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Published in:
BMJ Open

DOI:
10.1136/bmjopen-2019-032019

Publication date:
2019

Document version
Final published version

Document license
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Citation for published version (APA):
Møller, M., Juvik, B., Olesen, S. C., Sandstrøm, H., Laxafoss, E., Reuter, S. B., & Bodtger, U. (2019). Diagnostic property of direct referral from general practitioners to contrast-enhanced thoracoabdominal CT in patients with serious but non-specific symptoms or signs of cancer: a retrospective cohort study on cancer prevalence after 12 months. BMJ Open, 9(12), [e032019]. https://doi.org/10.1136/bmjopen-2019-032019

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Download date: 08. May. 2020
Diagnostic property of direct referral from general practitioners to contrast-enhanced thoracoabdominal CT in patients with serious but non-specific symptoms or signs of cancer: a retrospective cohort study on cancer prevalence after 12 months

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ABSTRACT

Objectives To describe the diagnostic properties of thoracoabdominal contrast-enhanced CT (ceCT), when general practitioners (GPs) managed referral to ceCT through the non-specific symptoms or signs of cancer: a retrospective cohort study on cancer prevalence after 12 months. BMJ Open 2019;9:e032019. doi:10.1136/bmjopen-2019-032019

Primary and secondary outcomes Our primary objective was to estimate the negative and positive likelihood ratios for being diagnosed with cancer within 1 year after ceCT. Our secondary outcomes were prevalence and final diagnoses of malignancy (including temporal trends since implementation of NSSC-CPP), the prevalence of revision of CT scans and referral patterns based on ceCT results.

Results In total, 529 subjects underwent ceCT and malignancy was identified in 104 (19.7%) patients; 101 (97.1%) during initial workup and 3 patients during the subsequent 12 months follow-up.

Eleven patients had a false-negative ceCT, and revision classified the ceCT as ‘probable/possible malignancy’ in eight (73%) patients. The negative predictive value was 98% and positive predictive value 63%. Negative and positive likelihood ratios for malignancy was 0.1 and 7.9, respectively.

Conclusion Our study shows that ceCT as part of GP-coordinated workup has a low negative likelihood ratio for identifying malignancy; this is important since identifying patients for further workup is vital.

INTRODUCTION

The Danish Board of Health initiated the Danish National Cancer Plan in 2000, including first diagnostics and treatment, and later on referrals, prevention, education, rehabilitation and palliation. Cohesive plans for varying types of cancer, cancer patient pathways (CPP), were structured as clinical guidelines in accordance with the latest international evidence in 2005. The CPPs are continually updated and revised by multidisciplinary editorial teams. The first organ-specific CPP was implemented in 2008 and included a guideline as well as a description of selected alarm symptoms, investigations, specialist departments involved, and lastly, timeframes for all phases in the workup (for instance, time from referral to first consult).1

Approximately 50% of patients diagnosed with a malignancy presents with organ-specific symptoms, and these patients are referred through the cancer-specific CPP. However, 20% of patients suffering from malignancy present with non-specific but serious symptoms, and 30% with vague ‘low-risk but not no-risk’ symptoms to their general practitioner (GP).2
Patients with non-specific symptoms or signs of cancer (NSSC) have an overall inferior survival, higher disease stage and lower performance compared with patients referred through the organ-specific cancer pathways.\textsuperscript{3–6} The reason for this may be doctors delay and therefore, a quick diagnostic workup of patients with uncharacteristic symptoms like weight loss, fatigue, fever, bone pain or just GPs ‘gut feeling’ was warranted.\textsuperscript{3–6}

Therefore, the urgent referral pathway for NSSC was implemented in 2011–2012.\textsuperscript{7} The NSSC-CPP aimed to minimise the time-to-workup in patients with non-specific symptoms, by providing new referral possibilities for GPs.\textsuperscript{5}

The Danish healthcare system is run by five regional health administrations each providing healthcare for approximately 1.1 million citizens. The NSSC-CPP has been implemented with significant regional variations exemplified by differences in the role of GP (involved in NSSC-CPP or referring to secondary centre for workup) and in choice of initial imaging: chest X-ray plus abdomino-ultrasound, low-dose CT of chest plus abdomino-ultrasound, low-dose thoracoabdominal CT or thoracoabdominal contrast-enhanced CT (ceCT).\textsuperscript{3,4,7,9,10}

In our region (Region Zealand, \textasciitilde800 000 inhabitants), the NSSP-CPP consists of two steps and is initiated and coordinated by the GP. Step 1: medical history, physical examination and paraclinical screening (urine dipstick, ECG, faecal occult blood test; blood tests for complete blood count, renal function tests, liver function tests, albumin, pancreas-specific amylase, C-reactive protein, glucose, thyroid stimulating hormone, myeloma protein and IgG, IgA and IgM).

If inconclusive, the GP initiates step 2: a thoracoabdominal ceCT (performed within 4 days), and the GP summarises the results of the NSSP-CPP and refers accordingly.\textsuperscript{7}

Approximately 20% of patients referred through the NSSC-CPP are found to have a malignant disease.\textsuperscript{2,8,10,11} When the GP has direct access to imaging and blood tests, it reduces costs and time spent by a specialist completing diagnostic workup.\textsuperscript{11} Our study aimed at describing the diagnostic properties of ceCT, when GPs manage referral to ceCT through the NSSC-CPP. Our primary objective was to estimate the negative and positive likelihood ratios for being diagnosed with cancer within 1 year from ceCT. Our secondary outcomes were prevalence and final diagnoses of malignancy (including temporal trends since implementation of NSSC-CPP in 2012), the prevalence of revision of CT scans and referral patterns based on ceCT results.

**METHODS**

**Design and patient inclusion**

This is a retrospective cohort study based on data from hospital health records of patients referred by the GP through the NCCS-CPP to a thoracoabdominal ceCT performed at the Department of Radiology (Zealand University Hospital, Roskilde, Region Zealand, Denmark) from July to December in 2013 and from July to December in 2015. By choosing these two separated periods, we aimed at exploring possible temporal trends in reference pattern as a secondary endpoint.

Approval from the Danish Patient Safety Authority and the Danish Data Protection Agency was obtained before any study-related activity.

**Data collection**

Patient Electronic Health Records and National Health databases were searched for demographics, radiological rapports, referral patterns (including hospital departments and diagnostic procedures) and final diagnosis. We defined the date of ceCT as study inclusion date. We excluded patients if someone other than the primary care physician acted on the ceCT results.

**Computed tomography**

CT of the chest, abdomen and pelvis was performed with a multiple row detector CT scanner (Philips 64 Brilliance or Philips 256 ICT; Philips Healthcare, Best, The Netherlands).

CT acquisition parameters were $64 \times 0.625$ mm collimation on both systems, kV 120, mAs/slice 150–250, rotation time 0.75, reconstruction thickness $3$ mm (1 mm thickness also reconstructed and used when necessary), increment $3$ mm, a $5$ mm maximum intensity projection was reconstructed for the lungs, increment $5$ mm, pitch 1.078, field of view (FOV) from $35$ to $45$ cm and matrix $512 \times 512$.

Iomeprol $350$ mg/mL (Iomeron 350 Bracco Imaging) was injected intravenously, in patients with normal renal function (defined as estimated glomerular filtration rate (eGFR) $>45$) in a dose of $100$ mL. Patients with eGFR $<45$ were scanned without intravenously contrast. CT was performed after a delay of $20$ s (arterial phase) for the liver, and $70$ s for thorax, abdomen and pelvis (portal venous phase).

In the daily clinical routine, all examinations were described by a general radiologist. For this study, all primary descriptions have been assessed and compared with the clinical outcome of the patient.

**Definitions**

Radiological findings were categorised as:

1. No cancer and no abnormal findings.
2. Abnormal but benign findings with no suspicion of cancer, findings warranted workup (eg, aortic aneurysms, renal enlargement).
3. Possible cancer, abnormal findings that could be malignant.
4. Probable cancer.

A final diagnosis of malignancy was defined as an unequivocal diagnosis of cancer within 12 months after ceCT, either by a statement in the patient’s medical records or by review of results in the Danish National Pathology Registry (a nationwide database covering all tissue samples since 1990\textsuperscript{15}).
False-negative ceCTs were defined as patients diagnosed with cancer within 12 months of follow-up, in which the original ceCT report had not found any suspicion of cancer (groups 1 and 2). All false-negative ceCT scans were rereviewed by an expert in oncoradiology (H Sandstrøm) who was blinded to the specific diagnosis of malignancy.

In the case of equivocal findings on CT, we choose to apply a worst-case scenario; all indeterminate ceCT results were categorised as being false-negative (in those with a malignancy) or false-positive (in all others).\textsuperscript{13}

Statistics

Statistical analyses were performed using dedicated software (SPSS V.23.0; IBM). Continuous data are presented as median (range), and intergroup differences were assessed using the $\chi^2$ test. Categorical data are presented as prevalence (%), and intergroup differences analysed with the Mann-Whitney U test. Statistical significance is defined as $p<0.05$. Based on a classification of the suggested diagnoses as true-positive, true-negative, false-positive, false-negative, we calculated the sensitivity, specificity, positive likelihood ratio (LR+), negative likelihood ratio (LR−), positive predictive value (PPV) and negative predictive value (NPV). Bayesian statistics were used to calculate the post-test probability of malignancy; according to the Bayesian method, estimates of post-test probability for malignancy are a function of disease prevalence (pretest probability). Using the prevalence of malignancy in the target population, and the LR− and LR+ of ceCT, it is possible to calculate the probability of having a malignancy if the ceCT is without findings suggestive of malignancy, respectively suspicious for malignancy (including 95% CI).

Patient and public involvement

Nor patients or the public were involved in the planning of the study.

RESULTS

In total, 555 patients were referred to ceCT in the study period. Of these, 26 (4.7%) were excluded because ceCT was not performed, images were not available (ceCT performed at another location) or someone other than the GP had acted on the ceCT. Thus, 529 subjects were found eligible for inclusion.

Final diagnosis of cancer

Table 1 shows that 101 (19%) patients were diagnosed with cancer during initial workup and, in addition, 3 (0.7%) patients during the 12 months of follow-up, totaling 104 (19.7%) patients. The majority (n=92; 88.4%) were classified as ‘probable/possible cancer’ by ceCT.

Table 1 shows that 21 patients died in the group with a ceCT classified as ‘malignancy not suspected’ including three patients who were diagnosed with malignancy. Six of the 18 patients died in hospital. No postmortem analyses were made, but none of the medical files provided a clinical suspicion of an underlying, missed cancer as the cause of death. However, according to the worst-case scenario, all these fatalities were included as false-negative cases to challenge our estimates.

False-negative initial workup

Of the 104 patients diagnosed with malignancy, 3 (0.7%) were diagnosed during follow-up of all 428 patients with non-malignant results after initial work-up. Two of these patients had a false-negative ceCT. Case 1 was diagnosed with localised breast cancer, and ceCT was described as normal both initially and at unblinded review by an oncoradiologist. Case 2 was diagnosed with colorectal cancer and peritoneal carcinomatosis 10 months after the initial ceCT, and the scan was described as normal both initially and at review. The last case was suspected of having colorectal cancer and peritoneal carcinomatosis at ceCT (‘probable cancer’); however, initial workup and post ceCT endoscopy were normal. After 4 months, the patient developed obstructive ileus and was subsequently diagnosed with colorectal cancer and peritoneal carcinomatosis.

False-negative ceCT results

In addition to the first two patients above, nine patients were diagnosed with cancer during initial workup, despite the CT was classified as ‘malignancy not suspected’ (groups 1 and 2; table 1). Thus, the prevalence of false-negative ceCT was 2.9% (11/382).

Unblinded review of these scans (including the above cases) resulted in a regrouping of five patients (lung and colorectal cancer) to ‘probable cancer’ (group 3) and three patients (breast cancer, pancreatic cancer and splenic lymphoma) to ‘possible cancer’ (group 4), respectively. Thus, postdiagnosis CT review resulted in redesignation in eight (73%) cases towards possible/probable malignancy, equaling 2.0% of ceCT classified as ‘malignancy not suspected’ (groups 1 and 2).

Diagnostic accuracy

Table 2 shows the diagnostic values of ceCT for diagnosing malignancy, including a worst-case scenario in which patients who died during follow-up, with no known malignancy, were classified as false-negative.

Clinical application

The prevalence of malignancy is 19.7%, which is similar to other findings in Europe and Denmark.\textsuperscript{8,14,15}

When considering the actual case scenario, the findings of a positive CT (LR+7.9), would increase this probability to 63% (56%–68%), whereas a negative result (LR− 0.10) would decrease the probability of malignancy to 2% (1%–4%).

According to the worst-case scenario, the findings of a positive CT (LR +5.9), would increase this probability to 64% (58%–70%), whereas a negative result (LR− 0.26)
Table 1  Demographic and clinical data stratified by results of the ceCT

|                                | Malignancy not suspected (groups 1+2) | Malignancy possible/probable (groups 3+4) | P value |
|--------------------------------|---------------------------------------|------------------------------------------|---------|
| **Total, n (%)**               | 382 (72)                              | 147 (28)                                 |         |
| **Demographic data**           |                                       |                                          |         |
| Female sex, n (%)              | 200 (52)                              | 81 (55)                                  | 0.6     |
| Age, median (range)            | 68 (26–94)                            | 72 (44–99)                               | <0.05   |
| **Actions after ceCT**         |                                       |                                          |         |
| **Referrals based on ceCT result** |                                       |                                          |         |
| Organ specific cancer pathway, n (%) | 22 (6)                               | 119 (81)                                | <0.05*  |
| Diagnostic centre, n (%)       | 5 (1.3)                               | 13 (9)                                   |         |
| Other: non-cancer pathway, n (%) | 33 (9)                                | 2 (1.4)                                  |         |
| Total number referred, n (%)   | 60 (16)                               | 134 (91)                                 |         |
| **Referrals not based on ceCT results** |                                   |                                          | <0.05*  |
| Organ-specific cancer pathway, n (%) | 22 (6)                               | 0                                       |         |
| Diagnostic centre, n (%)       | 36 (9)                                | 0                                       |         |
| Other: non-cancer pathway, n (%) | 44 (12)                               | 2 (1.4)                                  |         |
| Total number referred, n (%)   | 102 (27)                              | 2 (1.4)                                  | <0.05   |
| Total number referred (any cause) | 162 (42)                              | 136 (93)                                 |         |
| **Diagnosis of malignancy**    |                                       |                                          | <0.05   |
| All malignancies, n (%)        | 9 (2.4)                               | 92 (63)                                  |         |
| **Cancer subtypes**            |                                       |                                          | 0.05*   |
| Lung cancer, n (%)             | 2 (20)                                | 25 (27)                                  |         |
| Pancreas cancer, n (%)         | 0                                     | 13 (14)                                  |         |
| Colorectal cancer, n (%)       | 2 (20)                                | 17 (19)                                  |         |
| Urogenital cancer, n (%)       | 1 (10)                                | 11 (12)                                  |         |
| Haematology, n (%)             | 3 (30)                                | 5 (4)                                    |         |
| Upper gastrointestinal, n (%)  | 0                                     | 12 (13)                                  |         |
| Malignant melanoma, n (%)      | 0                                     | 2 (2.2)                                  |         |
| Breast, n (%)                  | 1 (10)                                | 3 (3.3)                                  |         |
| Unknown origin or rare, n (%)  | 0                                     | 4 (4.4)                                  |         |
| **Mortality, 12 months**       |                                       |                                          | <0.05   |
| All cases, n (%)               | 21 (6)                                | 50 (34)                                  |         |
| In the malignant cases, n (%)  | 3/9 (33)                              | 48/92 (52)                               | 0.3     |
| In the benign cases, n (%)     | 18/373 (5)                            | 2/55 (4)                                 | 1.0     |
| **Malignancy during follow-up, n (%)** | 2/373 (0.5)                       | 1/55 (1.8)                               | 0.3     |

*p for trend (Chi²- test)

ceCT, contrast-enhanced CT.

would decrease the probability of malignancy to 7% (5%–10%).

**Actions and referral patterns after ceCT**

The referral patterns varied between ceCT groups (table 1). As expected, referrals based on ceCT results were more prevalent in patients with CT suggestive of probable or possible cancer (91%), whereas non-CT related findings promoted referral in the group with low or no suspicion of cancer at ceCT (16%).

If the ceCT was classified as ‘malignancy not suspected’ (groups 1 and 2), more than half of the patients were not referred for further evaluation (58%, table 1).

If the ceCT was classified as ‘possible/probable cancer’ (groups 3 and 4), the CT results did not lead to referral in 13 (9%) patients. Two patients were referred in the non-cancer pathway due to other findings, and two of the remaining 11 (18%) patients died within 12 months after ceCT. We have no data on causes for non-referral.
Compared with previous findings (11%–16%).

14–17 Cancer prevalence in our study was 20%, somewhat higher than that, in some patients with signs of disseminated cancer.

Time from CT to diagnosis

In patients with ceCT classified as ‘possible/probable cancer’, median duration from CT to first visit in the CPP clinic was 82–19 days, and from ceCT to final diagnosis 24 (10–69) days.

DISCUSSION

This study shows that thoracoabdominal ceCT, as part of a GP-coordinated workup of NSSC, has a high NPV and a moderate PPV for diagnosing malignancy. Among patients with no suspicion of malignancy at the initial evaluation and on ceCT, 0.57% were diagnosed with malignancy during the follow-up period. This is in agreement with the 6 months prevalence of 0.23% found in a large-scale, Danish epidemiological study from 2017. The cancer prevalence in our study was 20%, somewhat higher compared with previous findings (11%–16%).

In patients with a ceCT not suspicious for cancer, we found that no additional investigations were performed in 57%. We suspected that serious disease might be missed in several cases; however, only two (0.5%) of these non-referred patients were diagnosed with cancer within the follow-up period.

One patient was diagnosed with localised breast cancer, and one patient had ceCT performed after 10 months which showed signs of peritoneal carcinomatosis in which subsequent investigation led to a diagnosis of colorectal cancer.

In 13 (9%) patients with ceCT classified as ‘possible/probable malignancy’ (groups 3 and 4), no further investigations were performed. Our data do not show why these patients were not referred; however, we speculate that, in some patients with signs of disseminated cancer who are not suitable for treatment, further investigations would be futile.

The strength of our study is that it shows the everyday use of the NSSC-CPP and utility of ceCT for fast evaluation of possible cancer. This result is of utmost importance, as vague symptoms are well known to indicate underlying malignancy. A prospective study, in England, is evaluating several aspects comparable to this study. However, a significant difference is that the GPs refer patients with ‘low-risk but not no-risk of cancer symptoms’ for workup to a hospital-based clinic. The GP suspects cancer in 4%–6% of all patient contacts in primary care, and cancer is only confirmed in 1/30. Several types of malignancy are unlikely to be detected by ceCT (of the chest and abdomen), for example, leukaemia and lesions in other anatomical regions (colorectal cancer is undetected in 20% of abdominal CT examinations).

Thus, ceCT is not a standalone test, and negative results should always be interpreted carefully in relation to signs and symptoms. It should be noted that the NSSC-CPP in our region also includes a predefined set of blood samples identifying, for example, haematological diseases. Our study focused on ceCT.

We only evaluated the prevalence of malignant diseases, yet, patients might also suffer from life-threatening benign conditions. The numerous referrals for further workup in patients with a CT non-suspicious for malignancy reflect this. Previous studies have found that 22% of patients referred through the NSSC-CPP were subsequently diagnosed with a serious non-malignant disease, dominated by treatable rheumatic and gastrointestinal diseases.

A limitation of our study is that it does not allow for investigation of symptoms-based risk scores, as we did not have access to data from primary care. Additionally, we did not include analyses from blood, urine and stool, or the combination thereof. However, the positive likelihood ratios of various biochemical tests for diagnosing

Table 2 Cross-tables and diagnostic values of filter CT for a diagnosis of malignancy during the study period: (A) actual case scenario, (B) worst-case scenario (non-malignant fatalities considered as false-negative malignant cases) and (C) diagnostic values for either scenario

|       | No malignancy | Malignancy | Total |
|-------|---------------|------------|-------|
| A     |               |            |       |
| Malignancy not suspected (groups 1+2) | 373         | 9          | 382   |
| Malignancy possible/probable (groups 3+4) | 55          | 92         | 147   |
| Total | 428           | 101        | 529   |
| B     |               |            |       |
| Malignancy not suspected (groups 1+2) | 355         | 27         | 382   |
| Malignancy possible/probable (groups 3+4) | 53          | 94         | 147   |
| Total | 408           | 121        | 529   |

C Sensitivity Specificity Negative predictive value Positive predictive value Positive likelihood ratio Negative likelihood ratio

2a 91.1% 87.2% 97.6% 62.6% 7.1 0.1
2b 77.7% 87.0% 92.9% 64.0% 6.0 0.3
malignancy (e.g., white blood cell count (LR+1.3) and elevated bilirubin (LR+2.3)) were low and the LR− was not reported. Furthermore, we did not have access to cause of death; thus the true number of missed cases of malignancy is unknown. However, it is unlikely that all fatalities were due to missed cancers, so our worst-case scenario is probably too conservative, as we have included all fatalities as false-negative cases (table 2).

Our study found that the usage of NSSC-CPP increased from 2013 to 2015, parallel to a decrease in the prevalence of malignancy. The same pattern has been reported from secondary care, where the cancer prevalence dropped from 22% in 2011 to 16% in 2013 in a Diagnost Centre that manages the NSSC-CPP in a secondary care setting. This could be due to a reduced threshold for referral, as well as highlighting the blurred lines between serious signs and vague symptoms.

Our study is unique in several ways. Most significantly, we have not found other studies that comprehensively describe the use and results of ceCT in a primary care setting. In previous studies of the NSSC-CPP in primary care, patients have had different types of diagnostic imaging and not a consequent use of ceCT. Also, our study is unique in that we performed 12 months of follow-up and an oncological review of false-negative ceCT scans. Most previous studies used 3–6 months follow-up and to our knowledge, none included CT review. The extended follow-up makes it unlikely that we missed false-negative cases of malignancy except in patients who died during follow-up.

We therefore included a worst-case scenario, burdening the diagnostic strength by classifying patients with no known malignancy who died during follow-up as false-negative.

The worst-case scenario did not change the NPV, PPV and likelihood ratios considerably (table 2).

An unblinded review of initially false-negative ceCTs (‘malignancy not suspected’, groups 1 and 2) reclassified >50% of these scans as ‘possible/probable malignancy’ (group 3 and 4).

The initially false-negative ceCT scans constituted <2% of all negative ceCTs; however, revision of all CT scans was not performed, thus the exact inter-observer agreement ratio is unknown.

However, the low prevalence does not support the implementation of routine review of ceCTs by specialised oncoradiologists.

CONCLUSION

Our study shows that ceCT as part of GP-coordinated workup has a low negative likelihood ratio for identifying malignancy; this is important since identifying patients for further workup is vital.

In addition, the hit rate for detecting malignancy, in patients with non-specific symptoms and signs of cancer, seems comparable to other fast-track workup plans for patients with disease-specific symptoms.

REFERENCES

1 Sundhedsstyrelsen T, Kraeftpakker, historisk overbiik, cancer pathway historical overview, 2019. Available: https://www.sst.dk/da/videos/Kraeft/Kraeftpakker/Historisk-overbiik
2 Jensen T, 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.
3 Vedsted P, Olesen F, A differentiated approach to referrals from general practice to support early cancer diagnosis – the Danish three-legged strategy. Br J Cancer 2015;112:S56–9.
4 Tørring ML, Frydenberg M, Hansen RP, et al. Evidence of increasing mortality with longer diagnostic intervals for five common cancers: a cohort study in primary care. Eur J Cancer 2013;49:2187–98.
5 Neal RD, Tharmanathan P, France B, et al. Is increased time to diagnosis and treatment in symptomatic cancer associated with poorer outcomes? systematic review. Br J Cancer 2015;112:S92–107.
6 Organization WH. Who guide to cancer early diagnosis. 2017. Available: http://www.who.int/cancer/publications/cancer_early_diagnosis/en/
7 Sundhedsstyrelsen T. Diagnostisk pakkeforløb for patienter Med uspecifikke symptomer på alvorlig sygdom. Der kunne være kræft. Diagnostic pathway for patients with non-specific symptoms of serious illness that might be cancer, second ED. Available: https://www.sst.dk/da/udgivelser/2016-/media/028409D2A0F94772B19868ABEF06B626.ashx
8 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.
9 Sundhedsstyrelsen T. Diagnostisk pakkeforløb. Oversigt over indgang til pakkeforløb til brug i almen praksis – Diagnostic pathway, Guide to referral for General Practice. Available: https://www.sst.dk/da/sygdom-og-behandling/kraeft/pakkeforloeb/-media/2AADDDF3495C4E6B3AF95E6B2E851B4.ashx
10 Services) SdopptCH. Alvorlig sygdom der kunne være kræft, Diagnostiske Enheder Aarhus, Horsens og Randers - Serious illness that could be cancer, Diagnostic departments at Aarhus, Horsens, Horsens

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Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

Ethics approval Approval from the Danish Patient Safety Authority and the Danish Data Protection Agency were obtained before any study-related activity.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request.

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Møller M, et al. BMJ Open 2019;9:e032019. doi:10.1136/bmjopen-2019-032019
and Randers, Denmark, 2018. Available: https://www.sundhed.dk/sundhedsfaglig/information-til-praksis/midtjylland/almen-praksis/patientforloeb/forloebesbeskrivelser/a-almen-og-uspecificeret/avlorig-sygdom-kraeft-oest/

11 Guildbrandt LM, Fenger-Grøn M, Folkersen BH, et al. Reduced specialist time with direct computed tomography for suspected lung cancer in primary care. Dan Med J 2013;60:A4738.

12 Bjerregaard B, Larsen OB. The Danish pathology register. Scand J Public Health 2011;39:72–4.

13 Cohen JF, Korevaar DA, Altman DG, et al. Stad 2015 guidelines for reporting diagnostic accuracy studies: explanation and elaboration. BMJ Open 2016;6:e012799.

14 Bislev LS, Bruun BJ, Gregersen S, et al. Prevalence of cancer in Danish patients referred to a fast-track diagnostic pathway is substantial. Dan Med J 2015;62:A5138.

15 Moseholm E, Lindhardt B Ø. 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.

16 Jørgensen SF, Ravn P, Thorsen S, et al. 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.

17 Næser E, Fredberg U, Møller H, et al. Clinical characteristics and risk of serious disease in patients referred to a diagnostic centre: a cohort study. Cancer Epidemiol 2017;50:158–65.

18 Lebech A-M, Gaardsting A, Loft A, et al. Whole-Body 18F-FDG PET/CT Is Superior to CT as First-Line Diagnostic Imaging in Patients Referred with Serious Nonspecific Symptoms or Signs of Cancer: A Randomized Prospective Study of 200 Patients. J Nucl Med 2017;58:1058–64.

19 Nicholson BD, Oke J, Friedemann Smith C, et al. The suspected cancer (scan) pathway: protocol for evaluating a new standard of care for patients with non-specific symptoms of cancer. BMJ Open 2018;8:e018168.

20 Lacey K, Bishop JF, Cross HL, et al. Presentations to general practice before a cancer diagnosis in Victoria: a cross-sectional survey. Med J Aust 2016;205:66–71.

21 Lyratzopoulos G, Neal RD, Barbieri JM, et al. Variation in number of general practitioner consultations before hospital referral for cancer: findings from the 2010 National cancer patient experience survey in England. Lancet Oncol 2012;13:353–65.

22 Lyratzopoulos G, Wardle J, Rubin G. Rethinking diagnostic delay in cancer: how difficult is the diagnosis? BMJ 2014;349:g7400.

23 Horton KM, Abrams RA, Fishman EK. Spiral CT of colon cancer: imaging features and role in management. Radiographics 2000;20:419–30.

24 Klang E, Eifer M, Kopylov U, et al. Pitfalls in diagnosing colon cancer on abdominal CT. Clin Radiol 2017;72:658–63.

25 Næser E, Møller H, Fredberg U, et al. Routine blood tests and probability of cancer in patients referred with non-specific serious symptoms: a cohort study. BMC Cancer 2017;17:817.