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PATIENTS FROM GENERAL PRACTICE WITH NON-SPECIFIC CANCER SYMPTOMS: A RETROSPECTIVE STUDY OF SYMPTOMS AND IMAGING

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Abstract

Background. Patients with non-specific symptoms or signs of cancer (NSSC) present a challenge as they are a heterogeneous population that are not candidates for fast-track work-up in an organ-specific cancer preplanned pathway. Denmark has a cancer preplanned pathway for this population (NSSC-CPP), but several issues remain unclarified, e.g. distribution and significance of symptoms and findings and choice of imaging.

Aim. We investigated symptoms, cancer diagnoses, and diagnostic yield of CT and $^{18}$F-FDG-PET/CT in NSSC-CPP patients to improve the overall diagnostic process.

Design and setting. A retrospective medical chart review in a one-year consecutive cohort (2020).

Methods. We reviewed 802 referrals for diagnostic imaging in patients with NSSP from general practices, specialist practices or the local hospital diagnostic centre responsible for NSSC-CPP.

Results. We included 248 patients: 21% had cancer, most frequently gastrointestinal cancer (27%). The most frequent symptom was weight loss (56%). CT had a sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of 85%, 87%, 65% and 96%, respectively. For $^{18}$F-FDG-PET/CT, the numbers were 82%, 62%, 33% and 94%. Patients frequently underwent subsequent examinations following initial imaging.

Conclusions. Our findings were in accordance with the literature. Patients with non-specific symptoms or signs of cancer had a cancer prevalence of 21%, most frequently gastrointestinal. The most frequent symptom was weight loss and even as the only symptom, it is a potential marker for cancer. CT and $^{18}$F-FDG-PET/CT were sensitive with high NPV, whereas PPV was superior in CT. Better stratification by symptoms or findings is an obvious focus point for future studies to further optimize the NSSC-CPP workup strategy.

How this fits in

Patients with non-specific signs or symptoms of cancer are a heterogeneous and clinically challenging group in general practice (GP). A significant proportion is diagnosed with underlying cancer, but the most suitable diagnostic strategy for GP remains controversial. We found a 21% cancer prevalence, most frequently gastrointestinal, and symptoms and signs reflected the literature with weight loss as the most prevalent one. The current strategy with CT of chest and abdomen or $^{18}$F-FDG-PET/CT performed well in this population with high sensitivity and negative predictive values but more moderate specificity and positive predictive values especially for $^{18}$F-FDG-PET/CT.

Introduction

Correct and timely treatment of cancer requires a fast and accurate diagnostic strategy. Recognizing relevant symptoms is the first step, but only half of cancer patients present with alarm symptoms. 1, 2, 15% of the general population experience alarm symptoms during a year 3, 4, whereas annual cancer incidence is much lower, e.g. < 1% in Denmark 5. The diagnostic process is even more difficult if the cancer presents with non-specific symptoms and signs of cancer.
In the late 1990s, cancers were diagnosed later in Denmark than in other European countries, and the mortality rates were higher\textsuperscript{7, 9-11}. As a result, Danish Health Authority introduced national cancer pre-planned pathways (CPP) to ensure fast work-up\textsuperscript{2, 12} for specific cancer suspicions and alarm symptoms, and also for NSSC (NSSC-CPP)\textsuperscript{13, 14}. Patients with NSSC are investigated in GP or hospital-based diagnostic centres\textsuperscript{12}. Initial work-up usually include clinical examination, standard blood tests and diagnostic imaging; usually either CT of chest and abdomen or a positron emission tomography with \textsuperscript{18}F-labelled fluorodeoxyglucose ([\textsuperscript{18}F]FDG-PET/CT). Only diagnostic centres may refer directly to a \textsuperscript{18}F]FDG-PET/CT scan, and it remains controversial if CT or \textsuperscript{18}F]FDG-PET/CT is the most appropriate first line modality in NSSC, e.g. diagnostic yield and false positive findings\textsuperscript{15, 16}.

The NSSC-CPP are organized slightly different in each Danish region\textsuperscript{17} and data is sparse on basic demographics, symptoms, cancer prevalence, and imaging in the NSSC populations at our hospital; this is currently debated between referring physicians and radiology departments.

The study objective was to contribute novel insights into NSSC-CPP patients including the distribution and significance of symptoms and the diagnostic yield of CT and \textsuperscript{18}F]FDG-PET/CT with the aim to improve the overall workup process.

**Methods**

This was a retrospective review of medical charts. We included all patients with novel NSSC referred from GP, specialist practice, or local diagnostic centre for CT of chest and abdomen or \textsuperscript{18}F]FDG-PET/CT at our hospital from 1 January-31 December 2020. We excluded patients with known cancers, cancer of unknown primary, referrals to specific CPP, and suspected non-melanoma skin cancer.

Primary outcome was the proportion of NSSC patients diagnosed with cancer. Any finding on a scan that was considered suspicious of cancer was classified as true or false positive or negative using the final diagnosis from the medical charts as reference standard.

We followed patients for a maximum of one year after the initial scan, but stopped in case they were diagnosed with cancer. We verified cancer diagnoses from biopsy results in The Danish Pathology Register\textsuperscript{18} and grouped them according to ICD-10 chapters C00-D49. When no biopsy was performed despite suspicious scans, e.g. due to patient frailty, an experienced onc-radiologist re-analysed the scans to assess whether the findings were consistent with cancer.

Secondary endpoints included the most frequent initial symptoms and the number of subsequent examinations during the diagnostic workup process.

We registered the most frequent cancer symptoms the patients presented with to their GP or diagnostic centre, and seven well-known warning signs of cancer, i.e. long-term dysphagia, weight loss, long-term coughing or hoarseness, changed bowel habits, unexplained bleeding, changed moles or non-healing wounds, changing lumps or swellings\textsuperscript{19}. We limited the list to 20 symptoms/signs plus ‘no symptoms’ and ‘doctor’s gut feeling’.

In addition, we registered data on subsequent examinations induced directly by the scan, i.e. imaging, endoscopy, or biopsy performed within the follow-up period after initial referral, i.e. for instance control scans of known findings were not included.

Study data was collected and managed using REDCap (Research Electronic Data Capture), hosted by the Region of Southern Denmark\textsuperscript{20, 21}.
Statistics were performed using Stata/BE 17 (StataCorp, Texas US) with continuous data reported by mean and standard deviation if normally distributed, and compared using Student’s t-test. Discrete or non-normal data were presented by median and range. Categorical data was represented as prevalence, and differences tested using chi-square or Fisher’s exact test. Statistical significance level was defined as 0.05.

Results

Of 802 referrals (178 from the diagnostic centre and 624 from GP or specialist practice), 248 matched the inclusion criteria (123 men and 125 women) (Figure 1). Table 1 presents baseline demographics and characteristics.

Findings indicative of cancer were found in 81/248 (33%) scans. Ultimately, 52/248 patients (21%) were diagnosed with cancer (Table 1).

The most common cancer sites were the digestive organs (27% of 52), respiratory system (15%), and lymphoid or haematopoietic malignancies (14%) (Figure 2). Figure 2 illustrates the frequency of cancers and cancer suspicions in the initial scan: initial imaging detected 85% (44/52) of cancers.

Patients presented to the referring physician with 0-8 symptoms with a median of 2 (Table 1). The most frequent symptom was weight loss (56% of the patients), and 78/248 (32%) had only one symptom. Some symptoms were more frequently associated with cancer: changed bowel habits (8/16), blood in the urine (1/2), or pain (23/80) (Figure 3). When no symptoms were reported, the reasons for referral was usually abnormal results of blood samples or suspicious imaging findings.

After correlation of scans with final diagnoses, the diagnostic yield of initial CT and $^{18}$F-FDG-PET/CT was calculated as presented in Table 2. Cancer prevalence was 22% (41/190) in the CT group and 19% (11/58) in the $^{18}$F-FDG-PET/CT group, respectively.

Seven patients with findings suspicious of cancer on the initial CT scan had no biopsies. When CT scans were reanalysed, four of the patients had obvious cancer based on imaging alone and died during follow-up; these could arguably be classified as true positives.

Two non-solid haematological cancers (leukaemia) were not detected by $^{18}$F-FDG-PET/CT (Figure 2). These should be diagnosed by blood samples and not imaging. $^{18}$F-FDG-PET/CT is suitable for the detection of solid tumours and hematologic cancers could be categorised as true negatives with respect to solid tumours.

The diagnostic yield after applying these modifications can be found in Table 2.

After the initial scan, patients often underwent additional examinations; patients without cancer went through 0-5 subsequent examinations (median of 1). Of those, 62 underwent one examination and 44 underwent more. CT scans and endoscopies were the most common supplementary examinations (Table 3); 87 underwent endoscopies, in 40 cases with biopsy performed.

Discussion

Summary

Twenty-one percent of included patients were diagnosed with cancer, most frequently in the digestive organs, respiratory system, and lymphoid or hematopoietic system. The most common
initial symptoms were weight loss, pain, or fatigue. CT and $^{18}$F-FDG-PET/CT had comparably high sensitivity and NPV, whereas CT had superior specificity and PPV.

**Strengths and limitations**

This is a retrospective study with the inherent limitations by this design, e.g. important data may unavailable and data is prone to bias and confounders that are difficult to control. To minimize the risk of selection bias, we included all referrals to CT received as part of a NSSC-CPP at our institution in 2020 regardless if they originated from GP, specialist clinic, or diagnostic centre. We also used biopsy as the reference standard and retrieved cancer diagnoses directly from the national pathology database to minimize the risk of misclassification and recall bias. This ensured that we did not miss a diagnosis even if a patient moved to a different region of Denmark.

On the negative site, the number of patients and scans in our dataset is relatively limited leading to some wide confidence intervals of all diagnostic properties (sensitivity, specificity, PPV, NPV) especially in the case of $^{18}$F-FDG-PET/CT. Thus, a misclassification would have a considerable impact on diagnostic properties.

Also, our study was observational with no interventions, meaning that the patients in our study were preselected for CT and $^{18}$F-FDG-PET/CT depending on the clinical setting and the referring physicians discretion. Therefore, the two groups were not directly comparable, although the cancer prevalence was similar in both groups.

Some patients were undoubtedly diagnosed with non-malignant diseases that where relevant as differential diagnoses in the context of NSSC, but due to technical issues after a regional switch to a new electronic patient record, we did not have full access to historic electronic patient charts. Therefore, we could not investigate this further or verify any post-scan clinical procedures or examinations except endoscopies.

We registered initial symptoms based on referral text and there could be reporting bias if referring doctors disregarded some symptoms or findings in the referrals.

**Comparison with existing literature**

Our study found 21% had a biopsy proven malignancy. Another 1.6 % (4 / 248) had imaging findings in keeping with malignancy not confirmed by biopsy. Arguably, our prevalence is 23 % and within the range in the literature. Møller et al. found a prevalence of 20 % in a cohort from GP. Prevalence of cancer with NSSC in Denmark, Sweden, UK, The Netherlands, Australia and Spain are found to be 9-35%13, 14, 23-30. The COVID-19 pandemic stressed healthcare systems in 2020 and a general decrease in cancer incidence was observed31, 32. The prevalence of cancer in our study is similar to studies before COVID-1914, 23, 26, 33 and any influence of the COVID-19 pandemic could not be detected in our result.

In adherence to Danish GDPR legislation, we had to keep our overall groupings of malignant findings relatively broad; the most common cancer sites were the digestive organs (27%), respiratory system (15%), and lymphoid or haematopoietic malignancies (14%). These results were in keeping with the literature, for instance Chapman et al. found the three most common cancers to be GI-cancers (upper and lower) (35%), lung (22%), and haematological (13%)24. Several other national and international studies found comparable results albeit with variations in numbers25, 26, 29, 34.

In agreement with other studies13, 15, 26, 34, more than half of patients (56% overall, 12% of those with a cancer diagnosis) were referred with weight loss. For instance, in a large British study,
Chapman et al. found weight loss in 66%, in 20% it was monosymptomatic. Unintended weight loss is associated with cancer, but not often explored in a standardized manner. Interestingly, it was recently discussed at our institution whether monosymptomatic weight loss is enough to qualify a patient for the NSSC-CPP. Given the frequency of this symptom among NSSC patients, weight loss may warrant further studies to investigate if it could predict cancer in itself. The second and third most common symptoms/findings in our study was pain (32% overall, 9% of cancer patients) and fatigue (28% overall, 5% of cancer patients). Chapman et al. found similar results, i.e. pain and fatigue was the third and fifth most common (32% and 19%, respectively).

Of note, 6.4% of the patients in our cohort presented with changed bowel habits, which would actually qualify them for the national colorectal CPP, and the reason why they entered the NSSC-CPP is unknown, but probably just signifies the complexity of this population.

Our cohort consisted of patients with NSSC from both GPs and the diagnostic center of our institution: NSSC are common and can be a challenge to GPs. Organisation of CPP vary among institutions both nationally and internationally and there is an ongoing effort to gather information to optimize the efforts.

Imaging is routinely used in the diagnosis, staging and follow up of cancer, and although several studies address the diagnostic yield of advanced imaging in patients with NSSC, timing, first-line choice, and cost-effective use of imaging in patients with NSSC remains controversial. For instance, a current protocol is testing rapid CT in this context, and in Denmark there are disagreements over conventional CT or [18F]FDG-PET/CT as first-line modality.

Initial scans detected 85% (44/52) of cancers in our series. Møller et al. investigated the diagnostic properties of contrast enhanced CT in NSSC-CPP referred from GP. Cancer prevalence was 20%, and 92% had CT results classified as possible or probable cancer: a positive CT raised the probability of a cancer diagnosis to 62%, whereas a negative one decreased the probability to 2%. Similar results were reported by Ormstrup et al.

[18F]FDG-PET/CT has been suggested instead of CT as initial imaging in NSSC for more timely diagnoses and cost-effectiveness. Our results found that CT and [18F]FDG-PET/CT had comparable and reasonable sensitivity and high negative predictive values. CT had better specificity and higher PPV than [18F]FDG-PET/CT, i.e. PPV of 65% for CT versus 33% for [18F]FDG-PET/CT. Thus, [18F]FDG-PET/CT was as sensitive as CT and as effective in ruling out cancer suspicion, but induces further examinations and it is still less available and more expensive. These results are consistent with other studies, although Lebach et al. found higher PPV for [18F]FDG-PET/CT than CT, but it was not statistically significant. However, they classified [18F]FDG-PET-positive lesions without clear anatomic CT substrate as negative for cancer, and [18F]FDG-PET-negative but malignant-looking tumour on the CT part of [18F]FDG-PET/CT as positive for cancer on FDG-PET. By doing so, they may inadvertently have introduced a bias by removing false positive cases from [18F]FDG-PET/CT and introducing more false positives on CT.

Most malignant diagnoses in our study were established during the initial work-up process, but in two cases, the diagnoses were not established until six months and 1 year, respectively, after referral. One patient presented with fatigue, weight loss, and gastrointestinal symptoms and was diagnosed with metastatic breast cancer 150 days later. The other presented with fatigue and dizziness and findings in keeping with arteritis on [18F]FDG-PET/CT. This patient was diagnosed with chronic lymphocytic leukaemia 300 days later. It is unclear if their symptoms were related to their final malignant diagnosis.
Suspicion of prostate cancer was raised twice on $^{18}$F-FDG-PET/CT but not reported as suspicious on CT (Figure 2). Hypertrophy of the prostate was reported in both patients with prostate cancer, but CT is not considered diagnostic in the routine workup for prostate cancer.

Some patients were initially CT scanned before entering the NSSC-CPP and were subsequently referred for $^{18}$F-FDG-PET/CT. Generally, patients without cancer went through multiple examinations like endoscopy illustrating the diagnostic challenges in this patient group. More than half of the non-cancer patients underwent at least one additional examination after the initial scan before the workup process was concluded. Other studies showed a similar trend. $^{18}$F-FDG-PET/CT may identify incidental gastrointestinal findings potentially representing malignancy, thus, patients without cancer with initial $^{18}$F-FDG-PET/CT underwent relatively more endoscopies compared to those with initial CT.

**Conclusions**

Our findings in NSSC-CPP patients were in accordance with the literature. We found a cancer prevalence of 21%, most frequently in the digestive organs. The most frequent symptom was weight loss as reported by more than half of the patients and even as the only symptom, it is a potential marker for cancer. CT and $^{18}$F-FDG-PET/CT were sensitive with high NPV, whereas PPV was superior in CT. Patients without a cancer diagnosis underwent subsequent examinations following initial imaging with CT or $^{18}$F-FDG-PET/CT.

**Implications for clinical practice**

Our data underlines the heterogeneous presentation of NSSC-patients with a multitude of potential symptoms and findings. Our data also supports the current imaging strategy in NSSC-CPP. CT and $^{18}$F-FDG-PET/CT both have a place, but based on our data, it was not possible to establish why patients were referred for CT or $^{18}$F-FDG-PET/CT. Future, prospective studies are needed to better stratify patients according to presentation to further optimise the NSSC-CPP workup strategy.

**Ethical approval**

Relevant permissions according to Danish legislation were obtained from the regional council (22/24999) and the hospital (22/21408) before the study began. In retrospective studies, informed consent is not required under Danish law.

**Acknowledgements**

We wish to extent our sincere gratitude to the remaining members of Imaging Research Initiative Southwest for fruitful discussions and constructive comments throughout the process. We are especially grateful to our administrative officer, M.Sc. Louise Klok Ingvartsen for keeping everything together.
Funding
Nothing to report.

Competing interests
Nothing to report.

References


30. Damhus CS, Siersma V, Birkmose AR, et al. Use and diagnostic outcomes of cancer patient pathways in Denmark - is the place of initial diagnostic work-up an important factor? BMC Health Serv Res. 2022;22(1):130.


Figure 1 Flowchart showing enrolment of patients.

602 referrals screened

554 excluded
357 only abdomen or chest CT scan
84 other cancer preplanned pathway
56 from a specialist doctor's clinic
11 control scans of existing cancer
16 on different indication than NSSC

248 included

162 diagnostic centre
86 general practice
Figure 2 Types of cancers seen on initial scan grouped by the modality of the initial scan. A bar represents the number of cancer types detected in the group that was initially scanned using CT or [18F]FDG-PET/CT. The dark area shows how many of the cancers that were suspected on the initial scan (true positives (TP)).
Figure 3 Overview of the symptoms reported by the included patients. The dark coloured bars represent the proportion of cancer patients who report each symptom. Each patient may present with multiple symptoms. ‘No symptoms’ was used when the patient was referred due to abnormal blood test results, suspicious findings on imaging, or any other finding that led the physician to refer the patient.
<table>
<thead>
<tr>
<th></th>
<th>General practice (n = 86)</th>
<th>Diagnostic centre (n = 162)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women, n</td>
<td>43 (50%)</td>
<td>82 (51%)</td>
<td>0.926</td>
</tr>
<tr>
<td>Men, n</td>
<td>43 (50%)</td>
<td>80 (49%)</td>
<td></td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total, mean (±SD)</td>
<td>69.8 (±11.1)</td>
<td>67.3 (±14.4)</td>
<td>0.160</td>
</tr>
<tr>
<td><strong>Modality</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CT, n</td>
<td>85 (98.8%)</td>
<td>105 (64.8%)</td>
<td>&lt;0.000</td>
</tr>
<tr>
<td>[18F]FDG-PET/CT, n</td>
<td>1 (1.2%)</td>
<td>57 (35.2%)</td>
<td></td>
</tr>
<tr>
<td><strong>Cancer</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cancer, n</td>
<td>25 (29.1%)</td>
<td>27 (16.7%)</td>
<td></td>
</tr>
<tr>
<td>Non-cancer, n</td>
<td>61 (70.9%)</td>
<td>135 (83.3%)</td>
<td>0.009</td>
</tr>
<tr>
<td>Total</td>
<td>86</td>
<td>162</td>
<td></td>
</tr>
<tr>
<td>Number of symptoms</td>
<td>2 (0 - 7)</td>
<td>2 (0 - 8)</td>
<td>0.002</td>
</tr>
<tr>
<td>Total</td>
<td>86</td>
<td>162</td>
<td></td>
</tr>
</tbody>
</table>

Table 1 characteristics of patients (n=248). Patients are divided into two groups depending on the referral site.

C: chi² test
F: Fisher’s exact
T: t-test
<table>
<thead>
<tr>
<th>Modality</th>
<th>Sensitivity (95%-CI)</th>
<th>Specificity (95%-CI)</th>
<th>PPV (95%-CI)</th>
<th>NPV (95%-CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT (n = 190)</td>
<td>85% (71% - 94%)</td>
<td>87% (81% – 92%)</td>
<td>65% (51% – 77%)</td>
<td>96% (91% – 98%)</td>
</tr>
<tr>
<td>[18F]FDG-PET/CT (n = 58)</td>
<td>82% (48% – 98%)</td>
<td>62% (46% – 76%)</td>
<td>33% (17% – 54%)</td>
<td>94% (79% – 99%)</td>
</tr>
<tr>
<td>CT (n = 190)</td>
<td>87% (73% - 95%)</td>
<td>90% (84% – 94%)</td>
<td>72% (58% – 84%)</td>
<td>96% (91% – 98%)</td>
</tr>
<tr>
<td>[18F]FDG-PET/CT (n = 58)</td>
<td>100% (66% – 100%)</td>
<td>63% (48% – 77%)</td>
<td>33% (17% – 54%)</td>
<td>100% (89% – 100%)</td>
</tr>
</tbody>
</table>

Table 2 Sensitivity, specificity and predictive values of initial CT and [18F]FDG-PET/CT before and after re-evaluation of scans. Modifications consisted of treating obvious cancer suspicions on CT as true positives and evaluating [18F]FDG-PET/CT on its ability to detect solid tumours (raw numbers are found in Supplementary data Table 1-4)

CI = confidence interval. PPV = positive predictive value. NPV = negative predictive value. CT = computed tomography. [18F]FDG-PET/CT = positron emission tomography with the glucose analogue 18F-labelled fluorodeoxyglucose
<table>
<thead>
<tr>
<th>Examination</th>
<th>CT group (n=149)</th>
<th>[18F]FDG-PET/CT group (n=47)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT</td>
<td>44 (29.5%)</td>
<td>14 (29.8%)</td>
</tr>
<tr>
<td>Endoscopy</td>
<td>12 (8.1%)</td>
<td>12 (25.5%)</td>
</tr>
<tr>
<td>MRI</td>
<td>13 (8.7%)</td>
<td>4 (8.5%)</td>
</tr>
<tr>
<td>[18F]FDG-PET/CT</td>
<td>12 (8.1%)</td>
<td>2 (4.3%)</td>
</tr>
<tr>
<td>X-ray</td>
<td>7 (4.7%)</td>
<td>5 (10.6%)</td>
</tr>
<tr>
<td>Bone marrow biopsy</td>
<td>5 (3.4%)</td>
<td>2 (4.3%)</td>
</tr>
<tr>
<td>Ultrasound</td>
<td>5 (3.4%)</td>
<td>3 (6.4%)</td>
</tr>
<tr>
<td>Mammography</td>
<td>3 (2%)</td>
<td>2 (4.3%)</td>
</tr>
<tr>
<td>Other</td>
<td>19 (12.8%)</td>
<td>11 (23.4%)</td>
</tr>
<tr>
<td>Total</td>
<td>120</td>
<td>55</td>
</tr>
</tbody>
</table>

Table 3: Types of supplemental examinations each non-cancer patient (n=196) underwent grouped according to the initial imaging (CT or [18F]FDG-PET/CT). The category ‘Other’ included bronchoalveolar lavage, thyroid scintigraphy, and pleuro-/paracentesis. Data was registered from The Danish Pathology Register and the radiology information system of the hospital.

CT = computed tomography. MRI = magnetic resonance imaging. [18F]FDG-PET/CT = positron emission tomography with the glucose-analogue 18F-labelled fluorodeoxyglucose.