PET/CT may change diagnosis and treatment in cancer patients

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ABSTRACT

INTRODUCTION: The national focus on cancer has propelled the use of PET/CT for cancer imaging in Denmark. We believe that first-year experiences from a large PET centre may be of interest to new users.

MATERIAL AND METHODS: Data from all scans made in the period from February 28 2006 to March 1 2007 with a single PET/CT scanner and 18F-fluoro-deoxyglucose (FDG) were collected prospectively along with information on action diagnosis, study purpose, etc. Referring departments indicated if PET/CT had changed or confirmed diagnosis, staging and treatment plan.

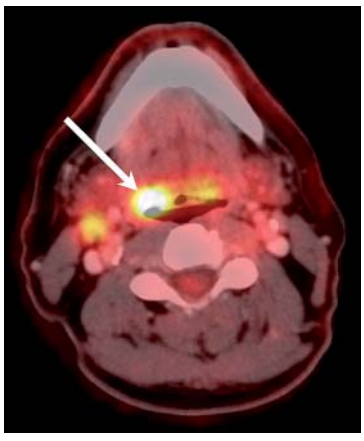
RESULTS: A total of 970 scans were made in 826 patients, 14% had 2-5 scans performed. Diagnostic CT was performed in 53%. In all, 792 referrals came from Odense University Hospital. Nearly 85% were from the specialities of oncology (31%), haematology (24%), surgery (14%), internal medicine (9%) and gynaecology (6%). PET/CT for primary diagnosis was mainly used in lung cancer and in cases with unknown primary tumour. In malignant lymphomas and colorectal cancer, the technique was mainly employed for response evaluation. Use of PET/CT for staging and recurrence was more evenly distributed across specialities. PET/CT changed the primary diagnosis in 16% and induced a change in staging and treatment plan in 28% to 32% of cases, respectively.

CONCLUSION: FDG PET/CT was mainly used for diagnosis in lung cancer and in cases with an unknown primary tumour, and for response evaluation in lymphomas and colorectal cancer. PET/CT caused a change of staging and treatment plan in 25-33% of cases.

PET was used in cardiac, brain and bone research for over 30 years before achiev-ing its clinical breakthrough in the past decade. The first PubMed item on clinical PET appears to be a 1980 US report in the German journal Herz [1]. For the year 1985, the keyword "pet" yields 163 PubMed hits of which 55% are related to PET, while the remaining hits mainly refer to animal pets. Since then, the number of PET publications has doubled every five years. Two factors played a major role in the clinical breakthrough of PET. One was the introduction of 18F-fluoro-deoxyglucose (FDG) for cancer imaging. This glucose analogue appeared in 1974, but only gained importance during a five-year period around the millennium when the U.S. Food and Drug Administration and Centers for Medicare and Medicaid Services accepted clinical PET and offered Medicare coverage for FDG PET in selected cancers, and then, as from 2005, in almost all cancers. The latter modification came with the clause that application be recorded in a national database [2-4]. The second factor of importance for the clinical breakthrough of PET was the appearance in 2001 of the combined PET/CT scanner, which became such a success that as from 2005, PET scanners without CT have no longer been manufactured.

The past years' national focus on cancer and the Danish Regions' 2007 resolution on a "National Danish Invitation to Tender for the Delivery of Cancer Scanners" have doubled the Danish stock of PET/CT scanners in a few years. Thus, we imagine that coming users may be interested in hearing our early experiences. The first sod for the PET and Cyclotron Centre at Odense University Hospital (OUH) was turned on 8 October 2004, and the first patient was examined on 28 February 2006 (**Figure 1**). Staff members had been trained at Rigshospitalet's PET centre and had attended courses at home and abroad. In the first year covered by this study, only a single scanner was in operation using FDG supplied by Rigshospitalet or Research Center Risø until the OUH achieved permission to produce FDG. All patients were

FIGURE 1



Fused positron emission tomography/computed tomography (PET/CT) image showing focal accumulation of 18F-fluoro-deoxyglucose (FDG) in a suspected tongue root tumour. All prior biopsies before PET/CT imaging were negative. A single PET-guided biopsy gave the diagnosis.

ORIGINAL ARTICLE

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registered consecutively including information of their disease, the PET/CT scan and its impact on management. All data were recorded in an electronic database, the contents of which forms the basis for this article which will later be followed by a review of the progress made over time.

MATERIAL AND METHODS

All studies were performed in patients with known or suspected cancer using a General Electric Discovery STE PET/CT scanner with a 16-slice CT scanner and a PET scanner with bismuth germinate crystals arranged in a ring around the patient covering 15.4 cm per field of view. Patients were injected with approximately 400 MBq FDG (4-6 MBq/kg body weight) and instructed to lie completely still in the first 20-30 min. after injection in a designated injection room. In case oral contrast was given, the patient drank this in a waiting room 20 min. before the scan, which typically lasted 20-25 min. A whole-body scan (from base of skull to upper thighs) was performed approximately one hour after injection. The acquisition time was 2.5 min. per field of view.

Survey data were recorded prospectively on prefabricated data sheets containing questions about action diagnosis, study purpose (diagnosis, staging, recurrence, response evaluation, target definition, follow-up or research) and the scan itself (before, during, after). Prior to the PET Centre's establishment, most of the potential user departments in the region had declared their support and written commitment to provide relevant clinical information to the Centre in order to assess the clinical value of PET. On this background, the referring departments received both the scan report and a survey questionnaire with a few questions about the extent to which the PET/CT scan had changed or confirmed the diagnosis, staging and treatment plan. If the form was not returned, reminders were sent out twice within six months. If the reminders were unsuccessful, the answers were considered lost. Results are presented as numbers and percentages, as appropriate.

RESULTS

Scans

A total of 970 scans were made in 826 patients, including 52.0% men (average age 57.8 years), 47.6% women (average age 59.6 years) and four boys. The majority of patients (86.0%) were only examined once, while 10.6% had two scans, 3.2% three scans, 0.1% four scans and 0.1% five scans. Diagnostic CT was performed in 53% of cases and only during the last nine months, while in the first three we exclusively performed low-dose CT scans for attenuation correction of PET images, since agreement on radiological assistance to describe the diagnostic CT scans had not yet been obtained.

There were minor problems with 27 scans (2.8%) including discomfort, anxiety, phobia, etc. (n = 11), problems with needle insertion or injection of X-ray contrast (n = 9) and technical problems with the scanner (hardware and/or software, n = 7). However, all studies were completed and PET scanning was not cancelled one single day because of technical issues. The number of examinations rose gradually to approx. 20-25 per week with slightly lower figures in the Easter and summer, and the number stayed at that level until the arrival the following year of scanners 2 and 3 and the initiation of our own production of FDG. We performed about 45 scans per week with approximately 35 diagnostic CT scans in the autumn of 2007. The corresponding figures in 2009 were 75 PET scans, 45 of which were diagnostic CTs, plus an additional 15 CT angiographies per week. Several research projects were planned during the first year, but none were implemented until the other scanners had been deployed.

Referrals

Among the 970 referrals, 792 were from departments at the OUH, 79 from Funen Hospital (Sygehus Fyn), while the remaining 99 came from other counties than Funen. Categorized by specialties at the OUH, almost 85% of the referrals came from five specialties: oncology (31%), haematology (24%) (malignant lymphoma), parenchymal surgery (14%) (particularly colorectal and breast cancer), internal medicine (9%) (especially lung cancer) and gynaecology (6%). The remaining referrals originated from thoracic surgery (4%), urology (3%), head and neck surgery (3%), plastic surgery (3%) and other specialities (3%). For more information on the distribution of cancer types and their association with indications, diagnosis, staging, recurrence and response evaluation, see **Table**

TABLE 1

Distribution of cancer types on the four most common indications for positron emission tomography/computed tomography.

Cancer type	Diagnosis	Staging	Recurrence	Response evaluation
Lung	40.8	20.0	11.0	2.3
Unknown primary	33.1	-	-	-
Gastro-intestinal	1.7	9.8	20.7	12.3
Malignant lymphoma	2.2	5.4	9.0	48.0
Female genitalia	-	13.7	8.3	2.9
Breast	2.2	6.3	7.2	2.9
Malignant melanoma	-	9.3	-	-
Urologic	-	9.3	-	-
Bone	-	-	9.3	-
Male genitalia	-	-	4.8	-
Occult	3.0	-	-	-
Other	17.0	26.2	29.7	31.6

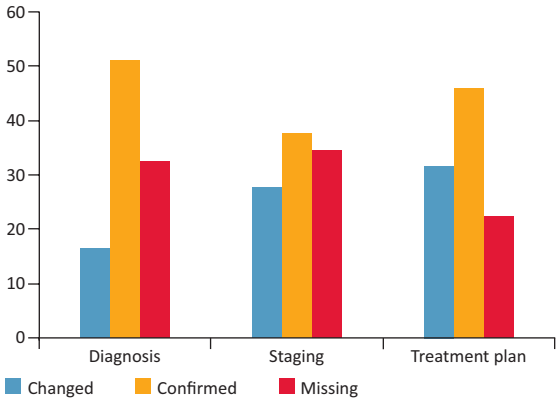
1. The table shows that PET/CT for primary diagnosis was mainly used in patients with lung cancer and an unknown primary tumour, while response evaluation was primarily applied for malignant lymphomas and to some degree gastrointestinal cancers. The use of PET/CT for staging and recurrence was more evenly distributed among the various cancers, whereas the indications of target definition, follow-up and research were hardly recorded in this first year (0.3%, 0.7%, 0.0%, respectively).

Clinical implications

Answers concerning whether PET/CT scans had changed or confirmed the diagnosis, staging and treatment were distributed as indicated in **Figure 2**. It appears that PET/CT yielded a change of the primary diagnosis in approximately 16% of cases, whereas PET/CT resulted in a change in staging and treatment plan in approximately 28% to 32% of the cases, respectively. In this survey, we unfortunately have no information to describe whether these changes were made on the basis of the PET-answer alone or if they were confirmed by other modalities.

FIGURE 2

Histogram showing the referring departments' use of positron emission tomography/computed tomography with regard to change or confirmation of diagnosis, staging and management plan.



DISCUSSION

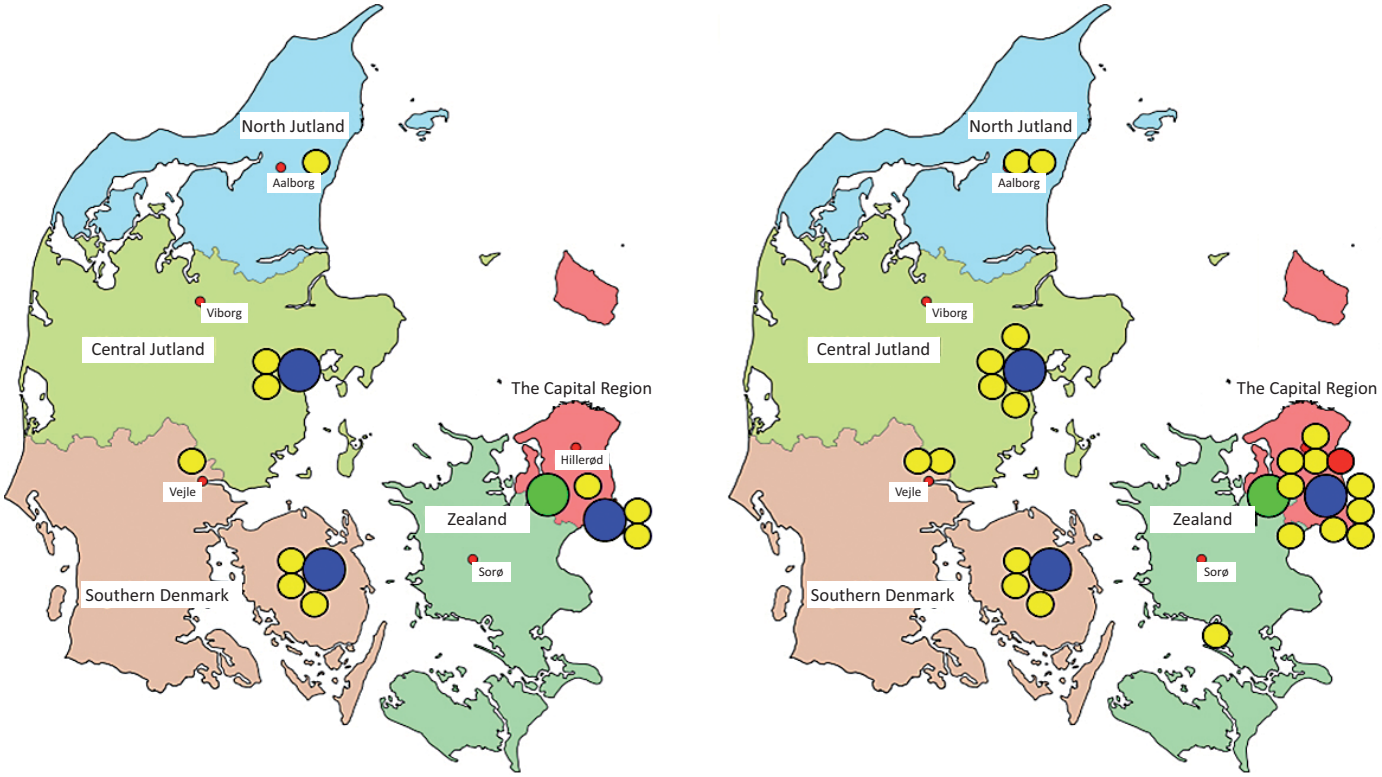
PET has been called "the fastest growing medical technology ever". It is difficult to ascertain whether this holds true or not. The PET technique is more than 50 years old and the starting time chosen for such a calculation is therefore crucial. However, recent developments in Denmark seem to partly back this claim. The first PET scanner in Denmark was a second-hand brain scanner imported from Canada to Rigshospitalet in 1989. In 1993, the second Danish PET centre opened in Aarhus with a focus on neurological research. In 2001, Rigshospitalet acquired the country's first and the world's second PET/CT scanner. This combined functional/anatomic modality gave impetus to the clinical use of PET as merging of the images (Figure 1) provided new evidence and higher diagnostic accuracy [5]. Herlev Hospital received its first PET/CT scanner in 2004 followed by Odense, where the country's third PET centre with cyclotron and radiochemistry was established in 2006-7. In 2007, there were 11 PET/CT scanners in Denmark available for clinical use, which is equivalent to approximately one for every 500,000 inhabitants. In early 2010, the number of scanners had doubled, corresponding to one PET/CT scanner per 250,000 inhabitants (**Figure 3**) and a couple of scanners were still in tenders.

The regions of Southern Denmark and Odense are good examples of the rapid development of the PET/CT once the technology has become known. Until the start in 2006 with one scanner at the OUH, clinical PET/CT scans were performed with the newly installed scanners at Rigshospitalet and to a lesser extent in Aarhus and in Herlev. Only in exceptional cases were patients outside the Copenhagen area examined by PET/CT, and staging and treatment control of the patients' cancers were not an option. The implementation of PET/CT at OUH was conducted in consultation with the clinical departments of primarily oncology and haematology, while extensive PR efforts were made by the PET Centre. These activities involved site visits, internal, local and regional lectures and presentations to disseminate knowledge of PET/CT, its clinical usefulness and scientific potential. Agreements on clinical research collaboration were made with a view to initiate studies once additional scanners had been installed. PET/CT became an important tool for clinicians managing cancer patients and planning their treatment course. The next step was the development and implementation of new tracers, which further increased the position of PET/CT in cancer management.

In 2007, the Danish Board of Health decided to create National, Integrated Cancer Pathways, 34 of which were ready in 2009 [6]. PET/CT was included as part of the work-up in only seven of these pathways (malignant lymphomas, head/neck, some childhood, oesophageal and gastric, ovarian, cervical and uterine cancer) and as an option in another four (biliary and lung cancer, malignant melanoma, sarcoma). In no pathway was PET/CT suggested for detection of recurrence, response evaluation, guidance for radiotherapy or long-term follow-up. This is somewhat surprising since the first comprehensive survey of the PET literature published in 2001 (before the advent of PET/CT) rather convincingly demonstrated the superiority of PET over imaging modalities like CT and magnetic resonance imaging for various purposes in breast, colorectal, lung, pancreatic and testicu-

FIGURE 3

The development of positron emission tomography/computed tomography (PET/CT) in Denmark starting before the national tender for cancer scanners in 2007 and ending early 2010. Small red dots = administrative capitals of Denmark's five regions; yellow dots = each one PET/CT scanner; blue dots = PET centres with cyclotron; green dot = research cyclotron at Risø National Laboratory; red dot = PET/CT at private hospital in Copenhagen.



lar cancer [7]. The root of this negligence may hide in statements like "lack of randomised trials" and "impact on survival never proved" which appeared in a 2002 report from the Danish National Board of Health [8], even if modern physicians will be aware that randomised studies are not the only source of reliable information and that improved survival is difficult to demonstrate as long as clinical practice does not fully exploit the advantages of a new technique. In 2007, a comprehensive health technology assessment of the clinical effectiveness of PET found that the diagnostic accuracy in colorectal and gastro-oesophageal cancer was 20% better than that of CT and superior to CT/endoscopic ultrasound [5]. However, this and similar information was not generally known to those responsible for the national Danish pathways for these cancers.

The same board and its institutions have delivered constantly increasing estimates of the need for PET and PET/CT scans primarily in cancer [8-10]. In accordance with such need, the number of PET scanners has doubled in few years (Figure 3). Nonetheless, the need for PET/CT scanning will continue to increase for years to come. Thus, in the latest report of the Danish National Board of Health from 2006, it was estimated that in 2008-2010 the need for PET in Denmark would reach approx. 38,000 scans per year including 25,500 cancer scans, and that the average production per scanner would be 1,200 per year [8]. There are currently 22 scanners in Denmark, and these figures accordingly testify to a deficiency corresponding to an additional ten PET/CT scanners in 2010. This estimate does, to some degree, take into account indications such as detection of recurrence, response evaluation, guidance for radiation therapy and long-term follow-up, but it does not estimate the effect of new tracers, the advent of which may considerably increase the need. Such tracers may, for example, include the new 18F-choline and 18F-acetate tracers used for prostate cancer. The implementation of these tracers is under investigation at a time when the incidence and prevalence of this disease is rapidly increasing. In Denmark alone, more than 10,000 men live with prostate cancer which may require PET/CT monitoring.

Molecular imaging with PET will increase for a long period to come. We suspect that in many cancers, first or early examination with PET/CT will substitute a

number of standard work-up procedures and that PET/CT will become the method of choice for monitoring and adjusting costly modern cancer therapies. In line with previous reports [11, 12], we found that even during its first year, FDG PET had a substantial impact on the staging, recurrence detection and planning of therapy. Similar tendencies were recently published by the US National Oncologic PET Registry. Based on data from 22,975 studies at 1,178 centres, it was determined that physicians changed their intended management in 36.5% of cases after PET [13]. Based on 10,497 studies at 946 centres, the referring physician felt that the PET scan results allowed them to avoid other imaging or invasive procedures in 90% of cases [14]. PET may not be flawless and will need further validation and standardisation [15], but it would be unwise not to recognize and utilise the potential of this unique technique for the benefit of patients and the healthcare community.

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