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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

Marie Møller,[1] Bue Juvik,[1] Stine Chabert Olesen,[1] Hanne Sandstrøm,[2] Erling Laxafoss,[3] Simon Bertram Reuter ,[4,5] Uffe Bodtger[1,4,5]

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For numbered affiliations see end of article.

Correspondence to
Bue Juvik;
rbju@regionsjaelland.dk

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-cancer patient pathway (NSSC-CPP).

Design Retrospective cohort study including patients from a part of Denmark.

Setting Department of Internal Medicine at a university hospital.

Participants In total, 529 patients underwent ceCT.

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 in 2012), 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.

Strengths and limitations of this study

- The study shows the utility of CT in everyday clinical patients with a vague suspicion for malignancy in primary care.
- Public, free healthcare system.
- High follow-up rate.
- Uses rereview of all false-negative CT scans by experienced oncoradiologist.
- Does not include biochemistry or clinical examination findings.

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]

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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.[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.[3–6]

Therefore, the urgent referral pathway for NSSC was implemented in 2011–2012.[7] The NSSC-CPP aimed to minimise the time-to-workup in patients with non-specific symptoms, by providing new referral possibilities for GPs.[8]

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 abdominal ultrasound, low-dose CT of chest plus abdominal ultrasound, low-dose thoracoabdominal CT or thoracoabdominal contrast-enhanced CT (ceCT).[3 4 7 9 10]

In our region (Region Zealand,~800 000 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.[7]

Approximately 20% of patients referred through the NSSC-CPP are found to have a malignant disease.[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.[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 64×0.625 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 512×512.

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[12]).

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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).[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 χ^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.[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)

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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			
All malignancies, n (%)	9 (2.4)	92 (63)	<0.05
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			
All cases, n (%)	21 (6)	50 (34)	<0.05
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 (Chi^2- 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.

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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

A	No malignancy	Malignancy	Total
Malignancy not suspected (groups 1+2)	373	9	382
Malignancy possible/probable (groups 3+4)	55	92	147
Total	428	101	529

B	No malignancy	Malignancy	Total
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

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 8[2–19] days, and from ceCT to final diagnosis 24 (10–69) days.

Time period (2013 vs 2015): the number of patients increased significantly from 202 in 2013 to 327 (+62%) in 2015, whereas the prevalence of malignancy decreased insignificantly from 22% to 17%.

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.[15] The cancer prevalence in our study was 20%, somewhat higher compared with previous findings (11%–16%).[8 14–17]

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.[2 3 8 16 18] A prospective study, in England, is evaluating several aspects comparable to this study.[19] 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.[19] The GP suspects cancer in 4%–6% of all patient contacts in primary care, but cancer is only confirmed in 1/30.[7 20–22] 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[23 24]).

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.[17]

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

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malignancy (eg, white blood cell count (LR+1.3) and elevated bilirubin (LR+2.3)) were low and the LR– was not reported.[17 25] 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 Diagnostic Centre that manages the NSSC-CPP in a secondary care setting.[14] This could be due to a reduced threshold for referral, as well as highlighting the blurred lines between serious signs and vague symptoms.[3]

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.[8 25] Also, our study is unique in that we performed 12 months of follow-up and an oncoradiological review of false-negative ceCT scans. Most previous studies used 3–6 months follow-up and to our knowledge, none included CT review.[11 15 17 25] 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.

Author affiliations
[1]Internal Medicine, Zealand University Hospital Roskilde, Roskilde, Sjaelland, Denmark
[2]Radiology, Zealand University Hospital Roskilde, Roskilde, Sjaelland, Denmark
[3]Orthopedic Surgery, Copenhagen University Hospital, Kobenhavn, Denmark
[4]Respiratory Medicine, Nastved Hospital, Nastved, Denmark
[5]Institute for Regional Health Research, University of Southern Denmark, Odense, Denmark

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ORCID iD
Simon Bertram Reuter http://orcid.org/0000-0002-2256-2034

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