

Original Article

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Cancers detected by thoracoabdominal computed tomography in patients with nonspecific symptoms

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ABSTRACT

INTRODUCTION Use of an urgent fast-track pathway comprising contrast-enhanced computed tomography (CECT) is a recognised method for diagnostic evaluation of patients with non-specific symptoms. This study focused on a subgroup of patients with non-specific symptoms who are diagnosed outside of fast-track pathways. To investigate the cancer prevalence in patients with non-specific symptoms outside of fast-track pathways undergoing a thoracoabdominal CECT.

METHODS This was a retrospective observational study including patients referred for a thoracoabdominal CECT. Patients with non-specified symptoms were included. All pathology reports were reviewed to confirm histopathological findings. Data were collected during a one-year period from the Department of Radiology, Vejle Hospital.

RESULTS A total of 238 patients were included; 125 (52.5%) women and 113 (47.5%) men. The median age was 69 years (range: 29-99 years). Fifty (21%) patients (25 men and 25 women) were diagnosed with malignant conditions by computed tomography (CT), all of which were confirmed by biopsy (median age = 68 years, range: 43-87 years). An additional ten patients had CT findings consistent with malignancies that were not confirmed by biopsy (median age = 86 years, range: 58-93 years).

CONCLUSION We found a 21% prevalence of cancer.

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Early cancer detection improves the outcome for patients with cancer. General practitioners (GP) play an important role in healthcare as their suspicion of cancer is important in securing early cancer diagnosis. The GP sees up to 75-85% of all patients with cancer when symptoms appear [1]. It is important that a GP can issue an urgent referral for diagnostic imaging when patients present with non-specific symptoms. Patients presenting with specific alarm symptoms will be referred to an urgent cancer fast-track pathway, whereas non-specific alarm symptoms may be difficult to fit into an urgent fast track cancer pathway. In the year preceding cancer, investigations increase 2-6 months before diagnosis [2]. A recent study found that GPs were more likely to suspect cancer in patients who were worried about cancer [3]. The GPs' cancer suspicion has been reported to be associated with referral for an urgent fast-track pathway. Furthermore, in up to 50% of abdominal cancer patients, the GP had no initial suspicion of cancer [4]. Non-specific symptoms typically include unexplained weight loss, fatigue and abdominal pain [5].

Since 2007, it has been possible for GPs to refer patients with non-specific symptoms directly for open access abdominal ultrasound, chest X-ray and thoracoabdominal contrast-enhanced computed tomography (CECT) at the Department of Radiology, Vejle Hospital. This formed the basis for an urgent clinical fast-track pathway for specific cancers in Denmark [6, 7]. Urgent fast-track pathways were implemented nationally in 2011 [8]. However, choice of radiology packages varies among the five Danish regions; some GPs can refer patients for chest X-ray and abdominal ultrasound, whereas others can also refer patients for a low-dose computed tomography (CT) of the lungs and thoracoabdominal CECT.

Some concern has been voiced that urgent fast-track pathways would result in misuse of CT by GPs. However, no increase was observed in CT use in a study giving GPs direct access to CT [9]. An urgent fast-track pathway may positively influence the survival rate among cancer patients [10], e.g. 16% of patients investigated in an urgent fast-track were diagnosed with malignant disease [11]. Consequently, it is important to recognise GPs as essential assets in cancer diagnostics and provide them with expedited access to referring patients with non-specific symptoms directly for timely diagnostic imaging. The GPs, however, still suspect cancer more often than they refer patients for an urgent fast-track pathway [12].

The aim of this study was to estimate the one-year cancer prevalence in non-specific patients not following a fast-track pathway undergoing CECT, either with ultrasound or directly for thoracoabdominal CECT from the GP.

METHODS

This was a retrospective, descriptive study conducted at the Department of Radiology, Vejle Hospital, Denmark. The study was approved by the local Danish Data Protection Agency (2012-58-0018) and by the local hospital committee. Approval by the Regional Committee on Health Research Ethics was not required as collection of radiology data was completed before July 2020 at which time new provisions on radiology research came into force in Denmark.

Patients

Eligible were patients aged 18 years or older who were referred from their GP for a thoracoabdominal CECT with non-specified symptoms and outside any fast-track pathway.

The inclusion period was from 1 January to 31 December 2017. All patients were eligible provided all three criteria were met:

- Referred with non-specific symptoms
- Outside a fast-track pathway
- Radiology CECT report was sent directly to the GP.

To confirm the cancer diagnosis, all pathology reports were reviewed by searching the Danish National Pathology Registry database [13] using each patient's unique civil registration number. The final histopathological diagnosis of cancer was confirmed within 12 months after the CT examination. If an initial ultrasound examination was performed, this was noted. We searched the Danish National Pathology Registry database to ensure that excluded patients had not been diagnosed with cancer within a 24-month period.

Data collection and clinical database

The Radiology Information System database and Picture Archiving Communication System database were searched. The two databases include referral information, radiology and ultrasonic imaging, and reports on all

patients examined at the Department of Radiology, Vejle Hospital.

Computed tomography

The primary radiology reports were accessed and analysed as a joint effort by two of the authors; T.E.O and M.R.P. Three multiple-row detector CT scanners were used. In patients with a normal renal function, a non-ionic contrast agent Optiray 300 mg/ml (Bracco Imaging, Italy) was injected intravenously. No oral contrast agent was used. The scan was performed with a delay of 35 seconds upon reaching the trigger value (venous phase). No side-effects due to the contrast agent were encountered.

Data analysis

Descriptive statistics were used to display the results. All data were tabulated in Microsoft Excel (Office 2013, Microsoft Corp, USA). Data included patient age at the time of the CT, examination date, ultrasonography three months prior the CT, gender, final diagnosis, tumour or metastasis location, histopathological findings, survival and/or date of death and radiology report.

Trial registration: not relevant.

RESULTS

In total, 238 patients had a thoracoabdominal CECT performed in the study period; 125 (52.5%) women and 113 (47.5%) men. The overall median age was 69 years (range: 29-99 years).

Among the 238 patients, a total of 141 patients were referred directly for thoracoabdominal CECT with non-specified alarm symptoms without prior examinations and 97 patients (referred indirectly) had an ultrasound investigation performed up to three months prior to the thoracoabdominal CECT.

In the 141 patients (73 women and 69 men) referred directly for CT, a total of 13 (9.2%) had a cancer confirmed by biopsy. An additional nine patients had a finding on CT that was reconcilable with malignancy, but a biopsy was not performed. In total, 16% in this subgroup had cancer.

In total, 50 (21.0%) of the patients were diagnosed with cancer. The gender distribution was 25 women and 25 men with a median age of 68 years (range: 43-87 years). **Table 1** shows the cancer distribution (biopsy versus CT) with hepatobiliary and pancreas cancer as the most frequent diagnoses. One false negative finding was observed; this case was recognised retrospectively.

TABLE 1 Patient distribution of malignancy diagnoses in biopsy and computed tomography findings.

Type of cancer	CT findings consistent with malignancy, n	Biopsy-verified malignancies, n
Hepatobiliary and pancreas	16	15
Other ^a	28	18
Gastrointestinal	8	9
Lung	8	8
Total findings	60	50

CT = computed tomography.

a) A mix of cancer types such as leiomyosarcoma, breast cancer, lymphoma, urinary tract cancer, carcinoma genital interna, neuroendocrine cancer, haematological cancer and recurrence cancer: patients with recurrence cancer who were no longer in the follow-up programme.

Within one year, a total of 18 of the patients (36.0%) had died (median age = 73.5 years). The three most common malignancies among the deceased patients were cancers of the liver and bile duct, the pancreas and the lungs.

We found ten patients (4.2%) with CT findings that were consistent with malignancy, but which had not been confirmed by biopsy or histopathological examination (median age = 86 years, range: 58-93 years). The most common finding was recurrence of a previous histologically confirmed malignancy. All patients had died within two years of their CT. The median survival was 208 days (range: 20-664 days).

DISCUSSION

A total of 21.0% of the patients with non-specific symptoms were diagnosed with cancer confirmed by biopsy. Additional 4.2% were diagnosed by CT without biopsy confirmation. The 50 confirmed cancer patients counted a varied group with malignant clinical findings. No difference was observed in the detection rate of women and men.

The recorded 21% cancer prevalence in our study is in line with that of Møller et al. and Stenman et al. [14, 15], but some studies have found a lower prevalence of 11-16% [11, 16-18], whereas one found a high cancer prevalence of 30% [19]. Our results highlight the importance of enabling GP referral of patients with non-specific symptoms for diagnostic imaging, including CECT as appropriate. Other studies have agreed that action should be taken when GPs suspect serious disease due to a patient’s high risk of cancer or other serious illness [20]. Furthermore, we investigated the pathology register within a two-year period and no further cancer diagnoses were registered.

In ten patients (4.2%), the CT findings were consistent with malignancy but a biopsy was rejected by the patients.

Several reasons may explain this, e.g., old age (median age = 69 years) and survival time after the CECT (median = 208 days, range: 20-664 days). Some patients may have actively deselected any further invasive investigation due to their advanced age or comorbidity.

The high detection rate may indicate that GPs are able to select the right patients or that more patients need to be referred. Showing that only 40% of cancer patients in Denmark were referred to an urgent fast-track pathway, Jensen et al. [12] stressed the importance of providing GPs with direct access to diagnostic tools to achieve early diagnosis of cancer.

Similar to our findings, others have found a high prevalence of lung cancer [11, 14, 16, 17] and pancreatic cancer [11], although the prevalence of haematological and/or gastrointestinal cancer also seems to be high [11, 16, 17]. Few patients with breast cancers were found in this material. In general, women with symptoms have easy access to mammography and both GPs and women are highly aware of this disease. Furthermore, a limited number of patients were diagnosed with a recurrence cancer after the CT follow-up was completed.

It is a concern that patients with non-specific symptoms who do not fit into the established fast-track cancer pathways have a high prevalence of cancer. In general, GPs have an important but also challenging task and often they cannot trust one single symptom. It may be a puzzle to decide if a patient needs urgent fast-track investigation and to establish who may benefit from watchful waiting.

Besides having access to urgent fast-track pathways, GPs need to follow-up on information about symptom complexity and have information about patient characteristics.

On the other hand, a delay may be caused by a misinterpretation of the referral causing the patients not to be referred directly for an urgent fast-track pathway. In this group of patients, a short waiting time and acceleration of a potential diagnosis are important.

In case of a strong suspicion of cancer, the GP needs access to referring patients for timely and appropriate diagnostic imaging, i.e., CECT in elderly patients and abdominal ultrasound in patients under the age of 40. Abdominal ultrasound is an excellent first-choice image modality in patients presenting with non-specific symptoms, but the opportunity to refer for CECT is of high value. In general, ultrasound examination is primarily used as the first-choice option in younger patients (< 30 years), whereas CT is used in elderly patients. This is related to its ease of access as it is a drop-in investigation and to reluctance to refer to radiation exposure in the young population due to life-time attributable cancer risks since the stochastic radiation risks decrease substantially with age.

Strengths and weakness of the study

A major strength of this study was that the diagnoses were based on medical assessment, which increases reliability. Due to the retrospective design, there were no dropouts. Included patients were unselected describing an everyday clinical situation in a department of radiology.

Retrospective studies typically involve a higher risk of information bias, e.g., misclassification bias and reporting bias due to the study design. All data entered in the database were crosschecked by two of the authors. However, several advantages and disadvantages are related to obtaining information from patient files. Essentially, recall bias can be excluded. Thus, in some cases, it may be challenging to interpret information that was not obtained for the purpose of the study. Not including incidental findings that were probably benign but required further examination was a limitation of the study. Misclassification bias occurs when there are errors in measurements comparing groups and can lead to under or overestimation. To minimize misclassification bias, the database was reviewed several times, both by authors individually and by two of the authors simultaneously.

The small sample size is a limitation as it may affect the reproducibility and validity of the study. Furthermore, a risk of unconscious bias always exists.

CONCLUSION

In this study, patients with non-specific symptoms outside fast-track pathways who underwent CECT with or without an initial ultrasound examination had a high cancer prevalence of 21%.

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REFERENCES

1. Allgar VL, Neal RD. Delays in the diagnosis of six cancers: analysis of data from the National Survey of NHS Patients. *Cancer. Br J Cancer* 2005;92:1959-70.
2. Jessen NH, Jensen H, Falborg AZ et al. Abdominal investigations in the year preceding a diagnosis of abdominal cancer: a register-based cohort study in Denmark. *Cancer Epidemiol* 2021;72:101926.
3. Virgilsen LF, Jensen H, Pedersen AF et al. Patient's worry about cancer and the general practitioner's suspicion of cancer or serious illness: population-based study in Denmark. *Eur J Cancer Care* 2021;28:e13411.
4. Jessen NH, Jensen H, Helsper C et al. Cancer suspicion, referral to cancer patient pathway and primary care interval: a survey and register study exploring 10 different types of abdominal cancer. *Fam Pract* 2021;38:589-97.
5. Koo MM, Hamilton W, Walter FM et al. Symptoms signature and diagnostic timeliness in cancer patients: a review of current evidence. *Neoplasia* 2018;20:165-74.
6. Probst HB, Hussain ZB, Andersen O. Cancer patient pathways in Denmark as a joint effort between bureaucrats, health professionals and politicians-A national Danish project. *Health Policy* 2012;105:65-70.
7. Danish Health Authority. National cancer plan II - Denmark 2005 - National Board of Health recommendations for improving cancer healthcare services. Annex 6.1 Patient pathway organised in packages. 2005. <https://www.sst.dk/da/udgivelser/2005/national-cancer-plan-ii---denmark-2005---national-board-of-health-recommendations-for-improving-canc>
8. Danish Health Authority. Diagnostisk pakkeforløb for patienter med uspecifikke symptomer på alvorlig sygdom, der kunne være kræft. 2016. <https://www.sst.dk/da/udgivelser/2016/~media/3ACA5B705B44EAF84F62B9FBB16AC7A.ashx> (15 Jan 2021).
9. Mahncke Guldbrandt L, Fenger-Grøn M et al. Reduced specialist time with direct computed tomography for suspected lung cancer in primary care. *Dan Med J* 2013;60(12):A4738.
10. Møller H, Gildea C, Meechan D et al. use of English urgent referral pathway for suspected cancer and mortality in patients with cancer: cohort study. *BMJ* 2015;351:h5102.
11. Ingeman ML, Christensen MB, Bro F et al. The Danish cancer pathway for patients with serious non-specific symptoms and signs of cancer-a cross-sectional study of patient characteristics and cancer probability. *BMC Cancer* 2015;15:421.

12. Jensen H, Tørring ML, Olesen F et al. Cancer suspicion in general practice, urgent referral and time to diagnosis: a population-based GP survey and registry study. *BMC Cancer* 2014;14:636.
13. Bjerregaard B, Larsen OB. The Danish Pathology Register. *Scand J Public Heal* 2011;39:72-4.
14. Stenman E, Palmér K, Rydén S et al. Diagnostic spectrum and time intervals in Swedens first diagnostic center for patients with nonspecific symptoms of cancer. *Acta Oncol* 2019;58:296-305.
15. Møller M, Juvik B, Olesen SC et al. Diagnostic property of direct referral from general practitioners to contrast-enhanced thoracoabdominal CT in patients with seriously but non-specific symptoms or signs fo cancer: a retrospective cohort study on cancer prevalence after 12 months. *BMJ Open* 2019;9:e032019.
16. Bislev LS, Bruun BJ, Gregersen S, Knudsen ST. Prevalence of cancer in Danish patients referred to a fast-track diagnostic pathway is substantial. *Dan Med J* 2015;62(9):A5138.
17. Jørgensen SF, Ravn P, Thorsen S, Worm SW. Characteristics and outcome in patients with non-specific symptoms and signs of cancer referred to a fast track cancer patient pathway; a retrospective cohort study. *BMC Cancer* 2017;17:809.
18. Moseholm E, Lindhardt BØ. Patient characteristics and cancer prevalence in the Danish cancer patient pathway for patients with serious non-specific symptoms and signs of cancer - a nationwide, population-based cohort study. *Cancer Epidemiol* 2017;50:166-72.
19. Bosch X, Escoda O, Nicolás D et al. Primary care referrals of patients with potentially serious diseases to the emergency department or a quick diagnosis unit: a cross-sectional retrospective study. *BMC Fam Pract* 2014;15:75.
20. Baughan P, Keatings J, O' Neill B. Urgent suspected cancer referrals from general practice: audit of compliance with guidelines and referral outcomes. *Br J Gen Pract* 2012;62:e700-e706.