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The diagnostic impact of direct referral from general practitioners to contrast-enhanced thoraco-abdominal CT in patients with serious but non-specific symptoms or signs of cancer.

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Title

The diagnostic impact of direct referral from general practitioners to contrast enhanced thoraco-abdominal CT in patients with serious but non-specific symptoms or signs of cancer.

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Abstract

Introduction

In Denmark, a national strategy for an urgent referral pathway for patients with non-specific symptoms or signs of cancer (NSSC) was implemented in 2012. The optimal organization of this service is currently debated. Our study aimed at evaluating the diagnostic properties of contrast enhanced thoraco-abdominal CT (ceCT), where general practitioners (GPs) are responsible for referring and responding to CT-results.

Methods

Our study is a retrospective cohort study based on data collection from hospital health records and National Health databases of patients, referred by a GP to our department for ceCT through the NSSC cancer patient pathway, in 2013 and 2015. CeCT results were classified as either "malignancy not suspected" or "probable/possible malignancy". We reviewed false-negative ceCT scans. A worst-case scenario was evaluated, classifying mortalities in the "malignancy not suspected group" as false-negative.

Results

In total, 529 subjects underwent ceCT, and malignancy was identified in 104 patients (19.7%); 101 (97.1%) during initial workup, and three 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 8 patients (73%). 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.

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Strengths and limitations of the study:

- Shows the utility of CT in every day clinical patients with a vague suspicion for malignancy in primary care
- Public, free health-care system
- High follow-up rate
- Uses re-review of all false negative CT scans by experienced onco-radiologist
- Do not include biochemistry or clinical examination findings

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Introduction

Approximately 50% of patients diagnosed with a malignancy presents with organ-specific symptoms, 20% with non-specific but serious symptoms, and 30% with vague "low-risk-but-not-no-risk" symptoms to their general practitioner (GP) (1).

Patients with non-specific symptoms or signs of cancer (NSSC) have an overall inferior survival compared with patients referred through organ-specific cancer pathways (2-5).

The reason for this may be because of doctors-delay, and therefore, a quick diagnostic workup of patients with uncharacteristic symptoms (including vague or "low-risk-but-not-no-risk") symptoms is warranted (2-5).

When the GP has direct access to imaging and blood tests, it reduces the cost and time spent by a specialist completing diagnostic workup (6). In Denmark, a national strategy for an urgent referral pathway (cancer patient pathway, CPP) for NSSC was implemented in 2012 (NSSC-CPP). Inter-regional differences in the setup of NSSC-CPP were allowed and the workup may include chest x-ray, abdominal ultrasound, low-dose computed tomography (CT) or contrast-enhanced thoraco-abdominal CT (ceCT) (2, 3, 7).

In our region (Region Zealand, 800 000 inhabitants), GPs manage the initial workup of the NSSC-CPP (clinical examination and history supplemented by a predefined set of blood tests).

If the initial workup is inconclusive, the GP can refer the patient directly to ceCT, and if necessary, to further investigations at a specialist (8, 9). In other regions of Denmark, GPs refer patients suspected of NSSC to a diagnostic center or other secondary care unit that manage the workup. Approximately 20% of patients investigated through the NSSC-CPP have cancer (2, 8, 10, 11)

Our study aimed at describing the diagnostic properties of ceCT, when GPs managed referral to ceCT through the NSSC-CPP. Our primary objective was negative and positive likelihood ratios for being diagnosed with cancer within one year after ceCT. Our secondary outcomes were incidence and final diagnoses of malignancy, the prevalence of revision of CT scans and -referral patterns based on ceCT results.

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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 contrast-enhanced thoraco-abdominal CT (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.

Approval from the Danish Patient Safety Authority and the Danish Data Protection Agency were 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 Healtcare, Best, The Netherlands). CT acquisition parameters were 64 x 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, FOV from 35-45 cm and matrix 512 x 512.

Iomeprol 350 mg/ml (Iomeron ® 350 Bracco Imaging), was injected intravenously, in patients with normal renal function (defined as 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 seconds (arterial phase) for the liver, and 70 seconds 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 to the clinical outcome of the patient.

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Definitions

Radiological findings were categorized as

1) No cancer and no abnormal findings
2) Abnormal but benign findings with no suspicion of cancer, findings warranted workup (*e.g.* 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)). 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 re-reviewed by an expert in oncoradiology (H Sandstrøm) who was blinded to the specific diagnosis of malignancy.

Statistics

Statistical analyses were performed using dedicated software (SPSS 23.0; IBM, Chicago, USA). Continuous data are presented as median (range), and inter-group differences were assessed using the Chi^2-test. Categorical data are presented as incidence (%), and inter-group differences analyzed 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 (TP), true-negative (TN), false-positive (FP), false-negative (FN), 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.

Patient and Public Involvement

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

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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 upon the ceCT. Thus, 529 subjects were found eligible for inclusion.

Final diagnosis of cancer

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

False-negative initial workup

Of the 104 patients diagnosed with malignancy, three (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 localized 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 four 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" (group 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 (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, post-diagnosis CT-review resulted in re-designation in eight (73%) cases toward possible/probable malignancy, equaling 2.0% of ceCT classified as "malignancy not suspected" (group 1 and 2).

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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

According to the Bayesian method, estimates of post-test probability for malignancy is a function of disease prevalence (pretest probability). The incidence of malignancy is 19.7%, which is similar to other findings in Europe and Denmark (8, 9, 13).

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) would decrease the probability of malignancy to 7% [5-10%].

Referral patterns

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" (group 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" (group 3 and 4), the CT results did not lead to referral in 13 patients (9%). Two patients were referred in the non-cancer pathway due to other findings, and two of the remaining 11 patients (18%) died within 12 months after ceCT. We have no data on causes for non-referral.

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.

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Time periods: 2013 vs. 2015

The number of patients increased significantly from 202 in 2013 to 327 (+62%) in 2015, whereas the incidence of malignancy decreased insignificantly from 22% to 17%.

Discussion

This study shows that contrast-enhanced thoraco-abdominal CT (ceCT), as part of a GP-coordinated workup of non-specific symptoms and signs of cancer, has a high negative predictive value and a moderate positive predictive value 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 incidence of 0.23% found in a large-scale, Danish epidemiological study from 2017 (9). The cancer-incidence in our study was 20%, somewhat higher compared to previous findings (11-16%) (8-10, 13, 14).

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 2 (0.5%) of these non-referred patients were diagnosed with cancer within the follow-up period. One patient was diagnosed with localized 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 patients (9%) with ceCT classified as “possible/probable malignancy” (group 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.

A 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 (1, 2, 8, 10, 11). A prospective study, in England, is evaluating several aspects comparable to this study (15). 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 (15).

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The GP suspects cancer in 4-6% of all patient contacts in primary care, but cancer is only confirmed in 1/30 (7, 16-18). Several types of malignancy are unlikely to be detected by ceCT (of the chest and abdomen) *e.g.* leukemia and lesions in other anatomical regions (colorectal cancer is undetected in 20% of abdominal CT examinations (19, 20)).

Thus, ceCT is not a stand-alone-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, *e.g.* hematological diseases. Our study focused on ceCT.

We only evaluated the incidence 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 (14).

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 malignancy (*e.g.* white blood cell count (LR+ 1.3) and elevated bilirubin (LR+ 2.3) were low and the LR- was not reported (14, 21).

Our study found, that the usage of NSSC-CPP increased from 2013 to 2015, parallel to a decrease in the incidence of malignancy. The same pattern has been reported from secondary care, where the cancer incidence dropped from 22% in 2011 to 16% in 2013 in a Diagnostic Center that manages the NSSC-CPP in a secondary care setting (13). This could be due to a reduced threshold for referral, as well as highlighting the blurred lines between serious signs and vague symptoms (2).

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 (6, 9, 14, 21). 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”, group 1 and 2) re-classified >50% of these scans as “possible/probable malignancy” (group 3 and 4).

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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 incidence does not support the implementation of routine review of ceCTs by specialized 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 work-up plans for patients with disease-specific symptoms.

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Author Contributions

(I) Conception and design: All authors
(II) Administrative support: U Bodtger, B Juevik
(III) Provision of study materials or patients: M. Møller, U Bodtger, B Juevik
(IV) Collection and assembly of data: M. Møller
(V) Data analysis and interpretation: All authors
(VI) Manuscript writing: All authors
(VII) Final approval of manuscript: All authors

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Background (Appendix)

Beginning at the turn of the millennium, the Danish Board of Health was tasked by the Government to develop a national strategy for mapping, diagnosing and treating malignancies. The resulting initiative; The Danish National Cancer Plan, was followed by subsequent updates and expansions in 2005, 2010 and 2016 (22).

The aims have expanded along the way to include, amongst others; prevention, education, rehabilitation and palliation, but diagnosis and treatment remain essential tasks.

As part of the implementation of the recommendations following the second revision in 2005, cohesive plans for referrals, diagnostics and treatment were outlined for varying types of cancer. These plans, termed Cancer Patient Pathways (CPP), were structured as clinical guidelines in accordance with the latest international evidence and are continually updated and revised by multidisciplinary editorial teams (23).

The Cancer Patient Pathway provides the framework for the decentralized organization of the inherent efforts by regional health sector administrations. One of these initiatives was aimed at creating an urgent referral pathway for patients with vague symptoms, therefore, the urgent referral pathway for non-specific serious symptoms or signs of cancer (NSSC) was implemented in 2011-2012 (7). The NSSC aimed to minimize the time-to-work up in patients with non-specific symptoms, by providing new referral possibilities for general practitioners (GP) (8).

The GP suspects cancer in 4% of the contacts equaling 244 patient each year (7, 24). The rate of new cancer diagnosis per year for each of the registered general practitioners in Denmark (n=3436 in 2017) is between 8 and 10 (7, 24).

Far from all patients have organ-specific symptoms and for patients presenting with serious non-specific symptoms, the urgent referral pathway for non-specific serious symptoms provides a setup for diagnostic workup (2, 3, 7, 25).

Denmark is, according to geography and demographics, divided into five semi-autonomous regional health administrations providing public health in Denmark. The detailed setup of the recommendations in the cancer patient pathway has been implemented with some slight variation between the individual regions (26, 27).

In our region, Region Zealand, the NSSP-CPP is coordinated by GPs. Early protocolized screening prompted by suspicion is instigated and followed up by the GP.

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In cases where the preliminary screening is inconclusive, a contrast-enhanced thoraco-abdominal CT-scan is performed. The GP then receives the CT-scan rapport with a detailed description of the findings, and on the basis hereof, determines whether to refer the patient to a diagnostic center for further workup. In cases where the workup at the GP is sufficient to indicate an organ-specific cancer diagnosis, the patient is referred via the relevant cancer patient pathway to a specialized department for further investigations and treatment.

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Table 1, Demographic and clinical data stratified by filter-CT results

	Malignancy not suspected (groups 1+2)	Malignancy possible/ probable (groups 3+4)	*p*
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
Referrals based on CT			
Organ specific cancer pathway, *n* (%)	22 (6%)	119 (81%)	<0.05*
Diagnostic center, *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 based on other than CT			0.05*
Organ specific cancer pathway, *n* (%)	22 (6%)	0	
Diagnostic center, *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 by 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%)	
Hematology, *n* (%)	3 (30%)	5 (4%)	
Upper GI, *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

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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

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Section & Topic	No	Item
TITLE OR ABSTRACT		
	1	Identification as a study of diagnostic accuracy using at least one measure of accuracy (such as sensitivity, specificity, predictive values, or AUC) P: 1
ABSTRACT		
	2	Structured summary of study design, methods, results, and conclusions (for specific guidance, see STARD for Abstracts) P: 2
INTRODUCTION		
	3	Scientific and clinical background, including the intended use and clinical role of the index test P: 5
	4	Study objectives and hypotheses P: 4+5
METHODS		
Study design	5	Whether data collection was planned before the index test and reference standard were performed (prospective study) or after (retrospective study) P: 5
Participants	6	Eligibility criteria P: 5
	7	On what basis potentially eligible participants were identified (such as symptoms, results from previous tests, inclusion in registry) P: 5
	8	Where and when potentially eligible participants were identified (setting, location and dates) P: 5
	9	Whether participants formed a consecutive, random or convenience series P: 5
Test methods	10a	Index test, in sufficient detail to allow replication P: 5-6
	10b	Reference standard, in sufficient detail to allow replication P: 5-6
	11	Rationale for choosing the reference standard (if alternatives exist) P: 5-6
	12a	Definition of and rationale for test positivity cut-offs or result categories of the index test, distinguishing pre-specified from exploratory P: 5-6
	12b	Definition of and rationale for test positivity cut-offs or result categories of the reference standard, distinguishing pre-specified from exploratory P: 5-6
	13a	Whether clinical information and reference standard results were available to the performers/readers of the index test P: 5-6
	13b	Whether clinical information and index test results were available to the assessors of the reference standard P: 5-6
Analysis	14	Methods for estimating or comparing measures of diagnostic accuracy P: 5-6
	15	How indeterminate index test or reference standard results were handled P: 5-6
	16	How missing data on the index test and reference standard were handled P: 5-6
	17	Any analyses of variability in diagnostic accuracy, distinguishing pre-specified from exploratory P: 5-6
	18	Intended sample size and how it was determined NA
RESULTS		
Participants	19	Flow of participants, using a diagram NA
	20	Baseline demographic and clinical characteristics of participants P: 16
	21a	Distribution of severity of disease in those with the target condition P: 16
	21b	Distribution of alternative diagnoses in those without the target condition P: 16
	22	Time interval and any clinical interventions between index test and reference standard NA
Test results	23	Cross tabulation of the index test results (or their distribution) by the results of the reference standard P: 17
	24	Estimates of diagnostic accuracy and their precision (such as 95% confidence intervals) P: 17
	25	Any adverse events from performing the index test or the reference standard P: 8
DISCUSSION		
	26	Study limitations, including sources of potential bias, statistical uncertainty, and generalisability P: 9-10
	27	Implications for practice, including the intended use and clinical role of the index test P: 9-10
OTHER INFORMATION		
	28	Registration number and name of registry NA
	29	Where the full study protocol can be accessed NA
	30	Sources of funding and other support; role of funders P: 11

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BMJ Open

The diagnostic property of direct referral from general practitioners to contrast enhanced thoraco-abdominal 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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Title

The diagnostic property of direct referral from general practitioners to contrast enhanced thoraco-abdominal CT in patients with serious but non-specific symptoms or signs of cancer: a retrospective cohort study on cancer prevalence after 12 months.

Authors

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Abstract

Introduction

In Denmark, a national strategy for an urgent referral pathway for patients with non-specific symptoms or signs of cancer (NSSC) was implemented in 2012. The optimal organization of this service is currently debated. Our study aimed at evaluating the diagnostic properties of contrast enhanced thoraco-abdominal CT (ceCT), where general practitioners (GPs) are responsible for referring and responding to CT-results.

Methods

Our study is a retrospective cohort study based on data collection from hospital health records and National Health databases of patients, referred by a GP to our department for ceCT through the NSSC cancer patient pathway, in 2013 and 2015. CeCT results were classified as either "malignancy not suspected" or "probable/possible malignancy". We reviewed false-negative ceCT scans. A worst-case scenario was evaluated, classifying mortalities in the "malignancy not suspected group" as false-negative.

Results

In total, 529 subjects underwent ceCT, and malignancy was identified in 104 patients (19.7%); 101 (97.1%) during initial workup, and three 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 8 patients (73%). 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.

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Strengths and limitations of the study:

- Shows the utility of CT in every day clinical patients with a vague suspicion for malignancy in primary care
- Public, free health-care system
- High follow-up rate
- Uses re-review of all false negative CT scans by experienced onco-radiologist
- Do not include biochemistry or clinical examination findings

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Introduction

Approximately 50% of patients diagnosed with a malignancy presents with organ-specific symptoms, 20% with non-specific but serious symptoms, and 30% with vague "low-risk-but-not-no-risk" symptoms to their general practitioner (GP) (1).

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 organ-specific cancer pathways (2-5). A reason for this may be doctors-delay and therefore, a quick diagnostic workup of patients with uncharacteristic symptoms (including vague or "low-risk-but-not-no-risk") symptoms is warranted (2-5). When the GP has direct access to imaging and blood tests, it reduces the cost and time spent by a specialist completing diagnostic workup (6). In Denmark, a national strategy for an urgent referral pathway (cancer patient pathway, CPP) for NSSC was implemented in 2012 (NSSC-CPP). Inter-regional differences in the setup of NSSC-CPP were allowed and the workup may include chest x-ray, abdominal ultrasound, low-dose computed tomography (CT) or contrast-enhanced thoraco-abdominal CT (ceCT) (2, 3, 7).

In our region (Region Zealand, 800 000 inhabitants), GPs manage the initial workup of the NSSC-CPP (clinical examination and history supplemented by a predefined set of blood tests).

If the initial workup is inconclusive, the GP can refer the patient directly to ceCT, and if necessary, to further investigations at a specialist (8, 9). In other regions of Denmark, GPs refer patients suspected of NSSC to a diagnostic center or other secondary care unit that manage the workup. Approximately 20% of patients investigated through the NSSC-CPP have cancer (2, 8, 10, 11)

Our study aimed at describing the diagnostic properties of ceCT, when GPs managed 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 one 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.

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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 contrast-enhanced thoraco-abdominal CT (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 were 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 Healtcare, Best, The Netherlands). CT acquisition parameters were 64 x 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, FOV from 35-45 cm and matrix 512 x 512.

Iomeprol 350 mg/ml (Iomeron ® 350 Bracco Imaging), was injected intravenously, in patients with normal renal function (defined as 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 seconds (arterial phase) for the liver, and 70 seconds 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 to the clinical outcome of the patient.

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Definitions

Radiological findings were categorized as

1) No cancer and no abnormal findings
2) Abnormal but benign findings with no suspicion of cancer, findings warranted workup (*e.g.* 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)). 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 re-reviewed 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 was categorized 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 23.0; IBM, Chicago, USA). Continuous data are presented as median (range), and inter-group differences were assessed using the Chi^2-test. Categorical data are presented as prevalence (%), and inter-group differences analyzed 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 (TP), true-negative (TN), false-positive (FP), false-negative (FN), 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 is 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%

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confidence intervals).-

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 upon the ceCT. Thus, 529 subjects were found eligible for inclusion.

Final diagnosis of cancer

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

False-negative initial workup

Of the 104 patients diagnosed with malignancy, three (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 localized 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 four 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" (group 1 and 2) (Table 1). Thus, the prevalence of false-negative ceCT was 2.9% (11/382).

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Unblinded review of these scans (including the above cases) resulted in a regrouping of five (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, post-diagnosis CT-review resulted in re-designation in eight (73%) cases toward possible/probable malignancy, equaling 2.0% of ceCT classified as "malignancy not suspected" (group 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, 9, 14).

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) 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" (group 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" (group 3 and 4), the CT results did not lead to referral in 13 patients (9%). Two patients were referred in the non-cancer pathway due to other findings, and two of the remaining 11 patients (18%) died within 12 months after ceCT. We have no data on causes for non-referral.

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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 periods: 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 contrast-enhanced thoraco-abdominal CT (ceCT), as part of a GP-coordinated workup of non-specific symptoms and signs of cancer, has a high negative predictive value and a moderate positive predictive value 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 (9). The cancer-prevalence in our study was 20%, somewhat higher compared to previous findings (11-16%) (8-10, 14, 15).

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 2 (0.5%) of these non-referred patients were diagnosed with cancer within the follow-up period. One patient was diagnosed with localized 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 patients (9%) with ceCT classified as "possible/probable malignancy" (group 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.

A 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 (1, 2, 8, 10, 11). A prospective study, in England, is evaluating several aspects comparable to this study (16). 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

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clinic (16).

The GP suspects cancer in 4-6% of all patient contacts in primary care, but cancer is only confirmed in 1/30 (7, 17-19). Several types of malignancy are unlikely to be detected by ceCT (of the chest and abdomen) *e.g.* leukemia and lesions in other anatomical regions (colorectal cancer is undetected in 20% of abdominal CT examinations (20, 21)).

Thus, ceCT is not a stand-alone-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, *e.g.* hematological 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 (15).

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 malignancy (*e.g.* white blood cell count (LR+ 1.3) and elevated bilirubin (LR+ 2.3) were low and the LR- was not reported (15, 22).

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 Center 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 (2).

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, 22). 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 (6, 9, 15, 22). The extended follow-up makes it unlikely that we missed false-negative cases of malignancy except in patients who died during follow-up.

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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", group 1 and 2) re-classified >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 specialized 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 work-up plans for patients with disease-specific symptoms.

Competing Interests

There are no competing interests for any authors. This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Data Availability Statement

Data are available opon request

Author Contributions

(I) Conception and design: MM, BJ, SO, HS, EL, SR, UB
(II) Administrative support: BJ, UB
(III) Provision of study materials or patients: MM, BJ, UB
(IV) Collection and assembly of data: MM
(V) Data analysis and interpretation: MM, BJ, SO, HS, EL, SR, UB
(VI) Manuscript writing: MM, BJ, SO, HS, EL, SR, UB
(VII) Final approval of manuscript: MM, BJ, SO, HS, EL, SR, UB

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Background (Appendix)

Beginning at the turn of the millennium, the Danish Board of Health was tasked by the Government to develop a national strategy for mapping, diagnosing and treating malignancies. The resulting initiative; The Danish National Cancer Plan, was followed by subsequent updates and expansions in 2005, 2010 and 2016 (23).

The aims have expanded along the way to include, amongst others; prevention, education, rehabilitation and palliation, but diagnosis and treatment remain essential tasks.

As part of the implementation of the recommendations following the second revision in 2005, cohesive plans for referrals, diagnostics and treatment were outlined for varying types of cancer. These plans, termed Cancer Patient Pathways (CPP), were structured as clinical guidelines in accordance with the latest international evidence and 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 raising the suspicion for malignancy, which investigations to include in the follow-up, which specialist departments to refer to, and lastly, timeframes for all phases in the workup (for instance, time from referral to first consult) (23).

The Cancer Patient Pathway provides the framework for the decentralized organization of the inherent efforts by regional health sector administrations. One of these initiatives was aimed at creating an urgent referral pathway for patients with vague symptoms, therefore, the urgent referral pathway for non-specific serious symptoms or signs of cancer (NSSC) was implemented in 2011-2012 (7). The NSSC aimed to minimize the time-to-work up in patients with non-specific symptoms, by providing new referral possibilities for general practitioners (GP) (8).

The GP suspects cancer in 4% of the contacts equaling 244 patient each year (7, 24). The rate of new cancer diagnosis per year for each of the registered general practitioners in Denmark (n=3436 in 2017) is between 8 and 10 (7, 24).

Far from all patients have organ-specific symptoms and for patients presenting with serious non-specific symptoms like weight loss, fatigue, fever, bone pain or just GPs “gut feeling”, the urgent referral pathway for non-specific serious symptoms provides a setup for diagnostic workup (2, 3, 7, 25).

Denmark is, according to geography and demographics, divided into five semi-autonomous regional health administrations providing public health in Denmark.

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The detailed setup of the recommendations in the cancer patient pathway has been implemented with some slight variation between the individual regions (26, 27).

In our region, Region Zealand, the workup of the NSSP-CPP is coordinated by the GP. The NSSP-CPP consists of two steps. Step one is history, a clinical examination (including urine dipstick, electrocardiogram and fecal occult blood test) supplemented by a predefined set of blood tests (containing hemoglobin, erythrocyte mean cell volume (MCV), mean cell hemoglobin concentration (MCHC), leukocyte differential (L+D), reticulocyte index, thrombocyte count, C-reactive Protein (CRP), sodium, potassium, creatinine, estimated glomerular filtration rate (eGFR), calcium (total), albumin, glucose, bilirubin, alanine aminotransferase (ALAT), alkaline phosphatase, pancreas specific amylase, lactate dehydrogenase (LDH), Immunoglobulin G-A-M, thyroid-stimulating hormone (TSH), myeloma-protein and prothrombin time INR)).

In cases where the above is inconclusive or without any pathologic findings, a contrast-enhanced thoraco-abdominal CT-scan is performed (step two). The GP then receives the CT-scan rapport with a detailed description of the findings, and on the basis hereof, determines whether to refer the patient to a diagnostic center for further workup. In cases where the workup at the GP is sufficient to indicate an organ-specific cancer diagnosis, the patient is referred via the relevant cancer patient pathway to a specialized department for further investigations and treatment. If all findings are negative, the GP can choose to terminate the work-up (7).

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Table 1, Demographic and clinical data stratified by results of the contrast-enhanced CT (ceCT)

	Malignancy not suspected (groups 1+2)	Malignancy possible/ probable (groups 3+4)	*p*
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 center, *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 center, *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%)	
Hematology, *n* (%)	3 (30%)	5 (4%)	
Upper GI, *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

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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

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Section & Topic	No	Item
TITLE OR ABSTRACT		
	1	Identification as a study of diagnostic accuracy using at least one measure of accuracy (such as sensitivity, specificity, predictive values, or AUC) P: 1
ABSTRACT		
	2	Structured summary of study design, methods, results, and conclusions (for specific guidance, see STARD for Abstracts) P: 2
INTRODUCTION		
	3	Scientific and clinical background, including the intended use and clinical role of the index test P: 5
	4	Study objectives and hypotheses P: 4+5
METHODS		
Study design	5	Whether data collection was planned before the index test and reference standard were performed (prospective study) or after (retrospective study) P: 5
Participants	6	Eligibility criteria P: 5
	7	On what basis potentially eligible participants were identified (such as symptoms, results from previous tests, inclusion in registry) P: 5
	8	Where and when potentially eligible participants were identified (setting, location and dates) P: 5
	9	Whether participants formed a consecutive, random or convenience series P: 5
Test methods	10a	Index test, in sufficient detail to allow replication P: 5-6
	10b	Reference standard, in sufficient detail to allow replication P: 5-6
	11	Rationale for choosing the reference standard (if alternatives exist) P: 5-6
	12a	Definition of and rationale for test positivity cut-offs or result categories of the index test, distinguishing pre-specified from exploratory P: 5-6
	12b	Definition of and rationale for test positivity cut-offs or result categories of the reference standard, distinguishing pre-specified from exploratory P: 5-6
	13a	Whether clinical information and reference standard results were available to the performers/readers of the index test P: 5-6
	13b	Whether clinical information and index test results were available to the assessors of the reference standard P: 5-6
Analysis	14	Methods for estimating or comparing measures of diagnostic accuracy P: 5-6
	15	How indeterminate index test or reference standard results were handled P: 5-6
	16	How missing data on the index test and reference standard were handled P: 5-6
	17	Any analyses of variability in diagnostic accuracy, distinguishing pre-specified from exploratory P: 5-6
	18	Intended sample size and how it was determined NA
RESULTS		
Participants	19	Flow of participants, using a diagram NA
	20	Baseline demographic and clinical characteristics of participants P: 16
	21a	Distribution of severity of disease in those with the target condition P: 16
	21b	Distribution of alternative diagnoses in those without the target condition P: 16
	22	Time interval and any clinical interventions between index test and reference standard NA
Test results	23	Cross tabulation of the index test results (or their distribution) by the results of the reference standard P: 17
	24	Estimates of diagnostic accuracy and their precision (such as 95% confidence intervals) P: 17
	25	Any adverse events from performing the index test or the reference standard P: 8
DISCUSSION		
	26	Study limitations, including sources of potential bias, statistical uncertainty, and generalisability P: 9-10
	27	Implications for practice, including the intended use and clinical role of the index test P: 9-10
OTHER INFORMATION		
	28	Registration number and name of registry NA
	29	Where the full study protocol can be accessed NA
	30	Sources of funding and other support; role of funders P: 11

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BMJ Open

The diagnostic property of direct referral from general practitioners to contrast enhanced thoraco-abdominal 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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Title

The diagnostic property of direct referral from general practitioners to contrast enhanced thoraco-abdominal CT in patients with serious but non-specific symptoms or signs of cancer: a retrospective cohort study on cancer prevalence after 12 months.

Authors

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Abstract

Objectives

To describe the diagnostic properties of contrast-enhanced thoraco-abdominal CT (ceCT), when GPs managed referral to ceCT through the 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 one 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 patients (19.7%); 101 (97.1%) during initial workup, and three 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 8 patients (73%). 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.

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Strengths and limitations of the study:

- Shows the utility of CT in every day clinical patients with a vague suspicion for malignancy in primary care
- Public, free health-care system
- High follow-up rate
- Uses re-review of all false negative CT scans by experienced onco-radiologist
- Do not include biochemistry or clinical examination findings

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Introduction

The Danish Board of Health initiated the Danish National Cancer Plan in 2000, including firstly 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 to patients referred through the organ-specific cancer pathways (3-6). A 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 minimize the time-to-work up in patients with non-specific symptoms, by providing new referral possibilities for general practitioners (GP) (8).

The Danish health-care system is run by five regional health administrations each providing health-care 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 center for work-up) and in choice of initial imaging: chest x-ray *plus* abdominal ultrasound, low-dose computed tomography (CT) of chest *plus* abdominal ultrasound, low-dose thoraco-abdominal CT, or contrast-enhanced thoraco-abdominal 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, electrocardiogram, fecal 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 immunoglobulins G, A and M).

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If inconclusive, the GP initiates Step 2: a thoraco-abdominal ceCT (performed within 4 days), and the GP summarizes 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 manages 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 one 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 contrast-enhanced thoraco-abdominal CT (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 were 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 Healtcare, Best, The Netherlands).

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CT acquisition parameters were 64 x 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, FOV from 35-45 cm and matrix 512 x 512.
Iomeprol 350 mg/ml (Iomeron ® 350 Bracco Imaging), was injected intravenously, in patients with normal renal function (defined as 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 seconds (arterial phase) for the liver, and 70 seconds 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 to the clinical outcome of the patient.

Definitions

Radiological findings were categorized as

1) No cancer and no abnormal findings
2) Abnormal but benign findings with no suspicion of cancer, findings warranted workup (*e.g.* 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)).
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 re-reviewed 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 was categorized as being false-negative (in those with a malignancy) or false-positive (in all others) (13).

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Statistics

Statistical analyses were performed using dedicated software (SPSS 23.0; IBM, Chicago, USA). Continuous data are presented as median (range), and inter-group differences were assessed using the *Chi*^{2}-test. Categorical data are presented as prevalence (%), and inter-group differences analyzed 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 (TP), true-negative (TN), false-positive (FP), false-negative (FN), 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 is 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% confidence intervals).-

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 upon the ceCT. Thus, 529 subjects were found eligible for inclusion.

Final diagnosis of cancer

Table 1 shows that 101 patients (19%) were diagnosed with cancer during initial workup and, in addition, 3 patients during the 12 months of follow-up (0.7%) totaling 104 patients (19.7%). 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 post-mortem analyses were made, but none of the medical files provided a clinical suspicion of an underlying, missed cancer as the cause of death.

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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, three (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 localized 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 four 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" (group 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 (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, post-diagnosis CT-review resulted in re-designation in eight (73%) cases toward possible/probable malignancy, equaling 2.0% of ceCT classified as "malignancy not suspected" (group 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.

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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) 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" (group 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" (group 3 and 4), the CT results did not lead to referral in 13 patients (9%). Two patients were referred in the non-cancer pathway due to other findings, and two of the remaining 11 patients (18%) died within 12 months after ceCT. We have no data on causes for non-referral.

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 periods: 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%.

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Discussion

This study shows that contrast-enhanced thoraco-abdominal CT (ceCT), as part of a GP-coordinated workup of non-specific symptoms and signs of cancer, has a high negative predictive value and a moderate positive predictive value 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 to 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 2 (0.5%) of these non-referred patients were diagnosed with cancer within the follow-up period. One patient was diagnosed with localized 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 patients (9%) with ceCT classified as “possible/probable malignancy” (group 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.

A 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) *e.g.* leukemia and lesions in other anatomical regions (colorectal cancer is undetected in 20% of abdominal CT examinations (23, 24)).

Thus, ceCT is not a stand-alone-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, *e.g.* hematological 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-

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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 malignancy (*e.g.* 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 Center 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”, group 1 and 2) re-classified >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.

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However, the low prevalence does not support the implementation of routine review of ceCTs by specialized 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 work-up plans for patients with disease-specific symptoms.

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This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Competing Interests

There are no competing interests for any authors.

Data Availability Statement

Data are available upon request

Author Contributions

(I) Conception and design: MM, BJ, SO, HS, EL, SR, UB
(II) Administrative support: BJ, UB
(III) Provision of study materials or patients: MM, BJ, UB
(IV) Collection and assembly of data: MM, BJ, SO
(V) Data analysis and interpretation: MM, BJ, SO, HS, EL, SR, UB
(VI) Manuscript writing: MM, BJ, SO, HS, EL, SR, UB
(VII) Final approval of manuscript: MM, BJ, SO, HS, EL, SR, UB

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Table 1, Demographic and clinical data stratified by results of the contrast-enhanced CT (ceCT)

	Malignancy not suspected (groups 1+2)	Malignancy possible/ probable (groups 3+4)	*p*
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 center, *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 center, *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%)	
Hematology, *n* (%)	3 (30%)	5 (4%)	
Upper GI, *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

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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

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Section & Topic	No	Item
TITLE OR ABSTRACT		
	1	Identification as a study of diagnostic accuracy using at least one measure of accuracy (such as sensitivity, specificity, predictive values, or AUC) P: 1
ABSTRACT		
	2	Structured summary of study design, methods, results, and conclusions (for specific guidance, see STARD for Abstracts) P: 2
INTRODUCTION		
	3	Scientific and clinical background, including the intended use and clinical role of the index test P: 5
	4	Study objectives and hypotheses P: 4+5
METHODS		
Study design	5	Whether data collection was planned before the index test and reference standard were performed (prospective study) or after (retrospective study) P: 5
Participants	6	Eligibility criteria P: 5
	7	On what basis potentially eligible participants were identified (such as symptoms, results from previous tests, inclusion in registry) P: 5
	8	Where and when potentially eligible participants were identified (setting, location and dates) P: 5
	9	Whether participants formed a consecutive, random or convenience series P: 5
Test methods	10a	Index test, in sufficient detail to allow replication P: 5-6
	10b	Reference standard, in sufficient detail to allow replication P: 5-6
	11	Rationale for choosing the reference standard (if alternatives exist) P: 5-6
	12a	Definition of and rationale for test positivity cut-offs or result categories of the index test, distinguishing pre-specified from exploratory P: 5-6
	12b	Definition of and rationale for test positivity cut-offs or result categories of the reference standard, distinguishing pre-specified from exploratory P: 5-6
	13a	Whether clinical information and reference standard results were available to the performers/readers of the index test P: 5-6
	13b	Whether clinical information and index test results were available to the assessors of the reference standard P: 5-6
Analysis	14	Methods for estimating or comparing measures of diagnostic accuracy P: 5-6
	15	How indeterminate index test or reference standard results were handled P: 5-6
	16	How missing data on the index test and reference standard were handled P: 5-6
	17	Any analyses of variability in diagnostic accuracy, distinguishing pre-specified from exploratory P: 5-6
	18	Intended sample size and how it was determined NA
RESULTS		
Participants	19	Flow of participants, using a diagram NA
	20	Baseline demographic and clinical characteristics of participants P: 16
	21a	Distribution of severity of disease in those with the target condition P: 16
	21b	Distribution of alternative diagnoses in those without the target condition P: 16
	22	Time interval and any clinical interventions between index test and reference standard NA
Test results	23	Cross tabulation of the index test results (or their distribution) by the results of the reference standard P: 17
	24	Estimates of diagnostic accuracy and their precision (such as 95% confidence intervals) P: 17
	25	Any adverse events from performing the index test or the reference standard P: 8
DISCUSSION		
	26	Study limitations, including sources of potential bias, statistical uncertainty, and generalisability P: 9-10
	27	Implications for practice, including the intended use and clinical role of the index test P: 9-10
OTHER INFORMATION		
	28	Registration number and name of registry NA
	29	Where the full study protocol can be accessed NA
	30	Sources of funding and other support; role of funders P: 11

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