Clinical value of 18F-FDG-PET/CT in suspected serious disease with special emphasis on occult cancer

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ABSTRACT (296 words)

Purpose: Suspected serious disease (SSD) is a disease designation often given to patients with one or more non-specific symptoms of severe disease that could be due to cancer; the optimal diagnostic strategy is largely left to the clinician's discretion. Being a sensitive non-invasive whole-body imaging modality ^{18}F-FDG-PET/CT may have a potential role in this cancer-prevalent group of patients to confirm or refute suspected malignancy. We aimed to investigate the diagnostic value of ^{18}F-FDG-PET/CT in SSD using long-term follow-up as reference.

Methods: We retrospectively studied results obtained in all SSD patients referred for ^{18}F-FDG-PET/CT at a single institution in 2010-2011 retrieving the following clinical data in all patients: journal entries, examinations, and evaluations made from six months before the scan and until the latest recorded entry. A true positive PET scan was a positive scan with a subsequently biopsy-confirmed diagnosis of cancer in the same target organ, whereas a false positive scan had no subsequent cancer diagnosis. A true negative PET scan was a negative scan without a cancer diagnosis during follow-up, whereas a false negative PET scan was one with a subsequently confirmed cancer diagnosis.

Results: Ninety-three patients, aged 67 years (range 25-89) were included and followed for up to 7.3 years (median 6). Of these, 21 (22.6% [95% CI: 15.3-32.1]) turned out to have cancer. With ^{18}F-FDG-PET/CT, the sensitivity was 81.0% (95% CI: 60.0-92.3), specificity 76.4% (95% CI: 65.4-84.7), positive predictive value 50% (95% CI: 34.1-65.9), and negative predictive value 93.2% (95% CI: 83.8-97.3). Five patients with negative scans were subsequently diagnosed with cancer.

Conclusion: Cancer prevalence is substantial among patients with SSD. ^{18}F-FDG-PET/CT is a promising option in this setting, in particular because a high negative predictive value equals a low incidence of cancer during follow-up. Further studies are needed to establish the role of ^{18}F-FDG-PET/CT in SSD.

INTRODUCTION

Suspected serious disease (SSD) is a designation often given to patients presenting with a multitude of often vague, non-specific symptoms not directly related to a specific organ system **(Table 1)**. In Denmark, due to so-called integrated cancer pathways introduced in 2009, it is a relatively well-defined "entity", but in the international literature it is often referred to as suspected occult cancer although the underlying diseases need not be malignant. It is important not to confuse SSD with cancer of unknown primary, a different and more well-defined population. SSD represents a major challenge to clinicians and healthcare at large because of substantial overlap with harmless and self-limiting conditions and since it may be difficult to distinguish malignant from benign conditions [1]. Patients are heterogeneous, and often undergo several, possibly invasive, procedures en route to diagnosis. The literature on SSD is limited, but studies have found cancer prevalence in SSD populations of 10-22% [1-5]. In 2009, increasing awareness of diagnostic delay in SSD patients in Denmark led to the introduction of a diagnostic fast-track for these patients (SSD-FT), and now an estimated 20,000 subjects of a population of 5.7 million are referred to the SSD-FT every year [1].

Currently, there is no consensus on imaging strategy in SSD, and combined positron emission tomography/computer tomography with 18F-fluorodeoxyglucose (^{18}F-FDG-PET/CT) is not used routinely in SSD-FT patients. An increase in referral of these patients from clinicians of various specialities prompted us to investigate the matter further. As ^{18}F-FDG-PET/CT is a sensitive, whole-body, non-invasive functional imaging technique, we speculated that it might serve well as potential first-line modality as it had already proven useful in similar equivocal settings such as infection or inflammation of unknown origin and suspected paraneoplastic syndromes [6, 7]. Challenges with ^{18}F-FDG-PET/CT would be poor spatial resolution and consequent relatively low sensitivity in early stage malignant diseases like sub-centimetre pre-malignant colon polyps and liver metastases, and an inherent FDG non-avidity in certain cancers (e.g., diffuse breast cancer,

subsets of gastric cancers, and metabolically relatively inactive cancers like prostate cancer and neuroendocrine tumours [8, 9]). However, in patients with an established diagnosis, or a strong suspicion of cancer, ^{18}F-FDG-PET/CT is a powerful tool to characterize disease, extent and severity [10, 11]. Thus, in selected cancer-prevalent groups like SSD patients, ^{18}F-FDG-PET/CT might shorten time-to-diagnosis and be able to effectively refute a malignancy suspicion, whereas the relative non-specificity of FDG may cause unnecessary additional diagnostic procedures.

The objective of this study was to investigate the prevalence of cancer in a retrospective cohort of SSD patients referred for ^{18}F-FDG-PET/CT and to investigate the diagnostic value of this modality in confirming or rejecting a suspicion of malignancy using long-term follow-up as reference.

MATERIALS AND METHODS

Patient population and data retrieval

All patients referred for ^{18}F-FDG-PET/CT at the Department of Nuclear Medicine, Odense University Hospital in 2010-2011 under ICD10 code DZ031 ("Observation due to suspected cancer") were eligible; only patients with specific mention of SSD or suspected occult cancer (without a designated target organ) in their report or referral were included. Patients with specific cancer suspicion or known cancer at the time of scan were not included **(Figure 1)**.

Clinical data were retrieved from electronic medical charts and records, i.e. all entries, examinations, and evaluations regarding each patient from six months before the scan and until the latest recorded entry. In patients with multiple ^{18}F-FDG-PET/CT scans during the disease course of SSD only the first scan was evaluated; subsequent scans were read as a part of the general record. We noted the following specific information: referring departments, indicators of SSD (symptoms, clinical findings, and/or abnormal biochemistry), findings in the ^{18}F-FDG-PET/CT report, the final

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diagnosis, including confirmatory biopsies, follow-up information until last recorded entry, and time of death, if applicable. If a patient was diagnosed with cancer, no further diagnoses were assigned. If no cancer was found, any outcome diagnoses in the discharge summary were registered.

Interpretation of ^{18}F-FDG-PET/CT results

No new image assessments were undertaken; based on the original report we used the following definitions regarding the PET/CT findings. A true positive (TP) result was defined as a positive ^{18}F-FDG-PET/CT scan suggesting malignancy in an organ with a subsequent cancer diagnosis. A false positive (FP) result was a finding suggestive of malignancy which led the clinician to request further diagnostic procedures and/or initiate treatment, but with no subsequently confirmed cancer diagnosis. A true negative (TN) result was defined as a scan with no findings suggestive of malignancy or only findings that did not lead the clinicians to any further actions (e.g., physiologic uptake or inconspicuous foci), in patients with no subsequent cancer diagnosis or sign of other severe disease in the ensuing 12 months. Correspondingly, false negative (FN) findings were negative scans or results that did not make the clinicians take further actions in patients, who nonetheless had a cancer diagnosis made within the next 12 months. We assessed the rate of missed cancers in the immediate period after the scan (i.e. during the first 12-month), but also evaluated the long-term negative predictive value for up to 7 years. Patients with normal scans who were alive, but did not have any contact with the hospital system during follow-up were presumed healthy and TN.

SSD may be caused by cancer, but is not limited to malignancies. In this study of SSD we primarily looked for cancer, but also noted if patients were diagnosed with severe non-malignant diseases. Such findings (e.g., rheumatoid arthritis, human immunodeficiency virus, or vasculitis) were considered FP, if the ^{18}F-FDG-PET/CT report raised suspicion of malignancy, but TN if the

PET report suggested a non-malignant illness.

Imaging protocol

All ^{18}F-FDG-PET/CT scans were performed and interpreted in accordance with guidelines of the European Association of Nuclear Medicine [12]. All examinations were performed on a GE Discovery PET/CT scanner (GE Healthcare, Milwaukee, WI) with either low-dose CT scan without contrast enhancement or diagnostic quality exam with contrast enhancement. Data were reconstructed with a standard filter into transaxial slices with a field of view of 50 cm, matrix size of 512x512 (pixel size 0.98mm), and a slice thickness of 3.75mm. The CT scan was followed immediately by a PET scan performed using a standard whole-body acquisition protocol with 6 or 7 bed positions and an acquisition time of 2.5 minutes per bed position (adjusted to patient size). The scan field of view was 70 cm. Attenuation correction was performed using the CT scan. The PET data were reconstructed into transaxial slices with a matrix size of 128x128 and a slice thickness of 3.75mm using iterative reconstruction algorithms, and displayed in coronal, transverse, and sagittal planes. Corrections for attenuation, randoms, dead time, and normalization were done inside the iterative loop. Analysis of the PET and fused PET/CT data was performed using a GE Advantage Workstation v. 4.4 or a GE Advantage Server 2.0 (GE Healthcare). At the time of FDG administration, all patients had fasted for at least 6 hours. ^{18}F-FDG-PET/CT image acquisition commenced 60±5 minutes after the administration of a weight adjusted dose of 4 MBq/kg FDG (200-400MBq) [13].

Statistics

Study data were collected and managed using Research Electronic Data Capture (REDCap) electronic data capture tools, a secure, web-based application designed to support data capture for

research studies [14]. Descriptive statistics were derived according to data type. Estimates were supplemented by Wilson score-based 95% confidence intervals (95% CIs). All analyses were performed with STATA/IC 15.0 (StataCorp, College Station, Texas 77845 USA).

Ethics

The study was approved by the Danish Health Authorities (case no. 3-3013-1393/1/) as well as the Danish Data Protection Agency (case no.15/48429) and conducted in accordance with Danish legislation, which does not require informed consent in retrospective studies.

RESULTS

Patient characteristics

Ninety-nine patients were eligible, but five patients were lost to follow-up, i.e. no entries in the electronic charts (n=4), and a foreign citizen (n=1). One patient was excluded due to disseminated cancer at the time of the scan (well-known, but not mentioned at referral). Thus, 93 patients were included (cf. **Figures 1A and 1B);** median age was 67 years (range 25-89), and 45 patients (48.4%) were male, 48 patients (51.6%) were female. The most common symptoms/clinical findings leading to referral were unexplained weight loss (59.1%), pain (26.8%), and anaemia (23.6%) **(Figure 2)**, some had several simultaneously. Patients were referred from 14 different medical specialties, five patients had a hereditary disposition to cancer, six patients were transplantation patients treated with immunosuppressants.

Cancer prevalence and mortality

Of the 93 patients, 21 were subsequently diagnosed with cancer (**Table 2**) yielding a cancer prevalence of 22.6% (95% CI: 15.3-32.1). Forty-five patients (48.4%) died during follow-up and of

these, 21 (46.7%) had cancer; thirteen patients died with cancer during the initial course (2010-2011), while eight died with cancer during follow-up. Twenty-four (53.3%) patients died due to other conditions than cancer, seven during the initial course, and seventeen during follow-up (**Figure 3**). Forty-eight (51.6%) patients were alive at the end of follow-up and of these 45 (93.8%) did not develop cancer. Three patients diagnosed with cancer during the initial course survived the entire follow-up period (7.3 years).

Diagnostic yield in the immediate short-term period

Seventeen cases were considered TP, 17 were FP, 55 TN, and 4 FN in the immediate course. Thus, the sensitivity of ^{18}F-FDG-PET/CT was 81.0% (95% CI: 60.0-92.3), specificity was 76.4% (95% CI: 65.4-84.7), positive predictive value (PPV) was 50% (95% CI: 34.1-65.9), and negative predictive value (NPV) was 93.2% (95% CI: 83.8-97.3). Examples of TP, FP, and FN are provided in **Figure 4**.

Diagnostic yield after long-term follow-up

The mean and median follow up periods were 4.6 years (standard deviation 2.54 years) and 6.0 years, respectively (range 0.01-7.37 years). Sensitivity, specificity, PPV, and NPV were reassessed at end of follow-up to include subsequently detected cancers to assess long-term predictive values: Seventeen scans were still considered TP, 17 were FP, 54 were TN, and 5 were FN (i.e. one TN was reclassified as FN, cf. below). Corrected for findings during follow up, sensitivity and specificity was 77.3% (95% CI: 56.6-89.9) and 76.1% (95% CI: 65.0-84.5), respectively. PPV remained unchanged, and NPV was 91.5% (95% CI: 81.6-96.3).

Additional results related to true negative, false negative, false positive PET/CT findings

In eight TN cases, scans pointed correctly towards non-malignant clinically relevant diseases; i.e. Crohn's disease, vasculitis (n=2), pneumonia (n=2), rheumatoid arthritis (n=2), and a HIV patient with typical findings (FDG-avid lymphadenopathy). In FP patients (i.e., scans raised suspicion of cancer, but the findings were later refuted), further diagnostic examinations also led to clinically relevant non-malignant diagnoses; one case of Addison's disease, a case of primary sclerosing cholangitis, a case of silicosis, one case of Whipple's disease, and a case of pneumonia.

Nine patients with negative scans were subsequently diagnosed with cancer **(Table 3);** four during the initial course and five during follow-up. Two were diagnosed with two separate cancers, i.e. a total of 11 cancers were diagnosed. The four cancers detected during the immediate short-term period were considered false negative according to our definition (a case of gastro-oesophageal junction cancer, a case of glioblastoma, and two patients with non-solid, indolent cancers). During long-term follow-up, five additional cancers were diagnosed; one case of parotid gland neuroendocrine tumor diagnosed after 14 months was re-classified from TN to FN.

Four FP scans led to futile invasive procedures; two colonoscopies, a gastroscopy, a breast biopsy, and a biopsy of the tongue.

DISCUSSION

We assessed ^{18}F-FDG-PET/CT for patients with SSD and found a high prevalence of cancer, an acceptable sensitivity, moderate specificity and PPV, and a high NPV. The most prevalent finding leading to SSD and subsequent referral for ^{18}F-FDG-PET/CT was unexplained weight loss, but several non-specific signs, symptoms, and findings were commonly encountered **(Figure 2)**. This is in agreement with the definition, as SSD is often based on vague and non-specific symptoms or findings **(Table 1)** [1]. Thus, we consider our cohort representative of SSD patients, albeit to some extent selected – our cohort comprised consecutive patients referred for ^{18}F-FDG-PET/CT, but not

all patients with SSD are referred for ^{18}F-FDG-PET/CT routinely. Patients were referred from a multitude of medical specialties, i.e. SSD patients are highly heterogeneous, challenging, and ubiquitous in the healthcare system.

Seventeen scans (TP) either clearly indicated or strongly suggested malignancy; all but one cancer were histopathologically confirmed, one patient died beforehand, but the scan clearly showed disseminated cancer and was included as TP. The patients had either undergone extensive but futile diagnostic workup prior to the scan or presented findings or symptoms too vague to suggest a specific diagnostic strategy. ^{18}F-FDG-PET/CT is currently not routine in the SSD-FT; it may be ordered at the clinicians' discretion or through a multidisciplinary team conference. The ^{18}F-FDG-PET/CT proved highly beneficial in directing clinicians towards the area of subsequent diagnosis and helped ensure correct and timely treatment.

Of the four scans considered FN **(Table 2)**, one patient was subsequently diagnosed with cancer of the gastro-oesophageal junction and one with glioblastoma. The former cancer type is commonly FDG non-avid [9], and in glioblastomas high physiologic FDG-uptake in normal brain tissue generates a high background activity which may obscure pathologic lesions that may also present variable uptake themselves [15]. Hence, FN results are not surprising in these particular settings. Two patients with non-solid, indolent cancers that went undetected **(Table 2)** were also defined as FN, but ^{18}F-FDG-PET/CT cannot always detect low-grade malignant haematological disease, and referring clinicians must be aware of this well-known shortcoming [16].

Seven cancers developed during follow-up in five patients with negative scans **(Table 3)**. A neuroendocrine tumour in the parotid gland was discovered 14 months after the scan, and was considered TN according to our 12 months cut-off. However, a cancer during follow up so close to the cut-off should be considered FN, although FDG-avidity of neuroendocrine tumours may be highly variable [8, 10]. When considering the scan as FN instead of TN, sensitivity and NPV

decreased slightly to 77.3% and 91.5%, respectively. All other cancers developed >2 years after the scans. Cancer incidence increases with age, so five new cancers in a population of 72 middle-aged persons over the course of >7 years is hardly surprising or unexpected. Acute myelogenous leukaemia and small cell lung cancer are aggressive fast-growing cancers that would not necessarily have been present in the patient at the time of scan; hence, these were still considered TN. In the case of hepatic cancer, the time from scan to diagnosis was six years, deeming it unlikely that cancer was detectable or even present at the time of scan. Prostate cancers are low-metabolic, and the excretion of FDG through the urine may hamper the assessment of urinary tract cancers, but both cases were diagnosed >4 years after the scan, so we consider it unlikely that these cancers were detectable or present at the time of scan [10]. After follow-up the total number of TN was 54 and the total number of FN was five. Thus, the data, however sparse, from this study and previous ones, strongly suggests that a patient with SSD and a negative ^{18}F-FDG-PET/CT is indeed free of malignancy at least for the ensuing couple of years as long as symptoms do not worsen or new symptoms arise. However, ^{18}F-FDG-PET/CT is challenged in certain cancers, e.g. cancers of the gastro-oesophageal junction, glioblastomas, neuroendocrine tumours, or indolent haematological malignancies.

While this study mainly focused on cancer, we shall also briefly discuss other clinically relevant ^{18}F-FDG-PET/CT findings. The number of FPs was also high in this project, but only four of these 17 scans lead to further and futile invasive procedures. This was probably partly because many had already been extensively examined prior to the scan. Thus, we consider SSD patients generally at risk of receiving a number of potentially unnecessary procedures including invasive ones, but in our opinion ^{18}F-FDG-PET/CT does not necessarily cause many more examinations; it may actually reduce the number of futile procedures if implemented upfront to guide clinicians towards more specific procedures.

The overall mortality in the cohort was high, most notable among patients with a cancer diagnosis **(Figure 3).** This echoes results previously seen in general practice where more than half of the SSD patients with cancer were dead within one year after diagnosis [2]. Although patients with a median age of 67 year are also prone to co-morbidities that may negatively impact prognosis, the high mortality in SSD settings may be attributable to unfavourable diagnostic delay [2, 5], which suggests that the diagnostic strategy needs improvement in this vulnerable patient group.

Our study is among the first to assess the clinical value of ^{18}F-FDG-PET/CT in patients with SSD; a substantial patient group with 20,000 annual referrals to SSD-FT in Denmark, but nonetheless hitherto largely ignored in the literature. The study had a long-term follow up, which allowed for a robust evaluation of the sensitivity and NPV. This is important in order to establish the quality of a diagnostic test in this context – the ability to detect cancers and the ability to rule them out. This is not straightforward in the heterogeneous and difficult clinical setting of SSD, but with the literature largely devoid of this subject, a study of 93 patients contributes important data. All patient data and diagnoses were based on comprehensive chart review including biopsy confirmation of malignant disease.

Nonetheless, a retrospective study has by default several limitations. The data from medical records reflect daily clinical practice with a purpose of documentation rather than research. Thus, the obtained information may be difficult to interpret. The study cohort was from 2010-2011, and clinical practice has undergone transformations in the ensuing seven years; ^{18}F-FDG-PET/CT has become more commonplace and the SSD-FT has been introduced and is now applied in a more stringent manner. Therefore, there is a certain risk that changes in the clinical approach towards SSD have reduced the generalisability of our results. However, we are currently assessing the contemporary use of ^{18}F-FDG-PET/CT in SSD-FT patients at a newly established PET-centre in a rural area 350-bed primary care hospital with a dedicated SSD outpatient clinic using the same

criteria as in a historic cohort (these data from the first year of operation from 1 November 2016-1 November 2017 are yet unpublished): in this new cohort 59 patients were included, 49% males and a median age of 68 years (range 37-89). Nine patients were diagnosed with cancer (prevalence 15.3%; 95% CI: 8.2-26.5), and all were correctly detected with ^{18}F-FDG-PET/CT (TP). Forty-one were TN, nine were FP and there were no FN (although the short follow up period in the majority of patients must be kept in mind). Thus, with sensitivity, specificity, PPV, and NPV of 100% (95% CI: 70.1-100), 82% (95% CI: 69.2-90.2), 50% (95% CI: 29.0-71.0), and 100% (95% CI: 91.4-100), respectively, these preliminary results are very similar and support a general applicability of the results from the current older cohort.

A recent prospective Danish study included patients with non-specific symptoms and signs of cancer, a population similar to SSD, and 197 patients were randomized 1:1 to ^{18}F-FDG-PET/CT or CT of the thorax and abdomen. Cancer prevalence was 20%, and ^{18}F-FDG-PET/CT was superior to CT in diagnosing malignancy with sensitivity of 83% versus 70%, specificity 96% versus 85%, accuracy of 94% versus 82%, PPV of 83% versus 54%, and NPV of 96% versus 92%, although only specificity and accuracy reached statistical significance. Interestingly, the number of additional diagnostic procedures was higher in the CT group compared to ^{18}F-FDG-PET/CT (41 versus 26), and this study also found clinically relevant benign diseases in a significant proportion of the patients [4]. These data corroborate our finding of usefulness of the modality in this selected patient group. However, SSD is still sparsely represented in the literature, and the patient group is large and heterogeneous.

As mentioned in the introduction, there is good rationale in considering ^{18}F-FDG-PET/CT in settings of unresolved patients suspected of systemic diseases, including malignancies [6, 7]. Others have found similar results in comparable settings, e.g. patients without known cancer but elevated carcinogenic embryogenic antigen [17]. However, the use of ^{18}F-FDG-PET/CT may be a double-

edged sword if it is used in too non-specific populations; one point of critique against ^{18}F-FDG-PET/CT is FP findings [10, 11], but studies have also demonstrated limited sensitivity when ^{18}F-FDG-PET/CT is used as a general screening tool in unselected, non-symptomatic patients [18, 19]; thus, Terauchi et al. found a detection rate of 0.96% with sensitivity and PPV of 17.8% and 11.2%, respectively. It is possible that the combination of PET and magnetic resonance imaging (MRI) may be of additional value when it is employed in more specific settings, as it has been shown by Sekine et al. in their comparison of PET/CT and PET/MRI in patients suspected of occult tumors [20]. Overall, further and larger studies are warranted, including more firm analysis of the consequences of FN and FP scans as well as cost-benefit analysis of early ^{18}F-FDG- PET/CT versus alternative or conventional diagnostic strategies.

CONCLUSION

Our study showed substantial cancer prevalence among SSD patients and a clear potential for ^{18}F-FDG-PET/CT in this setting, in particular due to at high NPV with a low incidence of cancers during follow up. Patients with normal findings may avoid excessive examination and unnecessary concern without missing malignancy as long as the clinicians are aware of the well-known limitations of the modality in certain cancers and if implemented early in the diagnostic pathway. ^{18}F-FDG-PET/CT could potentially shorten time-to-diagnosis without leading to an adverse increase in diagnostic procedures due to FP results. Current preliminary results from a newly established PET-centre support our findings. However, to more firmly establish the validity of these findings and suggestions, prospective studies of ^{18}F-FDG-PET/CT in SSD are warranted.

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COMPLIANCE WITH ETHICAL STANDARDS

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FIGURE 1: Flow charts of initial patient eligibility **(1A)** and final patient selection **(1B)**. ICD-10 = International Classification of Diseases (version 10); ^{18}F-FDG-PET/CT = ^{18}F-fluorodeoxyglucose positron emission tomography/computer tomography; SSD = suspected serious disease; TN = true negative; FN = false negative; TP = true positive; FP = false positive.
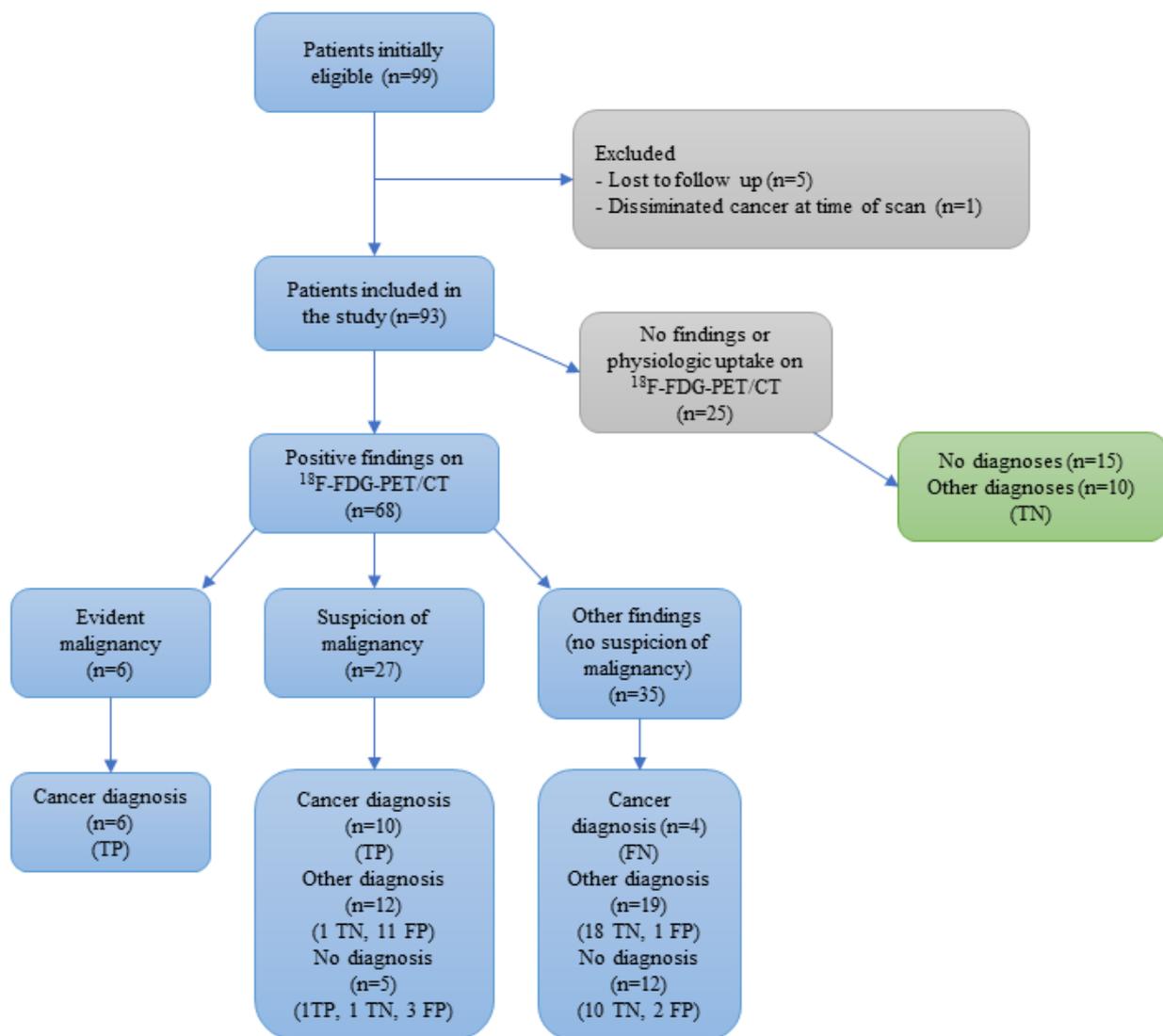
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                              │              │ - Lost to follow up (n=5)                │
                              │              │ - Dissiminated cancer at time of scan (n=1)│
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                    │  the study (n=93)   │        │ No findings or      │
                    └─────────────────────┘───────▶│ physiologic uptake on│
                              │                     │  18F-FDG-PET/CT     │
                              │                     │     (n=25)          │
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                    │ Positive findings on│                   └───────▶│ No diagnoses (n=15) │
                    │   18F-FDG-PET/CT    │                            │ Other diagnoses (n=10)│
                    │       (n=68)        │                            │        (TN)         │
                    └─────────────────────┘                            └─────────────────────┘
            ┌───────────────┼───────────────────────┐
            ▼               ▼                       ▼
    ┌──────────────┐ ┌──────────────┐    ┌──────────────────┐
    │   Evident    │ │ Suspicion of │    │  Other findings  │
    │  malignancy  │ │  malignancy  │    │ (no suspicion of │
    │    (n=6)     │ │    (n=27)    │    │   malignancy)    │
    └──────────────┘ └──────────────┘    │      (n=35)      │
            │               │            └──────────────────┘
            ▼               ▼                       ▼
    ┌──────────────┐ ┌──────────────┐    ┌──────────────────┐
    │Cancer diagnosis│ │Cancer diagnosis│   │     Cancer       │
    │    (n=6)     │ │    (n=10)    │    │ diagnosis (n=4)  │
    │    (TP)      │ │    (TP)      │    │     (FN)         │
    └──────────────┘ │Other diagnosis│   │ Other diagnosis  │
                     │    (n=12)    │    │     (n=19)       │
                     │ (1 TN, 11 FP)│    │  (18 TN, 1 FP)   │
                     │ No diagnosis │    │  No diagnosis    │
                     │    (n=5)     │    │     (n=12)       │
                     │(1TP, 1 TN, 3 FP)│ │  (10 TN, 2 FP)   │
                     └──────────────┘    └──────────────────┘
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FIGURE 2: Overview of symptoms and findings leading to referral for 18F-fluorodeoxyglucose positron emission tomography/computer tomography (percentages of all included patients). CRP = c-reactive protein; SR = sedimentation rate.
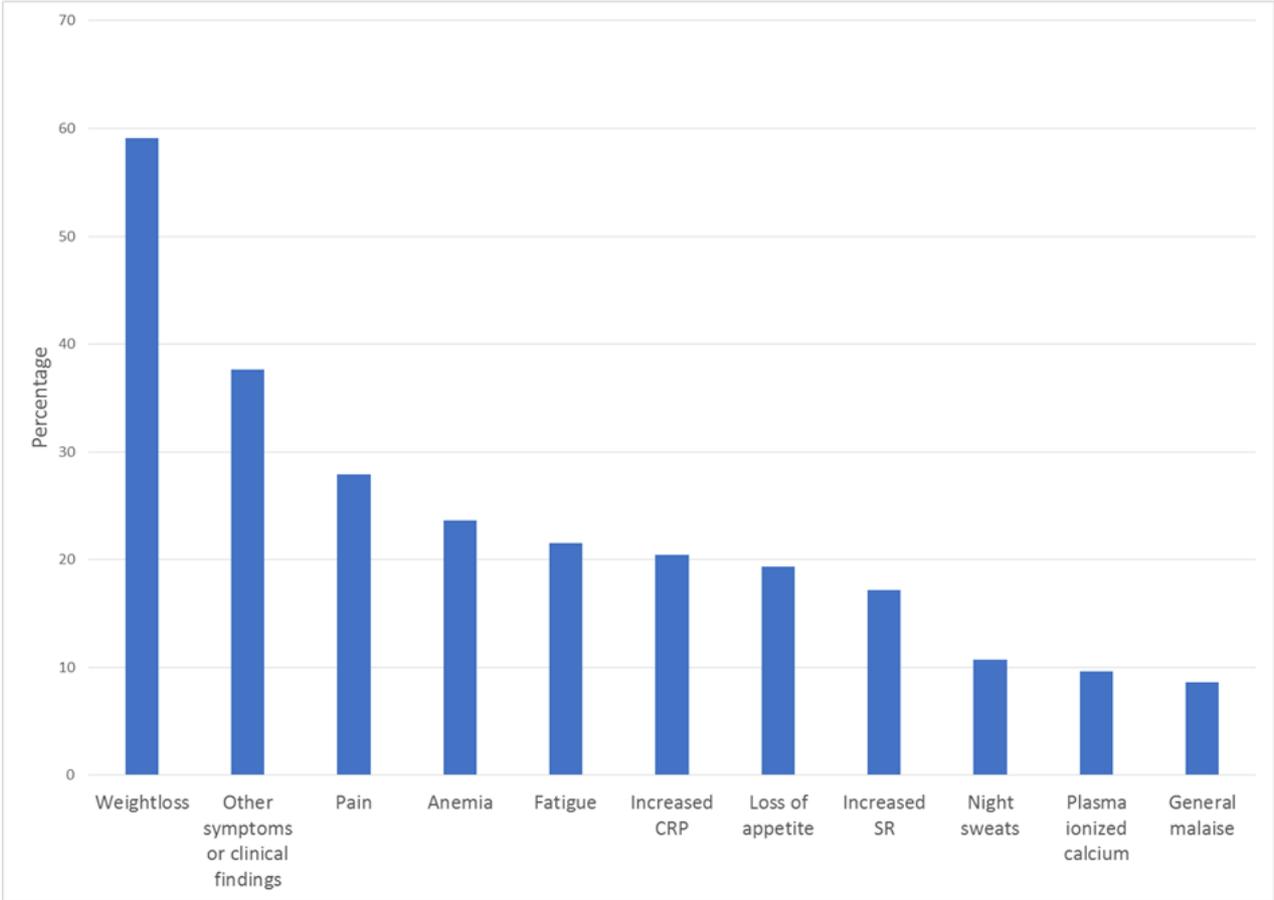
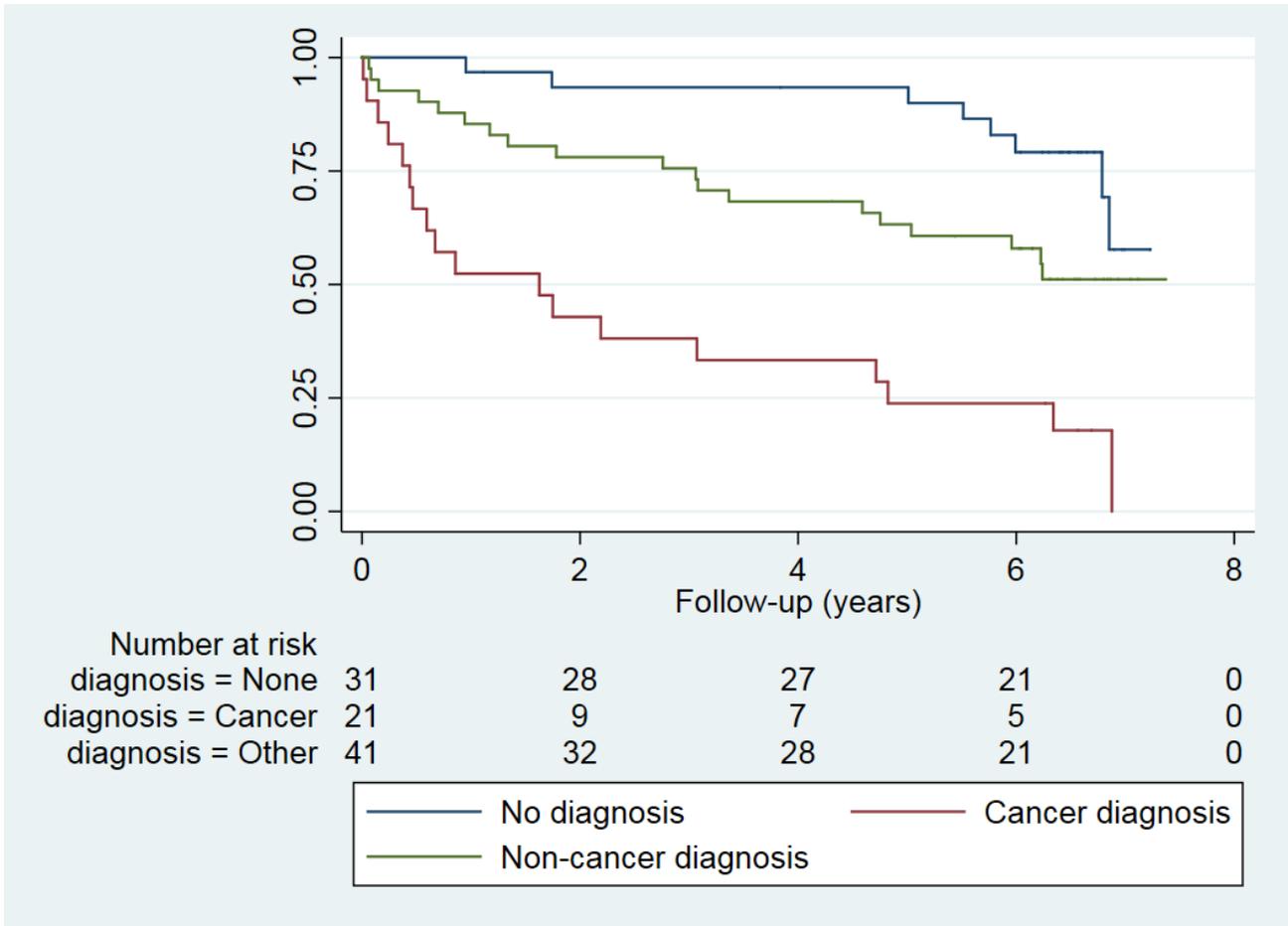**FIGURE 3:** Kaplan-Meier plot for overall mortality by diagnosis group.

FIGURE 4: Patient examples. (A) True positive scan: 65-year-old female with a pancoast tumor of the left lung *(blue arrow)*. Histopathology confirmed small cell lung cancer. (B) False positive scan: 75-year-old male with asymmetric focal FDG-uptake in the left tonsil *(blue broken arrow)*. Biopsy found only benign inflammatory changes. (C) False negative scan: 79-year-old male with normal whole-body FDG-distribution. The patient was subsequently diagnoses with an adenocarcinoma at the gastro-esophageal junction.
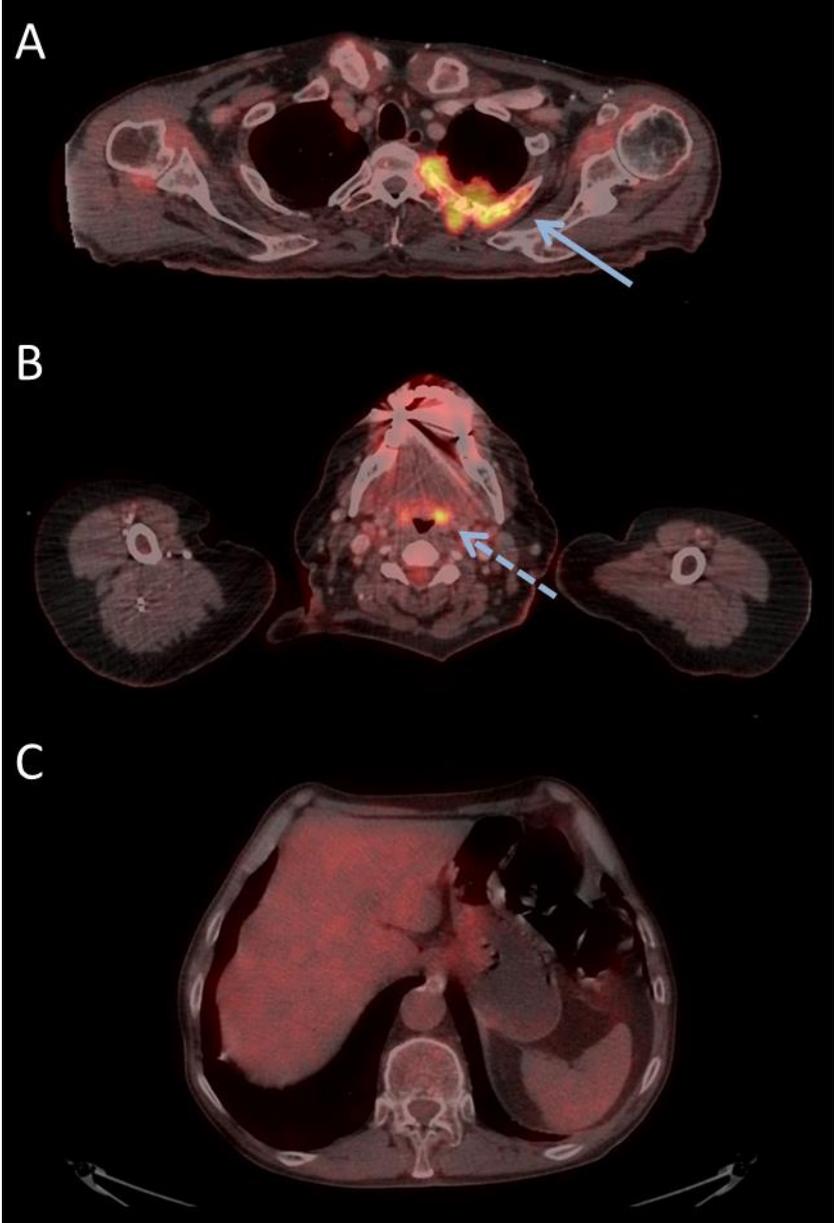
TABLE 1. Newly occurring symptoms or clinical findings that may give rise to suspected serious disease or occult cancer [1]. Values in parentheses represent results from our study.

General malaise (8/93; 8.6%)
Fatigue (20/93; 21.5%)
Large unintended weight loss (55/93; 59.1%)
Unexplained anaemia (21/93; 22.6%)
Diffuse bone pain 25/93; 26.9%)
Fever of unknown origin
Abdominal pain >4 weeks
One or more unexplained abnormal blood sample results
Significant and sudden increase in contacts to the health care system
Significant and sudden increase in medicinal use e.g. antibiotics or analgesics

TABLE 2. Cancer types encountered in the included patients.

Detected on PET/CT (TP) N= 17	Prostate cancer
	Cutaneous T-cell lymphoma
	Colon cancer (n=3)
	Chronic myelomonocytic leukaemia
	Neuroendocrine tumour
	Myelomatosis (n=2)
	Non-small celled lung cancer
	Cancer of the uterus
	Pancoast tumour
	Breast cancer
	Bladder cancer
	Kidney cancer
	Cancer of unknown primary
	Metastasis of unknown primary
Not detected on PET/CT (FN) N=4	Cardia cancer
	Chronic T-cell lymphoma
	Glioblastoma
	Myeloproliferative disease

TABLE 3. Cancers diagnosed after a negative ^{18}F-FDG-PET/CT scan.

	2010	2011	2012	2013	2014	2015	2016	2017	Total
Cancer types	Cancer of the gastro-oesophageal junction	Chronic T-cell lymphoma Glioblastoma Myeloproliferative disease	Parotid cancer		Cancer of the larynx[2] Acute myeloid leukaemia	Small celled lung cancer[2] Prostate cancer	Prostate cancer[1] Hepatic cancer		
Frequency	1	3	1	0	2	2	2	0	11

[1] Different cancers in the same patient

[2] Different cancers in the same patient