference in mortality between these two stages [84].

We wanted to test whether there was a difference in the use of the fast-track pathway and the PPV for lung cancer between intervention GPs and control GPs. This would indicate whether the possible effect of the new diagnostic modality and the CME focusing on lung cancer diagnosis was a general effect or if it was related to the possibility to refer directly to CT. Patients referred

to fast-track evaluation for lung cancer were coded DZ 03.1B (lung cancer observation). This code combined with the GP provider number gave information about referral to the fast-track pathway.

Other variables in Paper IV

Patient comorbidity was obtained from the GP questionnaire where the GP stated if comorbidity was present or not. For each identified lung cancer patient, the socio-economic position was collected from Statistics Denmark and dichotomised as in Paper I. We used DADI to gather information about the deprivation score in the different GP clinics' populations.

Statistical analysis

Paper III

Patient characteristics were described and duration of symptoms was calculated as medians with interquartile intervals (IQI). GP groups were compared using the Wilcoxon's rank-sum test for ordinal or continuous data or Pearson's χ^2 test for unordered or dichotomous, categorical data.

We calculated the referral rates to direct low-dose MDCT and fast-track based on the number of patients referred by the GP per project month per list size for patients aged 25 years and above. We used sex and age standardisation to compare the referral rates between CME-attending GPs and non-attending GPs. We used the CME-attending GPs as the standard population and calculated the referral rates for the patients listed with the GPs for 10-year age groups (25-34, 35-44, etc.). These expected rates were then applied to the non-attending GP list. We calculated the standardised referral rate ratio as the number of referrals divided by the expected numbers if the age- and sex-specific rates were the same as those of the standard population. The age-sex referral rate was then obtained by multiplying the referral rate ratio by the crude referral rate of the standard population.

Paper IV

We compared baseline characteristics and crude study outcomes in patients listed with intervention GPs with patients listed with control GPs using Pearson's chi-squared test or Wilcoxon rank-test.

Primary analyses were performed by standard intention to treat with participants analysed according to their GP's randomisation. The primary care and the diagnostic interval were presented as medians with IQI. We used general linear models (GLM) for the binomial family to calculate associations between long intervals and the patients' randomisation status. Long intervals were defined as the 4th quartile of similar intervals from Danish lung cancer patients in 2010 as calculated in Paper I. In these analyses, we accounted for clusters of patients within GPs using cluster robust variance estimation and adjusted for patient age and presence of comorbidity as it has previously been shown that these factors can influence the lengths of the intervals (Paper I).

In supplementary analyses, we corrected for non-compliance by comparing patients listed with GPs who participated in the CME with patients from a similar group of patients listed with control GPs [93]. These estimates were not diluted by lack of compliance as they are in standard intent-to-treat analyses.

Referral rates were calculated based on the number of patients referred by the GP per project month per patient aged 25 years and above. For the non-compliance analyses on referral rates, we used the risk of having a low referral rate (defined as among the 25% lowest referral rates for the two groups together).

Ethics and approvals

Paper I

The study was approved by the Danish Data Protection Agency (J. no.: 2010-41-4694) and The Danish Health and Medicines Authority (J. no.: 7-505-29-1484/1 and J. no.: 7-604-04-2/195/EHE). According to the Research Ethics Committee of the Central Denmark Region, the Danish Act on Research Ethics Review of Health Research Projects (s. 8(3) of Act No. 402 of 28 May 2003) did not apply to this project.

Paper II, Paper III and Paper IV

The study was approved by the Danish Data Protection Agency (Ref. no.: 2011-41-6872) and the Danish Health and Medicines Authority (Ref. no.: 7-604-04-2/357/KWH). According to the Research Ethics Committee of the Central Denmark Region, the Danish Act on Research Ethics Review of Health Research Projects did not apply to this project (Ref. no.: 118/2011) as CT is already a widely used technology. Clinicaltrials.gov: NCT01779726 (Paper II) and NCT01527214 (Papers III and IV).

RESULTS IN SUMMARY

PAPER I

GP Involvement

GPs were involved in the diagnosis of 68.3% of the lung cancer patients. If the GPs were involved, a fast-track referral was initially used in 40.9% of the cases. In total, 27.4% of all patients in the study were diagnosed by presenting to the GP and then by referral to the fast-track pathway.

Intervals

The overall median primary care interval was 7 days (IQR: 0-30), whereas the median diagnostic interval was 29 days (IQR: 12-69). Older age was statistically significantly associated with an increased likelihood of longer intervals of both kinds. Patients referred to a fast-track route experienced statistically significantly shorter median diagnostic intervals than patients not referred to a fast-track route (23 days (IQR: 11-52) vs. 34 days (IQR: 12-88)). Patients with advanced disease stages had statistically significantly shorter diagnostic interval than patients with localised disease, but, surprisingly, their primary care interval was similar. An increased likelihood of a long primary care interval (adjusted PR: 4.8 (2.8-8.2)) and a long diagnostic interval (adjusted PR: 2.4 (1.5-3.9)) was seen if the GP interpreted presented symptoms as "vague" than if the GP interpreted symptoms as "alarm" symptoms.

Activity

During the 90 days before diagnosis, 85.6% of the patients had at least one radiograph and 33.6% had at least two. The proportion of patients who had one radiograph was higher among patients referred to the fast-track route (66%) than among those who did not go through the fast track (49.4%). We found that among patients for whom the GP interpreted the symptoms as 'serious, but unspecific', the proportion of those who two or more radiographs was higher than among patients for whom the GP stated 'alarm symptoms' (35.9% vs. 22.1%). Furthermore, the proportion of patients who had two or more radiographs was higher among patients with comorbidity (41.6%) than among patients with no co-morbidity (26.8%).

PAPER II

Numbers of CE-MDCT

A total of 508 patients were eligible and included during the 11-month study period. Ten patients in the intervention group did not have a CT (4.1%, 95% CI: 2.0-7.3%); seven patients in the control group had no CT (2.8%, 95% CI: 1.1%-5.8%). The difference in "CTs not conducted" between the two groups was -1.3% (95% CI: -4.4-2.0%; $p = 0.454$).

Time

Time was measured at 48 consultations, and the difference in time spent per patient between the intervention group (one visit) and the control group (two visits) was 13.3 min. (min.-max.: 7.7-19.5 min.). For every 100 patients evaluated in the fast track with direct CE-MDCT, the department would save 22.2 hours (min.-max.: 12.9-32.4 h) in comparison with the usual organisation.

Satisfaction

The focus group interview identified a range of advantages of the new organisation:

"The patients are very satisfied. They understand the logic behind first receiving the scan and subsequently seeing the doctor. This is a good thing for the patients" (nurse). "Many patients can save a parking ticket, and most of the patients can be seen in the morning by the nurse, they can be at work at nine o'clock" (nurse). "The new organisation has reduced the number of medical consultation hours involving a doctor; hours that we can spend on the patients in need of care" (physician 1). "The new organisation provides greater flexibility for the unit when scheduling the daily programme. Patients can be seen by a nurse while the doctor is engaged elsewhere" (physician 2).

PAPER III

Patient characteristics and LDCT use

During the study period of 19 months, 648 low-dose MDCTs were performed. The mean age of scanned patients was 62.1 years. The most prominent symptom was coughing (78.2% of the patients referred). The duration of symptoms varied from a median of 1.5 weeks (haemoptysis) to a median of 8.0 weeks (coughing). A total of 133 GPs had access to direct LDCT. This possibility was used by 68.4% of the GPs. Most GPs referred two patients during the study period. The unadjusted referral rate for all GPs was 0.10 per 1000 patients (≥ 25 years of age) per month. When we excluded the GPs who did not use the possibility of direct CT, the unadjusted GP referral rate was 0.18 per 1000 patients (≥ 25 years of age) per month. There was no difference in GP age, gender, type of clinic (solo or more GPs together), list size or levels of deprivation in relation to the use of LDCT scans.

CME

In total, 48.1% of the GPs participated in the CME meetings. When adjusting for patient age and gender and GP list size, the referral rate was 61% higher for GPs working in a clinic with one or more CME-participating GPs than the referral rate for non-participating GPs.

LDCT outcome

Of the 648 patients who underwent CT, 36.1% patients had a normal scan, while lung nodules were found in 22.7% of the patients. Cancer suspicion was raised in 13.0% of the scans, and suspicion of other lung diseases was raised in 30.9%. For 47.2% of the patients, no further diagnostic work-up was needed.

During the study, 30 (4.6% of the scanned) patients were diagnosed with a severe lung disease (tuberculosis, sarcoidosis or interstitial lung disease). In addition, in 44 patients (6.8%) (not

known with any lung disease), signs of COPD were identified. Furthermore, 15 (2.3% of the scanned) patients were diagnosed with NSCLC, none had SCLC. Stage distribution was as follows: 9 (60%, 95%CI: 32.3-83.7%) in early stage and 6 (40%, 95%CI: 16.3-67.7) with advanced disease. Six (40.0%, 95%CI: 16.3-67.7) were stage I tumours. In addition to the lung cancers, we identified eight (1.2% of all scanned) patients with other cancers (three breast cancers, two lymphomas, one rectal cancer, one hepatocellular carcinoma and one mesothelioma).

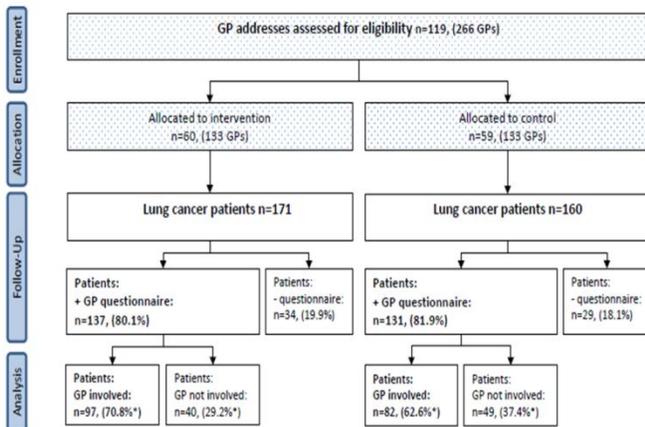
Use of fast-track pathway and fast-track lung cancer PPV

The GPs referred 335 patients to the existing lung cancer fast-track route during the study period (33 lung cancer diagnoses; PPV for cancer: 9.9%). The referral rate to the fast-track pathway was 0.19 per 1000 patients \geq 25 years for CME-participating GPs compared with 0.15 for non-participating GPs (p-value: 0.451). The PPV for a lung cancer diagnosis as a result of referral to a fast-track lung cancer pathway was 13.3% for CME-participating GPs and 6.1% for non-participating GPs (p-value: 0.027), which is equivalent to a 2.2 higher hit rate.

PAPER IV

During the study period of 19 months, 331 incident lung cancer patients were diagnosed at the Department of Pulmonary Medicine at Aarhus University Hospital; 171 were listed with intervention GPs and 160 with control GPs. There was no statistically significant difference in questionnaires returned or in involvement in diagnosis between control and intervention GPs (Figure 1).

Figure 1: The flow of GPs and patients.



Baseline data

The GPs in the intervention group were slightly older (mean 53.6 years compared with 51.6 years), more were working in a solo practice and their patients were slightly more deprived. Sixty-four (48.5%) of the GPs in the intervention group who were offered CME participated in the CME.

Lung cancer patients (for whom the GP returned the questionnaire) from both intervention and control GPs were similar with respect to age, gender, education, marital status and comorbidity.

The intervals

For all patients, the median primary care interval was 16 days (IQI: 4-56) and the overall median diagnostic interval was 39 days (IQI: 17-93). There was no statistically significant difference in

intervals between patients in the intervention group and patients in the control group.

There was no difference in the proportions experiencing long primary care or diagnostic intervals between patients from the control and the intervention groups. Within the intervention group, both primary care and diagnostic intervals were statistically significantly lower if the GP (or a GP in the clinic) participated in the CME (primary care interval median: 9 days vs. 37 days, p=0.048; diagnostic interval median: 23 vs. 66, p=0.008).

When correcting for non-compliance, we found a statistically insignificantly higher risk for having a long diagnostic interval for patients from the control group (risk difference (RD): 13.5% (95%CI: -11.0-37.9%, p-value=0.280)); no difference in risk for having a long primary care interval was observed (RD: 1.1% (95%CI: -23.9-26.1%, p-value=0.929)).

Stage

The cancer was localised in 34.7% of the lung cancer patients. There was no difference in stage distribution between patients from control or intervention GPs in the non-adjusted analyses. We found no difference in the risk of having localised stage when adjusting for non-compliance (RD: 1.5, 95%CI: -31.8-34.9, p-value=0.927).

General effects on other diagnostic strategies

The GPs referred 836 patients to the lung cancer fast-track pathway during the study period. Among these patients, 81 were diagnosed with lung cancer. This corresponds to a PPV for lung cancer diagnosis when referring patients to a fast-track lung cancer pathway of 9.7%. The proportion of patients with advanced disease was 59.3%, with no difference in stage distribution between patients from intervention and control GPs. The unadjusted referral rate to fast-track was 0.17 per 1000 adults listed with the GP per month (95% CI: 0.12-0.25) for intervention patients compared with 0.15 (95% CI: 0.11-0.24) for control GPs (p-value: 0.417). When correcting for non-compliance, we found no difference in PPVs between the groups (risk difference (RD): 1.1% (95%CI: -5.8-8.2, p-value: 0.740)), but a statistically insignificantly higher risk for having a low referral rate (below the lowest referral rate quartile) to the fast-track pathway for control GPs (RD: 6.3% (95%CI: -22.7-35.3, p-value: 0.670)).

DISCUSSION OF METHODS

This chapter addresses the strengths and weaknesses of the four papers by discussing the internal and external validity of the studies in relation to design, sampling, data quality, interventions, outcome measures and analyses.

DATA VALIDITY

Design

The cohort study (Paper I)

In Paper I, we conducted a national registry-based cohort study encompassing the entire population of newly diagnosed lung cancer patients in Denmark. The data were collected in 2010 by a colleague at the Research Unit for General Practice, Aarhus University who used a validated sampling procedure [90] (see later). The data were collected as part of the Danish Cancer in Primary Care (CaP) project which aims to support epidemiological and health services research within the field of cancer diagnostics [90].

Questionnaire data in this study were collected retrospectively, which make them more vulnerable to bias (see later). A prospective cohort study will usually provide more detailed infor-

mation on exposures and other key variables than the retrospective design [94]. However, as GPs encounter only approximately one new lung cancer patient every year, it would not have been feasible to use a prospective design in which symptomatic patients were followed, milestones were registered and data on those who got cancer were extracted for analysis.

The strengths of this study were the unique Danish possibility for gathering nearly 1000 patients through a valid sampling procedure [90] and combining data on these patients with valid registry and questionnaire data.

The randomised controlled trial (Paper II)

In Paper II, we conducted a randomised trial on all patients referred from general practice to the existing fast-track pathway at one single department of pulmonary medicine. We chose a RCT design as it is in general regarded as superior to non-experimental designs for establishing the effectiveness of an intervention owing to its ability to minimise selection bias and information bias and, in particular, to control for confounding [95-97]. Thus, the strength of this study was the randomised design that produced two comparable groups with no statistically significant differences. We were able to measure outcomes during one time period for two different organisations rather than making before-after-comparisons or comparisons between two settings.

We chose a simple randomising procedure based on the birth month of the patient referred. This was done to ensure that the randomisation process was as pragmatic as possible. The patients were randomised by one of two chest physicians when they triaged the patients who were referred from primary care to the fast-track pathway. This randomisation process is also a potential weakness in the study. If GPs had been aware of the allocation of their patients, they might have used the diagnostic system differently. However, the GPs were unaware of the study; thus, the problem is probably non-existing in the present study.

The cluster-randomised, controlled trial (Paper III and Paper IV)

In Paper III, we choose to report outcomes from the intervention arm solely as a cohort study nested in the RCT. This was done to elaborate on the complex intervention and the outcomes of the LDCTs. The study is descriptive and provides only the results of the first scan. In order to measure the full impact gained by the direct LDCT option, a follow-up study is needed. This is necessary to obtain information on lung cancers diagnosed from the repetitive CTs on nodule follow-up indications, other diagnoses made, and the additional number of diagnostics needed as a result of the follow-up scans. The research group has planned to conduct a follow-up study two years after the baseline scan.

A major strength of this study is its well-defined study population and the large number of patients included. The data obtained from the referral letters and the CT records were complete as were the data on GP participation in the CME on lung cancer. However, a limitation is that we have no knowledge about the kind of diagnostic tool (e.g. chest radiograph or fast-track referral) applied by the GP if (s)he were allowed to refer to a direct LDCT.

In Paper IV, we chose the design of a cluster-randomised trial with GP practice addresses as the randomisation level. Compared with individually randomised trials, cluster-randomised trials require more participants to obtain equivalent statistical power because observations on individuals in the same cluster tend to be correlated (non-independent). This reduction in effective sample size depends on the average cluster size and the degree of correlation between clusters (i.e. how much patients listed at one GP correlate with patients listed at another GP) [92,98]. However,

we found individual patient randomisation non-suitable for this study because the intervention was targeted at the GP. If we had chosen to randomise at the individual patient level, one GP would potentially have patients randomised both to the intervention and to the control group. Nor was it possible to intervene at the single GP level because we anticipated a large risk of contamination (risk of spill-over) between GPs at the same practice address if one GP had the opportunity to refer directly to CT and another GP did not have this opportunity.

Sampling

Sampling of lung cancer patients (Paper I)

The lung cancer patients were sampled as part of a national cohort of all newly diagnosed cancer patients (except non-melanoma skin cancer) aged 18 years or older during a 4-month period from 1 May 2010 to 31 August 2010. During the inclusion period, cancer patients were identified consecutively from the Danish National Patient Register (NPR) [77].

A major concern in a cohort study is whether the cohort resembles the source population [99]. However, the patients in this database were initially sampled using a predefined algorithm. This algorithm has been shown to have a high PPV for sampling incident cancer patients whose case-mix resembles the case-mix of the same year in the DCR (considered as gold-standard) [79].

In this study, patients were sampled from administrative registries. Alternatively, patients could have been sampled directly from hospital wards. This could potentially have increased the possibility of on-time inclusion of patients. However, such a sampling approach would have required massive personal resources. Its success would also depend on the individual hospitals' willingness and ability to participate which would have entailed a considerable risk of incomplete sampling.

Sampling of patients referred to the existing fast-track pathway (Paper II)

Patients referred to the traditional fast-track pathway from general practice were sampled by a combination of the unique code for fast-track, DZ 031.B (lung cancer observation), and the referral code from primary care (the GP provider number). All patients with this combination were sampled during the study period (1 January 2012 to 1 December 2012). This sampling procedure was simple and easy to conduct. Some patients may have been referred from primary care to the fast-track pathway, but may initially have been seen at another department. Such cases would not have been sampled by the algorithm. However, these patients may differ from the standard fast-track referrals directly from primary care. The crucial issue is that the sampling procedure ensured that all patients were followed according to the number of performed CTs and lung cancer diagnoses. The CPR number was used to ensure precise follow-up on all patients.

Sampling of GPs (Paper III and Paper IV)

Before randomisation, we identified all practice addresses allowed to refer patients to the Department of Pulmonary Medicine, Aarhus University Hospital. This permission is held by all general practices located in the Aarhus municipality. GPs in the outer area of this district may have patients on their list who are living in other municipalities. These patients may therefore be referred mainly to hospitals other than the Aarhus University Hospital. In order to minimise this problem, we chose to exclude general practices in the outer area of the municipality. This helped ensure that we gained information on all patients from all randomised practice addresses. Furthermore, with this proce-

ture, we were sure that all patients were diagnosed and treated at the Aarhus University Hospital, which, in turn, ensured a homogenous patient care pathway for all patients included in the study. One the downside, this procedure decreased the number of included GP practice addresses which, finally, meant that fewer lung cancer patients were included in the study.

Sampling of lung cancer patients (Paper IV)

The outcomes at patient level in Paper IV were based partly on questionnaire data from the patients' GPs and partly on data from registries. Thus, we needed to identify all newly diagnosed lung cancer patients from Aarhus University Hospital listed with both the intervention GPs and the control GPs. The aim of the sampling procedure was to make sure that all patients with lung cancer were identified, that no GP received a questionnaire concerning a patient who did not have cancer and, finally, that the questionnaires were sent to the GP as close in time to the diagnosis as possible in order to minimise the risk of recall bias (see later).

One approach could be to extract lung cancer patients from the DCR. Unfortunately, it is not possible to extract on-time information from the DCR due to its comprehensive quality control and validation procedures. Within a year, almost 90% of the tumours in the DCR are validated [79]. Inversely, data in the NPR are on-time because the registry serves as a basis for the payment of hospitals. The validity of the data in the NPR has been examined continuously since reporting became mandatory in the late 1970s. Several studies conclude that minor misclassifications do exist in the NPR, but these misclassifications do not influence the overall validity of the NPR data [77,100-102]. In order to minimise the risk of misclassification, we combined the data extracted from the NPR with the data extracted from the DLCR. The DLCR contains information from departments of thoracic surgery, pulmonary medicine and oncology. Each department is responsible for including patients in the registry, which is primarily done by physicians. Since 2003 the registry has covered more than 90% of all lung cancer patients in Denmark. Every month data were extracted from both the DLCR and the NPR. If the patient was included in both registries or in the DLCR alone, we sent a questionnaire to the patient's GP. If the patients were listed only in the NPR, we used the patient hospital records to check whether the diagnoses were correct.

The intervention (Papers III and IV)

The intervention in Paper III and in Paper IV consisted of granting GPs direct access to LDCT and giving the GP an up-date on early lung cancer diagnosis (the CME). Initially, we wanted to test the two components of the intervention (CT and CME) separately in order to be able to separate the effects of the intervention, which would make interpretation of the results easier. However, two things made this approach impossible. Firstly, when planning the intervention, it became evident that offering the GPs a new diagnostic technology without offering some education in how to use this technology would be wrong and inefficient, and we would risk that the GP used the technology inappropriately or not at all. Secondly, a separation of the two elements of the intervention would imply that the RCT had to be designed with three arms. This would decrease the number of practice addresses in each arm and therefore the number of lung cancer cases, too, which would entail an increased risk of an underpowered study. One way to handle this problem could be to expand the study area. However, this would increase the risk that patients were diagnosed and treated at other hospitals which could potentially introduce bias. We therefore decided to unite the two com-

ponents of the intervention into one arm, not only for the above-mentioned reasons, but also because we think this approach resembles the way such a technological upgrade would be introduced in a real healthcare setting.

The CME

A Cochrane review from 2009 concludes that educational meetings alone or combined with other kinds of interventions can improve professional practice and patients' outcomes. However, the effect is most likely to be small [103]. Another review on educational intervention for GPs designed to promote early diagnosis of cancer supports these findings [104]. We chose to design the CME as small group meetings located at strategic places around the intervention area. The CME was interactive and included case stories for the GPs to discuss. The GPs were reminded about the meetings per letter a least twice, and some of the larger GP practices with many GPs were contacted to arrange meetings within the practice during lunch breaks. These initiatives were taken because existing research has found that strategies to increase attendance that use mixed interactive, various didactic formats and focus on outcomes are likely to be perceived as serious and may increase the effectiveness of the educational meeting [103].

The CME was completely voluntary. This implies that the clinicians who agreed to participate may have taken a special interest in lung cancer, and this group of GPs may already have performed differently from other GPs when diagnosing lung cancer. This would potentially underestimate the effect of training. We found that the patients from intervention GPs participating in the CME had much shorter diagnostic intervals than patients from non-participating GP practices. This either implies that the intervention was a success or that the intervention GPs who participated in the CME already performed better than the rest of the intervention group.

Unfortunately, only about half of the invited GPs participated in the CME and, moreover, the GPs who did were the ones who used the direct CT access. When adjusting for non-compliance, we induced a statistical power problem. The research group was unfortunately not aware of this problem when the study was planned, and we did not take into account that the number of patients should have been doubled at the least.

The LDCT scan

During the initial two months of the study, we used full-dose, contrast-enhanced MDCT (the same protocol as used in patients referred to the fast-track pathway) because we wished to use the currently best modality for lung cancer diagnosis. However, after these first two months, we had to change the modality and to use a low-dose MDCT. This change was primarily rooted in a need to speed up the investigations owing to a high referral rate at that time. The CE-MDCT is more time-consuming both as far as the scan is concerned and because it is necessary to prepare patients for the scan.

In retrospect, the LDCT should have been the first choice. In the research group, we are not aware of any studies comparing the sensitivity of CE-MDCT and low-dose MDCT for lung cancer. However, the CE-MDCT modality is superior to the LDCT for characterising an infiltrate in the lung parenchyma. In the present study, we wanted to provide the GPs with a diagnostic test that would disclose whether the patient referred had a lung infiltrate or not. In these cases, we know that the low-dose MDCT is much more sensitive than the chest radiograph which is the diagnostic

tool currently available to the GP [59]. If an infiltrate was observed by the low-dose scan, the next step was to order a CE-MDCT to characterise the infiltrate. Furthermore, in favour of the LD-MDCT speaks that this technology utilises a lower radiation dose than other modalities and that it may be conducted much more quickly than the MDCT. This makes the low-dose MDCT superior as a direct test (and also in screening), and the results of this study would have been less relevant if we had continued to use the contrast-enhanced MDCT.

There were no differences in CT outcomes according to lung cancer between patients scanned during the initial two months of the study and patients scanned in the rest of the study period (16 months). However, the number of lung diseases diagnosed with the CE-MDCT would probably have been higher than with the LDCT owing to the fact that the CE-MDCT has a higher sensitivity for detection of lung diseases, but, again, the number of lung disease detected by low-dose MDCT is higher than that detected by a radiograph with which it would be most obvious to compare our intervention technology.

QUALITY OF DATA

Register data

The use of Danish registries for research has many advantages. The data are easy available, can be obtained at low costs and can be linked through the patient's CRN. The registries are considered to have high completeness and patient data are considered to be valid. The present thesis discusses the quality and the advantages of the individual registers in the chapters describing their use rather than in a separate section. However, some disadvantages will be mentioned here. In the DCR, the overall completeness of the TNM staging for NSCLC is high, but it decreases with increasing levels of comorbidity and at ages above 80 years [85]. In Paper I, the completeness of data on stage was high; and we used a recommended algorithm to define stage in the presence of missing T, N or M values [85].

Furthermore, calculation of the CCI based on the NPR holds a risk of underestimating the degree of comorbidity as the patient has to have been admitted to the hospital for the ICD-10 code to be registered. This means that we have no information on patients with Charlson comorbidity conditions who were not diagnosed at a hospital. However, this concern seems to have little influence on the results as most of the diseases used in the CCI are so serious that the patients would have been seen at a hospital [86].

Questionnaire data

Paper I and Paper IV

The GP questionnaire used in Paper I was developed by a group of colleagues in 2010 as part of the CaP cohort [90] established by the Research Unit for General Practice, Aarhus University. There were no pre-designed questionnaires addressing the specific purpose of Paper I (cancer diagnostics) and Paper IV (lung cancer diagnostics in primary care), and they therefore had to be developed by the research groups. Whenever possible, questions and definitions from earlier questionnaires were used to enhance the validity of the new questionnaires. Items addressing symptoms, dates in the diagnostic pathways, reasons for delay and symptom interpretation have previously proved effective in describing a Danish population [26,27,90,105], and they were therefore used again. The content validity of the questionnaire was optimised in a pilot-test by GPs at the research unit. The use of a validated questionnaire or scales for determining especially the milestones would have strengthened the discussion of the validity of the results. However, no such instrument yet exists. On the

other hand, we used items established by the research group (time intervals, milestones) on which there is international consensus [31]. This makes the results as reliable as currently possible.

The focus group interview

In Paper II, we used a focus group interview to explore changes in the organisation of the fast-track pathway at the Department of Pulmonary Medicine in Aarhus. The method can be defined as "a research technique that collects data through group interaction on a topic determined by the researcher" [106]. It is well established that the method is useful and effective when a researcher explores processes whereby a group jointly constructs meaning about a topic [107,108]. The focus group participants were two chest physicians and one nurse, all involved in the lung cancer diagnostic in the fast-track pathway. The aim of the focus group interview was to explore the pros and cons of the traditional versus the new organisation of the fast-track. This issue was explored primarily to ensure that we induced no harm that had not been duly considered when the new organisation was introduced.

Contrary to asking the staff at the department, we could have asked the patients examined through the fast-track pathway. This approach would have given us more precise knowledge about the pros and cons of the new organisation from the patient's view. Adopting this approach, the challenge would be that because most of the patients are only examined in the fast-track pathway, they would not be able to compare the two different settings. We could also have asked patient from both settings and have compared their satisfaction with the diagnostics. This, on the other hand, would be time consuming and the results would probably be difficult to interpret.

OUTCOME MEASURES AND STATISTICAL ANALYSES

Diagnostic intervals

In Papers I and IV, the primary care and the diagnostic intervals were calculated. Information about milestones in the diagnostic pathway was obtained from the GP questionnaires (except for the date of diagnosis, see later). This information could also have been obtained by reading the patients' records. One advantage of such an approach would have been that the GP could not have interpreted the information they offered in the questionnaire in the light of his/her knowledge of the patient's cancer diagnosis. Research indicates that the GPs interpret their medical records differently than a blinded researcher [109]. However, resources for external coding of the medical records would have been very costly and it would have been very time-consuming.

The validity of the intervals is considered to be high because the intervals are calculated on the basis of factual dates that can be found in patients' records and in registries. However, information on the intervals was restricted to the patients for whom the GP returned the questionnaire and for whom the GP was involved in the diagnosis. Several statistical methods can be used for imputation of missing data, but none of these methods were suitable in the present study because the missing data were factual and could not be estimated based on other factors. We instead included patients only with available dates in the analyses, which can introduce bias (see later).

An alternative approach to measure time in primary care could be to measure the number of contacts to the GP before diagnosis. The hypothesis is that the more pre-diagnostic consultations, the longer the patient had to wait for the diagnosis [44,45]. This may be misleading as 1) it would introduce a relative

measure compared with others presenting to the GP, 2) it is arbitrary to use the number of consultations as some patients would need three contacts to be properly examined (e.g. three in a week) and some would have three consultations in a year, 3) it should be within a specific time interval and 4) it should be related to the cancer and not to other diseases. If the above-mentioned is not fulfilled, the connection between numbers of consultations and time may not be valid.

In Paper I, the date of diagnosis was defined as the day the hospitalisation or outpatient visit during which the diagnosis was made was initiated. This choice implies that the diagnostic intervals were shorter than if we had chosen the date of the histological diagnosis. However, as we wanted to examine the number of X-rays performed before the diagnosis and primarily those initiated by the GP, this definition increased the validity of the diagnostic activity by being truly pre-diagnostic.

Analyses

The time intervals were not normally distributed, and some intervals were very long. The mean allows the extremes to affect the results. All the time intervals (Papers I and IV) were therefore presented as median rather than as mean to prevent any overestimation. In Paper I, a cut point for long intervals was defined as the upper quartile in the group studied. Prevalence ratios were preferred to odd ratios which would tend to overestimate the associations as the prevalence of the outcome measure was above 20% [91].

In Paper IV, primary analyses were performed by the standard intention-to-treat principle with participants analysed according to their GP's randomisation. Patients listed within the same practice are likely to share features; and in these analyses, we accounted for clusters of patients within GPs using cluster robust variance estimation. However, the clustering effect may be very small as the study GPs only had one or two lung cancer patients listed.

Diagnostic activity

In Paper I, we wanted to measure the diagnostic activity prior to the diagnosis of lung cancer. We used chest radiographs as a proxy for the activity. One limitation concerning the radiographs was that we had no indication as to why they were performed. Thus, we may have overestimated the diagnostic activity as some of the radiographs may have been conducted due to congestive heart failure, for example. Still, also in these instances, many GPs would intend to rule out the possibility of cancer, too. Some of the radiographs may have been repeated to rule out false negative radiographs, while others may have been repeated on rational, clinical grounds.

Chest physician time

In Paper II, we measured time per patient spent by the chest physician. One limitation was that we only measured time for a sample of the patients. We chose this approach to approximate the time spent per patient in a period in which the two different kinds of organisation had been running for some time, and we believe that this time per consultation was stable throughout the entire study period.

Patient characteristics and CT outcome

In Paper III, we calculated the duration of symptoms. The information was obtained from the GP referral notes. The GPs were told to describe symptoms, smoking habits and known lung diseases in the notes. The referral notes differed somewhat in how many details the GP presented which is a limitation when interpreting the results. Another approach could have been to obtain the information by asking (either by interview or a questionnaire) all patients referred to direct CT. If we had done so, we would

probably have obtained a more detailed description of the patients, and we could have examined patient satisfaction with the direct CT. However, this procedure would have been much more time consuming and more expensive. One concern was that if the GPs were responsible for handing out the questionnaires, they could find this inconvenient in a busy schedule and they would therefore maybe have more reluctant to refer patients.

GP variation and use of fast track

In Paper III, the referral rate to LDCT was measured for all GPs and, additionally, only for GPs who used the referral option (excluding the GPs who had no referrals to the direct CT, the zero count GPs). The latter was done under the presumption that most of the zero count GPs probably never would use this opportunity within the study period. We wanted to estimate the highest use of the direct CT scans as we would expect it to be if the opportunity was implemented in Denmark. We believe that the real use of the CTs, if implemented, is more accurately estimated when the zero count GPs are not included.

Stage at diagnosis of lung cancer

Stage at diagnosis in Paper I was obtained in the DCR, whereas information on stage in Papers III and IV was obtained from the DLCR. This was done based on the fact that contrary to the DLCR, the DCR, as mentioned above, does not contain on-time information. If we had decided to use the DCR, we would have had to wait for the information to be validated and that was outside the time limits of this PhD study. On the other hand, we have no knowledge that the data regarding staging should be less precise in the DLCR than in the DCR.

As mentioned in the methods section, the two registers differ in the way the TNM is defined. The DLCR contains only one TNM stage (which can be either cTNM or pTNM), while the DCR contains both cTNM and pTNM if available. This implies that the stage distribution between Paper I and Paper IV is not directly comparable as approximately 10% more patients will have an early-stage lung cancer in the DLCR than in the DCR. This issue does not seem to represent any particular problem as long as data for comparison of stage is gathered from either the DLCR or the DCR.

STATISTICAL PRECISION

Power calculation

In this thesis, we aimed to test whether direct CT access from general practice combined with a lung cancer CME would decrease the diagnostic intervals. In 2008 half of the Danish lung cancer patients waited 33 days or more (the median) from their first presentation to primary care until diagnosis of lung cancer [27]. In the research group, we discussed what would be a clinically relevant decrease in time; a difficult subject to measure as the time for a possible stage shift in lung cancer is unknown. Ultimately, we wanted to be able to show a decrease in the diagnostic interval to a level where only 25% of the patients had to wait for 33 days or more. Thus, the proportion of patients waiting 33 days or more should be halved. With a one-sided alpha of 5% and a power of 80%, we had to include 54 lung cancer patients in each arm with a 1:1 randomisation.

It can be assumed that lung cancer patients are randomly distributed among GPs. However, the incidence of lung cancer could be higher in some areas with many smokers and in practices with many elderly patients. To account for an unknown intracluster correlation coefficient (ICC), we included a design effect of 1.25 [92]. In this way, we were able to account for the fact that individual subjects can choose a specific practice, and this may result in a within-practice correlation of characteristics such as age,

gender or ethnic group. The ICC on 0.25 was based on previous research of cluster-randomised trials in primary care [110]. Given the design effect, we had to include a total of $54 * 2 * 1.25 = 135$ lung cancer patients with questionnaire data and GP involvement in the diagnosis. Unfortunately, only approximately half of the intervention GPs participated in the CME. The power measurements should therefore have been at least doubled. However, the Aarhus municipality was chosen because the study area had to be sufficiently large to accommodate the variance of the outcome and the risk of random errors [96], but also sufficiently small to ensure precise follow-up and homogenous patient pathways. Furthermore, the length of the study period was primarily given by the length of the PhD study period.

INTERNAL VALIDITY

Selection bias

Selection bias is the systematic difference between the group selected and the full group from which the selected study group stems [94]. Descriptive studies are vulnerable to selection bias that arises from the procedures used to select subjects and from factors that influence study participation. This type of bias is likely in case-control and retrospective cohort studies because both the exposure and the outcome have occurred by the time the subjects are selected.

In Paper I, the risk of selection bias was minimised by sampling patients from valid registries independently of their GPs and the hospital wards. The questionnaire response rate among GPs was 71.1%, which is very satisfactory. The high response rate reduced the potential for selection bias. GP-induced selection bias was possible if patients of non-responding GPs had different diagnostic intervals than patients of responding GPs. If non-responding GPs were reluctant to respond because of long primary care intervals, our results are underestimating the actual intervals, thereby leading the estimate towards the null hypothesis. On the other hand, it might be that non-responding GPs were uninvolved in the diagnostic pathway more often than responding GPs. If that is the case, the diagnostic intervals may be shorter because those patients are diagnosed in hospitals in connection with another disease which would make us overestimate the overall intervals. Given this, it is difficult to predict the direction of the bias due to selection.

In Paper IV, a high response rate among the GPs of 81.0% minimised the risk of selection bias. This is supported by the fact that the lung cancer patients were quite similar regardless of whether they were listed at control GPs or intervention GPs. However, patients who were not included due to GP non-response may differ from patients of responding GPs in respect of diagnostic intervals, as discussed above. The GPs in this study had an economic incentive to participate as they received compensation for completing the questionnaires. This probably influenced their response rate, but not the estimated delays.

Information bias

Information bias is a flaw in measuring exposure, outcome data or confounding that results in variable quality (accuracy) of information between comparison groups. The most pronounced risk of information bias in this present thesis is that of GPs' recall bias when responding to the questionnaires used in Papers I and IV.

The retrospective nature of the questionnaire-based studies (Papers I and IV) makes them prone to recall bias. Recall bias will affect both the accuracy of the data (e.g. dates) and, in Paper I, the categorisation of patients according to initial symptom

presentation and the symptom interpretation. The GPs were encouraged to consult their electronic patient files when completing the questionnaire to reduce potential information bias. Danish GPs are legally bound to keep detailed medical records of their patients; this includes data on laboratory test results and hospital discharge letters [111]. Knowing that the patient was diagnosed with lung cancer may have influenced the GPs' answers when they stated the dates in the cancer care pathway, and it may have shaped their recollection of the patient's symptom presentation and their evaluation of the care pathway. In Papers I and IV, recall bias may occur if GPs intentionally downplay the delay when feeling responsible for the outcome. This implies that the intervals we reports are the minimum intervals. Furthermore, in Paper IV, recall bias may occur if GPs in the intervention group, who participated in the CME, estimated the intervals longer than the control GPs because they had recently received an up-date on lung cancer symptoms and because of the increased awareness of such symptoms in the daily practice. If the intervention GPs report long intervals because of increased awareness, this will equalise the possibly faster diagnosis owing to the intervention. This bias will underestimate a possible effect of the intervention on the two intervals and could be the reason for the non-significant difference in the primary care interval between groups.

A source of information bias in Paper III may be the referrals notes. The GPs who participated in the CME may filled in more accurate details about the patients referred than the GP who did not participate (a source of possible differential misclassification). On the other hand, the CME-participating GPs were also mostly the ones who used the direct CT option, which makes the problem a minor one.

Confounding

A confounder is a factor that is a risk factor for the outcome and associated with (unevenly distributed), but not a consequence of the exposure. Confounding is most simply defined as the mixing of effects between an exposure, an outcome and a third extraneous variable known as the confounder [94]. Randomisation is a mean of controlling for both known and unknown confounders because possible confounders are evenly distributed.

In Paper I, the effects of gender, age, education, comorbidity and marital status on the diagnostic intervals were mutually adjusted. The effect of the GP's symptom interpretation and use of the fast-track pathway on the diagnostic intervals were adjusted for gender, age, education, comorbidity and marital status. In addition, there might be residual confounding due, e.g., to GP or patient characteristics about which we had no information. However, we have no reason to believe that this residual confounding is unevenly distributed between the groups.

In Paper III, we choose not to adjust for any confounding variables when examining the difference in the proportion of cancers found through the usual fast-track evaluation between the CME participating GPs and the non-participating GPs. The number of lung cancers in a population depends primarily on smoking and age. We measured the proportion of all lung cancers diagnosed through the fast-track pathway. If we had adjusted for smoking and patient age, for instance, we would also have adjusted for the causal variables in getting lung cancer. The comparison of the CME-participants and the non-CME-participants in terms of the GP referral rate to direct CT was adjusted for the GP list gender and age composition because the risk of getting lung cancer increases with increasing age. GPs with many old patients listed will have more consultations regarding symptoms that could

indicate lung cancer, which would increase the referral rate for examinations.

EXTERNAL VALIDITY

Generalisability

In Paper I, we included a well-defined national study population of considerable size. In the light of the above discussion of selection and information bias, we believe that our sample of lung cancer patients is a random selection of the general lung cancer patient in Denmark. Thus, these patient's symptoms, routes to diagnosis and delays are comparable to those of the general lung cancer patient in Denmark. Extrapolation of the results to other countries requires careful consideration of the differences in organisation of the healthcare systems. However, the results of the present study may likely be generalised to other countries where GPs act as gatekeepers to the rest of the healthcare system and where fast-track systems are used for fast cancer diagnoses (e.g. within the other Nordic countries or the UK).

In Paper II, we included all patients referred from primary care to fast-track evaluation at a single department of pulmonary medicine. Whether these patients resemble patients referred to fast-track pathways in other parts of Denmark is partly unknown. However, as GPs in Denmark follow national guidelines when referring patients to fast-track diagnosis and treatment, we would argue that the sample is similar to the general patient population referred to a lung cancer fast-track pathway. One consideration is whether the change in organisation in this study is transferable to other settings. The findings should be interpreted carefully since outpatient clinics are organised differently in Denmark and around the world. Still, the decrease in the use of specialist time may be generalised to other departments.

In the Papers III and IV, this Danish single-setting, randomised, controlled trial with complete inclusion of patients holds the opportunity to generalise the characteristics of patients included to the general patient presenting to the GP with symptoms/signs of lung cancer (Paper III) or the general Danish lung cancer patient (Paper IV). Furthermore, the interventions conducted in this study are transferable to daily clinical practice around the country with only small organisational changes; and the experimental condition in these studies can be considered almost analogous to everyday conditions in the primary and the secondary healthcare system. Furthermore, we do find that the results may apply to other countries and settings in which general practice serves as the first line of healthcare.

ETHICS/HARMS

Careful consideration was given to the ethical aspects of the randomised study reported in the Papers III and IV. The CT scan is a widely used technology and the pros and cons of this diagnostic modality according to lung cancer diagnostics have been thoroughly examined in screening studies. On the contrary, these aspects have not been examined for LDCT used as a case-finding tool in general practice.

For lung cancer, CT has a high sensitivity, but a lower specificity. This implies that the method involves risk of patient distress because of a relatively high number of false positive scans. On the other hand, patients suffering symptoms and signs that could indicate lung cancer are at risk of distress as well; distress that may be eliminated by a fast, direct, thorough test showing no signs of cancer.

Furthermore, the size of the radiation dose and the risk of cancer secondary to radiation from the LDCTs and subsequent imaging used to evaluate positive screens were discussed. A US

study from 2013 addresses this problem in connection with LDCT screening studies [58]. Based on epidemiological data on radiation exposure, the authors calculate that assuming an annual LDCT from the age of 55 to age 74 (20 scans), the lifetime attributable risk of lung cancer mortality is estimated to be 0.07% for males and 0.14% for females. Furthermore, the radiation from one single LDCT amounts not even to half of the total annual radiation exposure from natural and human made sources. In addition, patients belonging to the group of patients referred to a LDCT may have a higher risk of having lung cancer or other important diseases, and the small radiation dose may contribute only very little to the other risks these patients are facing. Bearing these facts in mind, we did not find the radiation dose exposure to be a source of major concern.

Other considerations were based on how the responsibility for the patient changed throughout the examinations. Within the research group, there was a strong wish to place the responsibility for the patient with the GP. By letting the GPs keep the responsibility for the patient, we hypothesised that more GPs would use the direct CT possibility. We wanted to be sure that if the patient after the CT scan needed further examinations in secondary healthcare, the GP would, indeed, refer the patient to the correct department. This would happen only if the CT reports were of good quality. We discussed this issue in the research group and decided that all CT descriptions should contain a plain description **combined** with a conclusion with precise instruction to the GPs. Furthermore, at the CME meeting, we encouraged the GPs to make follow-up appointments with the patient a few days after the CT referral to make sure that the result of the scan and the possible implications were immediately discussed with the patient.

DISCUSSION OF RESULTS

PATHWAY TO DIAGNOSIS, DIAGNOSTIC INTERVALS AND DIAGNOSTIC ACTIVITY (AIM 1)

Pathway to diagnosis

Two thirds of all newly diagnosed lung cancer patients forming part of the patient cohort in Paper I were seen in general practice before diagnosis, and a quarter of these patients were diagnosed from general practice through the fast-track route. Our findings are comparable to the findings of a British retrospective study including 220 lung cancer patients [40] in which 61% were seen in general practice. In line with our results, another British study from 2012 found that 24% of the lung cancer patients were diagnosed through a fast-track referral [55]. However, in the latter study, 39% of the patients were diagnosed through emergency routes compared with 6% in our study. This difference could be explained by the algorithm used to identify pathways since we were able to detect whether the patients were already registered in a hospital-based pathway or not. This is supported by a British study from 2007 with results similar to ours where emergency referrals accounted for 5% of the cases and fast-track referrals for 23% of the cases [56].

Diagnostic intervals

For the newly diagnosed lung cancer patients, the overall median primary care interval was seven days (IQR: 0-30), whereas the median diagnostic interval was 29 days (IQR: 12-69). The length of the diagnostic interval was associated with patient age and with the GP's interpretation of symptoms and referral to the fast-track pathway. Patients with advanced disease had statistically significantly shorter median diagnostic intervals than patients with localised disease. This contra-intuitive association (the waiting

time paradox) has been found in many observational studies as well; patients with short diagnostic intervals have more advanced stage and a higher mortality than the rest [112,113]. Illustrating this paradox, many studies take the results to show that there is no association between delay and mortality [114]. However, this association could be caused by confounding by indication based on differentiated clinical triaging [115]. The bias arises when a GP gives priority to the seriously ill patient, whereas (s)he is more reluctant to refer the not so obviously ill patient [41]. Furthermore, in most cases patients presenting with advanced disease at the hospital need fewer examinations to obtain a diagnosis (e.g. a biopsy from the liver as the only examination), while more diagnostic tests are needed in patients with localised disease. In 2013, a Danish study addressed this problem and found a u-shaped association between length of diagnostic interval and mortality for five common cancers (including lung cancer)[109]. These results provide evidence for the hypothesis that longer diagnostic intervals cause higher mortality in cancer patients. Thus, the data on which factors result in long intervals (i.e. high patient age, presenting with unspecific symptoms and GPs not referring to the fast-track) provide important knowledge for healthcare planning in general and for a shortening of the clinical pathway and thereby an improvement in prognosis in particular. Lung cancer patients are often elderly and many present with unspecific symptoms. Furthermore, only a quarter of the patients are diagnosed through the fast-track route from general practice which implies that many patients are at risk of experiencing long intervals.

A British study in 2008 [40] reported a much longer primary care interval than the present study (primary care: 51 days (interquartile range: 17-165)). As discussed previously, this difference can be explained partly by different study designs. We obtained data on milestones in the diagnostic pathway through GP questionnaires, whereas the British study used research assistants to scrutinise medical records for nine predefined lung symptoms. There is a risk that intervals may be underestimated when we ask the GPs to report the date the patient presented with a symptom that could be due to cancer. On the other hand, there is also a risk of overestimating the length of intervals when going through the GP records searching for the first date a predefined symptom was reported. The true interval properly lies somewhere in between. The impact of this difference in study designs has also been shown for colorectal cancer [109].

A Danish study from 2006 [26], i.e. prior to the introduction of fast-track referral in Denmark, reported longer median primary (29 (IQI: 10-63)) and secondary care intervals (58 (IQI: 42-70)) than demonstrated in the present study. This may indicate an effect of the introduction of fast-track pathways and/or the increased focus on early cancer detection.

Diagnostic activity

In Paper I where the data are from 2010, we found that 87% of all the patients had at least one chest radiograph and 34% had at least two during the 12 months immediately before diagnosis. This is slightly more than in a British study from 2005 where 164 of 247 (66%) lung cancer patients had at least one chest radiograph requested from primary care in the year before the diagnosis [51]. This may imply an increased use of X-rays in Denmark compared with the UK. However, the difference may also just be due to different study designs or to changes over time.

The more frequent use of chest radiographs among patients diagnosed through the fast-track than through the non-fast-track route may indicate that GPs' decisions to order chest radiographs are not rooted only in their symptom appraisal but may serve a strategic purpose, viz. to pave the way for access to the fast-track

route. In light of the rather large risk of false negative chest radiographs this behaviour may in the end lead to delayed diagnosis. Patients, who were not referred from primary care to the fast-track route were more likely to have either none or more than two X-rays compared with patients referred to the fast-track route. Furthermore, if the GP interpreted the symptoms as 'serious, but unspecific', a higher proportion had two or more radiographs conducted. This may imply that these patients are more difficult for the GPs to diagnose or that the initial diagnostic activity did not reveal the lung cancer. Moreover, almost half of the patients admitted as acute patients had two or more X-rays, which could indicate that these patients were, indeed, seen and investigated in primary care without finding the cancer.

At least one third of the patients had two or more chest radiographs during the three months prior to the diagnosis, and some of these additional radiographs may have been taken because the first ones were false negative. This finding confirms previous research [26,50,51] and indicates a need for a more critical use of radiographs for patients suspected of having lung cancer.

Of all lung cancer patients, 15% had no radiographs, and the seeming lack of diagnostic activity before the diagnosis could be explained by patients not being seen by their GP or the patient's and/or the GP's unawareness of signs and symptoms. A British interview-based study found that patients extensively framed their symptoms of lung cancer as "normal features of lifestyle and ageing processes" which may cause them not to visit their GP or not to tell their GP about the symptoms [22].

NUMBER OF PERFORMED MDCTS AND CHEST PHYSICIAN TIME (AIM 2)

In the randomised trial presented in Paper II, we found no differences in the use of CT scans when comparing the new straight-to-CECT scan scheme with the traditional organisation in which a chest physician saw the patient before the CT scan was performed. There was a decrease in time spent per patient. The new organisation was highly accepted and, according to the staff, it also improved the patient's experience.

A few studies have analysed the effect of straight-to-test vs. traditional referral to secondary care. A British retrospective comparative study from 2011 found that straight access to CT scan after an abnormal radiograph reduced the diagnostic interval without significantly increasing the overall proportion of patients undergoing CT scans (from 87% before to 92% after) [116]. Similar results were found in a study from the Netherlands in 2011 [54], where open access to colonoscopy from primary care was found to reduce the diagnostic interval with only a minor increase in the number of endoscopies.

A British study from 2009 rejects a straight-to-test system. This prospective study on patients referred through a fast-track route for colorectal cancer found that the requested test types as entered in the GP referral letters were changed after an outpatient visit in 31% of the cases [117]. This is contrary to the findings in this present study in which reading of the GPs' referral notes showed that the chest physicians were able to select only 3-4% of patients for whom a CT scan was found to be unnecessary. This implies that the GPs were, indeed, able to select patients properly for CT scans.

USAGE OF LDCT AND FAST-TRACK, OUTCOME OF the LDCTS (AIM 3A)

Use of LDCT and fast-track pathway.

In Paper III, two thirds of the GPs used the direct access to LDCT. CME-participating GPs had a 61% higher LDCT referral rate

than non-participating GPs. In terms of variation, we found no association between GP characteristics (age, gender, type of clinic, list size or levels of deprivation) and the use of CT. A review from Scotland [118] concluded that variation in GP referral rates in general is largely unexplained. The study suggests that GPs with an interest in or training in a particular field had a higher referral rate in that specialty. This may explain the higher referral rate among GPs who participated in the CME. However, we can make no causal inference as these findings may be influenced by selection bias.

During the study period, 648 patients were referred to a direct CT. The most prominent referral symptom was coughing with a median duration of two months. The mean patient age was 62 years which is slightly younger than the mean age of Danish lung cancer patients (66 years). Slightly more referred patients were never smokers compared with patients diagnosed with lung cancer. As we have no knowledge of how the scans were introduced to the patients by their GPs in the consultation room, we do not know if this difference arises because the GPs were more willing to refer the slightly younger patient or if a larger number of older patients declined to have the CT scan performed. However, a similar participation bias is also seen in the Danish lung cancer screening trial where people volunteering to participate differed substantially in terms of socio-demographic and psychosocial factors from a matched sample of heavy smokers from the general population [119].

Opposite the screening trials, inclusion in our study embraced a wider population. By limiting GP access to the LDCTs with specific criteria (e.g. smokers or age above 50 years), the proportion of lung cancers diagnosed in our study would probably have been higher. However, the non-limited access shows the actual use and outcome if the direct access is going to be implemented without referral criteria.

CME participation was not associated with an increased use of the existing lung cancer fast-track pathway. However, CME participation was associated with a PPV that was more than twice as high as in intervention GPs who did not participate in the CME. This finding runs counter to our CME hypotheses. We cannot make any causal inference of the associations found as these may simply arise because we compared two essentially different groups of GPs. It is, however, interesting that CME and direct CT seemed to change the GPs' referral patterns, and this may imply that the GPs use the direct CT option for the low-risk patients, whereas they use the fast-track route for patients who are at a higher risk of having cancer.

Outcome of CTs

In Paper III, symptomatic patients consulted general practice, and the GP referred them to a direct LDCT. We found that 64% of the scans were abnormal, and half of the patients needed further diagnostic work-up. Furthermore, we found that 2.3% of the patients were subsequently diagnosed with lung cancer; 60% in early stage (TNM: I and II). In a US screening study (NLST) including participants aged 55-74 with at least 30 pack-years, 1.1% had lung cancer at baseline [59]. The authors reported 55% stage I cancers compared with 40% in our study. In the screening study, 27.9% of the patients needed follow-up scans. This is comparable to our numbers. Similar results were seen in the Danish randomised lung cancer CT screening trial (DLCST) (120), which included participants aged 50-70 with at least 20 pack-years; 0.83% of the participants were diagnosed with lung cancers (68% in stage I). The fact that we found 40% stage I cancers in symptomatic patients can be due to an increased awareness of early signs of cancer among GPs in combination with easy access to a direct test. It

may also be caused by the high sensitivity of LDCT for detection of small lung cancers. These small tumours may not have been detected with a standard chest radiograph, and the test would then have been false negative. This implies that the direct CT from primary care could be an effective tool for diagnosing lung cancer in earlier stages.

LDCTs may also be used to diagnose other lung diseases than lung cancer. The diagnosis of such lung diseases (e.g. tuberculosis, chronic obstructive pulmonary disease (COPD) or interstitial lung diseases) is an important issue in Danish healthcare. For example, COPD remains a major public health problem, and studies have shown that early intervention is of great importance [120]. Drawing on multiple scans conducted in connection with the Danish lung cancer screening study, a Danish study from 2012 found that LDCT is, indeed, able to characterise the presence of early emphysema [121].

TIME TO DIAGNOSIS AND STAGE AT DIAGNOSIS (AIM 3B)

Time to diagnosis

In Paper IV, we found no statistically significant difference in the primary care interval or the diagnostic interval between patients listed with the control GPs and patients listed with the intervention GPs. Just about half of the invited GPs participated in the CME. The correction for non-compliance addresses this problem, but the analyses increase the uncertainty of the estimates and the study may hence be underpowered. Still, the risk of experiencing a long diagnostic interval was 13% higher in the control group than in the intervention group that also participated in the CME. This means that CME combined with direct access to CT may have expedited the diagnosis; however, a larger study is needed to fully evaluate the effect as we cannot falsify that there was no effect. The intervention GPs in this study were offered CME. Those who agreed to participate may have been more interested in lung cancer, and this group of GPs may already have performed better than those who did not participate when diagnosing lung cancer. This would potentially have underestimated the effect of training if our results were generalised.

In Paper IV, the median primary care interval was 16 days. This is longer than the median primary care interval calculated in Paper I (median 7 days, IQR: 0-30). Whether this means that the diagnosis of lung cancer was less expedite in 2012-2013 than in 2010 remains unknown, but we suggest that it may rather be because of increased awareness of lung cancer symptoms and early diagnosis and therefore an earlier 'first symptom presentation'-date listed in the questionnaire.

Stage at diagnosis

Using LDCT, we detected 40% of cancers in stage 1. However, a high frequency of early-stage cancers is not advantageous in itself. It is only beneficial if it is accompanied by a decreased frequency of detection of late-stage cancers. This issue is debated when discussing screening. In the Danish lung cancer screening trial, a relative stage shift was found (the proportion of early-stage cancers diagnosed grew), but no absolute stage shift was observed (a smaller proportion of late stage cancers was not diagnosed) [70]. This could to some degree be a sign of 'overdiagnosis', viz. diagnosis of cancer that never would have progressed to clinical disease during a person's lifetime and thus would not have been identified without the screening [70,122,123]. However, it is questionable whether the issue of overdiagnosis is a real problem in the present study. At the time where a patient visits the GP due to signs or symptoms, the cancer has progressed to clinical disease, and the subsequent cancer diagnosis may thus not be categorised as an overdiagnosis.

We found no difference in stage at diagnosis between the intervention and control group patients. As lung cancer develops over a period of many years, a study period of 19 months may not have been sufficiently long to demonstrate the shift in stage towards more localised cancer detectable by CT.

Change in fast-track use and PPV for lung cancer

The intervention group referred statistically insignificantly more patients to the existing fast-track pathway than the non-intervention group, but the PPV for lung cancer (within the fast-track) was identical in the two groups of GPs. This may indicate that CME has a positive effect by encouraging the GPs to refer more patients to expedite investigations. The PPV (in the fast-track) was equal across all intervention and control GP groups although direct LDCT was an option, which may suggest that the intervention GPs are able to identify more patients at risk of cancer, maybe because of a greater awareness of lung cancer signs and symptoms.

The frequency of lung cancer detected by LDCT was 2.3% compared with approximately 10% for the existing fast-track route found in this study. This indicates that the patients referred to a direct CT formed a subgroup of patients with less pronounced symptoms and thus at a lower risk than patients whose symptoms were due to lung cancer. This group of patient is theoretically the group that we wanted to find using direct CT scan. Patients with "low, but not no risk" may be the ones most GPs find difficult to handle in primary care [72], and they are exactly the ones for whom the best strategy may be a direct, valid test performed with the GP as the responsible part.

CONCLUSION, PERSPECTIVES AND IMPLICATIONS

Referring to the aims of the present thesis as stated in Chapter 1, this chapter summarises the overall conclusions. Furthermore, the perspectives and implications of the main results are discussed.

PATHWAYS TO DIAGNOSIS, DIAGNOSTIC ACTIVITY AND DIAGNOSTIC INTERVALS (AIM 1)

Two thirds of lung cancer patients were seen in general practice before diagnosis, and Danish lung cancer patients follow several routes to diagnosis. Only a quarter of lung cancer patients were diagnosed directly from general practice through the fast-track route. Furthermore, 9 out of 10 of all lung cancer patients had a radiograph performed before receiving their diagnosis, and one third of the patients had two or more radiographs within the last 90 days before being diagnosed with lung cancer. The GP estimated that the primary care interval exceeded one month in 25% of the lung cancer patients. The diagnostic interval exceeded 69 days in 25% of the patients. The length of the diagnostic interval was associated with patient age, GP interpretation of symptoms and the referral pathway.

Perspectives and implications

Most lung cancer patients begin the diagnoses in general practice. Even though the median primary care interval is only 1 week, one fourth of all patients waited 1 month or more before being diagnosed. In order to shorten the delay in primary care, it may be necessary to help the GPs become better at investigating and interpreting early cancer symptoms, for example through continuous medical education (CME) or by allowing them to draw on a wider range of diagnostic options. These results are important for the organisation of the healthcare system. For the secondary sector, the advantage of the fast-track system lies in standardisation of diagnostics and close monitoring of time. For

the primary sector, however, the fast-track pathway may be less optimal because only a minority of the patients present with alarm symptoms justifying the fast-track referral. One solution to this apparent dilemma may be to offer general practice access to more sensitive direct tests. Furthermore, radiographs are often repeated in patients, which suggests that there is a need for access to better diagnostic tools (e.g. LDCT scans) than those currently available to primary care (viz. radiographs).

NUMBER OF CT SCANS, CHEST PHYSICIAN TIME SPENT AND SATISFACTION WITH THE FAST-TRACK PATHWAY (AIM 2)

Adoption of a strategy of straight-to-test with contrast-enhanced MDCT for patients in the lung cancer fast-track pathway was associated with a reduction of chest physician time per patient and with an increase in levels of staff acceptability, but the overall number of performed CTs remained the same.

Perspectives

This study opposes the idea that patients referred to special diagnostics at the hospitals need to be seen by a hospital physician before the diagnostic test. Such double-gate-keeping may be ineffective and time-consuming. These results may be important for the organisation of other outpatient's clinics. In addition, the study implies that GPs are able to select patients properly for fast-track CTs.

USAGE AND OUTCOMES OF LOW-DOSE MDCT, TIME TO DIAGNOSIS AND STAGE (AIM 3)

The direct, LDCT option was used by two thirds of the GPs. We found an association between participation in CME and the use of LDCT. Half of the referred patients needed additional diagnostic work-up, and 2.3% were diagnosed with lung cancer with a favourable stage distribution.

No statistically significant difference was found between the primary care interval and the diagnostic interval. However, when correcting for non-compliance, we found that patients were facing a higher risk of experiencing a long diagnostic interval if their GPs were in the control group than if they received CME. We found no difference in stage at diagnosis between patients listed with the control and the intervention GPs.

Perspectives and implications

These results imply that GPs will only truly benefit from the introduction of new diagnostic technology if they are taught how to use it. The fact that half of the patients needed further diagnostic work-up is also an important point that should be considered before a possible introduction of new technology. Furthermore, in light of the large number of patients who are diagnosed with serious lung disease or cancer (lung or other) by means of LDCT, this modality may also be considered a future diagnostic tool in primary care. Even for the group of patients presenting with symptoms or signs in primary care, many of the lung cancers diagnosed by the LDCT were low-stage cancers. This provides hope for finding ways to diagnose lung cancer earlier in primary care. One major challenge of using the LDCT is the frequent finding of nodules needing follow-up scans even though the cancer PPV is very low. Much research is currently being conducted to assist clinicians in distinguishing between benign and malignant nodules. If such research succeeds, the potential for direct LDCT from general practice would increase.

The fact that we found no significant outcomes measure to support the implementation of direct CT in the randomised trial may be rooted in a design problem. The results from Paper III are encouraging, and they are important for any further discussion about direct-to-test referral from primary care. Direct access to

LDCT scan may be an alternative to lung cancer screening. Furthermore, if a LDCT screening program was going to be implemented, one consideration could be to expand the program by granting GPs the opportunity to directly refer symptomatic, non-screened patients to CT.

The frequency of lung cancer detection by LDCT is lower than we initially expected (2.3%). In addition, it is lower than the frequency of detection of cancers in the fast-track pathway (10%). The question therefore remains, what is the right frequency/PPV for cancer diagnostics? Based on very low PPVs for lung cancer symptoms in primary care, how high a PPV can the secondary sector demand? If we want the GPs to refer and investigate the not-so-obviously-ill patients, more patients will have to be investigated. The question that begs an answer, not by the research group but by health decisions makers, is accordingly whether the frequency (and derived advantages) of such an approach will outweigh its costs.

It is possible to take a very nihilistic view that all NSCLC biologically are low-grade tumours, and that patients with such tumours would have survived almost whatever treatment they had, or had not, received. We may only speculate as to the existence of a group of patients with comparatively speaking less aggressive lung cancer that may be susceptible to cure if identified early, but which are not curable if identified late. However, long-term survival is not the only consideration when trying to improve lung cancer diagnosis: late diagnosis usually imposes a serious strain on patients and their relatives. Not only does the lateness of diagnosis obviate radical treatment options, it also prevents recruitment of appropriate medical and social inputs, including options that may optimise symptom control and the planning of care and which will afford the patient and his or her family with enough time to adjust to the diagnosis.

FUTURE RESEARCH

The results of the present thesis invite further research into a number of areas as outlined in this chapter.

- The fact that lung cancer patients are seen in primary care before diagnosis calls for further studies of the clinical trajectory in primary care to explore the unique patterns of the initial steps in cancer diagnosis. Such research could target the pre-diagnostic activity in the years before diagnoses, for example by quantifying the number of consultations, lung functions tests, X-rays and prescriptions of lung medicine in lung cancer patients compared with a matched comparison group. A comparison of the above-listed activities between lung cancer patients with regional or distant disease or between patients with or without a chronic lung disease would also be interesting. The potential is to help GPs become better at assessing the risk of lung cancer in primary care, which may ultimately improve the lung cancer diagnostics in general practice.
- The positive results obtained owing to the current fast-track cancer pathways (Paper II) invite further studies deploying a straight-to-test strategy in other cancer fast-tracks pathways, e.g. the colon cancer fast-track pathway with direct to colonoscopy.
- The results of Paper II concerning a straight-to-test from primary care strategy encouraged the Department of Pulmonary Medicine, Aarhus University Hospital, to change their fast-track organisation. As from December

2012, all patients referred from general practice to the lung cancer fast-track pathway are now CT scanned before the chest physician outpatient visit. A study should be performed to evaluate the organisational change and to test whether the GPs are now using the fast-track option differently from before this organisational change, e.g. if the stated indications for the scans have changed. This will be measured by comparing fast-track referrals and PPVs in the fast-track before and after the reorganisation.

- Furthermore, a follow-up study encompassing the 648 patients scanned with direct LDCT has been planned. It is expected that this study will be able to quantify the additional diagnostic work-up needed after the first CT and that it will be possible to calculate the number of lung cancers diagnosed by the derived CTs.
- Finally, a large-scale study with direct CT access from primary care should be performed to test whether direct LDCT from primary care may reduce the time to diagnosis and result in a lower disease stage at diagnosis. Furthermore, a study comparing LDCT screening with case-findings based on direct LDCT from primary care would be interesting because it may reveal which scenario performs best on outcomes like PPV of cancer, PPV of other lung diseases, costs, patients/doctor satisfaction, additional work-up, and cancer stage, among others.

LIST OF ABBREVIATIONS

CE-MDCT	Contrast enhanced multi-detector computed tomography
CI	Confidence interval
CME	Continuing medical education
CRS	The Danish civil registration system
CT	Computed tomography
cTNM	Clinical TNM
DADI	The Danish deprivation index
DCR	The Danish Cancer Registry
DLCG	The Danish Lung Cancer Group
DLCR	The Danish Lung Cancer Registry
ENT	Ear, nose and throat
GP	General practitioner
HSR	The Danish National Health Service Registry
ICD-10	The International Classification of Diseases, 10 th revision
IQI	Interquartile interval
LDCT	Low-dose computed tomography
LD-MDCT	Low-dose multi-detector computed tomography
LMG	Louise Mahncke Guldbrandt
MDCT	Multi-detector computed tomography
NPR	The Danish National Patient Registry
NSCLC	Non-small cell lung cancer
PET	Positron emission tomography
PPV	Positive predictive value
pTNM	Pathological TNM
PS	Performance status
PV	Peter Vedsted
RCT	Randomised controlled trial
TNM	Tumour, nodes, metastasis
SCLC	Small cell lung cancer

SUMMARY

This PhD thesis is based on the project “The effect of direct referral for fast CT scan in early lung cancer detection in general practice. A clinical, cluster-randomised trial”, performed in Denmark in 2010-2013. The thesis includes four papers and focuses on early lung cancer diagnostics in general practice.

INTRODUCTION

A total of 4200 new cases of lung cancer are diagnosed in Denmark annually. The stage of the disease is an important prognostic factor; thus, the opportunity for curative treatment declines with more advanced tumour stage. Lung cancer patients in Denmark (like in the UK) have a poorer prognosis than lung cancer patients in other European countries. One explanation could be delayed diagnosis. A fast-track pathway was therefore introduced in an attempt to expedite the diagnosis of cancer. However, it seems that not all patients can be diagnosed through this pathway. In order to ensure fast and early lung cancer diagnosis, it is crucial to examine the initial diagnostic process in general and the role general practice plays in lung cancer diagnostics in particular. The specific areas of investigation include the pathways to diagnosis, the characteristics of patients who are at special risk of delayed diagnosis and the level of pre-diagnostic activity in general practice.

A chest radiograph is often the first choice in the investigation of lung cancer. Unfortunately, radiographs are less suitable for central and small tumours. Low-dose computer tomography (LDCT), however, has a high sensitivity for lung cancer which implies that it can be used to detect patients with localised, potentially curable disease.

AIM

The aim of this thesis was to increase our knowledge of the initial stages of lung cancer diagnostics in general practice. The thesis also examined the effect of a direct referral from general practice to an additional diagnostic test, the LDCT. The aims of this thesis were:

- 1) To describe Danish patients' pathways to the diagnosis of lung cancer in general and the pre-diagnostic activity leading up to diagnosis in particular. An additional aim was to explore the diagnostic intervals for specific patient groups (Paper I).
- 2) In a randomised, controlled trial including all patients referred for the existing fast-track scheme to either direct chest and upper abdomen CE-MDCT or to evaluation by the chest physician, (i) to test:
Fast-track performance measured by the number of CE-MDCT scans and chest physician specialist time per diagnosis (Paper II)
- 3) In a two-arm, clinical, controlled, cluster-randomised trial where direct referral to CT together with a lung cancer update is compared with usual practice, (i) to test how CT is used in this group of patients and the outcome of CT (Paper III); and (ii) to test the effect of either modality on the time to lung cancer diagnosis, the TNM stage and the use of the fast-track pathway for lung cancer (Paper IV).

METHODS

Study I was a national registry-based cohort study of 971 consecutive, incident lung cancer patients in 2010 Data were derived

from national registries and questionnaires filled in by general practitioners (GPs).

Study II was a randomised, controlled trial enrolling 493 patients referred from general practice to a fast-track evaluation. Half of the patients were randomly assigned to the intervention and went straight to a chest CT before a chest physician evaluation.

Studies III and IV were a cluster-randomised, controlled trial (IV) and a cohort study nested in the trial (III). A total of 199 general practices with 266 GPs were randomised into two groups. Intervention GPs were offered direct access to a low-dose chest CT combined with a meeting on early lung cancer detection. Study III concerned the intervention arm solely and reported uses and outcomes of the scans. Study IV evaluated the effect of direct low-dose CT on the time to diagnosis and stage at diagnoses for patients from intervention and control GPs.

RESULTS

In Study I, we found that GPs were involved in 2/3 of all lung cancer diagnostic pathways. One quarter of the patients followed the obvious pathway from general practice to fast-track detection. At least one radiograph was performed in 85.6% of patients, whereas 1/3 of all patients had two or more radiograph performed during the 90 days preceding diagnosis. Patients with comorbidity or unspecific symptoms more often had two or more X-rays performed than patients without these characteristics.

In Study II, there was no difference between the groups in the number of CTs performed. In the intervention group, chest physicians spent mean 13.3 minutes less per referred patient than in the control group.

In Study III, we found that 648 patients were referred to low-dose CT during a 19-month period. Half of the referred patients needed further work-up, and 15 (2.3%) of the patients had lung cancer, 60% in a localised stage. For all patients, 6.8% were diagnosed with a severe lung disease. In all, 2/3 of the GPs used the CT opportunity; and the referral rate was 61% higher for GPs participating in the lung cancer meeting than for GPs who did not participate in such meetings.

In Study IV, we found that direct, low-dose CT from primary care did not significantly influence stage at diagnosis and had only a limited impact on time to diagnosis.

CONCLUSION AND PERSPECTIVES

This thesis contributes to the knowledge of the early diagnosis of lung cancer in Denmark. General practice was found to play an important role, but only a small part of Danish lung cancer patients were diagnosed from general practice through the fast-track pathway. This together with the fact that a high proportion of patients had two or more radiographs within the 90 days preceding the diagnosis indicate that other diagnostic strategies should be tested in an attempt to provide GPs with the best opportunity for early diagnosis.

This thesis provides evidence that GPs are, indeed, able to refer patients straight-to-test in the fast-track pathway. This knowledge may be used when organising other fast tracks. Furthermore, GPs participating in education about early lung cancer diagnosis were willing to refer patients direct to low-dose CT (LDCT) from primary care. Half of the patients needed further diagnostic work-up, and 2.3% of all patients referred were diagnosed with lung cancer. In addition, many lung diseases were diagnosed by LDCT. No effect on time to diagnosis or stage at diagnosis was found when patients from intervention GPs were compared with patients from control GPs.

The effect of combining direct access to LDCT with referral to the existing fast-track pathway should be analysed as it may ensure earlier and faster lung cancer detection in primary care. Direct access to LDCT scan may also be an alternative to lung cancer screening. Furthermore, if a LDCT screening program is going to be implemented, it should be considered to supplement the program with access to CT directly from primary care for the symptomatic, not-screened patients.

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