The diagnosis of suspected lung cancer: Impact of practice organization on timeliness and distress

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INTRODUCTION AND OUTLINE

INTRODUCTION

Lung cancer is the leading cause of cancer related mortality worldwide, accounting for around 27% of all cancer deaths.[1] In the Netherlands specifically, well over 11.000 new patients are diagnosed with lung cancer every year.[2] Lung cancer is roughly divided by histology into Small Cell Lung Cancer (SCLC) and Non-Small Cell Lung Cancer (NSCLC), of which the latter accounts for 85-90% of all cases.[3] During the last decade, the medical professional has witnessed that lung cancer, especially NSCLC, has become much more complex and treatment has gained a more individualized character. The diagnosis of lung cancer nowadays requires more than just pathological confirmation of the diagnosis. Accurate staging is necessary to ascertain the extent of the disease as this stratifies patients into lower and higher risk groups, which is important for prognostication, patient management and optimal treatment decisions. Furthermore, in recent years lung cancer therapy for the higher incurable stages has become driven by tumor type[4] and for the large group of NSCLC adenocarcinoma subtype patients by gene mutation status.[5] Both developments have led to the necessity of performing multiple diagnostic procedures, of which ^{18}F-fluorodeoxy-glucose-Positron Emission Tomography and contrast enhanced Computed Tomography (FDG-PET/CT) precluded probably the most important change in diagnostic care for lung cancer. Compared to conventional Computed Tomography (CT), FDG-PET/CT proved to be superior in defining lung cancer stage mostly by revealing occult metastasis but also in more accurately predicting lymph node metastases.[6-8] Management decisions for individual lung cancer patients were influenced to such an extent that FDG-PET/CT rapidly became a primary diagnostic tool in lung cancer, and implementation in all major guidelines followed.

Pathological confirmation of diagnosis and disease stage may require – even within the same patient – several procedures including (but not exclusively) bronchoscopy, percutaneous needle biopsy, esophageal endoscopic ultrasound (EUS), endobronchial ultrasound (EBUS) or mediastinoscopy; often

multiple of these techniques are used in the same patient. In combination with the high lung cancer incidence rates described above this can be challenging for medical practice and requires, besides resources, organization and timing of health care. Timeliness of care has gained attention in recent years: Not only may delays adversely affect disease stage[9,10] and survival,[10-13] it can also be seen as a care quality indicator. And still, although maximum acceptable waiting times for referral, diagnosis and start of therapy in lung cancer have been explicitly formulated in both national and international guidelines,[14-17] these intervals are often reported to be longer than recommended.[18] It has been shown that diagnostic algorithms in the sense of a Rapid Outpatient Diagnostic Pathway (RODP) – in the past also referred to as 'one stop' or 'two stop' pathway – most successfully improved timeliness,[18] but these improvements were demonstrated in an era that preceded introduction of most of all previously mentioned diagnostic and staging tools that presently have such importance and comprise much more than just 'two steps'.

Despite all abovementioned developments that have broadened the diagnostic and therapeutic horizon for certain subgroups of patients, lung cancer has at diagnosis often already advanced to an extent that excludes curative treatment, resulting in a very modest overall 5 year survival rate that has shown only a small improvement over the last decades and is presently estimated at 18%.[1] From a patient's perspective, the confrontation with a possible diagnosis of lung cancer may be very distressing[21] not only because of this poor prognostic nature of the disease, but possibly also in face of the sometimes invasive diagnostic procedures that may be required to ascertain diagnosis and stage. Notably, lung cancer patients experience distress levels that are among the highest of all cancer types ranging from 20 to even 50% anywhere during the course of their disease;[19,20] as such they may be seen as a patient group that is more at risk.

Distress is usually characterized by anxiety or depressive symptoms and is best described by the National Comprehensive Cancer Network (NCCN) definition as 'a multifactorial unpleasant emotional experience of psychological (cognitive, behavioral, emotional), social and/or spiritual nature that may interfere with the ability to cope effectively with cancer, its physical symptoms and its treatment'. [22] And although medical practice strives to provide answers to the physical and mental needs of lung cancer patients in terms of curative and palliative care, the needs of suspected patients facing the pos-

sibility of this diagnosis receive much less attention despite the fact that these patients experience multiple more or less invasive diagnostic procedures during a period of uncertainty. Moreover, a considerable number of patients are eventually *not* diagnosed with cancer but undergo the same procedures and experience similar distress. Furthermore, if the recent calls for implementation of lung cancer screening[23] are adopted, numbers of suspected lung cancer patients that undergo diagnostic analysis for an eventual benign result will increase substantially. It is important to realize that for many patients this 'benign outcome' does not automatically result in a 'benign experience', as has been exemplified by breast cancer screening studies showing that psychological consequences of screening may persist in patients with benign results.[24]

In order to address both timeliness and the substantial number of new suspected patients that is referred on a daily basis, medical practice needs to review diagnostic care thoroughly and implementation of an RODP may be the most logic step further. Moreover, a timely diagnosis could actually reduce distress levels by drastically shortening the period of uncertainty. National discussion on this subject among medical professionals[25-27] but also patient advocate non-governmental institutions[28] is still alive today. However, the debate on the specific advantage or disadvantage of an RODP in patient distress remains unsettled since it is based on assumptions and personal experience, but not empirics.

The studies presented in this thesis address the diagnostic pathway in suspected lung cancer patients and focus on the possible improvements in diagnostic timeliness, patient reported distress and quality of life (QoL), when a standardized fast track approach by means of an RODP is used. Furthermore, these studies investigate the diagnostic performance of FDG-PET/CT when incorporated as a first-line diagnostic tool within the RODP.

OUTLINE OF THIS THESIS

This thesis provides a comprehensive analysis of the characteristics of the RODP of the Radboud university medical center (Radboudumc) and focuses on the diagnostic performance of FDG-PET/CT, which is included in this RODP as a routine diagnostic tool. Furthermore, distress and QoL during the diagnostic episode of a possible malignancy will be described in an overview of published literature and the beneficial effects of an RODP in reducing distress will be discussed.

CHAPTER 2 describes the diagnostic results of the RODP for suspected lung cancer patients, including routine FDG-PET/CT and the characteristics of all analyzed patients during the first ten years after its implementation at Radboudumc in 1999. It explores the accuracy of the diagnosis in this rapid setting and puts timeliness of diagnostic care for suspected lung cancer patients in the perspective of delays described in literature[12] and the limitations as published in guidelines.[8-11] Furthermore, it describes the impact of symptomatology and referral type on different types of delay (patient, referral, diagnostic and therapeutic delay) and it addresses the complex question whether these delays can be related to disease stage and patient outcome. **CHAPTER 3** focuses specifically on the subset of patients in this RODP whose referral was based on an abnormal chest X-ray. This is an important subgroup of the cohort described in the previous chapter, as in the clinical practice of primary care most lung cancer suspicions start with the abnormal chest X-ray that the general practitioner has ordered. Therefore, the diagnostic performance of the FDG-PET/CT in separating malignancy from benign lesions within the programmed setting of an RODP is vital, as the FDG-PET/CT is not performed after diagnostic CT in the regular sequential setting.

The next two chapters attempt to answer the question whether an RODP will influence distress and QoL. In the past, some research has been performed on this subject but these results do not automatically lead to straightforward

answers as different measures have been used in different circumstances to different patient subgroups. CHAPTER 4 systematically reviews the literature regarding distress and QoL during the diagnostic evaluation of a suspected malignancy in order to attempt to shed light on whether a rapid diagnosis should be preferred in this respect, with the subgroup of suspected lung cancer patients in mind which might be generally more at risk.[19,20] RODPs have been developed for different cancer types but the effect of this different approach on suspected lung cancer patients' distress levels and QoL had not yet been prospectively evaluated. We therefore decided to perform a study in suspected patients who underwent an RODP and patients who underwent a regular Standard Diagnostic Approach (SDA). This PENELOPE study (Pulmonary Evaluation of NEoplastic Lesions in Outpatients and it's Psychological Effects) was performed in a prospective cohort design in four different medical centers in the Netherlands, which enabled inclusion of a large number of patients that were analyzed in an RODP or SDA. Results are described in CHAPTER 5. The thesis concludes with a summary and discussion of the main results of our research in CHAPTER 6.

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TIMELINESS OF LUNG CANCER DIAGNOSIS AND TREATMENT IN A RAPID OUTPATIENT DIAGNOSTIC PROGRAM WITH COMBINED ^{18}FDG-PET AND CONTRAST ENHANCED CT SCANNING

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ABSTRACT

INTRODUCTION: Delays in the diagnosis of lung cancer are under debate and may affect outcome. The objectives of this study were to compare various delays in a rapid outpatient diagnostic program (RODP) for suspected lung cancer patients with those described in literature and with guideline recommendations, to investigate the effects of referral route and symptoms on delays, and to establish whether delays were related to disease stage and outcome.

METHODS: A retrospective chart study was conducted of all patients with suspected lung cancer, referred to the RODP of our tertiary care university clinic between 1999 and 2009. Patient characteristics, tumor stage and different delays were analyzed.

RESULTS: Medical charts of 565 patients were retrieved. 290 patients (51.3%) were diagnosed with lung cancer, 48 (8.5%) with another type of malignancy, and in 111 patients (19.6%) the radiological anomaly was diagnosed as non-malignant. In 112 (19.8%) no immediate definite diagnosis was obtained, however in 82 of these cases (73.2%) the proposed follow-up strategy confirmed a benign outcome. The median first line delay was 54 days, Interquartile Range (IQR) 20–104 days, median patient delay 19 days (IQR 4-52), median referral delay was 7 days (IQR 5-9 days), median diagnostic delay 2 days (IQR 1-19 days). In 87% a diagnosis was obtained within 3 weeks after visiting a chest physician and 52.5% started curative therapy within 2 weeks after diagnosis. Patients presenting with hemoptysis had shorter first line delays. The RODP care was generally far more timely compared to literature and published guidelines, except for both referral and palliative therapeutic delay. No specific delay was significantly related to disease stage or survival.

CONCLUSIONS: An RODP results in a timely diagnosis well within guideline recommendations. Patient and first line delay account for most of total patient delay. Within the limitations of this retrospective study, we found no association with disease stage or survival.

INTRODUCTION

Lung cancer is the leading cause of cancer related mortality in men and second in women. The 5 year survival rate of the various types of lung cancer for both Europe and the United States is approximately 16% and did not significantly improve in the last decade, despite emergence of new diagnostic and therapeutic developments.[1] The necessity to perform diagnostic procedures such as ^{18}fluorodeoxyglucose Positron Emission and contrast enhanced Computerized Tomography scan (FDG-PET/CT), mediastinoscopy or Esophageal endoscopic Ultrasound (EUS) and Endobronchial Ultrasound (EBUS), in combination with the high lung cancer incidence rates can be challenging and, besides resources, requires organized and timely health care. Timeliness has gained attention in the recent years since delays may affect disease stage[2,3] and survival.[2-6]

Although consensus based, maximum acceptable waiting times for referral, diagnosis and start of therapy in lung cancer have been explicitly formulated in several guidelines.[7-10] These can be as general as 2 months for referral, diagnosis and start of therapy together,[8] or rather specific: Referral delay is then limited to 1 week[7] or 80% of patients seen within 5 days;[9,10] diagnostic delay to 2 weeks,[7] or 80% of patients diagnosed in either 3 weeks or 5 when mediastinoscopy is needed;[9,10] therapeutic delay can take 1 to 6 weeks depending on urgency and therapy type.[7-10] A recent comprehensive review of the literature on timeliness of lung cancer care shows however that time intervals to diagnosis and treatment are often longer than guidelines recommend.[11] It furthermore demonstrates that most published literature addresses timeliness of treatment or referral and that diagnostic delay is discussed to a much lesser extent although it can be a deeply disturbing experience for suspected cancer patients accompanied by high distress levels.[12] The fact that distress in the diagnostic phase has been shown to be reduced by shortening this period[13-17] indicates this should be addressed by effective interventions such as implementation of urgent referral guidelines,[18] multidisciplinary meetings,[19-21] nurse-led care,[22] or specific diagnostic algorithms.[23] These algorithms and more complicated two-stop pathways most successfully improve timeliness[11] although the evidence so far is limited to a few studies[24,25] and did not include FDG-PET/CT, nowadays being considered the best imaging technique in lung cancer.[26,27]

With the present study, we hope to add to the knowledge on rapid pathways. We retrospectively reviewed all patients referred between 1999 and 2009 to

the two-day Rapid Outpatient Diagnostic Program (RODP) including the unique feature of FDG-PET/CT for all patients with suspected lung cancer that was implemented in the Radboud University Nijmegen Medical Centre (RUNMC) in 1999. Our aims were to describe the diagnostic results of the RODP, to evaluate the impact of symptomatology and referral type on different types of delay, to establish whether delays were related to outcome and stage, and to compare the delays with those described in literature and guideline recommendations. To our knowledge this is the first study reporting on timeliness of an RODP incorporating integrated FDG-PET/CT.

METHODS

A retrospective chart review was conducted of all consecutive patients referred to the RODP between August 1999 and April 2009. In this period, all outpatients with a radiological suspicion of lung cancer without clinical need for hospitalization or obvious stage IV disease were diagnosed in this program in our centre. All patients underwent a full diagnostic workup (FDG-PET/CT, consultation of a chest physician, pulmonary function tests, bronchoscopy) and disclosure of the cytology results (based on Papanicolau and Giemsa staining), in two days time as explained in Table 1.

DAY 1 (Wednesday)
Lab, electrocardiogram
^{18}FDG injection
PET/CT and contrast enhanced chest CT
Multidisciplinary evaluation of PET/CT
Pulmonary function testing
Physician visit, physical examination, discussion of PET/CT
DAY 2 (Thursday)
Bronchoscopy
Discussion of cytology results

TABLE 1 **RODP schedule, capacity 4 patients weekly**

Demographic data, clinical characteristics and dates required to calculate delays and survival were retrieved from medical charts. Since the RUNMC is a large university hospital and a tertiary referral center for oncology, many patients were referred by other specialist consultants. In order to assess and compare both tertiary and primary care, demographic characteristics, diagnostic results and outcome were recorded by referral (general practitioner (GP) or specialist). Finally we defined the patient subgroup with a histologically or cytologically confirmed lung cancer diagnosis. Patient characteristics and delays were compared within groups. All patients were staged according the international staging system version 6.[28]

Different delays were defined as shown in Figure 1: Patient delay as the time from first symptom until the first visit to a GP, GP delay as the time between first GP visit and referral to a chest physician, referral delay as the time between referral (written or by phone) and first RODP day, diagnostic delay as the time between first RODP day and date of final (accurate) diagnosis, therapeutic delay as the time between diagnosis and start of treatment. In agreement with several studies[11] and both British Thoracic Society (BTS)[7] and Dutch[10] guidelines defining diagnostic delay as the interval between first visit and start of treatment, we also calculated this interval ('diagnostic + therapeutic delay') to facilitate comparison. All waiting time intervals were calculated in calendar days (including weekend and holidays) only if both dates defining that delay had been recorded.

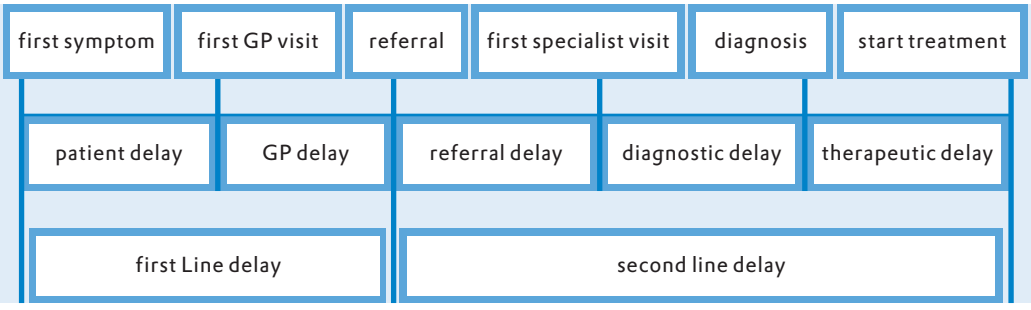

FIGURE 1 **Schematic representation of delays**

All data were analyzed using the SPSS 16.0 statistical software program (SPSS, Chicago, IL). Descriptive statistics were used to summarize the demographic data. We report the mean and standard deviation (SD) in case of

normally distributed continuous variables, and median and interquartile range (IQR) for variables that are not normally distributed. Continuous variables were compared using the unpaired t-test or Mann-Whitney-U test, categorical variables were compared using the χ^2-test, delay per stage was compared using the Kruskal-Wallis test. The Cox proportional hazard model was used to analyze survival per delay. Differences were considered statistically significant if $p < 0.05$.

RESULTS

DEMOGRAPHIC DATA

Of the total of 570 RODP patients, of 565 medical charts could be retrieved. Table 2 shows demographic patient data. Two hundred and eight patients had been referred by their GP, 355 by a specialist. The remaining 2 patients were self-referrals to the emergency ward, included in the RODP afterwards. Two patients (indicated by ECOG performance status 5 in table 2) died either before start of, or during the RODP but were included in calculations of prior delays. For all 565 patients mean age was 63.9 years, 66.5% were male and 10.8% were never smokers. Prevalence of COPD was 59%, with 6.7% Global initiative for Chronic Obstructive Lung Disease (GOLD) stage III or IV. A history of some form of cancer was noted in 324 patients (41.4%), significantly more often in specialist referred compared to GP referred patients (51.0 versus 25.5%) as was non-pulmonary co-morbidity (62.5% versus 49.0%, both $p<0.05$). Table 3 shows that 290 patients (51.3%) were diagnosed with lung cancer, of which 261 patients (90%) had Non-Small Cell Lung Cancer (NSCLC), 16 (9.0%) Small Cell Lung Cancer (SCLC) and 3 (1.0%) a double tumor consisting of both cell types. In 211 of all 290 lung cancer cases (72.8%) additional staging procedures to define clinical and/or pathological tumor stage were required. One hundred and fifteen patients (20.4%) had a certain benign diagnosis (most often infection) and from 112 patients (19.8%), no cytologically or histologically confirmed diagnosis was obtained. In 82 of these indefinite cases (73.2%) the proposed follow-up strategy (median follow-up 32 months, range 9 weeks to 10 years) confirmed a benign outcome. The remaining 28 (26.8%) were estimated to have a probable lung cancer but further analysis was abandoned because of poor performance status or patient refusal of further diagnostic procedures.

	PATIENTS
N	565
Mean age	65.9 (10.0)
Sex: Male	376 (66.5)
Female	189 (33.5)
ECOG Performance status at presentation	
0	387 (68.5)
1	138 (24.4)
2	32 (5.7)
3	6 (1.1)
4	2 (0.4)
Weight loss > 10%	60 (10.6)
Significant co-morbidity*	324 (57.3)
COPD:	332 (58.8)
GOLD I + II	291(51.5)
GOLD III + IV	41 (7.3)
Cigarette smoking:	
current	152 (45.4)
ex-smoker	162 (48.8)
never-smoker	16 (4.8)
Mean pack year history (min-max)	32.8 (1-125)
Any history of cancer	234 (41.4)
History of more than one cancer	34 (6.0)
History of cancer >1 and < 5 years	62 (11.6)
History of cancer < 1 year	74 (13.1)
Symptoms	
Any	387 (68.5)
None or nonspecific	218 (38.6)
RODP inclusion based on:	
Chest X-ray	413 (73.5)
CT-scan	144 (52.5)
PET-scan	6 (1.1)

TABLE 2 **Patient characteristics**

Numbers (%) or means (SD); ECOG: Eastern Cooperative Oncology Group; COPD: Chronic Obstructive Pulmonary Disease; GOLD: Global initiative on Obstructive Lung Disease; GP: General Practitioner; * non-pulmonary co-morbidity requiring treatment or follow-up by specialist physician in the last 5 years.

		TOTAL GROUP	LUNG CANCER GROUP
N		565	290
Diagnosis:			
NSCLC		261 (46.2)	261 (90.0)
SCLC		26 (4.6)	26 (9.0)
Synchronous NSCLC & SCLC		3 (0.5)	3 (1.0)
Benign		115 (20.3)	
Metastasis		43 (7.6)	
Mesothelioma		4 (0.7)	
Thymoma		1 (0.2)	
No tissue diagnosis		112 (19.8)	
most likely benign		82 (14.5)	
most likely cancer		28 (5.0)	
patient died before diagnosis		2 (0.4)	
Underwent bronchoscopy		533 (94.3)	279 (96.2)
Diagnosis by RODP, no other procedures		240 (42.5)	165 (56.8)
Pathology diagnosis by other procedure		207 (36.6)	125 (43.3)
RODP-cytology	(% of final diagnosis)*:		
NSCLC	(NSCLC)		127 (43.8)
Non-malignant	(NSCLC)		124 (42.8)
SCLC	(SCLC)		13 (4.5)
Non-malignant	(SCLC)		11 (3.8)
NSCLC	(SCLC)		2 (0.7)
SCLC	(NSCLC)		2 (0.7)
Lung cancer therapy:	Curative		151 (52.1)
	Palliative		85 (29.3)
	BSC		54 (18.6)

TABLE 3 **RODP diagnostic results (all patients), numbers of patients (%)**

NSCLC: Non Small Cell Lung Cancer; SCLC: Small Cell Lung Cancer; BSC: best supportive care.
*Of the 3 SCLC/NSCLC synchronous tumours, cytology diagnosis was correct in 1, yielded squamous cell carcinoma in another, and non-malignant in the last.

TIMELINESS – ANALYSIS OF DELAYS

Thirteen patients with exceptionally long diagnostic delays were excluded for delay analysis for the following reasons: solitary pulmonary nodules assigned to routine follow-up showing growth after more than 1 year (after re-evaluation malignancy (n=7, mean interval 385 days) and atypical mycobacteriosis (n=1, 126 days)), the necessity to perform surgery for other cancers prior to starting the further diagnostic work-up for the pulmonary lesion (n=3, mean 58 days), or postponement of procedures by the patient (n=2, mean 65 days).

Results of the delay analysis for the remaining 552 patients are summarized in Table 4. Within first line delay, median patient delay was 19 days for all, and 22 days for lung cancer patients. GP delay stretched 15 days and 18 days respectively. Median referral delay of the RODP was 7 calendar days (5 working days), 80% of all patients were seen by a chest physician within 12 calendar days (or 8 working days since the RODP was fixed to Wednesdays and Thursdays). Patient and referral delay were not statistically different between GP and specialist referred groups. Median diagnostic delay was 2 days, 80% of patients were diagnosed within 20.8 days. Lung cancer patients reviewed separately had equal diagnostic delay with 80% diagnosed within 20.0 days; if these patients required surgical staging by means of mediastinoscopy, 80% was diagnosed and staged within 29 days. Median diagnostic delay was significantly longer for specialist referred patients (6 days (IQR 1-20)) compared to GP referred patients (1 day (IQR 1-6)), and also when CT guided needle biopsies or mediastinoscopy were required, but not in case of EUS, cerebral CT or MRI.

Median therapeutic delay for curatively intended (stage I-IIIa) and palliative (stage IIIB-IV) therapy was 18 (IQR 0-25) days and 21.5 (IQR 12-33.5) days, respectively. Eighty percent started palliative therapy within 40.0 days and curatively intended therapy within 27.2 days, 31.4 days if a mediastinoscopy was required. The 26 patients diagnosed with small-cell lung cancer (SCLC) had a significantly shorter median therapeutic delay of 7.5 days (IQR 4.75-12.25), as compared to 20 days (IQR 6-28) for NSCLC (p=0.003). In our study the interval of 'diagnostic + therapeutic delay' spanned a median 26 (IQR 18-40, n 252) days; 80% of patients started therapy within 39 days. The 143 patients with curatively intended therapy for which we could calculate this interval had similar results (25 (IQR 19-35) days, 80% within 39 days, 41 days if mediastinoscopy was needed).

		ALL PATIENTS (N=552)		LUNG CANCER PATIENTS (N=280)
		N	Median (IQR)	N	Median (IQR)
Patient delay		107	19.0 (4-52)	63	22.0 (7-78)
GP delay		120	15.0 (6-35.5)	69	18.0 (6-46)
First Line delay		211	54.0 (20-104)	130	60.0 (24.75-119.5)
Referral delay		473	7.0 (5-9)	236	7.0 (5-9)
Diagnostic delay		450	2.0 (1-19)	280	2.0 (1-17.5)
Diagnostic + Therapeutic delay*				215	25.0 (18.0-39.0)
Therapeutic delay	Any			215	19.0 (6.5-27)
	Curative therapy			143	18.0 (0-25)
	Palliative therapy			72	21.5 (12-33.5)
Second Line delay				219	36.0 (26-46)

TABLE 4 **Timeliness: delays in days**

N = patients with known dates, see figure 1. *this interval has been used by some other studies to define 'diagnostic delay'.

TIMELINESS - LUNG CANCER STAGE AND OUTCOME

Clinical and pathological lung cancer stage for all NSCLC patients and their survival are presented in Table 5. Between GP and specialist referred groups, the only statistically significant difference was seen in the incidence of clinical stage Ia (4.3% versus 13.8%, $p < 0.05$) and pathological stage Ib (10.1% versus 33.3%). When all defined delays were analyzed per stage, diagnostic delay was inversely related to clinical stage (Kruskal-Wallis, p=0.008), while therapeutic delay showed the opposite being longer for higher stage patients (p=0.001). However, when patients with a diagnostic thoracotomy (with longer diagnostic and short therapeutic delay) were excluded, none of the delays showed a relation with clinical stage and no specific delay was related with pathological stage. Limiting the analysis to GP referred patients did not change the outcome.

Median overall survival for all NSCLC patients was 17 months (95% CI 29.5-41.3). When survival time was analyzed per delay, the Cox proportional hazards model showed no relation between any delay and survival.

STAGE	CLINICAL (n=261)	MEDIAN SURVIVAL	PATHOLOGICAL (n=100)	MEDIAN SURVIVAL
Ia	40 (15.3)	45	35	*
Ib	43 (16.5)	35	26	110
IIa	3 (1.1)	32	2	6
IIb	6 (2.3)	17	17	35
IIIa	48 (18.4)	12	10	19
IIIb	43 (16.5)	16	7	10
IV	78 (29.9)	6	3	28
Overall		17		53

TABLE 5 Survival per clinical and pathological lung cancer stage

Patient numbers (%) and median survival per stage (months) for the 261 NSCLC patients, * median survival was not reached.

SYMPTOMS, DIAGNOSTIC PERFORMANCE OF RODP BRONCHOSCOPY AND DIFFERENCES BY REFERRAL

The most frequent single presenting symptom was cough (22.4%), followed by hemoptysis (8.5%), pain (5.8%), dyspnea (5.3%) and fatigue (4.1%). Considerably more patients (55.8%) in the specialist-referred group were asymptomatic or had non-specific symptoms like fatigue or weight loss compared to the GP referred group (9.6%, $p<0.05$). As presenting symptom, only hemoptysis was associated with shorter median patient, GP or referral delay (4, 6 and 6 days, respectively, $p< 0.05$).

Thirty two of the 565 patients did not undergo the RODP bronchoscopy for various reasons (most often exclusion of malignancy after reviewing the FGD-PET/CT, 28 cases). In the remaining 533 patients, RODP bronchoscopy tissue samples rendered a cytological or histological diagnosis in 240 (42.5%) patients and in 165 of the 279 lung cancer patients that underwent bronchoscopy (59.1%). Despite the fact that 170 lung cancer patients (60.9%) had no visible endobronchial abnormalities, cytological examination did yield malignant cells in 67 of these cases (39.4%). In 135 (48.4%) of the 279 lung cancer patients, the initial cytology samples rendered a benign diagnosis due to sampling error. For the remaining 144 lung cancer patients, RODP cytological diagnosis was accurate when compared to the bronchoscopy histology results that were reported in the same week in 140 cases (97.2%).

Specialist compared to GP referred patients were less frequently diagnosed with primary lung cancer but more often with pulmonary metastasis (45.4%

versus 60.6 % and 9.6% versus 4.3%, respectively, both p< 0.05). GP-referred patients received an accurate diagnosis based on the RODP findings alone in 58.2% of cases compared to 33.5% in the specialist referred patient group, which required significantly more often additional diagnostic procedures to confirm the diagnosis (p< 0.05).

DISCUSSION

Although FDG-PET/CT is considered the best imaging technique in lung cancer staging[26,27] and feasibility of FDG-PET/CT in an RODP setting has already been shown[29] it has not been used as standard care in RODP studies published so far. This is the first study to demonstrate that an RODP for suspected lung cancer patients including routine FDG-PET/CT is a feasible and accurate logistical outpatient program capable of reducing median diagnostic delay to only 2 days.

These findings are relevant since this may reduce the time of exposure to high distress levels awaiting a possible diagnosis of a cancer[12] with high incidence rates.[1] Moreover, the results show that timely care was achieved by a relatively simple program that can be instituted in any medical centre with access to an FGD-PET/CT. Other studies have demonstrated improvement of timeliness by a two-stop rapid pathway[24,25] or a centrally coordinated algorithm[23] yet not to this extent.

TIMELINESS

Timeliness of lung cancer care starts with timely recognition of symptoms by patients themselves, which is often inadequate or delayed.[30,31] This is illustrated by the fact that the median first line delay in our study lasted almost 2 months although the 19 day median patient delay was in the lower range of other values reported (median 14-42 days).[4,32-36] The patient samples for which patient and GP delay could be calculated were different and much smaller than for first line delay (n=107, 120, and 211, respectively, table 4) so whether patient or GP delay is the bigger factor within first line delay remains unclear. Furthermore, we could not correct for factors influencing whether and when patients actually seek help.[37]

Referral delay in our study was 7 days and, despite the fixed weekly schedule, shorter than most reported referral delays (ranging 7-12 days).[11] Only the UK study by Devbhandari et al. reported a shorter 1 day (IQR 0-5) median referral

delay.[38] The RODP however demonstrated the strongest effect on diagnostic and second line delay; the median diagnostic delay of 2 days for both the total group and lung cancer patients specifically is substantially shorter than reported delays of 7-37 days in other studies.[3,4,19,23-35,38,39] Obviously, for most patients the diagnostic episode was not completed yet and many patients required additional interventions to define disease stage. Nevertheless, the RODP succeeded to maintain timeliness compared to other studies since the median 'diagnostic + therapeutic delay' interval spanned 26 days (table 4) and 80% of patients started therapy within 39 days. Similarly defined reported median delays range 31-104 days.[20,32,40,41] An RODP by definition does not specifically reduce therapeutic delay. However, the median therapeutic delay of 19 days is in the low range of other studies reported (12.5-52 days).[1,42,43] On the other hand, lung cancer patients requiring surgical therapy had a longer median therapeutic delay of 34 days (IQR 27-43, n=87 patients).

Only 2 other studies specifically report on RODPs and delay in lung cancer; both were performed in an era when FDG-PET/CT was not yet available. Laroche et al.[24] reported on a two stop investigation service reducing the median consultation to surgery interval by 50% to 5 weeks; however only 9% of patients had to undergo further staging procedures. The numerically smaller study by Murray et al.[25] comprised all therapy types and showed this interval reduced to even 3 weeks, but did not report on further staging. Delay types other than consultation to therapy were not investigated in both studies.

DELAYS AND OUTCOME

We found no clinically relevant differences in any delay in patients diagnosed with either locoregional (stage Ia-IIIa) or advanced disease (stage IIIb-IV), except for shorter diagnostic delay in lower clinical stage patients and longer therapeutic delay in higher clinical stage patients. This difference may be explained by the 19 patients that underwent diagnostic thoracotomy for a suspicious nodule. Fifteen of these were diagnosed with NSCLC in a low disease stage (mostly Ia) with by our definition a long diagnostic delay (median 29.0 days) and short therapeutic delay (0 days). After exclusion of this category no differences in disease stage or survival could be attributed to any delay. The influence of delays on stage and survival is under debate as both positive[5,6,44] and negative effects[4,40,45,46] have been reported; our findings are in line with studies showing absence of any effect.[2,33,47-49] The fact that in our study, compared to the studies mentioned, more patients were referred by

specialists was not a factor: limitation of the analysis to GP referred patients (who more frequently had symptoms) did not change outcome.

COMPARISON WITH GUIDELINE RECOMMENDATIONS

Our median referral delay of 7 days complies with BTS, RAND corporation and American College of Chest Physicians (ACCP) guideline limits,[7-9] but is 4 days longer than recommended in the Dutch guideline.[10] This may be explained by the restriction of the RODP to fixed days in our center (Wednesday and Thursday) limiting instant access. However, longer referral delay was compensated by shorter diagnostic delay. The RODP was not specifically designed to reduce therapeutic delay, but adhered to BTS and RAND guidelines. The Dutch guideline defines therapeutic delay as the time elapsing between the decision to treat and actual start of treatment rather than the time between diagnosis and treatment in our study. Its aim is to start treatment for at least 80% of patients within 2 weeks, after a maximum diagnostic interval of 3 weeks (or 5 weeks if mediastinoscopy is required). For a more accurate comparison with this guideline, we calculated the interval between the second RODP day and start of therapy. Of the curatively treated patients 80% started therapy within 34 days, 41 days if mediastinoscopy was needed. However 80% of palliative treatment started within 42 days, which exceeds the guideline limit for palliative treatment (80% within 24 days). Whether this difference is justified can be debated, as large numbers of patients do not require immediate palliative therapy and the detrimental effect of a 2 week delay on start of palliative therapy on survival has never been established.

DIAGNOSTIC PERFORMANCE

The long diagnostic delay we found for a number of patients confirms that for a subgroup of patients it may be difficult to obtain a tissue diagnosis. This was illustrated by the fact that CT guided needle biopsy and mediastinoscopy significantly increased diagnostic delays in our study. Especially specialist referred patients needed more diagnostic procedures, probably due to the fact that these patients presented with smaller lesions which frequently require multiple diagnostic procedures. Local availability of diagnostic and staging techniques will influence timeliness particularly for this more difficult to diagnose subgroup, yielding opportunities for improvement.

In the RODP, bronchoscopy was used for nearly all patients, irrespective of type, localization or visibility of the intrapulmonary lesions. This might ex-

plain both the relatively high number of non-diagnostic pathology results and the mismatch of around half of the initial cytological diagnosis compared to the final lung cancer diagnosis. However, retrospectively this led to treatment strategy change in only 4 cases in which NSCLC had been mistaken for SCLC and vice versa; malignant cytology results were therefore very accurate. Bronchoscopic cytology yield may be improved by ultrasound guided biopsies or EBUS[50,51] but these techniques were not routinely used in the RODP between 1999 and 2009.

LIMITATIONS

This study has some limitations. Data were obtained from patient records and GP referral letters making them susceptible to recall bias and underreporting, and some of the retrospective data are incomplete, limiting the quality of conclusions on delays. Furthermore, this is a single (tertiary care) centre study which can lead to a certain referral bias. The fact that the Dutch oncology health care system, in contrast to e.g. the United States[42] has public hospitals only, rules out health care system bias. Finally, one fifth of all patients were finally diagnosed with benign disease: Although common in clinical practice, it is a confounding factor when comparing results with other studies. On the other hand, suspected patients eventually not diagnosed with cancer have similar emotional distress of the diagnostic episode[16,17,52] and may therefore equally benefit from a rapid diagnosis.

CONCLUSION

Despite not being influenced by an RODP, awareness among patients needs to be improved since patient delay is the largest of all defined delays. However, an RODP including FDG/PET-CT is a valid instrument to achieve, for the majority of suspected lung cancer patients, care that is both more timely than the shortest guideline limits, and more timely compared to what has been published so far.

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3

HIGH PERFORMANCE OF ^{18}F-FLUORODEOXYGLUCOSE POSITRON EMISSION TOMOGRAPHY AND CONTRAST-ENHANCED CT IN A RAPID OUTPATIENT DIAGNOSTIC PROGRAM FOR PATIENTS WITH SUSPECTED LUNG CANCER

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ABSTRACT

BACKGROUND: The diagnostic evaluation of patients presenting with possible lung cancer is often complex and time consuming. A Rapid Outpatient Diagnostic Program (RODP) including ^{18}F-fluorodeoxy-glucose-Positron Emission Tomography (FDG-PET) and contrast enhanced Computed Tomography (CT) as a routine diagnostic tool may improve timeliness, however the diagnostic performance of such RODP combined approach remains unclear.

OBJECTIVES: We evaluated timeliness of care and diagnostic performance of FDG-PET and contrast enhanced CT (FDG-PET/CT) in an RODP for all patients referred with a chest X-ray suspicious of lung cancer.

METHODS: Charts of patients referred to the two-day RODP of our tertiary care university clinic after an abnormal chest X-ray between 1999 and 2009 were reviewed. Between 1999 and 2005 co-registered FDG-PET and CT imaging took place; from September 2005 onwards a hybrid system was used. We analyzed timeliness of care and diagnostic performance of FDG-PET/CT to differentiate malignant from benign lesions.

RESULTS: In 386 patients available for analysis, 260 were diagnosed lung cancer, 23 had another type of malignancy, 78 had certain benign disease, and in 45 the diagnosis was not pathologically confirmed but a median 24.5 months follow up confirmed a benign outcome. Sensitivity, specificity, negative predictive value, positive predictive value and accuracy of FDG-PET/CT to differentiate lung cancer from benign disease were 97.7%, 60.2%, 92.5%, 84.0% and 85.8% respectively. Lung cancer patients had a median referral, diagnostic and therapeutic delay of 7, 2 and 19 days, respectively.

CONCLUSIONS: FDG-PET/CT in an RODP setting for suspected lung cancer has high performance in detecting cancer and facilitates timely care.

INTRODUCTION

Lung cancer is the leading cause of cancer-related death in both men and women. The 5-year survival rate in the western world of the various types of

lung cancer combined is approximately 16% and has not significantly improved in the last decade,[1] despite constant new diagnostic and therapeutic developments. Obtaining a correct lung cancer diagnosis and stage is complex and may require multiple modalities such as ^{18}F-fluorodeoxy-glucose-Positron Emission Tomography (FDG-PET), Computed Tomography (CT), bronchoscopy, Endoscopic Ultrasound (EUS), CT-guided biopsy and sometimes many more. In clinical practice this has a tendency to negatively influence timeliness of lung cancer care. Many interventions have been reported to improve diagnostic delay, such as implementation of urgent referral guidelines,[2] multidisciplinary meetings,[3-5] nurse-led care[6] or two-stop pathways.[7,8] The latter seems to have the most success in improving timeliness of care.[9] From a patient's point of view, shortening diagnostic delay can reduce emotional distress in suspected cancer.[10-13] Moreover, although many patients suspected of cancer eventually have a benign outcome they do share the distress of diagnostic evaluation.

In an effort to improve the rapidity of the diagnostic process, a two-day Rapid Outpatient Diagnostic Program (RODP) for patients with a radiological suspicion of lung cancer was implemented in the Radboud University Nijmegen Medical Centre (RUNMC) in 1999. As a first diagnostic step in all patients we implemented in this RODP both FDG-PET and contrast enhanced CT (FDG-PET/CT), a novel combination at that time that proved to be a superior imaging technique in lung cancer staging[14-17] compared to either FDG-PET with low dose CT or CT alone. Aukema et al. have already demonstrated in a modest sample size that FDG-PET/CT within an RODP was feasible with good negative predictive value (NPV) of 92% and positive predictive value (PPV) of 77%.[18] To our knowledge, the effect of an RODP including FDG-PET/CT on timeliness of care has not been described yet. The aim of this study was to assess the diagnostic performance of FDG-PET/CT as a first-line diagnostic tool and the effect on timeliness of care in patients referred to our RODP based on an abnormal chest X-ray.

MATERIALS AND METHODS

PATIENTS

A retrospective chart review was conducted in all 570 consecutive patients referred to the RODP between August 1999 and April 2009, after regional ethics committee approval. We selected all cases where referral was based on a chest X-ray, to prevent bias of referring highly suspected patients and to fa-

Day 1 (Wednesday)
Laboratory investigation, electrocardiogram
^{18}FDG injection
^{18}FDG-PET/CT
Multidisciplinary evaluation of PET/CT
Pulmonary function testing
Chest physician visit, physical examination, report of PET/CT results (first 2 patients)
Day 2 (Thursday)
Physician visit, physical examination, report of PET/CT results (second 2 patients)
Bronchoscopy
Report of cytology results

TABLE 1 **RODP schedule**

cilitate comparison with the usual referral pattern. On referral, outpatients with a radiological suspicion of lung cancer (e.g. a nodule, mass, hilar enlargement, widened mediastinum) without clinical need for hospitalization or evident stage IV disease were selected by a respiratory physician to enter the RODP. Patients then underwent a full diagnostic workup (table 1) in two-days comprising blood analysis, FDG-PET scanning, diagnostic CT-scanning, electrocardiography, pulmonary physician consultation, pulmonary function testing on the first day, followed by bronchoscopy and disclosure of the cytology results on the second. In case of benign results on FDG-PET/CT, bronchoscopy was cancelled. If further diagnostic or staging procedures were necessary, they were performed in a regular setting outside the RODP.

FDG-PET/CT

All patients underwent a whole body FDG-PET. Prior to ^{18}F-fluorodeoxyglucose (FDG) injection, patients fasted for at least six hours. Intake of sugar-free liquids was permitted. Patients were hydrated with 500 ml of water immediately prior to the procedure and 60 minutes after intravenous injection of approximately 250 MBq FDG (Covidien, Petten, The Netherlands) and 10 mg furosemide. Images were acquired from the area between the proximal femora to the base of the skull. Until September 2005, PET scans were acquired on an ECAT-EXACT full ring PET-scanner (Siemens/CTI, Knoxville, TN, USA) using three-dimensional emission for 10 min per bed position and employ-

ing attenuation correction based on two-dimensional germanium-68 transmission images for 2 min per bed position. PET scans were reconstructed using an iterative two-dimensional ordered subset expectation maximization (OSEM) algorithm using two iterations, eight subsets and a three-dimensional Gaussian filter of 5 mm. From September 2005 onwards, PET scans were acquired with a hybrid PET/CT scanner (Biograph Duo, Siemens Medical Solutions USA, Inc.) containing a 2-slice CT scanner. A low-dose CT scan for localization and attenuation-correction purposes was acquired in the caudocranial direction. Scanning parameters included 40 mA.s (50 mA.s for patient weight >100 kg and 60 mA.s for >120 kg), 130 kV, 5 mm slice collimation, 0.8 s rotation time, and pitch of 1.5, reconstructed to 3 mm slices for smooth coronal representation. Low dose CT scans were acquired during timed unforced expiration breath-hold. For PET, a 3-dimensional whole body emission scan was acquired during free breathing. The acquisition time per bed position was 4 minutes for emission only.

A full-dose CT scan with contrast enhancement of thorax and liver for diagnostic purposes was acquired in all patients. Using a dual slice spiral CT scanner thoracic images were acquired in a craniocaudal direction after a delay of 40 s after intravenous contrast injection with 100ml Optiray 300 (Covidien, Hazelwood, MO, USA) using care dose referenced at 80 mA.s with the following parameters, 110 kV, CTDI volume 5.36 mGy, rotation time 0.8, slice 3.0 mm with a pitch of 1.5 mm during a single breath hold. Scanning parameters for liver imaging were care dose referenced at 80 mA.s, 130 kV, CTDI volume 8.64 mGy, rotation time 0.8, slice 3.0 mm with a pitch of 1.5 mm during breath hold. A delay of 12 s was set to automatically shift to the abdominal imaging.

All FDG-PET/CT images were reviewed prior to bronchoscopy in a joint-reading meeting in presence of a nuclear medicine physician, a radiologist and pulmonary physician. If FDG uptake was present, reports were reviewed to determine whether extrathoracic metastases or synchronous extrathoracic tumours were detectable in the above defined areas scanned by diagnostic CT. If FDG uptake was absent, CT findings were reviewed and defined non-malignant in case of sclerotic bone lesions, nodules with benign calcification pattern, pleural plaques, infiltrates, or mediastinal bulging by goitre, mediastinal fat, or cardiomegaly.

STATISTICAL ANALYSIS

Descriptive statistics were used to summarize the demographic data collected. The mean and standard deviation (SD) for normally distributed continuous variables, and median and interquartile range (IQR) for variables that are not normally distributed, were reported. PPV and NPV were calculated. Different delays were defined as follows: Referral delay as the time between referral (written or by phone) and first RODP day, diagnostic delay as the time between first RODP day and date of final (accurate) diagnosis, therapeutic delay as the time between diagnosis and start of treatment. All time intervals were calculated in calendar days (including weekend and holidays) if both defining dates had been recorded. All data were analyzed using the SPSS 16.0 statistical software program (SPSS, Chicago, IL).

RESULTS

DEMOGRAPHIC DATA AND CLINICAL CHARACTERISTICS

A flowchart of the RODP patients included in the analysis is shown in figure 1. Of those evaluated in the RODP between August 1999 and April 2009 we found 565 patients with available charts, of which 386 patients were suitable for analysis and 184 were excluded. Referral based on abnormal radiological investigation other than a chest x-ray was the most frequent reason for exclusion.

Most patients were male (n=258, 66.8%) and mean age was 64.3 years (SD 11.0). Referral was initiated by a GP in 194 patients (50.3%), the remainder 192 by a specialist consultant. The majority of patients (n= 367, 94.0%) had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, and 37 patients (9.6%) suffered from diabetes mellitus. Cytological or histological results are described in table 2.

Pathology diagnosis was obtained by RODP bronchoscopy in 196 cases (50.8%). Other diagnostic procedures were CT-guided needle biopsy (23, 6.0%), thoracotomy or thoracoscopic surgery (73, 18.9%), mediastinoscopy (24, 6.2%), EUS (10, 2.6%) or a second bronchoscopy (5, 1.3%). In 236 patients (61.1%) a final diagnosis of lung cancer was made, all subtypes considered (Non-Small Cell Lung Cancer (NSCLC), Small Cell Lung Cancer (SCLC) or both). Twenty seven patients (7.0%) were diagnosed with malignant pleural mesothelioma or pulmonary metastases of a non-pulmonary tumour. Seventy eight patients (20.2%) had a certain benign diagnosis (predominantly

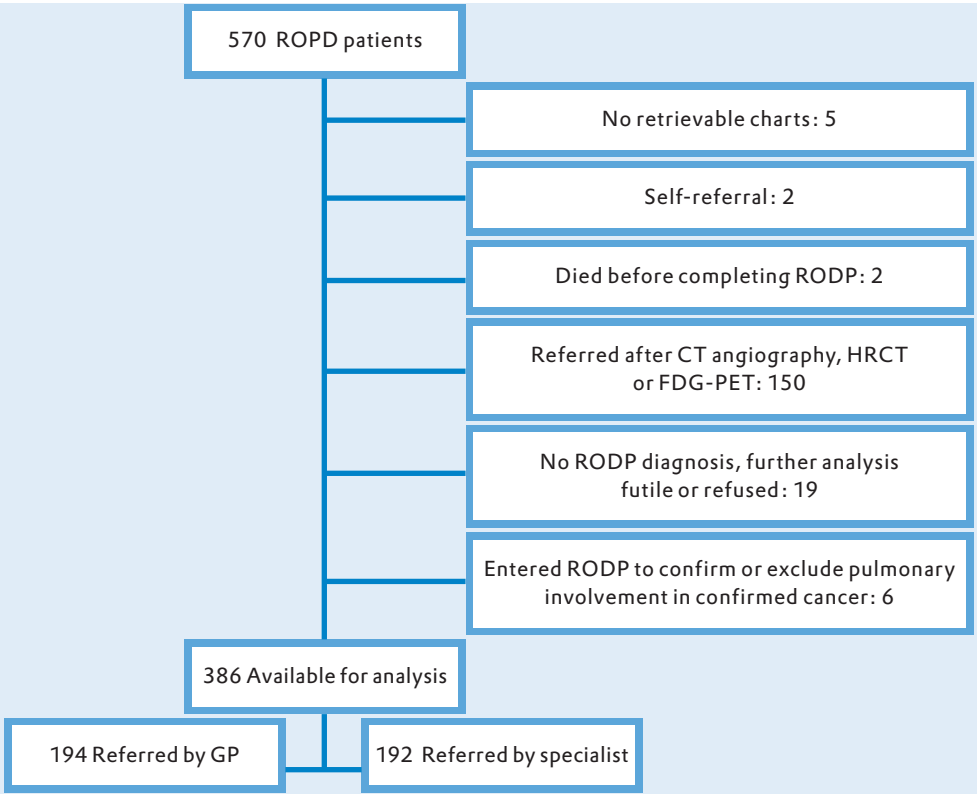

FIGURE 1 **Flow chart of the RODP patients**
HRCT: High resolution CT-scan

infectious, post-infectious or granulomatous abnormalities). In 45 patients (11.7 %), no definite pathological diagnosis could be established but according to the medical charts no malignancies were reported during a median 24.5 months (IQR 17.0-48.5) follow up in any of them.

Table 3 describes the clinical and pathological disease stages (according to the TNM6[19]) and shows that 122 lung cancer patients (51.7%) had clinically advanced (stage IIIb or IV) disease.

DIAGNOSTIC PERFORMANCE OF FDG-PET/CT AS A FIRST LINE DIAGNOSTIC TOOL

Performance of FDG-PET/CT was assessed in a cross table for all patients (table 4). For diagnosis of malignancy, sensitivity was 97.7% (95% CI 94.9-99.1%), specificity 60.2% (50.9-68.8%), negative predictive value 92.5% (83.8-96.9%) and positive predictive value 84.0% (79.3-87.8%). Accuracy, defined as

PATHOLOGY DIAGNOSIS	N (%)
Lung Cancer (all subtypes)	236 (61.1)
NSCLC	212 (54.9)
Adenocarcinoma	96 (24.9)
BAC	2 (0.5)
Squamous cell carcinoma	86 (22.3)
Large cell carcinoma NOS	12 (3.1)
Large cell neuro-endocrine carcinoma	4 (1.0)
Undifferentiated NSCLC	4 (1.0)
Mixed NSCLC subtypes	8 (2.1)
SCLC	2 (0.5)
Mixed NSCLC/SCLC	22 (5.7)
Pulmonary metastasis of other cancer	23 (6.0)
Mesothelioma	4 (1.0)
Benign	78 (20.0)
No diagnosis, benign at follow up	45 (11.7)

TABLE 2 **Cytological or histological diagnosis of all 386 evaluable patients**

NSCLC: Non-Small Cell Lung Carcinoma; BAC: Bronchoalveolar Carcinoma; NOS: not otherwise specified; SCLC: Small Cell Lung Carcinoma.

NSCLC and SCLC Stage		N (%)
Clinical Stage	Ia	26 (11.0)
(n = 236)	Ib	31 (13.1)
	IIa	2 (0.8)
	IIb	7 (3.0)
	IIIa	46 (19.5)
	IIIb	42 (17.8)
	IV	80 (33.9)
	Double tumor	2 (0.8)
Pathological Stage	Ia	24 (28.9)
(n = 83)	Ib	24 (28.9)
	IIa	1 (1.2)
	IIb	14 (16.9)
	IIIa	8 (9.6)
	IIIb	5 (6.0)
	IV	3 (3.6)
	Double tumor	3 (3.6)
pNx (incomplete pN stage)		1 (1.2)

TABLE 3 **Clinical and pathological disease stage**

Patients with no pathology confirmation before surgery were staged based on imaging and added to the clinical stage category.

	MALIGNANT	BENIGN	TOTAL
PET/CT Positive	257	49	306
PET/CT Negative	6	74	80
Total	263	123	386

TABLE 4 **Patient numbers of FDG-PET/CT result and final diagnosis of malignancy**

the proportion of true results, was 85.8% (81.4-90.0%). Performances of hybrid FDG-PET/CT and separate FDG-PET and CT (before and after September 2005 respectively) were not statistically different.

We found 19 cases (4.9%) where suspected lesions showed radiologically benign anomalies on CT scan and were FDG-PET negative (specified in table 5). In another 13 cases (3.1%) no abnormalities were found at all on FDG-PET or CT. In contrast, FDG-PET showed metastatic disease in 26 (6.7%) patients (10.8% in the lung cancer patient sample) and a synchronous tumour of other cancer type in 9 patients (2.3% of the total patient group), outside the volume scanned by diagnostic CT. Finally, there were 6 false negative cases, all with different histology: Adenocarcinoma (7mm), bronchoalveolar carcinoma (5mm), squamous cell carcinoma (29mm), malignant pleural mesothelioma (pleural fluid only), pulmonary metastasis of ovarian cancer (multiple nodules, largest 12 mm) and adenoid cystic carcinoma (multiple nodules ranging 15-23 mm).

TOTAL GROUP	386
Definite benign CT findings	32 (8.3)
CT without abnormalities	13 (3.4)
Clearly benign lesion on CT alone	19 (4.9)
Sclerotic bone lesion	7
Calcified nodule	3
Pleural plaque	3
Post-infectious infiltrate	3
Mediastinal mass (goitre, fat, cardiomegaly)	3

TABLE 5 **CT characteristics in patients with CT-confirmed benign definite findings**

DELAYS

For the total patient group, the median referral delay was 7 days (IQR 5-10), and median diagnostic delay 1 day (IQR 1-15). For patients ultimately diagnosed with lung cancer (NSCLC and SCLC), median referral delay was also 7 days (IQR 5-9), median diagnostic delay 2 days (IQR 1-17), median therapeutic delay 19 days (IQR 7-28), The median interval between RODP and all therapies spanned 25 days (IQR 18 -39): 23 days (IQR 18-32) for surgery, 27 days (IQR 14-41) for chemotherapy and 28 days (IQR 20-50) for radiotherapy.

DISCUSSION

This is so far the largest study evaluating FDG-PET/CT as a frontline diagnostic tool in an RODP setting for suspected lung cancer. We demonstrate that an RODP integrating FDG-PET/CT provides not only excellent diagnostic performance in detecting lung cancer in patients referred with an abnormal chest X-ray, but also minimizes diagnostic delay. RODPs have shown to successfully reduce the diagnostic delay in 2 other studies that evaluated a two stop service in suspected lung cancer and report a presentation to surgery delay of 5 weeks[7] and presentation to start of any treatment delay of 3 weeks,[8] respectively. These studies were however performed in an era when FDG-PET was not yet, in contrast with today, a standard imaging tool in the diagnostic work-up of lung cancer, with superior imaging capabilities.[14-17] One would expect the combination of an RODP with FDG-PET/CT to improve the overall diagnostic work-up quality in patients with suspected lung cancer. Our results confirm these expectations: with the demonstrated schedule of our RODP, the median time to establish a diagnosis was only one day, and treatment was initiated after a median 25 days. Both these diagnostic and therapeutic delays were shorter than the median 7-37 days for diagnostic[2,5,20-28] and 31-104 days for therapeutic delay[4,23,29,30] reported by others without an RODP.

Besides timeliness, our RODP including FDG-PET/CT had an excellent diagnostic performance with high sensitivity in diagnosing malignancy (97.7%). We herewith confirm the earlier results described by Aukema et al. showing good performance of RODP using FDG-PET/CT in diagnosing pulmonary malignancy. In 114 patients referred with an abnormal chest X-ray, they demonstrated similar sensitivity, specificity and accuracy for diagnosing malignancy (97%, 56% and 90%, respectively) despite a higher pre-test probability

of lung cancer (75% versus 61% in the present study). This difference might be explained by a different referral pattern to their centre with a specialized reference oncology status.[18] Specificity was relatively lower in both Aukema's and our study (56 and 60 %, respectively) and can be explained by the inclusion of patients on the basis of an abnormal chest X-ray: Studies evaluating the accuracy of FGD-PET/CT usually include patients with solitary pulmonary nodules on a CT scan, inherently lowering the probability of infectious or inflammatory disease compared to our selection of patients. FDG-PET/CT then demonstrates equal median sensitivity (97.0%, range 83-100%) but higher specificity (77.8%).[31]

The downside of incorporating both FDG-PET and a diagnostic CT in an RODP setting as a first line diagnostic tool for all patients referred with an abnormal chest X-ray is that retrospectively in some cases additional imaging with FDG-PET to exclude malignancy might not have been required: In 32 patients (8.3%) malignancy might have been excluded on CT alone as the lesions showed typical benign characteristics. This number is in line with the study by Aukema et al.[18] reporting around 10% abnormalities that could have been judged benign on CT alone (asbestos related benign pleural abnormality and residual abnormality after inflammation). However whether there is actually 'diagnostic overuse' in these cases cannot be judged retrospectively, as in both Aukema's and our study FDG-PET and CT images were jointly read. In contrast, in 35 patients (9.1%) FDG-PET/CT had significant added value as it detected metastases or synchronous tumours outside the chest that would not have been detected by CT alone. This result is in line with prior prospective studies detecting distant metastases in 6-18% of potentially curable lung cancer patients.[15,16, 32-34] FDG-PET/CT furthermore correctly suggested other than lung cancers in 9 RODP patients (2.3%) which is in line with other studies detecting unexpected synchronous tumors in 1.1-3.3%.[35,36] Whether detecting unexpected metastatic disease and synchronous tumours by FDG-PET/CT in the RODP counterbalances performing FDG-PET in case of radiologically benign lesions, cannot be answered by our study; this should involve comparison of other factors such as cost-effectiveness[37] and the prevention of futile thoracotomies.[15,35,38] Furthermore there might be a benefit of an RODP in quickly ruling out the possibility of cancer and reducing distress levels[13] that were raised by the chest X-ray. To address these issues, we have performed the multicenter PENELOPE study (Pulmonary Evaluation of NEoplastic Lesions in Outpatients and Psychological Effects) evaluating distress and quality of life in suspected lung cancer patients dur-

ing and after their RODP compared to regular stepwise outpatient evaluation. We expect to publish results in 2013.

CONCLUSION

Our findings add to the limited knowledge available on rapid outpatient programs, despite growing interest on performance of these programs and possible effects on patient distress. Our study shows that in patients referred with an abnormal chest X-ray, an RODP integrating FDG-PET/CT provides excellent diagnostic performance in detecting lung cancer with minimized diagnostic delay.

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4

THE FASTER THE BETTER? A SYSTEMATIC REVIEW ON DISTRESS IN THE DIAGNOSTIC PHASE OF SUSPECTED CANCER, AND THE INFLUENCE OF RAPID DIAGNOSTIC PATHWAYS

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ABSTRACT

OBJECTIVE: To perform a systematic review of articles published in the last 25 years on prevalence and course of distress and quality of life surrounding the diagnostic process of suspected cancer, and the influence of rapid diagnostic programs.

METHODS: Twenty-three articles were identified via Pubmed, PsycINFO, and reference lists of articles. Except for three randomized clinical trials and one case control study all studies were uncontrolled cohort studies.

RESULTS: Most studies involved patients with suspected breast cancer and therefore had a sex selection bias. Four studies on the effect of rapid outpatient diagnostic programs were found. Studies showed very high prevalence of anxiety, decreasing in case of a benign diagnosis but increasing or sustaining in patients waiting for results or after cancer diagnosis though not significantly more in rapid programs. Quality of life was low and showed varying patterns.

CONCLUSIONS: Distress in the diagnostic phase of cancer is a major problem and the rapid decrease of anxiety in patients eventually not diagnosed with cancer suggests a benefit of rapid diagnostic programs. The available evidence however is limited and shows some inconsistencies. Studies differ in subjects, objective and are limited by quality and quantity. Conflicting results prohibit a conclusion on patients ultimately diagnosed with cancer.

INTRODUCTION

Many cancer patients experience emotional distress in the course of their disease. In the oncology setting, emotional distress can be defined as an adjustment disorder and is most frequently characterized by anxiety or depression.[1] The prevalence of emotional distress among cancer patients, with numbers reported of a fifth to even half of all patients,[1-10] combined with high incidence rates of cancer in the western world,[11,12] suggest emotional distress in cancer patients is an ubiquitous problem. And indeed, emotional distress is a well-studied subject in cancer research; however, the emotional impact of the diagnostic phase is overlooked.

Receiving a diagnosis of cancer is a major cause of distress.[13,14] It has even been included as a potential trauma in the DSM-IV.[15] Authors report higher levels of distress directly after diagnosis compared to later in the course of the disease.[6,16-18] However, there are surprisingly few studies on emotional distress in the diagnostic phase itself although cancer patients, as well as large groups of patients eventually *not* diagnosed with cancer, go through several more or less invasive diagnostic procedures during a period of uncertainty. Cancer also affects Quality of life (QoL) which is a multidimensional composition of different contributing factors. It stands without reason that QoL has become a key factor in oncology; however as abundant literature assessing QoL in the therapeutic or post-therapeutic phase is, the more scarce it is around diagnosis.

The emotional impact of the diagnostic phase requires more emphasis, for the following three reasons. Firstly, as stated above, prevalence of emotional distress in cancer patients during the course of their disease is high, indicating this is a population at risk. Secondly, as anxiety, depression and QoL can be improved by psychosocial interventions in cancer patients,[19] early detection may be beneficial. Thirdly, the diagnostic phase can be substantially shortened by rapid diagnostic pathways (one- or two-stop diagnostic services) that have been implemented in the recent years, resulting in a shorter period of uncertainty and improved patient satisfaction. These pathways have been clinically or economically evaluated for different cancer types however information on the effect of these pathways on distress is limited and restricted to breast cancer patients.[20] However they also exist for other cancer types, mostly lung cancer.[21-23] Suspected lung cancer patients might be a unique subset, as lung cancer is the second most frequent malignancy with the highest death rate in the western world, requires in most cases multiple, sometimes quite invasive staging techniques and lung cancer patients are also known to have a higher distress prevalence during the course of their disease than other cancer types.[2]

In this paper we aim to establish the effect of this diagnostic phase on anxiety, depression and QoL and the effect of shortening diagnostic procedures to a one- or two-stop pathway. The following research questions are the objective of the systematic review:

- What are pre-diagnostic levels of anxiety in patients with suspicion of cancer?

- What are the effects of receiving a benign or malignant diagnosis on short-term distress and QoL?
- What are the effects of a rapid diagnostic pathway on emotional distress and QoL for different cancer types?

METHODS

SEARCH STRATEGY

We searched the Cochrane database of systematic reviews, Pubmed and PsycINFO from 1984 up to February 2009. We used the following keywords (Mesh-terms): Diagnosis, Neoplasm/psychology, anxiety/diagnosis, depression/diagnosis, stress, psychological, psychological stress, quality of life. The searches were limited to humans, all adult (over 19 years old) and English language. We checked all titles and abstracts. Full text copies were obtained when studies had possible relevance. Following the keyword search, we carried out a backward search by examining reference lists of all papers obtained. We reviewed all titles and abstracts for the following inclusion criteria: Patients with suspicion of cancer who were scheduled to undergo at least one invasive diagnostic procedure to obtain a cytological or histological diagnosis, use of validated or at least standardized measures of anxiety, depression or QoL, use of these measures before diagnosis prospectively, and in case of follow-up to do so within six weeks. To make a distinction between short and long term with respect to the diagnosis of cancer, we had defined the period of six weeks after diagnosis as short term. This definition is arbitrary, but chosen bearing in mind the acute stress disorder that restricts the period of acute distress symptoms to four weeks;[15] acute distress symptoms of the procedures and receiving the diagnosis will supposedly have subsided after six weeks. Moreover, distress levels after this period might be correlated with therapy or disease progression. Studies examining emotional distress around cancer screening procedures or cancer surgery and papers on the influence of cancer awareness were excluded, as were abstracts, case studies, small pilot studies, letters and editorials.

EXTRACTED INFORMATION

The following information was extracted from each study: report information (authors, year of study, journal name, type of cancer), study design, sample size, measures and questionnaires used, time intervals between measures or diagnosis, major findings and limitations with respect to answering our questions.

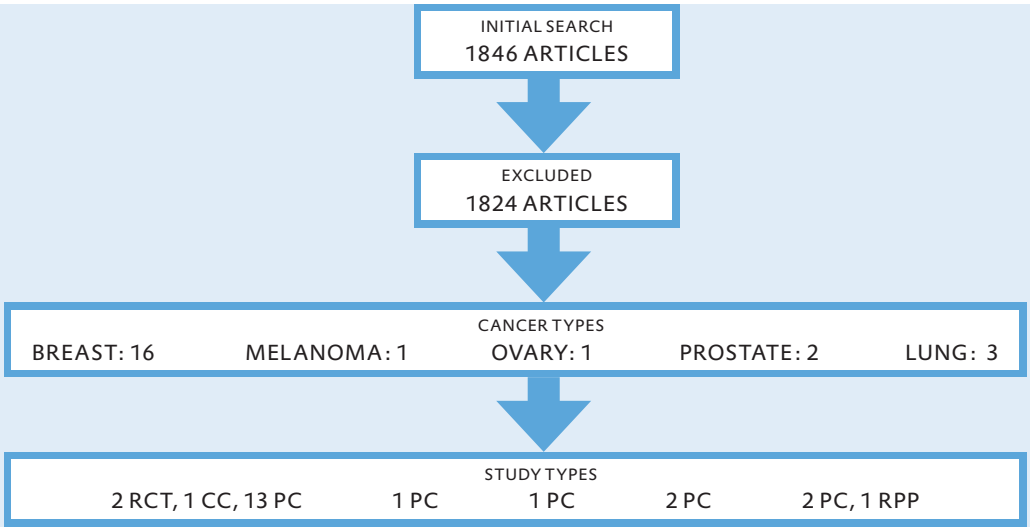

FIGURE 1 Overview of numbers and types of studies selected for review
RCT: randomized clinical trial, CC: case control study, PC: prospective cohort study, RPP: Randomized prospective pilot study.

RESULTS

SEARCH RESULT

Out of a total of 1846 articles, eventually 23 were eligible for review (see figure 1); 19 articles reported on anxiety and 7 on QoL or both. Since we had performed a broad search for which only rather non-specific keywords could be used, most articles were excluded; most frequent reasons for exclusion were studies being limited to the therapeutic rather than the diagnostic phase, measuring distress and QoL around surgical or other therapeutic procedures, and not including a pre-diagnostic measurement. Among the 23 articles finally reviewed, there were three articles reporting pre-diagnostic levels only.[24-26] All other articles also reported follow-up levels; in five studies these exceeded six weeks.[27-31] Finally, one article did not report absolute values but changes over time.[22]

PRE DIAGNOSTIC LEVELS OF ANXIETY

Pre-diagnostic levels of anxiety were reported in 19 studies and are presented in Table 1. Different measures for anxiety were used in these studies, most frequently the HADS (Hospital Anxiety and Depression Scale),[32] a 14-item questionnaire consisting of two subscales of anxiety and depression. Items are rated on a four-point scale, rendering a maximum total score of 21. On either subscale, scores of 0-7 are considered normal; scores of ≥11 are con-

sidered a significant 'case' of psychosocial morbidity, scores of 8-10 are considered 'borderline' and indicate potential clinical anxiety or depression. Suspected breast cancer patients had scores of ≥8 in 46-73% of cases,[28,33-35] Reported scores of ≥11 were 28-48%.[25,35,36] Mean HADS anxiety scores ranged from 7.7 to 10.6.[28,33,34] The study by Al-Shakli et al. on suspected malignant melanoma patients showed potential clinical anxiety in 27% of women (19% borderline plus 6% case anxiety) and 10% of men (6% borderline plus 4% case anxiety).[37] The one study on suspected lung cancer patients had 6% borderline and 10% case anxiety, with a mean anxiety score of 4.6.[27] In studies using the STAI (State-Trait Anxiety Inventory),[38] which is a 40-item questionnaire designed to measure state and trait aspects of anxiety adding up to a scale range from 20 to 80 (higher scores indicate more anxiety, and above a cut-off score of 44 is considered high anxiety), suspected breast cancer patients had mean state anxiety scores between 40.1 and 60.0.[25,31,33,35,39,40]

Remarkably, some patients with breast cancer were more anxious at baseline than patients with benign disease.[31,40] Japanese ovarian carcinoma patients had a similarly high mean score of 49.5, with 77.8% of patients above the 42 point cut-off (which was adapted for Japanese women).[41] In this particular study, an additional neuropsychiatric interview diagnosed 33% of suspected patients with an adjustment disorder. Again, patients in the study on malignant melanoma, that used a six item short form of the STAI (STAI-SSF) had lower mean scores of 10.6 in men and 12.7 in women.[37]

The two studies that used the POMS (Profile of Mood States) focused on patient factors that influence distress around breast and prostate biopsy; unfortunately the pre-biopsy results could not be compared to those from the other studies since no normative data exist on the scales that were used.[42,43]

Two breast cancer studies used the BSI (Brief Symptom Inventory),[44] a 53 items questionnaire designed to asses psychological symptom status, with higher scores indicating higher levels of distress. Moderate to high pre-diagnostic anxiety was reported (27.5 on the total scale) but substantially more in the group of patients that later would receive a cancer diagnosis – a phenomenon the authors could not explain.[45] Northouse et al. used the GSI (Global Severity Index, a BSI subscale) and similarly reported a score of 0.5 to 0.57, where 0.3 is the mean score of a normal population.[26]

FIRST AUTHOR	DESIGN	CANCER TYPE	SAMPLE	INTERVAL	MEASURES	PRE-DIAGNOSTIC ANXIETY
Harcourt [36]	RCT	Breast	583 females	6 days	VAS HADS	HADS-A ≥11: 28%
Ubhi [35]	PC	Breast	102 females	RP: 0 days RG: 1 week	STAI-SSF HADS	HADS-A≥8<11: 23.8% HADS-A≥11: 36.1% STAI-SSF: 49.0
Dey [33]	RCT	Breast	478 females	RP: 0 days RG: 1 week Assessments: 1 day and 3 weeks	STAI-SS HADS-A	HADS-A≥8: 58% mean 9.1 RP: STAI 48.4 RG: STAI 47.6
Al-Shakli [37]	PC	Malignant melanoma	195 females 126 males	0 days (clinically benign) 1 week (biopsy) 17 days (melanoma)	HADS STAI-SSF	HADS-A≥8: women 27%, men 10% STAI-SSF women 12.7 men 10.6
Lampic [34]	PC	Breast	509 females	0-15 days	HADS	HADS-A ≥8: 46 % Mean HADS-A: 7.7
Liao [40]	PC	Breast	127 females	Average 8.7 days (range 2-31) post consultation→ before biopsy→ diagnosis	STAI-SS	STAI-SS all: 60.0 benign: 56.93 cancer: 62.02@
Stanton [43]	PC	Breast	117 females	Average 7 days (diagnosis), 18 days (surgical breast biopsy)	POMS	POMS tension 11.24 (cancer) total POMNEG 39.8
Dekeyser [45]	PC	Breast	35 females	7-10 days and 14-20 days	BSI ASDS	BSI all: 27.5 benign: 19.07 cancer: 54.2@

TABLE 1 **Data extracted from articles found on anxiety around diagnosis; effect of a rapid diagnosis in upper 3 studies**

	DISTRESS CHANGE BENIGN DIAGNOSIS	DISTRESS CHANGE CANCER DIAGNOSIS	COMMENTS
	RP: 'case' anxiety 29.0%→ 11,3%* RG: 'case' anxiety 27.8%→ 19.5%# RP: HADS-D 3.50→ 2.32 RG: HADS-D 3.45→ 3.04$	RP: 'case' anxiety 22.5%→53.7% RG: 'case' anxiety 29.6%→ 41.4%$ RP: HADS-D 3.90→ 5.37@ RG: HADS-D 3.3.63→ 3.83#	Only 55 cancer patients (9%), possible perception of cues from surgeon on future result
	RP: STAI 52.44→ 37.95 RG: STAI 47.35→ 40.47	RP: STAI 44.67→ 51.85 RG: STAI 44.44→ 53.81$	No comparison of all patients after 1 week, only 16 cancer patients (16%)
	Benign and cancer patients (one day) RP: STAI 48.1→ 34.5* RG: STAI 47.2→ 39.8#	Benign and cancer patients (3 weeks) RP: HADS-A 8.9→ 7.3 RG: HADS-A 8.8→ 7.4$	Only 10 patients (3%) with malignant melanoma, no comparison of melanoma and benign cases after histological diagnosis, RP only for benign cases
	Clinically benign: STAI-SSF 11.49→ 8.88* Biopsy: STAI-SSF same day 12.73→ 13.91§# later day 12.89→ 13.79§#	STAI-SSF 14.4→ 16.0§ pre→ post-clinical→ 10.4* post-histological	Only 10 patients (3%) with malignant melanoma, no comparison of melanoma and benign cases after histological diagnosis, RP only for benign cases
	normal: HADS-A 8.0→ 4.0* cyst: HADS-A 6.8→ 2.7*	Significantly more anxiety when awaiting possible cancer diagnosis or surgery compared to immediate benign outcome	Variable interval, no detailed information on statistical significance of changes within groups in case of cancer, only 44 cancer patients (7%)
	STAI-SS 56.93→ 58.89§→ 45.40*	STAI-SS 62.02→ 62.24§→ 62.41§	Nonverbal cues might cause higher anxiety levels, variable interval, scores of Taiwanese probably higher than of western women
	POMS tension 11.24→ 4.59*	POMS tension 11.24→ 12.97*	Part of the post diagnosis distress attributed to upcoming surgery. Only 30 cancer patients (20% of total group) completed all measures
	BSI 19.07→ 13.4	BSI 54.2→ 54.7	No significance level reported for sequential anxiety changes, power analysis proved study too small, actual time intervals not reported, high pre- diagnostic anxiety in eventual cancer unexplained

Significance levels if given in articles:
* p< 0.05 before compared to after, # P< 0.05 rapid compared to regular,
@ p< 0,05 cancer compared to benign, § non-significant before compared to after,
$ non-significant rapid compared to regular.

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FIRST AUTHOR	DESIGN	CANCER TYPE	SAMPLE	INTERVAL	MEASURES	PRE-DIAGNOSTIC ANXIETY
Witek-[36] Januse k	C-PC	Breast	121 females	1 day 1 month	PSS, POMS STAI-SS	Benign: POMS tension and STAI higher than cancer or controls. Cancer: no difference
Sukegawa[41]	PC	Ovary	27 females	7-14 days	STAI-SS MINI	STAI all: 49.5, cancer 50.1 benign 49.1
Scott [39]	PC	Breast	85 females (benign)	6-8 weeks	STAI-SS	STAI 48.7
Perczek [39]	PC	Prostate	101 males	2 weeks	POMS	POMS distress score 0.68
Montazeri[39]	PC	Breast	168 females (cancer)	-	HADS	HADS-A≥8<11: 25% HADS-A≥11: 48% Mean HADS-A:10.6
Montazeri[27]	PC	Lung	77 males 52 females, (cancer)	-	HADS	HADS-A≥8<11: 6% HADS-A≥11: 10% Mean HADS-A: 4.6
Van der Steeg [31]	PC	Breast	202 females, (cancer)	-	STAI-SS	STAI all: 44.3. cancer 49.5 benign 40.1@
Madden [25]	RCT	Breast	50 females	-	STAI-SS	STAI 44.8
Nosarti [30]	PC	Breast	87 females (cancer)	-	GHQ-12	GHQ-12 case 33.8%
Chen [24]	PC	Breast	121 females	-	GHQ-12	GHQ-12 case 37.5%
Northouse [26]	PC	Breast	300 females, 265 husbands	-	BSI	Women overall distress: 0.57 Husbands: 0.37

TABLE 1 SEQUEL **Lower 7 studies with pre-diagnostic assessment only.**

	DISTRESS CHANGE BENIGN DIAGNOSIS	DISTRESS CHANGE CANCER DIAGNOSIS	COMMENTS
	POMS tension (but not STAI) still higher than controls	POMS tension and STAI higher than controls	Comparison with control group, but not exact levels or changes reported. Variable interval and not exactly reported
	STAI 49.1→ 31.7*	STAI 50.1→ 43.2*	Small sample, probably pre-surgery distress affecting first measure-ment, exact interval variable and not reported
	STAI 48.7→ 33*	-	Only patients with benign results, exact interval variable and not reported
	POMS distress 0.72→ 0.62 Significant group x time interaction	POMS distress 0.61→ 0.79 Significant group x time interaction	Study aim was role of optimism and coping, not distress before and after diagnosis, no comment on changes of distress levels found
	-	-	Only cancer patients
	-	-	Possible bias as part of study sample might have known diagnosis, only cancer patients
	-	-	Aim of study was determine in-fluence of personality traits in QoL
	-	-	Aim of study was effect of preparatory booklet
	-	-	Aim of study was course and risk factors of psychological morbidity during first year, only cancer patients
	-	-	Actual diagnostic procedure before assessment
	-	-	-

Significance levels if given in articles:
* p< 0.05 before compared to after, # P< 0.05 rapid compared to regular,
@ p< 0,05 cancer compared to benign, § non-significant before compared to after,
$ non-significant rapid compared to regular.

ARTICLE REFERENCE	DESIGN	CANCER TYPE	SAMPLE	INTERVAL	MEASURES	PRE-DIAGNOSTIC QOL
Harcourt [36]	RCT	Breast	583	6 days females	EORTC QLQ-C30	General QoL (GHS) 64.3-69.3
Murray [22]	RPP	Lung	55	6 weeks	EORTC QLQ-C30	-
Al-Shakli [37]	PC	Malignant melanoma	See table 1	See table 1	EORTC QLQ-C30	All: GHS 80.0 Melanoma: 82.5
Van der Steeg [31]	PC	Breast	202 females (cancer)	1, 3, 6 months	WHOQOL-100	Benign: Overall QoL 15.0 Cancer: 15.6@
Montazeri [29]	PC	Breast	167 female (cancer)	3, 18 months	EORTC QLQ-C30 QLQ-BR23	Global QoL 59.2
Lheureux [49]	PC	Lung	61 males 9 females	Mean 22.4	EORTC-QLQ-C30 QLQ-LC13	Global QoL 55.2
Ishihara [51]	PC	Prostate	141 males	≤6 weeks	MOS-SF-36 UCLA-PCI	SF-36 GH/MH: 50-59 years 64.2/67.6 60-69 years 60.2/64.6 70+ years 56.2 /65.1 Only MH lower than Japanese norm in 60-69 years group

TABLE 2 Data extracted from articles found on QoL around diagnosis; effect of a rapid diagnosis in upper 3 studies

Abbreviations in tables 1 and 2: RCT: randomized controlled trial, PC: Prospective Cohort, VAS: Visual Analogue Scale, HADS: Hospital Anxiety and Depression Scale, RP: RaPid pathway, RG: ReGular pathway, STAI: Spielberger State-Trait Anxiety Inventory STAI-SS: State Scale of STAI, STAI-SSF: STAI Six-item Short Form, POMS: Profile Of Mood States, C-PC: Controlled Prospective Cohort, BSI: Brief Symptom Inventory, ASDS: Adapted Symptom Distress Scale, GHQ-12: General Health Questionnaire short version of 12 items,

	QOL CHANGE BENIGN DIAGNOSIS	QOL CHANGE CANCER DIAGNOSIS	COMMENTS
	RP: improvement on several subscales#, general QoL 69.3→ 74.8# RG: 67.9→ 70.0#	RP: significant worsening of several subscales#, general QoL 68.1→ 57.1@ RG: 64.3→65.6§	See table 1. Pre-diagnostic QoL only reported for different groups. After 8 weeks groups were comparable on all measures
	-	RP: worse role, social, financial functioning#, other dimensions unchanged	Study aim was not primarily QoL, exact data not reported, only cancer patients were followed, twice as many patients had started chemotherapy in RP, unknown sex of sample analyzed
	-	RG: (all melanoma) GHS 82.5→ 50.0*, EF 75.3→ 50.8*	See table 1
	Non-significant	Non-significant	See table 1. Exact QoL change not reported.
	-	-	Only cancer patients included.
	-	Global QoL no significant change, deterioration of most functioning scales and arm pain	Only cancer patients were followed, all patients were hospitalized, time interval variable
	GH 56→ 58.4§ MH 64.2→ 63.6§	GH/MH§ for all different disease stages	SF-36 might lack sensitivity in detecting changes. Results reported by age group only, 50-59 years group was small (n=11)

MINI: MINI International Neuropsychiatric Interview, NKC: Natural Killer Cell, POMNEG: the five POMS subscales tapping negative mood, EORTC QLQ-C30: European Organization for Research and Treatment of Cancer 30 item Quality of Life Questionnaire, WHOQOL-100: World Health Organization 100 item Quality of Life Questionnaire, EORTC QLQ-B23: European Organization for Research and Treatment of Cancer 23 item Breast Cancer Quality of Life Questionnaire, EORTC-QLQ-LC13: European Organization for Research and Treatment of Cancer 13 item Lung Cancer Quality of Life Questionnaire, MOS-SFR-36: Medical Outcome Study 36 Item Short Form, UCLA-PCI: University of California at Los Angeles Prostate Cancer Index, GH: general Health scale, MH: Mental Health scale.

Nosarti et al[30] found 'cases', indicating potential clinical significant psychological distress, in 34% of patients with suspected breast cancer using the GHQ-12 (General Health Questionnaire – 12 item version) similar to the 37.5% of symptomatic breast lesion patients being probable cases in the study by Chen et al.[24]

EFFECTS OF RECEIVING A BENIGN OR MALIGNANT DIAGNOSIS ON SHORT-TERM DISTRESS

Detailed results and significance levels if reported are presented in Table 1. Patients receiving a benign diagnosis showed significant decreases in anxiety in all studies reviewed irrespective of cancer type,[34-73,39-42,45] except for the breast cancer study by Witek et al. in which anxiety levels were not analyzed as repeated measures; no difference was found compared to cancer patients, but significantly higher anxiety levels in all patients when compared to normal controls.[46]

Women eventually diagnosed with breast cancer had either increased[34-36,43] or sustained[40] anxiety levels; however increases were only reported to be statistically significant in one study.[43] Increased anxiety was also reported in prostate cancer patients.[42] On the other hand, in case of melanoma[37] or ovarian cancer[41] lower anxiety levels after diagnosis were found.

Short term depression was only reported in three breast cancer studies, one of which was a rapid pathway study in which depression scores after a cancer diagnosis in the one stop system were higher than in the two stop system but not for patients with benign results.[36] The other two studies reported a decrease in depression scores after diagnosis in cancer patients[34] or an increase, but also a decrease again after surgery.[43]

EFFECTS OF RECEIVING A BENIGN OR MALIGNANT DIAGNOSIS ON SHORT-TERM QUALITY OF LIFE

We found six studies assessing QoL around a cancer diagnosis with a before-and-after comparison and one with a before measure only,[47] presented in table 3. Suspected cancer patients scored much lower pre-diagnostic general QoL levels than compared to the random normal reference,[48] and suspected lung cancer patients scored worst.[49] Remarkably, one of three studies on suspected breast cancer patients also found lower values compared to general breast cancer patients.[29] For suspected lung and prostate cancer patients the reported pre-diagnostic values were somewhat lower than reference lung or

prostate cancer patients' values.[47,49,50] Surprisingly, suspected melanoma patients QoL levels exceeded both normal and melanoma patients' values.[37]

With respect to short term (within six weeks) effects on QoL, 3 studies showed decreases in several aspects of QoL in patients diagnosed with either breast, skin or lung cancer.[36,37,49] Prostate cancer patients[50] and patients in one breast cancer study[31] showed no significant changes before and after diagnosis in patients with both malignant and benign outcomes.

EFFECTS OF A SPEEDIER DIAGNOSTIC PATHWAY ON EMOTIONAL DISTRESS AND QUALITY OF LIFE

On the specific effect of rapid diagnostic evaluation on emotional distress we found three studies of suspected breast cancer patients,[33,35,36] presented in the top box of table 1. We found one study on QoL in suspected lung cancer[22] presented in table 2. We found no reports on depression in cancer patients in the rapid setting.

Numbers of patients, eventually receiving a cancer diagnosis were relatively small in all studies. Dey et al.[33] found a significantly larger reduction of anxiety after 24 hours in one-stop evaluation, compared to two-stop evaluation in which patients were still awaiting results. This difference disappeared after three weeks. In both other breast cancer studies patients who were given benign results in the rapid systems showed significantly less anxiety after one week than those still waiting for results (in regular or delayed systems), and in the study by Harcourt also a significant decrease in depression.[36] In contrast to the others, Ubhi et al.[35] compared absolute changes in anxiety scores after immediate or delayed communication of cytology results and found that immediate communication of a benign outcome resulted in a greater reduction of anxiety than when this was done one week later. For patients with cancer there was an equal increase irrespective of communication type. The last study in this category by Harcourt et al.[36] showed an increase in anxiety in patients being diagnosed with malignant disease, though not significantly more in the one stop patients than in those still waiting for results. Anxiety differences between one-stop and two-stop pathways disappeared after two months in this study, however one-stop patients then had unexplained significantly higher though subclinical (mean HADS-D 5.47) depression rates that had increased 1.54 clinically debatable points. This study was the single one of the abovementioned three including also a QoL measurement, showing significant deterioration of several aspects of QoL in

breast cancer patients in the one-stop group compared to two-stop, and a significant increase in patients having benign results. After two months, differences between both groups had disappeared. This seems comparable to the findings by Murray et al. reporting similar changes in role, social and financial functioning after diagnosis of lung cancer in patients randomized between a central (one day) arm and a conventional arm, however the true rapid pathway effect can be debated after a six week interval of the QoL measurements.[22] The study by Montazeri et al.[29] evaluating pre-diagnostic QoL in breast cancer patients added a long term (more than 6 weeks) follow-up, that was therefore not included in this analysis.

DISCUSSION

PRE-DIAGNOSTIC ANXIETY AND QUALITY OF LIFE

A diagnosis of cancer may lead to distress by several causes: The feeling of the threat of the disease itself, symptoms, disability, pain, as well as the treatment (surgery, radiotherapy, chemotherapy) or treatment-related toxicity.[13,14,51] This review shows that distress and QoL surrounding a potential cancer diagnosis are not well and abundantly studied. Many cancer patients suffering from psychological distress remain unidentified, due to either underestimation by physicians or underreporting by patients.[52,53] Pre-diagnostic distress is likely to remain unrecognized as well, but can reach extremely high levels, i.e. a 33%-60% prevalence of potential clinical anxiety. In other words: Suspected cancer patients have similarly or even more negatively affected anxiety and QoL compared to after a confirmed diagnosis during the course of their disease; patients who's diagnostic analysis renders a benign outcome are equally affected.

Though the possibility of a cancer diagnosis in our opinion can be seen as a factor in itself for the development of distress, one may assume that it is influenced by all the known risk factors predicting psychological morbidity in cancer: family or personal history of a psychiatric disorder, low socioeconomic position, lack of support, female gender, younger age, advanced or active disease, recent stressors and pain or other poorly controlled symptoms.[9,51,54] None of these factors could be taken into account in the studies reviewed, except for an inevitable sex bias due to overrepresentation of breast cancer studies and underrepresentation of studies on other prevalent cancer types like lung and gastro-intestinal cancer.

Then there is the cancer type as specific risk factor: We found pre-diagnostic distress levels to be very different compared to levels reported during the course of disease.[2] Suspected melanoma and lung cancer patients had lower anxiety levels in two studies.[27,37] The lower levels in melanoma patients could be explained by the relatively lower actual melanoma incidence found and by the generally definite effect of the diagnostic procedure being therapeutic at the same time. The relatively lower level in the study on lung cancer patients could be explained by the patient sample, consisting of only 40% females and the selective use of data leaving out all patients eventually not diagnosed with lung cancer for whom pre-diagnostic anxiety levels were significantly higher. Furthermore there's a possibility of awareness of the cancer diagnosis among 30% of the study sample since the authors state this in another article reporting on QoL of the same study sample.[47] Certainly for lung cancer, known to harbor the highest distress prevalence of all cancer types during the disease course, one would assume both higher anxiety scores and more studies on patients confronted with a possible lung cancer diagnosis.

The high anxiety scores in suspected ovarian cancer patients were possibly influenced by both pre-surgery distress, and the fact that other diagnostic procedures could have been done before first anxiety assessment.[41]

The results of this review with respect to pre-diagnostic levels of anxiety should be interpreted with caution. Distress as assessed in some studies focuses on a specific diagnostic procedure, rather than a diagnostic work-up as a whole. This could either lead to overestimation of distress when patients are interviewed shortly before the procedure or underestimation assuming multiple diagnostic procedures cause more distress than the single one. The true effect remains unclear.

THE EFFECT OF RAPID DIAGNOSTIC PATHWAYS ON SHORT TERM DISTRESS AND QUALITY OF LIFE

When evaluating the effect on short-term distress and the effect of a rapid one-stop or two-stop diagnosis, this review not only shows both statistically and clinically significant decreases of anxiety in case of benign disease irrespective of cancer type, but also that this concerns a large patient group. In case of confirmation of suspected cancer anxiety tends to increase or sustains. The single study evaluating depression in a one stop setting revealed more depression after a rapid cancer diagnosis though still on a subclinical

level with an in our opinion clinically irrelevant change. In all, this implies a beneficial effect of a rapid diagnostic pathway on distress in case of benign disease. This was confirmed by studies specifically aiming at rapid pathways, and also by two other studies that though not truly rapid pathway studies, can be interpreted as such: anxiety levels of patients presenting with a suspected skin lesion at a pigmented lesion clinic that was clinically diagnosed as benign decreased significantly but sustained when biopsy was needed;[37] the same effect was found in the breast cancer study by Lampic for patients having an immediate benign outcome.[37] This effect might be associated with the superior patient satisfaction in rapid diagnostic pathways.[20] The fact that no long-term sequelae of a rapid benign diagnosis were found in the studies reviewed, suggests absence of a long-term detrimental effect of the speedier benign diagnosis on anxiety. For patients that eventually receive a cancer diagnosis, anxiety levels show sustainment or increase (though the clinical relevance of this increase in several studies can be debated) suggesting at least non-inferiority of rapid compared to non-rapid diagnostic pathways. However most was reported in breast cancer patients, derived from relatively small studies and therefore careful interpretation of results is mandatory.

In general, QoL has a tendency to decrease after a cancer diagnosis, but decreased faster when the diagnosis was faster and reacted oppositely in case of benign disease, though in a single one stop study with hardly relevant changes in clinical point of view.[36] Of all cancer types of the studies reviewed, lung cancer has by far the worst prognosis. One might expect this to have an impact on QoL, but comparison based on the studies found is impossible: The study by Lheureux et al.[49] reported some decreases in several QoL scales after a mean diagnostic period of over three weeks; a bias however was that all patients had been hospitalized. In the single study on suspected lung cancer patients in a rapid outpatient pathway, follow-up levels of QoL were possibly influenced by the fact that far more patients in the rapid arm had already started therapy in the rather long six week interval of QoL measurement; actual QoL levels were not reported so no statement can be made on whether these changes also were clinically relevant.[22]

CONCLUSION

Patients confronted with a possible cancer diagnosis report very high distress levels and decreased QoL. The reduction of distress after exclusion of cancer implies a beneficial effect of a rapid diagnostic pathway for those with

a benign diagnosis. For those who eventually appear to have cancer, the rapid pathway shortens the period of diagnosis related distress and the relatively few studies we found on this specific subject suggest absence of a detrimental effect on anxiety compared to regular pathways. More research is needed to shed a light on the process suspected cancer patients go through, and special attention should be paid to cancer types with high prevalence and invasive diagnostic procedures.

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DISTRESS IN SUSPECTED LUNG CANCER PATIENTS FOLLOWING RAPID AND STANDARD DIAGNOSTIC PROGRAMS: A PROSPECTIVE OBSERVATIONAL STUDY

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ABSTRACT

OBJECTIVE: Timeliness may influence emotional distress during the diagnostic phase of suspected lung cancer patients. We performed a prospective observational study to compare distress and quality of life (QoL) in two medical centres with a Rapid Outpatient Diagnostic Program (RODP) and two using conventional Stepwise Diagnostic Approach (SDA) based on trained nurse led care.

METHODS: Outpatients with radiological suspicion of lung cancer completed the Hospital Anxiety and Depression Scale (HADS), European Organization for Research and Treatment of Cancer 30-item Quality of Life Questionnaire (QLQ-C30) and its 13-item Lung Cancer specific module (QLQ-LC13) upon first visit, two days later, thereafter weekly for five weeks and after three months.

RESULTS: The 72 SDA patients and 121 RODP patients had a mean pre-diagnostic HADS-total score of 13.5 (SD 7.6); 63.4% had a score ≥10. Baseline QLQ-C30 global QoL was 61.6 (SD 22.7) exceeding reference values for lung cancer patients. Generalized least square models showed a significant centre by time interaction effect: During the first 6 weeks HADS-total scores decreased in RODP patients (13.8 to 11.9) but sustained in SDA patients (13.1 to 13.6) while QoL showed no relevant changes. Times to diagnosis and discussion of therapy plan for RODP patients were 7 and 11 days shorter, respectively.

CONCLUSIONS: Suspected lung cancer patients had high baseline distress levels. A decrease over time was found in RODP compared to SDA patients. QoL did not change relevantly. Albeit observational, these data indicate that patients experience less distress in rapid diagnostic programs than in stepwise diagnostic evaluation.

BACKGROUND

Many cancer patients experience emotional distress. The National Comprehensive Cancer Network definition of distress is a multifactorial unpleasant emotional experience of psychological, social and/or spiritual nature that

may interfere with the ability to cope with cancer.[1] Distress is mostly characterized by anxiety or depressive symptoms and with prevalences ranging form 20-50%[2,3] these play an important role in cancer. Deservedly, distress has become a well-acknowledged issue in oncological supportive care[1] and should be considered equally significant at the moment of confrontation with the diagnosis. [4] Although studies are neither abundant nor uniform and mostly limited to breast cancer patients, they at least suggest very high distress levels (specifically anxiety) in patients confronted with the mere possibility of a cancer diagnosis, sustaining after confirmation of the diagnosis but reducing after exclusion of cancer.[5] The psychological impact of the diagnostic phase is additionally highlighted by studies on outcomes of breast cancer screening showing that patients eventually not diagnosed to have cancer still may experience psychological consequences afterwards.[6] Lung cancer patients report general distress levels during the course of disease that are among the highest of all cancer types.[2,3] In this respect they may be considered a different patient group which is more at risk, also around diagnosis; a substantial group as well if the recent calls for implementation of lung cancer screening[7] are adopted. Being diagnosed with cancer takes time, which can be minimized by a one-stop or two-stop pathway (for which we use the generalized term 'Rapid Outpatient Diagnostic Program' (RODP)). RODPs have been developed for several cancer types.[8] Especially in lung cancer, often requiring multiple diagnostic and staging procedures, an RODP is a valuable tool to improve timeliness.[9,10] An RODP shortens the diagnostic period and in turn the period of diagnosis-related distress, without detrimental effects on anxiety compared with conventional pathways as was demonstrated in breast cancer patients.[11-13] However suspected lung cancer requires a different usually more invasive diagnostic approach and patients might, as stated before, be more at risk. The present article addresses the question whether timeliness of the diagnostic evaluation has an effect on distress and quality of life (QoL) in patients with suspected lung cancer. We report the results of the PENELOPE study (Pulmonary Evaluation of NEoplastic Lesions in Outpatients and it's Psychological Effects) that was designed to evaluate patients in a prospective observational design using validated distress and QoL measures before and during the diagnosis of a possible lung cancer up to three months in four different medical centres in The Netherlands comparing RODP with regular standard diagnostic approach (SDA). We hypothesized that patients in an RODP would experience less distress and a better QoL during the diagnostic phase than during conventional SDA; furthermore we hypothesized equal distress and QoL scores at baseline before diag-

nostic analysis for both patient groups and higher scores than general reference values for lung cancer patients. Although studies on emotional distress usually focus on anxiety, we chose distress as primary endpoint; a broader term and a parameter that is more comparable after the 3 months interval when the acute anxiety symptoms usually play a less important role and depression may be the factor promoting distress.

METHODS

PARTICIPANTS AND PROCEDURES

Between January 2009 and July 2010 we performed the PENELOPE study for suspected lung cancer patients in two university medical centers (Radboud University Nijmegen Medical Centre (RUNMC) and University Medical Centre Groningen (UMCG)) and two general hospitals (Gelderse Vallei Medical Centre (GVMC) and Atrium Medical Centre Heerlen (AMCH)) in the Netherlands. In both subsets one center with an RODP and one using an SDA were selected. In the RUNMC RODP patients underwent laboratory investigation, integrated ^{18}F-fluorodeoxyglucose Positron Emission Tomography-Computed Tomography (FDG-PET/CT) scan, pulmonary function test, consultation with pulmonary physician, and bronchoscopy in two days time and received cytology results on the second day, Endoscopic Ultrasound (EUS) or Endobronchial Ultrasound (EBUS) and further pathology results later that week or ultimately the seventh day if applicable. The AMCH implemented an RODP based on a three day schedule: FDG-PET/CT, pulmonary function tests and laboratory investigation on the first, bronchoscopy on the second and/or EUS of EBUS on the third and pathology results on the seventh day. Both other centres used an SDA based on trained nurse-led care. For this study all patients with a radiological suspicion of lung cancer were eligible if they were over 18 years old and were able to complete printed questionnaires. Patients were given verbal and written information about the study. After obtaining informed consent, patients were asked to complete sets of questionnaires on that day (day one) and day three, and thereafter weekly for five weeks. A final questionnaire was sent by mail three months after the last to enable comparison of both groups' scores after the diagnostic process itself. Patients' baseline demographic and disease characteristics and final diagnosis were recorded and collected after the study was completed.

QUESTIONNAIRES

Questionnaires were completed at home and returned by mail. Sets consisted of the Hospital Anxiety and Depression Scale (HADS),[14] the European Organization for Research and Treatment of Cancer (EORTC) 30 item Quality of Life Questionnaire (QLQ-C30)[15] and its 13 item Lung Cancer specific module (QLQ-LC13)[16] and the EuroQol-5D questionnaire.[17] We present results of the first two questionnaires in this article because we were specifically interested in distress and QoL. Not relevant for this study was the EuroQol-5D questionnaire, measuring health states specifically for the valuation of health in health economy studies. The HADS is a 14-item questionnaire consisting of two subscales: anxiety and depression. Items are rated on a 4-point scale, rendering a maximum total score of 21. On either subscale, scores of 0–7 are considered normal; scores of over 11 are considered a significant 'case' of psychological morbidity, scores of 8–10 are considered 'borderline' and indicate potential clinical anxiety or depression. A large meta-analysis concluded that a total score of 10 or more is the optimal threshold for significant emotional distress.[18] The major advantage of the HADS is exclusion of physical symptoms of anxiety and depression such as weight loss and fatigue. It has been well validated against structured clinical interviews (the 'gold standard' for the assessment of mental disorders) and is considered a reliable, sensitive and specific screening tool for psychological distress in oncology.[19] The EORTC QLQ-C30 is a frequently used cancer specific QoL questionnaire, widely accepted for its validity[20] containing 30 items on patients' functioning, global QoL and both disease and treatment related symptoms. Raw scores are linearly transformed to give standard scores in the range of 0-100 for each of the functioning and symptom scales. Higher scores in the global and functioning scales and lower scores in the symptom scales indicate better QoL. A difference of 5-10 points in the scores represents a small change, 10-20 points a moderate change and greater than 20 points a large clinically significant QoL change.[21]

OUTCOMES

The outcomes of the study were distress (reflected by the HADS-total score), anxiety (HADS-anxiety subscale), depression (HADS-depression subscale) and QoL (QLQ-C30 global QoL) at baseline (day one) and during the entire diagnostic analysis (day one to week six).

STATISTICAL POWER

We calculated that, based upon a single measurement per sampling unit, for a power of 0.8 with α=0.05, 63 patients were needed in both RODP and SDA groups to show a significant 10-20 points 'moderate difference' in global QoL score QLQ-C30.[21]

DATA ANALYSIS

We used generalized least squares models to model the course of distress and QoL over the first 38 days, which enabled us to explore the dependency caused by the repeated measurements on the same patients. A Toeplitz correlation structure coupled with heterogeneous variances provided the best fit for these data, based on the Aikike information criterion. The dependent variables were distress levels (reflected by the HADS total score), HADS anxiety subscore levels and the QLQ-C30 global QoL score. Dependent variables were time (entered into the model as a factor with 7 levels), centre type (RODP and SDA) and the interaction between these two. A significant interaction implies that the course over time is different for the two centre types. Figures depicting the estimated marginal means (with standard errors) based on this model are presented. Analyses were repeated within strata defined by gender and diagnosis outcome (benign and malignant). The measurement at three months was analysed separately since the much larger time would necessitate a much more complex correlation structure; moreover, centre type was not expected to still have an effect on outcomes given the long interval since diagnosis. An advantage of generalized least square models is that subjects with a missing outcome on a certain time point can contribute to the results using the observations that are present, assuming that the few missing values did not influence outcome. All data were analyzed using the SPSS 19 statistical software program (SPSS, Chicago, IL). Continuous variables were compared using the unpaired t-test or Mann–Whitney-U test; categorical variables were compared using the χ^2-test. Differences were considered statistically significant if $p < 0.05$.

RESULTS

PATIENTS

Figure 1 shows a flow chart of the 407 patients that had been asked to participate between January 2009 and July 2010; eventually 193 patients returned one or more questionnaires. Three RODP patients and one SDA patient died before completing the last questionnaire at 3 months. Patient numbers per

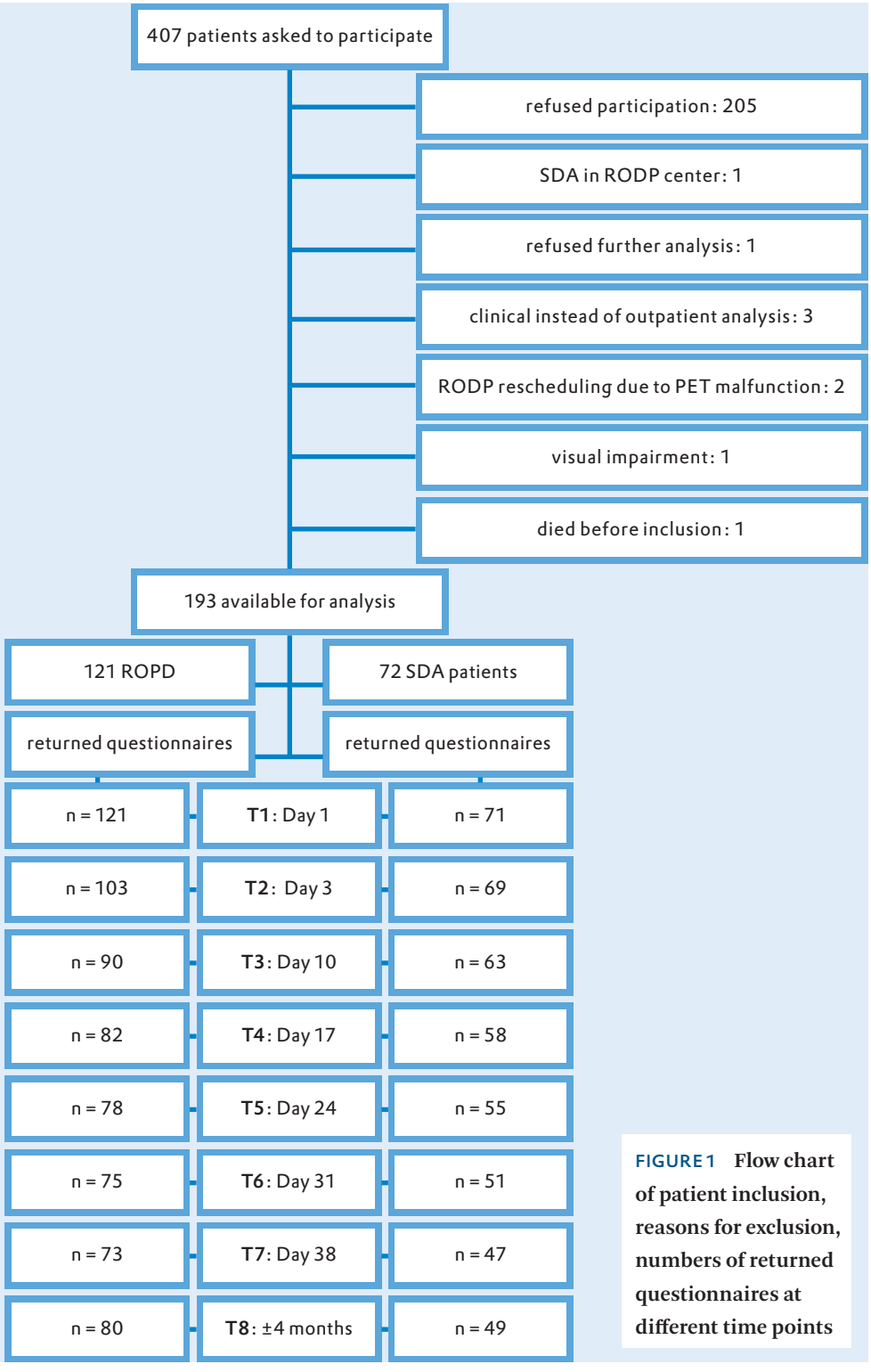


FIGURE 1 **Flow chart of patient inclusion, reasons for exclusion, numbers of returned questionnaires at different time points**

participating centre were as follows: RUNMC 87 (45.1%), AMCH 34 (17.6%), GVMC 55 (28.5%) and UMCG 17 (8.8%).

As shown in table 1, this resulted in significantly more tertiary care patients and more patients with synchronous or recent cancer diagnoses in the RODP group compared to the SDA group, however no significant differences in age, gender, lung cancer diagnosis and curative therapy were found. Separate analysis of the 104 lung cancer patients showed that significantly more patients in the RODP were surgically treated. Furthermore, as might be expected as a result of the different practice organizations, median times to reach a diagnosis and discuss therapy plan were 7 and 11 days shorter for RODP patients, respectively. However, the interval between first visit and actual start of therapy in case of lung cancer was not significantly different.

PRE-DIAGNOSTIC DISTRESS AND QOL

Pre-diagnostic distress as measured by the baseline mean HADS total score was 13.5 (SD 7.6), or from a different perspective, 63.4% of patients had a HADS-total score of 10 or higher, indicating significant distress. Furthermore, 51.8% of patients had a HADS-anxiety score over 7 (borderline anxiety) and 19.8% scored over 10 (case anxiety). Baseline mean HADS-total scores of patients with a cancer diagnosis were higher (14.7) when compared to patients with a benign outcome (11.8, p 0.010) as were mean HADS-anxiety scores (8.3 and 6.7 respectively, p 0.009); for HADS-depression scores there was a trend towards lower scores in SDA patients (6.4 and 5.2 respectively, p 0.052). Comparison of baseline EORTC QLQ-C30 and LC-13 subscales between patients with eventual malignant and benign results revealed significant and relevant (more than 10 points) differences only in physical functioning (74 and 84 respectively, p 0.002) and appetite loss (26 and 15 respectively, p 0.002). Mean HADS total scores at baseline were not statistically different between men and women (13.0 and 14.5 respectively, p 0.20), neither were HADS depression scores (p 0.71) although baseline mean HADS anxiety score tended to be higher in women (8.4) compared to men (7.2, p 0.502). Baseline HADS-total scores did not differ significantly between RODP and SDA patients, but HADS-anxiety scores did (8.2 and 6.5, respectively, p 0.01, table 1).Pre-diagnostic global QoL for all patients was 61.6 (SD 22.7) measured by the global QoL score of the QLQ-C30 and was not statistically different between RODP and SDA patients. Subscores were not significantly different between centres types, only fatigue was reported significantly more often in the SDA group (table 1).

CLINICAL CHARACTERISTICS	RODP CENTRES N = 121	SDA CENTRES N=72	P
Mean age (SD)	63.4 (9.6)	64.9 (8.9)	0.26
Tertiary Care centre	87 (71.9)	17(23.6)	< 0.001
Male	75 (62)	48 (66.7)	
Female	46 (38)	24 (33.3)	0.43
Cancer history:			
any history of cancer	34 (28.1)	9 (12.5)	0.01
over 5 years ago	18 (14.9)	6 (8.3)	0.18
1-5 years ago	15 (12.4)	3 (4.2)	0.06
less than 1 year and synchronous	16 (13.2)	1 (1.4)	0.01
Median time intervals in days:			
visit to diagnosis	7 (0-17)	14 (12-26)	< 0.001
visit to lung cancer therapy plan	8 (1-21)	19 (14-27)	< 0.001
visit to lung cancer therapy	31 (19-43)	37 (26-48)	0.08
Diagnosis lung cancer	62 (51.2)	42 (58.3)	
Other diagnosis:	59 (48.8)	30 (41.7)	0.34
non-malignant	49 (40.5)	24 (33.3)	
metastasis	8 (6.6)	1 (1.4)	
no diagnosis, follow up	2 (1.7)	5 (6.9)	0.03
Lung cancer clinical Stage (N=104):			
stage I-IIIA	37 (59.7)	18 (42.9)	
stage IIIB-IV	25 (40.3)	24 (57.1)	0.09
Lung Cancer Therapy (N=104):			
surgical	29 (46.8)	8 (19.0)	
non-surgical	29 (46.8)	26 (61.9)	
none	4 (6.5)	8 (19.0)	0.01
Lung Cancer Therapy (N=104):			
curative	40 (64.5)	24 (57.1)	
palliative	18 (29.0)	10 (23.8)	
none	4 (6.5)	8 (19.0)	0.14

TABLE 1 **Patient baseline clinical characteristics**

>>> continue on next page

N (%), or median (IQR).

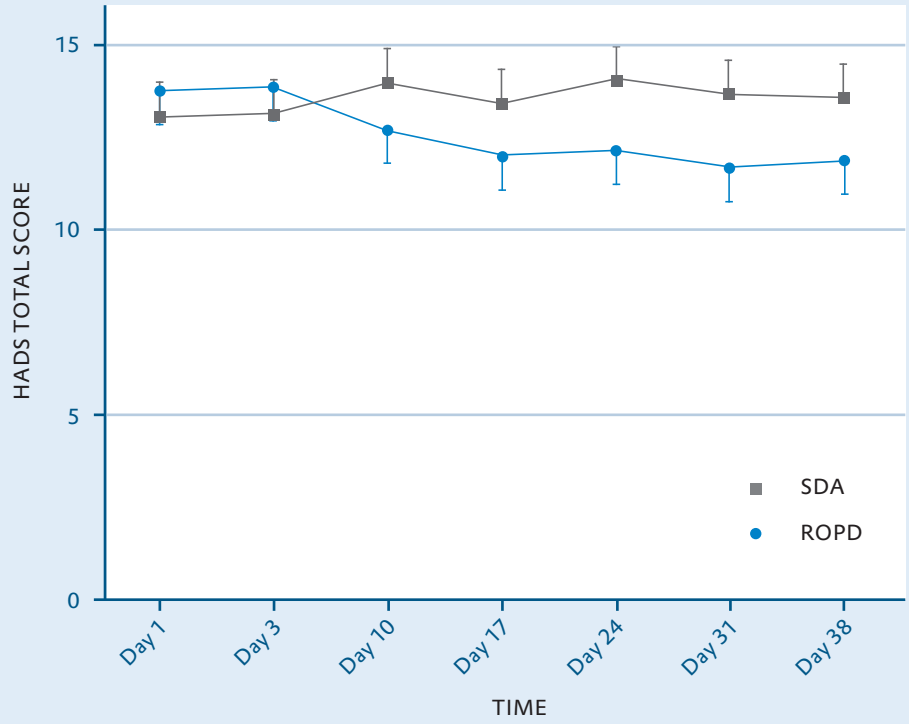
CLINICAL CHARACTERISTICS: MEAN BASELINE QUESTIONNAIRE SCORES	RODP CENTRES N = 121	SDA CENTRES N=72	P
HADS total score	13.8 (7.6)	13.1 (7.8)	0.55
HADS anxiety subscale	8.2 (4.2)	6.5 (4.0)	0.01
HADS depression subscale	5.5 (4.2)	6.5 (4.5)	0.11
Qlobal QoL			
QLQ-C30	63.6 (23.2)	58.2 (23.3)	0.11
QLQ-C30 functioning scores			
physical	78.5 (20.7)	78.4 (19.7)	0.99
cognitive	82.8 (17.5)	83.8 (19.9)	0.71
emotional	67.4 (21.9)	69.6 (22.8)	0.50
role	72.7 (29.2)	70.2 (29.9)	0.57
social	87.2 (20.4)	84.3 (19.1)	0.32
QLQ-C30 symptom scores			
financial difficulties	8.1 (19.8)	6.6 (17.5)	0.60
dyspnea	35.8 (31.4)	38.0 (32.0)	0.64
pain	17.2 (25.5)	24.4 (27.7)	0.07
fatigue	29.1 (24.8)	38.7 (27.1)	0.01
sleep	31.1 (33.3)	32.4 (31.9)	0.80
appetite loss	21.9 (31.0)	21.6 (29.9)	0.94
nausea	5.1 (11.4)	7.7 (17.8)	0.22
constipation	8.6 (19.6)	7.5 (18.0)	0.70
diarrhea	8.6 (18.6)	4.2 (13.7)	0.09

TABLE 1 SEQUAL

Baseline mean (SD) anxiety, depression, and QoL scores.HADS: Hospital Anxiety and Depression Scale, QLQ-C30 European Organization for Research and Treatment of Cancer 30 item QoL Questionnaire.

THE COURSE OF DISTRESS AND QOL

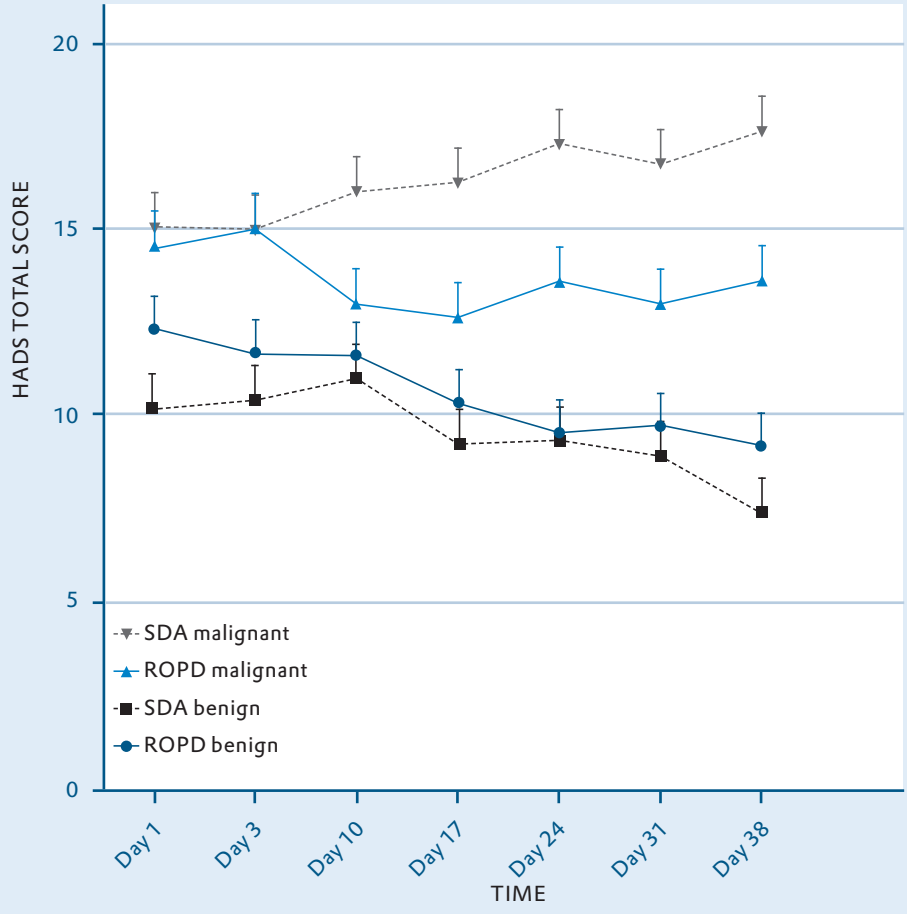
Distress levels measured with the total HADS scores during the course of the diagnostic evaluation of all patients are depicted in figure 2. Over time, HADS-total scores decreased in RODP patients from 13.8 at baseline to 11.9 on day 38 but sustained in SDA patients (13.1 and 13.6 respectively), showing a significant centre (2) by time (7) interaction effect ($p = 0.034$). The HADS-anxiety subscale showed a similar interaction effect ($p = 0.029$) over time. A small but statistically significant between-groups effect ($p = 0.038$) became apparent for HADS-D scores being slightly higher in SDA patients (differences between 0.4 and 2.0), however there was no interaction effect. After



	RODP	SDA
Day 1	13.8 (0.7)	13.1 (0.9)
Day 3	13.9 (0.8)	13.2 (1.0)
Day 10	12.7 (0.8)	14.0 (1.0)
Day 17	11.9 (0.8)	13.5 (1.0)
Day 24	12.1 (0.8)	14.1 (1.0)
Day 31	11.7 (0.9)	13.7 (1.1)
Day 38	11.9 (0.9)	13.6 (1.2)

FIGURE 2 **HADS-total scores of all SDA and RODP patients over time, means and standard errors of means**

three months, the differences in HADS-total scores between RODP and SDA patients disappeared (mean 11.5 and 11.8, respectively, p 0.91). Patients with a benign diagnosis reported lower scores than cancer patients (8.5 and 13.2 respectively, p 0.01).



	SDA malignant	ROPD malignant	SDA malignant	ROPD malignant
Day 1	15.0 (1.1)	14.5 (0.9)	10.2 (1.6)	12.3 (1.1)
Day 3	15.0 (1.2)	15.0 (1.0)	10.4 (1.6)	11.6 (1.1)
Day 10	16.0 (1.2)	13.0 (1.0)	11.0 (1.7)	11.6 (1.2)
Day 17	16.2 (1.3)	12.6 (1.1)	9.2 (1.6)	10.3 (1.2)
Day 24	17.2 (1.3)	13.6 (1.1)	9.4 (1.6)	9.5 (1.2)
Day 31	16.6 (1.3)	13.0 (1.1)	8.9 (1.8)	9.7 (1.4)
Day 38	17.6 (1.5)	13.6 (1.2)	7.4 (1.7)	9.2 (1.3)

FIGURE 3 **HADS-total scores in patients with benign and malignant diagnoses, means and standard errors of means**

Reviewing both genders separately, a centre type (2) by time (7) interaction effect (p 0.043) on HADS-total scores was found in men (p 0.043) but not in women (p 0.49). As for diagnosis, patients with a cancer diagnosis (lung and other) reacted significantly differently in RODP compared to SDA centres in terms of HADS total scores (figure 3, p 0.010) but patients with benign disease did not (p 0.78). In these patients, similar differences were found for both HADS-anxiety subscale (p 0.027 and 0.761, respectively), and HADS-depression subscale (p 0.005 and 0.603, respectively).

The mean QoL as indicated by the QLQ-C30 global scale showed neither significant differences between RODP and SDA patient groups (p 0.131) nor clinical relevant changes (i.e. less than 5 on the 0-100 scale[21]) over the 6 weeks that patients were followed. No differences were observed between both genders (p 0.214 for women, 0.56 for men). However in patients with benign diagnoses QoL improved 10.9 (moderate change) for SDA and 7.51 (light change) for RODP patients (p 0.40); patients with cancer did not show relevant changes during the course of the study. Since cancer history and surgery were more prevalent in RODP patients, we tried to determine whether these resulted in different patterns of HADS-total, HADS-anxiety and QLQ-C30 global scale but found no significant interaction effect.

DISCUSSION

This observational study shows that in patients in the diagnostic phase of suspected lung cancer, pre-diagnostic distress levels are very high, not only at baseline but also during the first weeks of diagnostic evaluation when almost two thirds of suspected lung cancer patients reach substantial distress levels.[14,18] Distress levels show different patterns over time: sustainment of distress in SDA patients and distress decrease in RODP patients. These findings are important since distress during the diagnostic phase of lung cancer has not been studied before[5] and many cancer patients suffering from psychological distress often remain unidentified.[22,23]

PRE-DIAGNOSTIC DISTRESS

Pre-diagnostic distress of suspected lung cancer has only been reported by Montazeri et al:[24] 16% of patients had HADS-anxiety scores over 7, and 10% over 10 - remarkably low compared to our findings (51.8% and 19.8% respectively), especially when taking into account the possible bias of this study in reporting results of patients with a confirmed lung cancer diagnosis only. In

fact, our results are much more in line with studies on suspected breast cancer patients reporting baseline HADS-anxiety levels over 8 in 46-63%[12, 13,24,25] and over 10 in 28-48%[11,12,26] of cases. Although other studies on pre-diagnostic anxiety used different instruments, high levels were reported in suspected breast, ovarian and prostate carcinoma patients.[9] This may confirm that the suspected lung cancer patient is not different from other suspected cancer patients in terms of distress levels, and moreover that the extreme levels in the present study are not unusual.

A remarkable outcome was that patients with an eventual cancer diagnosis in our study had significantly higher baseline distress levels compared to those with benign disease. Two studies in breast cancer patients[27,28] reported similar findings, possibly reflecting (non-verbal) cues that patients might have perceived from their physician.28 We cannot exclude that patients may have experienced more distress due to symptoms and therefore suspecting a worse outcome, as analysis of subscores of the QLQ-C30 and QLQ-LC13 questionnaires showed small but possibly relevant differences in patients with an eventual cancer diagnosis experiencing less physical functioning and more appetite loss. Furthermore, information given by the general practitioner at referral may have played a role and finally, since lung cancer is usually still smoking related, feelings of guilt due to previous smoking.

DISTRESS: THE EFFECT OF TIMELINESS

Regarding our hypothesis on the effect of an RODP in terms of distress, we found that over time distress reflected by HADS-Total and HADS-Anxiety scales decreasing faster in RODP patients. This may suggest a beneficial effect of the shorter time interval to reach a diagnosis and/or the programmed approach itself on patients' mental well-being. Post hoc analysis showed that this benefit was more profound in males and patients with an eventual cancer diagnosis. Eventually after three months, differences disappeared and distress levels decreased, although cancer patients were still far above the 10-point threshold indicating persisting distress.[18] Other studies in this respect are limited, small and focus on suspected breast cancer patients:[9] Dey et al.[13] found a significantly larger reduction of anxiety in one-stop evaluation compared with two-stop evaluation (in which suspected breast cancer patients were still awaiting results). This difference disappeared after three weeks. In two other studies,[11,12] suspected breast cancer patients who were given benign results rapidly experienced significantly less anxiety after one week than those still waiting for results. After communication of malignant

results, all studies showed equal increases of anxiety levels irrespective of diagnosis or diagnostic pathway.

QOL

Baseline global QoL was around six points higher than the reference lung cancer patients' values after diagnosis[29] and did not change relevantly despite the high distress levels and different diagnostic organisation types. This contrasts with the QoL results in the study by Harcourt et al.[11] in suspected breast cancer patients showing significant deterioration of several aspects of QoL in a one-stop diagnostic group compared with two-stop, and a significant increase in patients having benign results. Murray et al. reported similar decreases in role, social and financial functioning after diagnosis of lung cancer in patients randomized between one-day and conventional evaluation, however this comparison was performed after six weeks.[30]

CLINICAL IMPLICATIONS, LIMITATIONS AND STRENGTHS

Despite the descriptive and retrospective nature of the study, it has a wide socioeconomic and geographical range reflecting the population of lung cancer patients in present day practice in the Netherlands. The results should at least raise awareness among clinicians about the very high distress levels in suspected lung cancer patients; implementation of an RODP can be a relatively simple tool to address these.

This study features a substantial patient sample, followed over a longer period at fixed intervals during the diagnostic episode. To our knowledge, this has not been performed before. Although observational in design, it was performed as a multicentre study with university and general hospitals in both subsets of compared patients groups and relatively few missing data.

This study has some limitations. It is not a randomised trial, and although randomisation of this patient category is virtually impossible, should be interpreted with care. First, generalizability is restricted: more patients were included in ROPD centres compared to SDA centres, the largest contributing centre being a university hospital, although post-hoc analysis showed no interaction effect of surgery or cancer history (more frequent in the RODP patient sample) on the outcome parameters. Since PENELOPE is a descriptive study, we could not control for differences in atmosphere or in approach by medical personnel possibly influencing outcome variables, although the effect of the latter factor is probably limited as patients were seen by different

medical personnel per centre. Furthermore, smoking status was not recorded, and given the known associations between smoking and lung cancer, this may have been an important variable. Second, missing patient reported data required remodelling the course of distress and QoL by generalized least squares model. Third, post-hoc analysis showed that the interaction effect regarding HADS-total scores over time was different between genders, with male patients reporting highest scores; a remarkable finding since in various cancer types usually women (especially younger women) report higher scores than men. Therapeutic factors might have contributed to this difference, such surgery (which was less performed in SDA patients) or the intensity of the specific treatment.[31] Finally, half of all eligible patients refused participation. Questionnaire participation rates are rarely specifically studied, but the low rates in our patient category may not be unusual: Participation rates of 39-42% have previously been reported in smoking-related cancer studies[32,33] and were possibly related to smoking. Additionally, the substantial number of questionnaires in our study may have discouraged patients to participate.

CONCLUSION

Our study is the first to compare diagnostic pathways in terms of perceived distress in suspected lung cancer patients, and demonstrates high distress levels at baseline before diagnosis, remaining elevated during diagnostic analysis. Within the limitations of its descriptive nature the data suggest patients in an RODP approach experienced less distress. After 3 months, distress level differences between RODP and SDA patients disappeared. Despite the distress, QoL was relatively unaffected and increased in patients eventually not diagnosed with cancer. Clinicians should be aware of the very high distress levels in suspected lung cancer patients and may consider implementation of an RODP to address these.

ETHICAL APPROVAL

After consultation, the central ethics committee confirmed that approval was not necessary for this non-interventional study.

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6

SUMMARY AND GENERAL DISCUSSION

SUMMARY

Globally, lung cancer is the most prevalent cancer, the first cause of cancer death in men and second in women.[1] Since lung cancer is specifically smoking related, the lung cancer incidence rate showed a slow but steady decline in men in developed countries as a result of decreased tobacco consumption during the last quarter of the last century. In women, the incidence rose in the western world until recent stabilization.[2] However, in the Netherlands lung cancer incidence rates appear of epidemic proportions, with a nearly 30% increase in new lung cancer patients in 2011 compared to 2001 (11669 and 9009 cases respectively).[3] This quite alarming surge is mostly attributable to new cases in females in line with their increased tobacco consumption that commenced in the 1960's and 1970's.[4] This is illustrated by the fact that in 2012, Dutch women aged 45-64 still had a higher former smoking rate than women in any other European country.[5]

The overall five-year survival rate of lung cancer is presently estimated at 18% for all stages combined[6] and hardly improved over the last decades, despite the many efforts to find new therapies. With the usual focus on possible therapeutic improvements for this devastating disease, there has been less attention for the diagnostic episode despite the yearly increasing patient numbers, especially in the Netherlands. This thesis specifically evaluated different aspects of the diagnostic episode of suspected lung cancer, and more specifically the role of a rapid systematic approach towards the diagnosis of suspected lung cancer by means of a rapid outpatient diagnostic program (RODP). From the medical perspective, especially with the increasing patient numbers in mind, the value of an RODP in terms of timeliness and accuracy of diagnosis and disease stage was estimated. From a patient's perspective, the effects of analysis by RODP on the psychological distress that accompanies suspected lung cancer and on quality of life (QoL) were compared with analysis by a regular, stepwise approach.

TIMELINESS

During the last twenty years, timeliness of the diagnostic process of lung cancer has gained attention because of its supposed inverse relation to disease stage[7,8] and survival rates.[7-11] Guidelines on lung cancer care have been implemented stating specific criteria for referral, diagnostic and treatment delay[12-15] but research has shown that these were often not met in clinical practice.[16] In the Radboud University Medical Centre (Radboudumc), an RODP for suspected lung cancer patients was implemented in 1999. This RODP was based on a two-day schedule and included the specific novelty of a routine ^{18}F-fluorodeoxyglucose Positron Emission Tomography-Computed Tomography (FDG-PET/CT) scan. In **chapter 2** we investigated different aspects of diagnostic care in all 565 patients with retrievable medical charts out of the total of 570 who had been referred for suspected lung cancer in this RODP, during the first 10 years after its implementation. Apart from the fact that roughly one third of the patients were referred by a general practitioner (GP) and the other two thirds by a specialist consultant, the patient cohort was demographically representative with a mean age of 63.9 years, and 66.5% of all patients being male. Calculations based on specified dates revealed a median referral, diagnostic and curatively intended therapeutic delay of seven, two and eighteen days, respectively. After analyzing all defined delays per stage, diagnostic delay was inversely related to clinical stage, contrary to therapeutic delay which was proportionally related. For the subgroup of patients that had to undergo a diagnostic – and in case of cancer also therapeutic – thoracotomy, therapeutic delay, defined by the interval between diagnosis and therapy, could be extremely short and therefore causes a bias. After exclusion of this subgroup, none of the delays showed a relation with clinical or pathological stage. No relation between any delay and survival was found.

ACCURACY OF SAME DAY RAPID CYTOLOGY IN COMPARISON TO FINAL CYTOLOGY AND PATHOLOGY RESULTS

Lung cancer was diagnosed in 51.3% of all patients, of whom 90% had non-small cell lung cancer (NSCLC), 9.0% small cell lung cancer (SCLC) and 1.0% a double tumor consisting of both cell types. Malignant pleural mesothelioma or metastasis of another tumor type was found in 8.3% of patients. A certain benign diagnosis (usually infection) was found in 20.4% of patients, and in 19.8% no definite pathology diagnosis could be obtained. In 73.2 % of these indefinite cases follow-up confirmed a benign outcome; all others remained suspected lung cancer cases but further analysis was either deemed

futile because of poor performance status or was refused by patients themselves. In 59.1% of the 279 lung cancer patients who underwent bronchoscopy, tissue samples rendered a cytological or histological diagnosis, although this number was lower in the 170 patients without any visible endobronchial abnormalities (39.4%). The RODP cytological diagnosis of lung cancer was accurate when compared to the bronchoscopy histology results that were reported in the same week in 97.2% of cases; in four cases NSCLC had been mistaken for SCLC, or vice versa.

ACCURACY OF FDG-PET/CT WITHIN AN RODP

Out of all 565 patients, 144 were referred to the RODP with suspicion based on an abnormal chest CT-scan that usually had been performed for other reasons than a direct suspicion of lung cancer. A chest CT-scan can characterize a lesion much better as probably benign or malignant than a chest X-ray. It may indeed be a reasonable option in a stepwise approach towards a patient with an abnormal chest X-ray to first perform a CT. However, one of the specific characteristics of the RODP is that patients undergo FDG-PET/CT after a chest X-ray. When assessing the quality of the diagnostic performance of such an RODP this is an important patient subgroup and therefore in **chapter 3**, we studied patients that entered the RODP after an abnormal chest X-ray separately. This is an important subgroup in usual clinical practice, as in primary care most lung cancer suspicions start with an abnormal chest X-ray. In total 386 patients were analyzed in this cohort; 50.3% were referred by a GP. Lung cancer and certain benign diagnoses were eventually diagnosed in 61.1% and 20.2% of all cases, respectively. Other cancer types such as malignant pleural mesothelioma or pulmonary metastases of a non-pulmonary tumor were found in 7.0% of cases. The remaining 11.7% of patients had no pathological confirmation of their lesion(s) but these were considered benign after not showing growth on CT during follow-up. In 8.3% of all patients (8.3%) malignancy might have retrospectively been excluded on CT alone as the lesions showed typical benign characteristics, or for instance no abnormalities at all. For diagnosis of malignancy, sensitivity was 97.7% (95% confidence interval 94.9-99.1%), specificity 60.2% (50.9-68.8%), negative predictive value 92.5% (83.8-96.9%) and positive predictive value 84.0% (79.3-87.8%). Accuracy, defined as the proportion of true results, was 85.8% (81.4-90.0%). Analysis of delays within this subgroup revealed a median referral and diagnostic delay of seven days and one day, respectively. For patients in this cohort, ultimately diagnosed with lung cancer, median referral delay was also seven days, diagnostic delay two days and therapeutic delay 19 days.

DISTRESS OF THE SUSPECTED CANCER DIAGNOSIS AND EFFECT ON QUALITY OF LIFE

The subsequent two chapters shared patient reported outcomes in the diagnostic phase of suspected cancer mainly in terms of distress and Quality of Life (QoL). The National Comprehensive Cancer Network defined distress as an unpleasant emotional experience of psychological, social or spiritual nature interfering with the ability to effectively cope with cancer. Distress extends on a continuum ranging from common normal feelings of vulnerability, sadness and fears to problems that become disabling, such as depression and anxiety.[17] Quality of life refers to the functioning of patients on physical, psychological and social domains. In an attempt to answer the question on how much distress suspected patients encounter during the diagnostic episode, and what possible effects of an RODP are known, a systematic review of the available literature was performed. **Chapter 4** described this review which resulted in a collection of 23 publications out of a total of 1846 that were eligible for review based on publication of prospectively derived data on distress, anxiety, depression and QoL in suspected cancer patients before and after diagnostic evaluation. Notably, suspected lung cancer was hardly represented in these studies; most reported data concerned suspected breast cancer patients. Furthermore, the use of different measures for distress and QoL complicated comparison between studies. The most frequently used measure for anxiety was the Hospital Anxiety and Depression Scale (HADS), a 14-item questionnaire consisting of two subscales of anxiety and depression.[18] Items are rated on a 4-point scale, rendering a maximum total score of 21. On either subscale, scores of 0–7 are considered normal; scores of ≥ 11 are considered a significant 'case' of psychosocial morbidity, scores of 8–10 are considered 'borderline' and indicate potential clinical anxiety or depression. A HADS-total score of 10 or higher is presently regarded as best cut-off for screening for severe distress in cancer patients.[19] An important finding of the review was that pre-diagnostic anxiety as measured by the HADS Anxiety subscale (HADS-A), was high in suspected cancer patients (i.e. usually suspected breast cancer) showing 'borderline' and 'case' anxiety levels in 46-73% of patients.[20-25] The single study in this review that was performed in suspected lung cancer patients found these levels in 16% of all patients.[26] The low percentage may have been the result of sampling bias, since only data had been used of those patients who were eventually actually diagnosed with lung cancer and who were possibly aware of their lung cancer diagnosis in this particular study. As for QoL, suspected cancer patients' pre-diagnostic general QoL levels were much lower than the random normal

reference, with suspected lung cancer patients accounting for the lowest scores.[25,27-31]

With respect to the effect of a cancer diagnosis on distress, a beneficial effect of a rapid benign diagnosis on distress became apparent, in the form of both statistically and clinically significant decreases of anxiety in case of benign disease, irrespective of suspected cancer type. In case of confirmation of suspected cancer anxiety tended to increase or sustain, [22-25,28-37] with the exception of two studies reporting decreases of anxiety levels after diagnosis of melanoma and ovarian cancer patients.[38,39] In the end, only three relatively small studies in suspected breast cancer patients were found to report data on the effect of a rapid versus a non-rapid diagnosis, and thereby qualified as a comparison between an RODP and regular diagnostic care.[22,24,25] These studies revealed earlier improvements in anxiety scores for patients with benign results in rapid pathways, and equal increases of anxiety scores in case of malignant results in both rapid and non-rapid pathways. QoL was reported in only one of these studies[25] on rapid versus non-rapid breast cancer diagnosis and showed significant deterioration of several aspects of QoL in breast cancer patients in the rapid group, and a significant increase in patients having benign results.

The lack of studies regarding distress and QoL of suspected lung cancer, although known for its high distress levels compared to other malignancies[40,41] was perhaps one of the most striking conclusions of the reviewed literature. In order to address this lacuna and to provide answers for this patient group, we designed and performed the PENELOPE study (Pulmonary Evaluation of NEoplastic Lesions in Outpatients and its Psychological Effects). The study was described in detail in **Chapter 5**. PENELOPE included a large number of patients in a prospective cohort design to compare distress and QoL during the diagnostic episode of suspected lung cancer in two Dutch medical centers that had implemented an RODP and two that used a usual Standardized Diagnostic Approach (SDA) based on trained nurse led care. We compared patient distress and QoL in both diagnostic pathway types, by taking serial sets of questionnaires containing several measures. Of these, the results of the HADS, the European Organization for Research and Treatment of Cancer 30-item Quality of Life Questionnaire (QLQ-C30)[42] and its 13-item Lung Cancer specific module (QLQ-LC13)[43] were reported. The study included 193 patients who returned one or more questionnaires. Pre-diagnostic distress levels turned out to be very high; the baseline mean HADS total score was

13.5, or from a different perspective: 63.4% of patients had a HADS-total score of 10 or higher,[19] indicative of significant distress. Baseline HADS total scores were not statistically different between RODP and SDA patients, however, distress of patients with an eventual cancer diagnosis were higher (14.7) when compared to patients with a benign outcome (11.8, p 0.01). Pre-diagnostic QoL as measured by the QLQ-C30 global QoL score for all patients was 61.6 and was not statistically different between RODP and SDA patients. Over time, HADS-total scores decreased in RODP patients from 13.8 at baseline to 11.9 on day 38, but sustained in SDA patients (13.1 and 13.6 respectively), showing a significant centre (2) by time (7) interaction effect (p 0.03), which was similar for the HADS-anxiety subscale. When separately analyzed, this difference between RODP and SDA was seen in male (p 0.04) but not in female patients
(p 0.49), and in patients with a malignant (p 0.01) but not with a benign outcome (p 0.78). After three months, the differences in HADS-total scores between RODP and SDA patients had disappeared (mean 11.5 and 11.8, respectively, p 0.91), and patients with a benign diagnosis reported lower scores than cancer patients (8.5 and 13.2 respectively, p 0.01)). The mean baseline global QoL for all patients was within reference lung cancer patients' values after diagnosis,[44] not significantly different between RODP and SDA patients and did not change relevantly during the study period.

GENERAL DISCUSSION

Lung cancer care has been affected by major changes during the last decades. As mentioned before, especially in the Netherlands patient numbers are rising.[3] Accurate staging and tumor characterization are increasingly important due to the fact that management decisions increasingly depend on a combination of tumor stage, tumor type and partly on gene mutation status.[45,46] The role of the rapid diagnostic pathway may be seen as a pivotal one. This thesis shows that an RODP benefits different aspects of diagnostic care. Incorporation of an FDG-PET/CT enables the physician to diagnose and stage timely within guideline criteria and as confidently as in usual diagnostic care. Moreover, from the patient's perspective it has added value since the reported distress is lower in the first 2 months following RODP compared to SDA.

As extensively described in **chapters 2 and 3**, the Radboudumc RODP for suspected lung cancer started its programmed approach with FDG-PET/CT and included bronchoscopy as the primary diagnostic tool to deliver a tissue diagnosis. Whether both diagnostic entities should have this central role can be debated, especially regarding bronchoscopy which might not be an obvious first choice in case of a smaller or more peripherally located tumor and nowadays more often Endobronchial Ultrasound (EBUS) is chosen as a first diagnostic tool combining both staging and diagnostic properties. That being said, the utility of bronchoscopy in experienced hands was demonstrated by the fact that diagnosis was achieved by bronchoscopy in 59.1 % of all lung cancer patients. Furthermore, although in 60.9% of the lung cancer patients who underwent bronchoscopy, endobronchial abnormalities to guide direct biopsies were lacking, in 39.4% of cytological specimens malignant cells were nevertheless detected. Moreover, the malignant same-day cytological diagnosis on the bronchoscopy day was in 97.2% of cases confirmed as accurate by the final diagnostic results, reported in the same week. Although the smaller sample size of cytology compared to histology therefore not led to less accurate results, too small cytology specimens may complicate the analysis of gene mutation status. This is often crucial nowadays,[46] but not common practice during the years of the analyzed RODP cohort.

The most important (and within the RODP also the first) diagnostic tool was FDG-PET/CT, with radiological and nuclear images being conjointly read immediately after the scanning procedure. **Chapter 3** demonstrated that even for the important patient subgroup that had been referred with abnormal chest X-ray, sensitivity, NPV and PPV were within the published range of accuracy.[47] Although the demonstrated specificity of 60.2% may seem low compared to existing data, it is important to emphasize that other studies usually included patients with solitary pulmonary nodules on a CT scan, inherently increasing the pre-test probability of malignancy. Compared to our selection of chest X-ray referred patients, this resulted in a higher specificity (77.8%).

The obvious downside of an RODP that starts with an FDG-PET/CT is the risk of overuse in patients with a final benign diagnosis that appeared malignant at referral: Results of more than one third of patients (34.8%) were eventually definitely or probably (after follow up) benign. Supposedly, this risk may

be higher in patients referred with an abnormal chest X-ray, as a chest CT has a higher accuracy in the differentiation between benign and malignant lung lesions. In retrospect, in 8.3% of all cases of the chest-X-ray based referrals, CT without FDG-PET would have been sufficient in ruling out malignancy with high certainty. However, interposition of CT between chest X-ray and FDG-PET would have had an adverse effect on timeliness.

TIMELINESS

Essential for the value of the RODP was the fact that it resulted in a median diagnostic delay of two days (even one day for the subgroup of chest X-ray referred patients), which is within any guideline limitation and substantially shorter than reported delays of 7–37 days in other studies.[16] Although this was an important observation, also shorter waiting times before and after the diagnostic process contribute to the patient experience and the quality of cancer care. Analysis of diagnostic and therapeutic delays revealed possible benefits of the RODP as well. An RODP schedule inevitably increases waiting time for part of the referred patients when it is fixed to two weekdays (Wednesday and Thursday in case of the Radboudumc RODP). Nevertheless, the median waiting time before first visit was seven days and within guideline limitations, except for the Dutch Guideline stating a five day maximum.[12-15] Furthermore, it was shorter than presented in literature with the exception of only one study.[16,48] The delay of 18 days to curative therapy for lung cancer patients was in the low range of comparable reports[16] and within all guideline limitations.[12-15] These findings suggest that, despite the fact that the RODP was not designed to specifically reduce referral or therapeutic delay, the systematic and multidisciplinary approach to analyze all patients by RODP may have had a beneficial effect on both.

DISTRESS AND QUALITY OF LIFE AROUND DIAGNOSIS

WHAT DOES *PENELOPE* LEARN US?

Both positive and negative effects on lung cancer patients' wellbeing have been attributed to an RODP in the past. Discussions between proponents and opponents were supported by contrasting arguments. On the one hand the importance of the time the patient should need to get used to the dismal diagnosis was stressed, on the other hand the supposed benefit of shortening the period of uncertainty as much as possible was a main issue.[49-51] The argumentations were based rather on personal beliefs than science, since at the time not many studies existed on distress and QoL before or surrounding a potential cancer diagnosis, and as Chapter 4 demonstrated, even less on

the influence of an RODP. The PENELOPE study, presented in **chapter 5**, is the first large prospective study demonstrating a beneficial effect of an RODP: distress levels in suspected lung cancer patients analyzed in an RODP decreased faster over time compared to distress levels in patients analyzed in an SDA. This effect on patients' mental well-being may be explained by either the shorter time interval to reach a diagnosis or by the programmed approach itself, or by both. Obviously, we should realize that PENELOPE was not a randomized but a descriptive study and there were differences between including centers in terms of patient characteristics and inclusion numbers, which may have had an effect on results. On the other hand, just like the patient population described in the Radboudumc RODP, it has a wide socio-economic and geographical range that reflects the population of lung cancer patients in The Netherlands.

DISTRESS IN SUSPECTED CANCER

On top of the beneficial result for the suspected cancer patient in an RODP, two further findings of the PENELOPE study are of great importance. First, the very high distress levels that were found in referred suspected lung cancer patients: almost two thirds of patients had distress levels qualifying as suggestive of severe distress (HADS-total score of 10 or higher,[19] including a substantial number of patients that eventually had a benign outcome. In line with suspected breast cancer patients[22-24,27] these results confirm that the suspected lung cancer patient is not quite different in terms of distress levels as compared to other suspected cancer patients. This is contradictory to the single previous study in suspected lung cancer patients reporting much lower distress levels.[26] Moreover, this also suggests that these extreme levels found before diagnosis are not unusual. A second finding was that mean distress scores after three months for both RODP and SDA patients with lung cancer were still well above the 10-point distress threshold on the HADS-total scale, which confirms that lung cancer patients are indeed a group at risk for distress. These facts are all the more important since many cancer patients suffering from psychological distress often remain unidentified due to either patient underreporting or underestimation by physicians.[53,53] Pre-diagnostic distress may remain equally unrecognized as well.

FACTORS INFLUENCING DISTRESS LEVELS IN SUSPECTED CANCER

With respect to distress *after* diagnosis, different factors are known to be of importance and these have to be taken into account in the comparison and interpretation of the literature: Factors such as gender, age, or specific can-

cer type influence distress.[40,54,55] In other words, perhaps the most important question is whether the data of suspected breast cancer patients, inherently all female and perhaps younger, result in a selection bias when interpreting study results. Distress levels in these patients may not be equivalent to those in patients with other highly prevalent malignancies such as colorectal or lung cancer. Furthermore, different studies use different assessment measures, and certain studies assess distress around a specific diagnostic procedure, rather than around the diagnostic work-up as a whole. Despite of all the above, the studies reviewed in **chapter 4** demonstrated a beneficial effect of a rapid benign diagnosis on distress in general. In case of confirmation of suspected cancer, anxiety tended to increase or sustain, with the exception of two studies reporting decreases of anxiety levels after diagnosis of melanoma and ovarian cancer patients;[38,39] these different outcomes might be attributed to the specific cancer type (in case of melanoma), or the way the specific study was performed causing possible bias.[38] To equally compare the results of PENELOPE, we have to resort to three relatively small studies in suspected breast cancer patients analyzed by means of an RODP compared to a regular approach, revealing earlier improvements in anxiety scores for patients with benign results in rapid pathways, and equal increases in case of malignant results in both rapid and non-rapid pathways. In the PENELOPE study, it is a remarkable finding that the decrease of distress in an RODP appeared more profound in males is remarkable, since the female gender has been generally related to higher distress levels.[56,57]

The pattern over time of global QoL (EORTC QLQ-C30 global QoL scale) was different: in contrast to distress, baseline values positively exceeded the reference lung cancer patients' values after diagnosis by around 6 points.[58] After baseline, QoL did not relevantly change, either over time, or between diagnostic organization types despite the high distress levels, and in contrast to the deteriorating short term QoL that was found in two other studies on the effect of an RODP in breast[25] and lung cancer patients.[59]

THE FUTURE

An RODP has advantages to the regular stepwise approach, but further improvements are imaginable. For instance, in order to reduce patient radiation exposure and to increase cost-effectiveness, the effect of separating the diagnostic CT from the FDG-PET on both parameters could be evaluated. As mentioned, this may prevent patients from undergoing FDG-PET for benign lesions, but may increase the complexity of an RODP system and will pre-

clude a two-day schedule. Furthermore, the RODP should expand the techniques to obtain a tissue diagnosis by not only including bronchoscopy as the primary method but also transthoracic biopsies and/or endoscopic ultrasound guided procedures. This could further improve timeliness for those patients with peripheral lesions or non-bulky mediastinal metastases. Finally, another important subject to address is therapeutic delay: from the patient's perspective the interval between referral and start of therapy may be equally important.

Apart from the benefits of an RODP on timeliness and accuracy of diagnostic care, this thesis shows additional benefits in terms of distress levels. Until lung cancer is cured, distress will be following the patient after diagnosis, during treatment and beyond, in both curative and palliative settings. And since cure is by far not in sight, increased awareness among physicians of the risk of severe patient distress from the moment the suspicion of lung cancer is communicated, may be the second best thing.

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7

NEDERLANDSE SAMENVATTING

SAMENVATTING

Longkanker is wereldwijd de meest voorkomende soort kanker. Daarnaast is het de belangrijkste kanker-gerelateerde doodsoorzaak bij mannen en de op één na belangrijkste bij vrouwen.[1] Longkanker wordt in belangrijke mate veroorzaakt door roken. Als gevolg van de verminderde tabaksconsumptie in met name de westerse wereld valt er een lichte, maar gestage daling van het aantal nieuwe gevallen waar te nemen bij mannen. Bij vrouwen is dit aantal gestegen door toename van het aantal vrouwelijke rokers in de laatste decennia van de vorige eeuw. Toch lijkt het aantal globaal gezien te stabiliseren.[2] In Nederland is de incidentie van longkanker echter gestegen van 9009 nieuwe gevallen in 2001 tot 11669 in 2011, een toename van bijna 30%.[3] Deze alarmerende toename komt vrijwel geheel voor rekening van de vrouwelijke helft van de populatie, in lijn met de toegenomen consumptie van tabak door vrouwen in ons land sinds de jaren '60 en '70 van de vorige eeuw.[4] In 2012 bleken Nederlandse vrouwen in de leeftijdscategorie van 45-64 jaar frequenter te roken dan hun leeftijdgenoten in andere Europese landen.[5]

De vijf-jaars-overleving van longkanker, wanneer we alle stadia bijeen nemen, ligt momenteel rond de 18%.[6] Dit percentage is de laatste decennia nauwelijks veranderd, ondanks de vele wetenschappelijke inspanningen om betere vormen van behandeling te ontwikkelen. Opvallend is dat onderzoek bij longkanker meestal is gericht op therapeutische uitkomsten en niet op het diagnostische traject van de patiënt bij wie longkanker wordt vermoed, ondanks de zeker in Nederland jaarlijks toenemende aantallen. Juist van dit diagnostische traject worden in dit proefschrift diverse aspecten onder de loep genomen, en dan met name de invloed van een versnelde en systematische poliklinische analyse van patiënten bij wie longkanker wordt vermoed: de zogeheten sneldiagnostiek. Enerzijds wordt de meerwaarde ervan belicht voor het verkrijgen van niet alleen een tijdige, maar ook een correcte diagnose, anderzijds wordt de beleving in termen van psychisch welbevinden, angst en kwaliteit van leven vergeleken tussen patiënten met sneldiagnos-

tiek en patiënten die de reguliere stapsgewijze poliklinische analyse ondergaan.

DE TIJDSDUUR VAN HET DIAGNOSTISCHE TRAJECT

Het tijdig doorlopen van de diagnostiek voor longkanker heeft de laatste twintig jaar meer aandacht gekregen vanwege een verondersteld omgekeerd verband tussen het ziektestadium[7,8] en overlevingscijfers.[7-11] Diverse nationale en internationale richtlijnen zijn geïmplementeerd met specifieke maximale 'doorlooptijden' voor verwijzing, diagnosestelling en behandeling.[12-15] Onderzoek heeft echter ook laten zien dat in de dagelijkse praktijk deze doorlooptijden vaak veel langer zijn dan richtlijnen voorschrijven.[16] In het RadboudUMC in Nijmegen werd in 1999 een nieuw instrument voor diagnostiek en stadiëring van longkanker geïntroduceerd: de ^{18}F-fluorodeoxyglucose-Positron-Emissie Tomografie (FDG-PET) gecombineerd met Computer Tomografie met röntgencontrast (CT, samen FDG-PET/CT genoemd). Tegelijk hiermee werd een programma voor sneldiagnostiek ontwikkeld dat als specifiek novum startte met een FDG-PET/CT voor alle patienten die waren verwezen vanwege een radiologische verdenking van longkanker. In de eerste tien jaar na de introductie zijn in totaal 570 patiënten met behulp van dit programma geanalyseerd.

In **hoofdstuk 2** zijn diverse aspecten beschreven van de 565 patiënten uit die periode van wie medische gegevens konden worden achterhaald. Deze groep patiënten was representatief voor de reguliere longkankerpatiënt, gezien de gemiddelde leeftijd van 63.9 jaar en de verhouding mannelijk (66.5%) en vrouwelijk (33.5%) geslacht. Opvallend was wel het verwijspatroon, daar slechts een derde van de patiënten door een huisarts verwezen was, het overige deel door een medisch specialist. Door van iedere patiënt de doorlooptijd te registreren, waren voor de hele groep mediane doorlooptijden te berekenen voor verwijzing (door huisarts of specialist tot eerste bezoek), diagnose (eerste bezoek tot diagnose) en curatieve behandeling (diagnose tot eerste behandeling); deze kwamen uit op respectievelijk zeven, twee en achttien dagen. Bij vergelijking van hogere en lagere klinische stadia bleek een langere diagnostische doorlooptijd gerelateerd aan een hoger stadium; voor curatieve behandeling gold het omgekeerde. Van belang bleek ook de subgroep patiënten die een diagnostische thoracotomie had ondergaan, een zogenaamde 'proefthoracotomie' bij verdenking longkanker zonder vooraf vaststaande diagnose. In hun geval was de diagnostische doorlooptijd extreem kort en mogelijk verstorend voor de analyse. Na exclusie van deze groep bleek er geen verband meer aan te tonen tussen welke doorlooptijd

ook met een hoger of lager stadium van ziekte. Er viel evenmin een verband vast te stellen tussen doorlooptijd en overleving.

SNELLE DIAGNOSE: CYTOLOGIE VERSUS DEFINITIEVE RESULTAAT

Bij 51.3% van de patiënten was uiteindelijk sprake van een vorm van longkanker; deze groep bestond voor 90% uit niet-kleincellige longkanker (NSCLC), 9% uit kleincellige longkanker (SCLC) en in 1% kwamen beide vormen gelijktijdig voor. Metastasen van een andere soort kanker of een maligne mesothelioom kwamen voor in 8.3% van de gevallen. Bij 20.4% van de patiënten werd een zekere benigne diagnose gesteld, doorgaans een infectie. Van de gehele groep patiënten bleek bij 19.8% geen definitieve diagnose te stellen; bij bijna driekwart van hen (73.2%) bevestigde het vervolgen van de radiologische afwijkingen het vermoeden van een niet-maligne aandoening. Het overige deel hield wel een sterke verdenking op longkanker, maar werd niet verder geanalyseerd omdat dit hetzij medisch gezien zinloos werd geacht ten gevolge van bijvoorbeeld een sterk verslechterde algehele conditie, hetzij door de patiënt werd geweigerd. Van de 279 longkankerpatiënten die een bronchoscopie hadden ondergaan, werd bij 59.1% op basis van bronchoscopisch verkregen cytologisch of histologisch materiaal de specifieke diagnose verkregen. Dit lukte minder vaak als er geen endobronchiale afwijkingen zichtbaar waren, namelijk bij 39.4% van de patiënten. De voorlopige cytologische diagnose van longkanker was, vergeleken met de definitieve diagnose die dezelfde week werd afgegeven, correct in 97.2% van de gevallen; in 4 gevallen bleek deze niet correct te zijn en was een NSCLC gehouden voor een SCLC, of andersom.

HET DIAGNOSTISCH VERMOGEN VAN DE FDG-PET/CT BINNEN EEN SNELDIAGNOSTIEK-PROGRAMMA

Van alle bovengenoemde 565 beschreven patiënten met bekende medische gegevens waren er 144 verwezen naar het sneldiagnostiek-programma op basis van afwijkingen op een CT-scan, die meestal was gemaakt om andere redenen dan een vermoeden van longkanker. Met een CT-scan van de thorax valt het vermoeden dat een afwijking benigne of juist maligne is, veel beter in te schatten dan op basis van een X-thorax. In een stapsgewijze benadering van een patiënt met verdenking longkanker is het heel gebruikelijk om eerst een CT te maken. In het sneldiagnostiekprogramma was het juist een bijzonder kenmerk dat het mogelijk was dat patiënten met alleen een afwijkende X-thorax een FDG-PET/CT ondergingen. Dit is een belangrijke subgroep, omdat in de eerstelijns gezondheidszorg de verdenking van longkanker door-

gaans met een X-thorax begint. Daarnaast is het ook voor het beoordelen van de diagnostische waarde van de FDG-PET/CT binnen het sneldiagnostiekprogramma een belangrijke subgroep, die derhalve in **hoofdstuk 3** apart is beschreven.

Het cohort bestond uit 386 van de 565 patiënten uit de eerdere studie: 50.3% van hen was verwezen door een huisarts. Er bleek in 61.1% van de gevallen sprake van longkanker, in 20.2% van een benigne afwijking. In 7.0% van de gevallen was er sprake van een metastase van een andere tumor of een maligne mesothelioom. Bij de overige 11.7% van de patiënten is geen diagnose verkregen, maar werd de afwijking als benigne beschouwd en vervolgd zonder tekenen van groei. Bij 8.3% van dit cohort had retrospectief een CT-scan alleen reeds voldoende informatie kunnen geven om een maligniteit uit te sluiten, omdat de laesie radiologisch typisch benigne kenmerken vertoonde of omdat bijvoorbeeld geen enkele afwijking (meer) zichtbaar was. Ten aanzien van de diagnose maligniteit bedroeg de sensitiviteit 97.7% (95%-betrouwbaarheidsinterval 94.0-99.1%), specificiteit 60.2% (50.9-68.8%), negatief voorspellende waarde 92.5% (83.8-96.6%) en positief voorspellende waarde 84.0% (79.3-87.8%). Het percentage correcte resultaten bedroeg 85.5% (81.4-90.0%). Voor deze specifieke subgroep is ook de tijdigheid van de diagnostiek berekend: de mediane doorlooptijden van verwijzing en diagnose bedroegen respectievelijk zeven dagen en één dag, voor de patiënten die uiteindelijk longkanker bleken te hebben en behandeld werden respectievelijk zeven en twee dagen, met een mediane doorlooptijd tussen diagnose en behandeling van 19 dagen.

HET PSYCHISCH EFFECT VAN DE VERDENKING VAN KANKER, EN HET EFFECT OP DE KWALITEIT VAN LEVEN

De volgende twee hoofdstukken betroffen patiënt-gerapporteerde uitkomsten van onderzoek over het diagnostische traject van een verdenking van kanker, en dan in het bijzonder psychisch relevante nood, een begrip dat in het Engels het best wordt weergegeven door de term '*distress*' – en daarnaast kwaliteit van leven. Volgens de definitie van het National Comprehensive Cancer Network is *distress* een onprettige emotionele ervaring van psychologisch, sociaal of spiritueel karakter, die het de patiënt verhindert om de maligne aandoening op een effectieve manier het hoofd te bieden. Het betreft hier een continuüm, strekkend van normale gevoelens van kwetsbaarheid, verdriet en angsten tot problemen die aantoonbare klachten veroorzaken, zoals een angststoornis of depressie.[17] Kwaliteit van leven behelst vooral het

functioneren van de patiënt op het fysieke, psychische en sociale vlak. In een poging om te kwantificeren hoeveel *distress* patiënten in de diagnostische fase van een verdenking op kanker doormaken en het effect van een sneldiagnostiekprogramma hierop, is een systematische review van reeds gepubliceerde studies in de wetenschappelijke literatuur verricht. Dit resulteerde in **hoofdstuk 4** in een bespreking van een verzameling van 23 relevante wetenschappelijke artikelen uit een totaal van 1846 die in eerste instantie naar voren kwamen bij een elektronische zoekopdracht, waarbij in Engelstalige literatuur gezocht werd op prospectieve data over *distress,* angst, depressie en kwaliteit van leven bij patiënten met een verdenking van kanker, gemeten vóór en na diagnostische onderzoeken. Opvallend genoeg bleken er nauwelijks publicaties te zijn waarin het om een verdenking van longkanker ging; het merendeel betrof patiënten met een verdenking van een mammacarcinoom. Bovendien bleken er bij de verschillende studies ook verschillende soorten vragenlijsten te worden gebruikt, hetgeen onderlinge vergelijking en kwantificeren lastig maakt. De meest gebruikte vragenlijst was de Hospital Anxiety and Depression Scale (HADS), die bestaatuit 14 items, gelijkelijk verdeeld over twee schalen: angst (HADS-A) en depressie (HADS-D).[18] De items scoren op een schaal van 4 punten, waarbij opgeteld een maximale score van 21 punten mogelijk is. Een score van 0 tot 7 op één van beide schalen wordt normaal geacht, scores van 11 of hoger als een significant geval van psychopathologie; scores daartussen worden ' borderline' genoemd en kunnen indicatief zijn voor een potentiële angststoornis of depressie. Vodemaier stelde bovendien vast dat wanneer beide schalen opgeteld (HADS-totaal) een score van 10 of hoger opleveren, dit waarschijnlijk optimaal de mogelijkheid van een psychische stoornis aangeeft.[19]

Een van de opvallende bevindingen van dit review was dat pre-diagnostische angst, zoals gemeten met de HADS-A vóór het bekend worden van de diagnose, erg hoog lag bij patiënten die van kanker (weliswaar dus meestal borstkanker) verdacht werden: in 46 tot 73% van de gevallen was er sprake van 'borderline' of 'case' HADS-A scores.[20-25] De enige gepubliceerde studie over patiënten met een verdenking van longkanker vond deze scores bij slechts 16% van de gevallen.[26] Hier kan overigens sprake zijn geweest van het effect van selectie, omdat alleen patiënten die uiteindelijk daadwerkelijk longkanker bleken te hebben in deze studie waren opgenomen en het bovendien heel goed mogelijk is dat (een deel van de) patiënten reeds op de hoogte was van deze diagnose. Kwaliteit van leven voorafgaand aan de diagnose bleek bij patiënten die van kanker verdacht werden veel lager te zijn dan de bekende gemiddelde referentiewaarde, waarbij een verdenking op longkanker er nog verder in negatieve zin uitsprong.[25,27-31]

Er werd een gunstig (significant en relevant) effect van een benigne diagnose gevonden voor angst bij alle onderzochte soorten kanker. Indien het inderdaad een maligne diagnose betrof, bleven angstscores doorgaans gelijkwaardig aan die vóór de diagnose, of vertoonden ze een stijging.[22-25,28-37] Twee opvallende uitzonderingen die juist een daling van de angstscores lieten zien, betroffen een studie bij patiënten met een melanoom en een studie bij patiënten met een ovariumcarcinoom.[38,39]

Voor de vergelijking van het effect van een snellere diagnose op bovengenoemde aspecten of specifiek van sneldiagnostiek ten opzichte van reguliere, stapsgewijze diagnostiek bleken slechts drie studies die aan de zoekcriteria voldeden geschikt. Het betrof in alle drie de gevallen studies bij patiënten met een verdenking van borstkanker; de resultaten lieten zien dat angstscores bij een benigne diagnose sneller daalden bij sneldiagnostiek- patiënten, en vergelijkbaar stegen bij een maligne diagnose.[22,24,25] Kwaliteit van leven werd in slechts één van deze drie studies vergeleken[25] en bleek op verschillende dimensies te dalen bij patiënten met een diagnose mammacarcinoom, en juist significant te stijgen bij patiënten die een goedaardige aandoening bleken te hebben.

Samenvattend is er dus weinig bekend over *distress* en kwaliteit van leven bij een verdenking op longkanker, hetgeen opvalt vanwege het feit dat het gaat om een patiëntengroep die bekend staat om hoge angstscores gedurende het verdere verloop van de ziekte in vergelijking met andere maligniteiten.[40,41]

Om meer te weten te komen over juist deze patiëntengroep is de PENELOPE-studie ontworpen. PENELOPE is een acroniem voor Pulmonary Evaluation of NEoplastic Lesions in Outpatients and it's Psychological Effects, en is uitgebreid beschreven in **hoofdstuk 5**. In het kort betrof de PENELOPE-studie een prospectief cohortonderzoek, met daarin een groot aantal patiënten die een diagnostisch traject doorliepen in verband met een verdenking op longkanker. Het doel was om angst, depressie en kwaliteit van leven te vergelijken tussen een groep patiënten die in een sneldiagnostiekprogramma werden geanalyseerd, en een groep die deze analyse via stapsgewijze diagnostiek onderging. De groepen waren verdeeld over vier ziekenhuizen, twee daarvan met een sneldiagnostiektraject, en twee die patiënten stapsgewijs analyseerden. Patiënten beantwoordden wekelijks diverse vragenlijsten met betrekking tot angst, depressie en kwaliteit van leven op vaste momenten vóór en tijdens het diagnostische traject gedurende zes weken, met een laatste vra-

genlijst drie maanden daarna. De uiteindelijke analyse betrof de resultaten van de HADS waar het ging om angst en depressie,[18] en op het gebied van kwaliteit van leven de resultaten van de 30-items tellende European Organization for Research and Treatment of Cancer 30-item Quality of Life Questionnaire (QLQ-C30)[42] en de bijbehorende longkankerspecifieke module met 13 items (QLQ-LC13).[43] In totaal beantwoordden 193 patiënten tenminste één vragenlijst. De pre-diagnostische scores voor *distress* bleken zeer hoog. De gemiddelde HADS-totaalscore bedroeg 13.5, of anders gezegd: 63.4% van alle patiënten hadden een HADS-totaalscore van 10 of hoger, indicatief voor significante *distress*. Deze pre-diagnostische waarden verschilden niet tussen patiënten die sneldiagnostiek of stapsgewijze diagnostiek doorliepen. Opvallend was wel dat patiënten die uiteindelijk daadwerkelijk longkanker bleken te hebben, significant meer pre-diagnostische *distress* hadden in vergelijking met patiënten die een benigne diagnose kregen (14.7 versus 11.8, p = 0.01). De pre-diagnostische kwaliteit van leven, weergegeven door de globale kwaliteit van leven-schaal van de QLQ-C30 bedroeg 61.6 en dit verschilde niet tussen beide diagnostische trajecten. Bij sneldiagnostiekpatiënten daalde de gemiddelde HADS-totaalscore gedurende de eerste zes weken van de studie van 13.8 naar 11.9, maar bij patiënten die stapsgewijze diagnostiek doorliepen bleef deze hoog (respectievelijk 13.1 en 13.6), waarbij een significant (p = 0.03) interactie-effect zichtbaar werd tussen de soort diagnostiek (2) en tijd (7 meetmomenten). Een soortgelijke interactie werd gevonden voor de gemiddelde HADS-A subscore. Bij afzonderlijke analyse van bovenstaande gegevens bleek dit effect vooral voor mannen (p = 0.04) en patiënten met een maligne aandoening (p = 0.03) te gelden, maar niet voor vrouwen (p = 0.49) of patiënten met een benigne diagnose (p = 0.78). Op het laatste meetmoment na drie maanden bleek geen verschil meer te bestaan tussen de sneldiagnostiek en stapsgewijze diagnostiek waar het ging om de HADS-totaalscore (respectievelijk 11.5 en 11.8, p = 0.91). Wel lagen de scores van patiënten met de diagnose longkanker duidelijk hoger dan die van patiënten met een benigne diagnose (respectievelijk 13.2 en 8.5, p = 0.01). De gemiddelde pre-diagnostische globale QLQ-C30 kwaliteit van leven-score viel binnen de bekende referentiewaarden voor longkankerpatiënten[44] en verschilde niet tussen sneldiagnostiek en stapsgewijze diagnostiek. Evenmin viel er een relevante verandering waar te nemen tijdens de looptijd van de studie.

ALGEMENE DISCUSSIE

In de zorg voor patiënten met longkanker is de laatste decennia veel veranderd. Zoals eerder al genoemd, lijken vooral in Nederland de aantallen patiënten alleen maar te stijgen.[3] Het vaststellen van het exacte tumortype en het correcte stadium zijn steeds belangrijker geworden, omdat de keuze voor de behandeling sterk afhankelijk is geworden van de combinatie van stadium, tumortype en vaak ook mutatiestatus.[45,46] Hier kan sneldiagnostiek een centrale rol spelen. Dit proefschrift toont aan dat sneldiagnostiek enerzijds de longarts in staat stelt om longkanker zo goed te diagnosticeren en stadieren als binnen de reguliere diagnostiek mogelijk is, en wat de doorlooptijden betreft binnen de criteria van de richtlijnen te blijven. Het heeft anderzijds zeker ook voor de patiënt een meerwaarde vanwege een beter psychisch welbevinden in de periode rondom de diagnose.

HET SNELDIAGNOSTIEKPROGRAMMA VOOR LONGKANKER

DIAGNOSTIEK

Het sneldiagnostiekprogramma voor longkanker in het Radboudumc, dat in de **hoofdstukken 2 en 3** uitgebreid beschreven is, bestaat uit twee unieke elementen. Het programma start bij iedere patiënt met een diagnostische FDG-PET/CT. Daarnaast werd als primaire diagnostische modaliteit voor weefseldiagnostiek gekozen voor bronchoscopie. Met name het laatste is wellicht niet altijd de meest optimale keuze; indien er sprake is van kleinere of perifeer gelegen afwijkingen kan transthoracale biopsie, echo- of CT-geleid, of een bronchoscopie ondersteund met moderne navigatie technieken, meer geschikt zijn. Verder beschikken de meeste klinieken tegenwoordig over endobronchiale echografie (EBUS), waarmee diagnostiek en stadiëring van mediastinale lymfeklieren in één onderzoek zijn te combineren. Desondanks werd bij 59.1% van alle longkankerpatiënten de diagnose bronchoscopisch gesteld. Daar komt bij dat, hoewel bij 60.9% van alle longkankerpatiënten geen endobronchiale afwijkingen werden aangetroffen, bij 39.4% van hen toch maligne cellen werden aangetroffen. Dit wijst op een meerwaarde van de bronchoscopie in ervaren handen. De inspanning van de pathologische analyse voor een snelle diagnose is uiteraard ook van groot belang, maar bleek desondanks nog steeds kwalitatief hoogwaardig: in 97.2% van de gevallen van longkanker bleek de voorlopige diagnose die bronchoscopisch was geconstateerd en op dezelfde dag met de patiënt besproken werd, na volledige analyse van al het materiaal later in de week correct te zijn.

Hoewel de kleinere hoeveelheid materiaal voor diagnostiek bij cytologie (vergeleken met histologie) in een aanzienlijk deel van de gevallen correct kan zijn, houdt de beperkte hoeveelheid mogelijk wel een beperking in voor mutatie-analyse op het genetisch materiaal. Dit is inmiddels van toepassing op een deel van de longkankerpatiënten,[46] maar was nog niet gebruikelijk in de geanalyseerde jaren van het cohortonderzoek.

Het belangrijkste onderzoek in het sneldiagnostiekprogramma (ook het eerste dat de patiënt ondergaat) is de FDG-PET/CT, die door de radioloog en nucleair geneeskundige gezamenlijk terstond wordt verslagen. In **hoofdstuk 3** is aangetoond dat de sensitiviteit, zelfs voor de groep van patiënten die verwezen werd met een X-thorax, negatief en positief voorspellende waarde van de FGD-PET/CT binnen het sneldiagnostiekprogramma, gelijkwaardig zijn aan de diagnostische kwaliteiten zoals gedocumenteerd in de wetenschappelijke literatuur.[47] Weliswaar viel de specificiteit in deze vergelijking lager uit met 60.2% ten opzichte van gemiddeld 77.8%, maar dan moet wel benadrukt worden dat in andere studies over de diagnostische waarde van FDG-PET/CT het doorgaans solitaire noduli betrof op CT – en dat verhoogde uiteraard de voorafkans op maligniteit.

Een belangrijk nadeel van FDG-PET/CT als eerste onderzoek is overdiagnostiek bij patiënten die uiteindelijk geen maligne aandoening blijken te hebben. In het geanalyseerde cohort betrof dit 34.8% van alle patiënten met een eenduidige of waarschijnlijk (na poliklinisch vervolgen) goedaardige diagnose. Waarschijnlijk is het risico op overdiagnostiek groter bij patiënten die met een X-thorax verwezen worden in plaats van met een tussentijdse CT-thorax, aangezien een CT een afwijking veel beter als verdacht kan karakteriseren dan een X-thorax. Wanneer afzonderlijk gekeken werd naar de met FDG-PET en CT verkregen diagnostische gegevens, had retrospectief bij 8.3% van alle patiënten die met X-thorax waren verwezen een CT-thorax alléén met voldoende zekerheid maligniteit uit kunnen sluiten. Het afzonderlijk verrichten van CT vóór de FDG-PET kost echter meer tijd en kan een programma voor sneldiagnostiek logistiek ingewikkelder maken.

TIJDIGHEID

Wellicht het meest waardevolle aspect van sneldiagnostiek is de zeer korte doorlooptijd tot het verkrijgen van een diagnose: mediaan twee dagen, zelfs één dag voor de subgroep van patiënten die verwezen zijn met een X-thorax. Dit is aanzienlijk korter dan de criteria uit richtlijnen[12-15] en de gerappor-

teerde doorlooptijden uit studies, die 7 tot wel 37 dagen lang kunnen zijn.[16] Uit het perspectief van de patiënt en uit het oogpunt van kwaliteit van zorg zijn echter ook de doorlooptijden vóór en na de diagnose van groot belang. Nadere analyse van overige doorlooptijden leverde aanwijzingen voor aanvullend gunstige effecten van een programma sneldiagnostiek. De wachttijd van de diagnose tot de therapeutische behandeling voor longkanker bedroeg mediaan 18 dagen, hetgeen ruim binnen de norm valt van de richtlijnen[12-15] en in de lage regionen van andere studies.[16] De mediane wachttijd van verwijzing tot het eerste bezoek was 7 dagen, langer dus dan de maximaal acceptabele wachttijd van 5 dagen in de Nederlandse richtlijn,[15] maar vallend binnen de internationale richtlijnen.[12-14] Een schema op vaste dagen (in het geval van dit sneldiagnostiekprogramma woensdag en donderdag) zal onvermijdelijk leiden tot een vertraging van enkele dagen voor een deel van de verwezen patiënten. De verwijstijd is echter korter wanneer deze wordt vergeleken met de uitkomsten in de wetenschappelijke literatuur,[16] met uitzondering van één publicatie.[48] Dit suggereert dat, hoewel het sneldiagnostiekprogramma niet specifiek ontworpen is om de verwijsduur en wachttijd tot behandeling te verkorten, deze aanpak de gunstige effecten op dit gebied zou kunnen verklaren.

DISTRESS EN KWALITEIT VAN LEVEN RONDOM DE DIAGNOSE

LESSEN UIT *PENELOPE*

Er is veel discussie geweest over de mogelijke positieve dan wel nadelige effecten van sneldiagnostiek voor de patiënt met een verdenking op longkanker. Enerzijds is er altijd belang gehecht aan de tijd die een patiënt nodig zou hebben om te kunnen 'wennen' aan de kwalijke diagnose, anderzijds is beargumenteerd dat het zoveel mogelijk bekorten van de periode van onzekerheid voor patiënten beter zou zijn.[49-51] De argumenten over en weer waren echter meer gestoeld op persoonlijke voorkeur en gevoel dan op de resultaten van wetenschappelijk onderzoek. Er waren immers weinig publicaties over psychisch welbevinden en kwaliteit van leven rondom het diagnostische traject, en zoals in **hoofdstuk 4** beargumenteerd, al helemaal niet als het ging om de invloed van een sneldiagnostiekprogramma. De PENELOPE-studie, zoals beschreven in **hoofdstuk 5**, is feitelijk de eerste grote prospectieve studie geweest onder longkankerpatiënten naar de effecten van sneldiagnostiek. Bij patiënten die op deze wijze waren geanalyseerd bleek *distress* sneller te verminderen dan bij analyse door stapsgewijze diagnostiek. De mogelijke verklaring is het kortere tijdsinterval en daardoor een kortere periode van onzekerheid, of het positieve effect van een geprogrammeerde aanpak die de

patiënt gedurende het traject steun biedt. Uiteraard moet niet vergeten worden dat PENELOPE geen gerandomiseerde maar een beschrijvende studie was, en dat er verschillen waren in de kenmerken en aantallen van geïncludeerde patiënten tussen verschillende centra. Anderzijds vormt de totale patiëntenpopulatie (evenals die beschreven in de analyses van het sneldiagnostiekprogramma van het Radboudumc) een afspiegeling van de gemiddelde Nederlandse longkankerpatiënt.

Naast het positieve effect op het psychisch welbevinden van de sneldiagnostiekpatiënt, kwamen in de PENELOPE-studie twee andere bevindingen aan het licht. In de eerste plaats dat het niveau van *distress* bij patiënten bij wie longkanker wordt vermoed en die in afwachting zijn van het diagnostische traject zeer hoog is: bij bijna tweederde van de patiënten was dit dermate hoog (te weten een HADS-totaalscore van 10 of hoger)[19] dat feitelijk sprake zou kunnen zijn van een psychische stoornis. Dit is weliswaar enigszins vergelijkbaar met bevindingen uit de beperkte beschikbare literatuur,[22-24-27] maar in zekere zin toch een bijzondere uitkomst, omdat altijd rekening gehouden moet worden met het feit dat bij het vrouwelijk geslacht en bij een lagere leeftijd vaker sprake is van *distress*. Daarnaast is ook de soort kanker van invloed.[40,54-57] Gezien het feit dat de meeste gegevens over *distress* bij een mogelijke diagnose van een maligniteit afkomstig zijn uit studies die in grote meerderheid patiënten met een mammacarcinoom betreffen (die in studies alle van het vrouwelijk geslacht zijn en vaak jonger), lenen deze zich niet automatisch voor extrapolatie naar andere maligniteiten. Desondanks lijkt *distress* bij de in de PENELOPE-studie onderzochte longkankerpatiënten zo ernstig, dat geconcludeerd mag worden dat deze patiënten een risicogroep vormen. Daarnaast is dit een belangrijke bevinding, omdat de enige studie die eerder bij longkankerpatiënten is verricht, opvallend veel minder *distress* liet zien.[26] Daarbij moeten we opmerken dat in deze studie waarschijnlijk een deel van de patiënten al op de hoogte was van de diagnose. Verder bleek dat de HADS-totaalscore drie maanden na diagnose bij patiënten in beide diagnostische benaderingen nog steeds ruim boven de 10-puntengrens lag. Deze uitkomst bevestigt dat de longkankerpatiënt beslist een categorie vertegenwoordigt die een verhoogd risico loopt op psychische klachten. Dit besef is des te belangrijker omdat psychische klachten bij patiënten met kanker vaak niet aan het licht komen doordat ze niet gemeld worden, of doordat artsen ze onderschatten.[52,53] Dit geldt niet alleen na de diagnose en behandeling, maar ook ervóór.

HET EFFECT VAN SNELDIAGNOSTIEK

Naast de bovengenoemde factoren die van invloed zijn op het psychisch welbevinden, bracht **hoofdstuk 4** aan het licht dat bij de diverse publicaties die verschenen zijn over *distress* bij de diagnose van kanker verschillende vragenlijsten werden gebruikt, die onderling moeilijk vergelijkbaar zijn. Een andere potentieel verwarrende factor is dat bepaalde studies niet het gehele diagnostische traject in ogenschouw nemen, maar bijvoorbeeld slechts een enkele ingreep. Dit alles maakt het lastig om de effecten van de snelheid van een diagnose van kanker op het psychisch welbevinden te generaliseren. Desondanks is de conclusie gerechtvaardigd dat er een gunstig effect op psychisch welbevinden uitgaat van een snelle diagnose van een benigne afwijking, en dat bij bevestiging van het vermoeden van een maligniteit het psychisch welbevinden zeker niet nadelig beïnvloed wordt door een snellere diagnose. Omgekeerd is een gunstige invloed van een snelle maligne diagnose aangetroffen in twee studies; deze uitzonderingen zijn mogelijk te verklaren uit het feit dat één van beide studies patiënten met een melanoom betrof (waarbij de diagnostische excisie tevens vaak al de behandeling zelf betreft).[39] In het andere geval betrof het een studie waarbij patiënten bij wie een ovariumcarcinoom werd vermoed een diagnostische buikoperatie ondergingen en de auteurs het vermoeden van additionele preoperatieve *distress* als factor benoemen (en er dus sprake van verstoring zou kunnen zijn).[38] Eigenlijk lenen slechts drie publicaties zich voor vergelijking met de PENELOPE-studie. Het gaat om relatief kleine studies over patiënten met een verdenking van een mammacarcinoom, waarbij sneldiagnostiek vergeleken is met stapsgewijze diagnostiek.[22,24,25] In deze studies daalden de angstscores duidelijk eerder bij een snellere benigne diagnose in een traject van sneldiagnostiek. In tegenstelling tot de PENELOPE-studie, waarin *distress* niet significant verergerde na diagnose, was dit in deze studies wel het geval, waarbij overigens geen verschil viel aan te tonen tussen sneldiagnostiek en reguliere diagnostiek. Ter nuancering valt op te merken dat de studies slechts twee of drie meetmomenten hadden, mogelijk te kort om een daling van scores over de tijd waar te nemen. Bovendien waren er relatief weinig patiënten met een maligne diagnose (9-16%) en werd in de enige studie die de HADS als vragenlijst gebruikte, niet specifiek naar totaalscores gekeken.[25]

Het verloop van kwaliteit van leven in de PENELOPE-studie (de QLQ-C30 globale kwaliteit van leven schaal) was anders dan die van de HADS-totaalscore: de pre-diagnostische kwaliteit van leven bleek vergelijkbaar met de referentiewaarden voor longkankerpatiënten na diagnose[58] en liet daarna geen rele-

vante veranderingen zien. Noch over de tijd, noch tussen sneldiagnostiek en stapsgewijze diagnostiek. Opvallend is dat dit gegeven dan weer contrasteert met de dalende kwaliteit van leven-scores na sneldiagnostiek in de enige twee andere uit de literatuur bekende studies die kwaliteit van leven in dit kader bekeken.[25,59]

DE TOEKOMST

Sneldiagnostiek heeft wezenlijke voordelen ten opzichte van stapsgewijze diagnostiek, maar verbetering lijkt mogelijk. Om de stralenbelasting voor een deel van de patiënten te verminderen en wellicht de kosteneffectiviteit te verbeteren, valt bijvoorbeeld te kiezen voor het scheiden en separaat beoordelen van de CT-thorax en de FDG-PET. Hierdoor blijft een klein deel van de patiënten die radiologisch benigne afwijkingen hebben de FDG-PET bespaard, zij het dat de complexiteit van het programma hierdoor wel toeneemt. Bovendien zal een tweedaags programma hierdoor vrijwel onmogelijk worden. Een tweede mogelijkheid tot verbetering kan zijn om het primaire onderzoek met als doel een weefseldiagnose te verkrijgen niet te beperken tot bronchoscopie, maar uit te breiden met bijvoorbeeld transthoracale puncties en endo-echografie. Dit zal met name de tijdigheid van de diagnostiek verbeteren voor patiënten met perifeer gelegen afwijkingen of mediastinale metastasen. Tenslotte is, zeker uit het perspectief van patiënten, de wachttijd van verwijzing en die tot het starten van de behandeling tenminste zo belangrijk als de doorlooptijd van diagnostiek. Indien de aandacht hiervoor afneemt, heeft het minimaliseren van de diagnostische doorlooptijd weinig meerwaarde.

Dit proefschrift heeft laten zien dat sneldiagnostiek bij een verdenking op longkanker niet alleen evidente voordelen heeft voor een tijdige en correcte diagnose, maar bovendien vergeleken met stapsgewijze diagnostiek een gunstig effect heeft op het psychisch welbevinden van patiënten die de diagnostiek moeten ondergaan. Tot het moment dat er genezing wordt gevonden voor longkanker zullen deze patiënten een risicogroep blijven voor *distress*. Niet alleen in de periode van de diagnose, maar ook gedurende de behandeling, zowel curatief als palliatief, en daarna. Genezing is bij lange na niet in zicht, hetgeen de beroepsgroep zou moeten dwingen om alert te zijn op de mogelijke ernstige psychische klachten die kunnen ontstaan vanaf het moment dat een vermoeden van longkanker wordt uitgesproken.

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DANKWOORD

Een proefschrift zou gezien kunnen worden als het product van inspiratie en inspanning. De inspiratie ontstond door mijn omgang met patiënten, verdacht van een vorm van longkanker, die ik zag in het sneldiagnostiek-programma in het Radboudumc, en verdiepte zich na augustus 2005 met de publicatie van het artikel 'De Snelheidsduivel' in Medisch Contact. Een kritisch artikel, waarbij mij opviel dat de wetenschappelijke argumenten ontbraken die vóór sneldiagnostiek pleiten. Ook de stelling dat het bundelen van onderzoek en het gesprek over de uitslag emotionele consequenties kan hebben voor de patiënt, is mij bijgebleven. De verbazing over het ontbreken van bewijs in de conclusies bij een patiëntencategorie die me zo na aan het hart ligt, heeft het toen gewonnen van de argwaan over de omvang en de haalbaarheid van een promotieonderzoek. De inspanningen volgden niet geheel automatisch, maar wel gestaag. Door het combineren van mijn werk als longarts in het Radboudumc, later in het HAGA ziekenhuis, en het onderzoek kan ik bevestigen dat het stevig, maar haalbaar is. Het vereist coöperatie, keuzes en efficiëntie, maar bovendien het accepteren van teleurstellingen en tot slot flexibiliteit. Zoals met zoveel in het leven kan je dat natuurlijk niet alleen, en daarom wil ik een aantal personen graag bedanken.

In de allereerste plaats ben ik dank verschuldigd aan alle patiënten die belangeloos hebben meegewerkt aan de PENELOPE-studie, en aan de verpleegkundigen, nurse-practitioners en longartsen die zich voor hun deelname hebben ingezet.

Promotor Richard Dekhuijzen gaf mij het gevoel van onvoorwaardelijk vertrouwen en bleef mij motiveren door de jaren heen, niet alleen tijdens mijn opleiding tot longarts, maar ook in de periode daarna. Hij is een continue steun geweest voor het onderzoek en voor mijn carrière.

Judith Prins begon als copromotor, maar na haar eigen promotie tot hoogleraar beschikte ik over twee promotoren. Ik ben haar dankbaar voor alle inspanningen en steun, voor de flexibiliteit bij het vrijmaken van tijd voor overleg ondanks haar drukke werkzaamheden, maar bovenal voor haar positieve instelling en humor, die me

op een aantal momenten de juiste zet voorwaarts hebben gegeven. Tijdens de eenzame uren achter mijn computerscherm was zij als het nodig was op afstand toch steeds in de buurt.

Copromotor Erik van der Heijden wil ik graag bedanken vanwege zijn niet-aflatende enthousiasme voor het hele project, zijn sterke motivatie om sneldiagnostiek breed te analyseren en de tijd en steun die hij me daarvoor heeft gegeven. Mijn overgang naar Den Haag heeft niet verhinderd dat ik toch nog veel van hem heb kunnen leren, onder andere op endo-echoscopisch gebied. Ik heb de onderlinge samenwerking van Judith, Erik en mij als uniek ervaren, en zal deze missen.

Lioe-Fee de Geus-Oei werd copromotor vanaf het moment dat Judith plaats maakte, maar had hieraan voorafgaand al vele malen intensief meegekeken en meegedacht tijdens het schrijven van de artikelen over het sneldiagnostiek-programma in het Radboudumc en de rol van de PET/CT. Ik mocht profiteren van haar enthousiasme voor het hele project en haar ongeëvenaarde doorzettingsvermogen.

Ook had ik graag Ria te Winkel willen bedanken. Zij heeft een prominente plaats ingenomen en mij veel werk uit handen genomen door de antwoorden van alle vragenlijsten te digitaliseren. Het is heel triest dat zij ziek werd en overleed. Ik weet zeker dat ze de uitkomsten van het onderzoek boeiend had gevonden.

Door Hanneke van Helvoort werd de moeizame omgang met het niet altijd even gebruiksvriendelijke statistiekprogramma SPSS enigszins draaglijk. Ik heb bij herhaling mogen profiteren van haar toegankelijke, heldere inzicht en kwam zo weer op het goede spoor terecht.

Mijn collega's in het HAGA ziekenhuis, in alfabetische volgorde Harry Heijerman, Hassan El Bouazzaoui, Henk Schreur, Joey Brahim, Johnny Daflaar, Klara Rijnten, Renske van der Meer, Saar van Nederveen, Tessa Nizet, maar vooral mijn oncologische 'buddy' Henk Codrington, wil ik eveneens graag bedanken voor hun flexibiliteit

en steun tijdens de reguliere werkzaamheden en opleiding, waardoor ik in staat bleef tijd te besteden aan het onderzoek.

Coauteur Rogier Donders wil ik graag bedanken voor zijn inzet bij de analyses van de PENELOPE-studie en het bijbehorende artikel. Het is een ware kunst om statistische kennis over te brengen op een simpele longarts.

Ik mocht steunen op twee bijzondere paranimfen. Ik ben erg dankbaar dat ze op deze bijzondere dag aan mijn zijde willen staan. In Joris van Gulick heb ik al vele jaren een echte en unieke vriend, in goede en minder goede tijden. We mogen wat persoonlijkheid betreft verschillen, onze vriendschap bewijst dat je desondanks zoveel kan delen. De vriendschap met Annemarie Cottaar is op een andere manier uniek. Niet alleen doordat deze is ontstaan uit een arts-patiëntrelatie, maar vooral door de manier waarop we vervolgens een onvoorwaardelijke en diepe band hebben kunnen ontwikkelen die ik, ondanks de onzekere toekomst, nooit had willen missen. Zij heeft haar rol als paranimf beslist waargemaakt door, samen met haar man Wim Willems, een belangrijke motivator te zijn tijdens het schrijven van het manuscript. Haar contacten met vormgeefster Suzan Beijer en ervaringen met illustratoren en drukkers hebben mij veel zorgen uit handen genomen.

Ze zullen het vast heel vanzelfsprekend vinden, maar ik ben mijn ouders Ria en Jos erg dankbaar; niet alleen voor hun onvoorwaardelijke steun en interesse in de vele ontwikkelingen die ik van kinds af doormaakte, maar ook voor alle levenslessen die ik van hen heb gekregen. Evenals op mijn broer Reinout, weet ik dat ik altijd op hen kan rekenen.

En moet je je eigen partner bedanken? Jeroen had geen andere keuze dan deelgenoot te zijn van alle mooie en minder mooie kanten van het schrijven aan dit proefschrift. Hij zal het waarschijnlijk maar raar vinden dat ik hem bedank voor zijn geduld, zijn humor, zijn eerlijkheid en zijn vermogen om te delen in grote maar ook heel kleine dingen. Hij mag ervan denken wat hij wil, met niemand anders zou ik dit dankwoord willen besluiten.

CURRICULUM VITAE

PEPIJN BROCKEN is geboren op 13 maart 1975 in Boxtel. Na het gymnasium Beekvliet in St. Michielsgestel doorlopen te hebben, begon hij in 1993 aan de studie Geneeskunde in Nijmegen. Hij werkte tijdens zijn studie als huisarts-achterwacht, maar musiceerde ook als violist en altviolist in het Meijerijs Kamerorkest, Nijmeegs Studentenorkest en het Nederlands Studentenorkest. Na afronding van het artsexamen in 1999 werkte hij als Assistent Geneeskunde Niet In Opleiding (AGNIO) in het Canisius Wilhelmina Ziekenhuis te Nijmegen, waar hij vervolgens de opleiding startte tot internist. In 2003 besloot hij zich verder te specialiseren tot longarts in het Radboudumc, onder de hoede van opleider prof. dr. P.N.R. Dekhuijzen. In die tijd was hij als arts-assistent actief in het assistenten-bestuur en concilium van de Nederlandse Vereniging van Artsen voor Longziekten en Tuberculose (NVALT). In de latere fase van deze opleiding ontstond een steeds grotere interesse voor de pulmonale oncologie, en begon hij aan het onderzoek dat de basis vormde voor dit proefschrift. Na anderhalf jaar als chef de clinique gewerkt te hebben in het Radboudumc is hij sinds 2009 als longarts verbonden aan het HAGA ziekenhuis in Den Haag, met aandachtsgebied pulmonale oncologie en endobronchiale echoscopie.

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