Brady, Z. and Taylor, M. L. and Haynes, M. and Whittaker, M. and Mullen, A. and Clews, L. and Partridge, M. and Hicks, R. J. and Trapp, Jamie V. (2008) The clinical application of PET/CT: a contemporary review. *Australasian Physical and Engineering Sciences in Medicine* 31(2):pp. 90-109.

REVIEW ARTICLE

The clinical application of PET/CT: a contemporary review

Z. Brady[1,2], M.L. Taylor[2,3], M. Haynes[2,3], M. Whitaker[2,4], A. Mullen[2,5], L. Clews[2,6], M. Partridge[7], R. J. Hicks[5] and J.V. Trapp[8]

[1]*Radiology Department, The Alfred Hospital, Prahran, Australia*
[2]*Applied Physics, RMIT University, Melbourne, Australia*
[3]*William Buckland Radiotherapy Centre (WBRC), The Alfred Hospital, Prahran, Australia*
[4]*Royal Prince Alfred Hospital, Missenden Rd, Camperdown, Australia*
[5]*Peter MacCallum Cancer Centre, Australia*
[6]*Calvary Mater Newcastle, Warratah, Australia*
[7]*Joint Department of Physics, The Institute of Cancer Research, Sutton, UK*
[8]*School of Physical and Chemical Sciences, QUT, Brisbane, Australia*

Abstract

The combination of positron emission tomography (PET) scanners and x-ray computed tomography (CT) scanners into a single PET/CT scanner has resulted in significant improvements in the diagnosis and staging of disease, particularly in the field of oncology. A decade on from the publication of the details of the first PET/CT scanner, we review the technology and applications of the modality. We examine the design aspects of combining two different imaging types into a single scanner, and the artefacts produced such as attenuation correction, motion and CT truncation artefacts. The article also provides a discussion and literature review of the applications of PET/CT to date, covering detection of tumours, radiotherapy treatment planning, patient management, and applications external to the field of oncology.

Key words PET/CT, applications, oncology, treatment planning

Introduction

Multimodality imaging in medicine aims to exploit the complementary features of different medical imaging devices to provide physicians with an accurate tool for diagnosis and localisation of pathological tissue or assessment of tissue function. Typically, the procedure followed is that the patient is scanned by different devices, and the images from each device are then overlayed, resulting in a fused image. One challenge in multimodality imaging is the accurate co-registration of images to ensure that the patient's anatomy correctly 'lines up' in the fused image. Although advanced software is available to carry out this task[1] the patient typically needs to physically move from one imaging device to another. Apart from possible errors due to patient misalignment between scanners, the time delay between the non-simultaneous imaging sessions can occasionally be sufficient for changes to occur in the anatomy or physiology of the tissues being measured.

One solution to the above issues is the combination of different imaging modalities into a single scanner capable of simultaneous measurements by different techniques. Arguably, the most successful example of this to date is the combination of a positron emission tomography (PET) scanner, which primarily measures biochemical processes, and an x-ray computed tomography (CT) scanner, which primarily measures anatomical features, into a single unit referred to as a PET/CT scanner.

Although published clinical CT scans date back as early as 1973[2,3], and PET imaging even earlier (for a review of the history of PET the reader is directed to Muehllehner and Karp[4]), the development of a prototype PET/CT scanner was not reported until at least 1998[5,6] by a research group based at the University of Pittsburgh. The prototype scanner was a third generation Siemens Somatom AR.SP CT scanner placed in series with a Siemens ECAT ART PET scanner (Siemens Medical Solutions, Erlangen, Germany). The CT and PET scanners were housed in a single assembly with an axial separation of 60 cm such that the patient lay on an extended single couch which moved through the combined gantry. The PET and CT components were operated independently from separate consoles, but a

Corresponding author: J.V. Trapp, School of Physical and Chemical Sciences, QUT, GPO Box 2434, Brisbane, Queensland 4001, Australia; Tel: +61 7 3138 1386; Fax: +61 7 3138 1521
Email: j.trapp@qut.edu.au
Received: 6 January 2008; Accepted: 20 May 2008

software tool (developed in-house) allowed fused images to be displayed as colour PET images superimposing greyscale CT images.

In the few years since the University of Pittsburgh group published the details of their prototype scanner, PET/CT has proliferated in the medical industry. The first device to be made available commercially was the Discovery LS (GE Medical Systems, Milwaukee, WI, USA). This device involved simply combining their existing ADVANCE NXi PET scanner with a Lightspeed Plus 4-slice helical CT scanner and use of a newly designed patient bed. This system continued to operate with separate computers and software to control acquisition and processing of PET and CT respectively. Customized software was used for image fusion. Since 2001 a number of other medical equipment manufacturers have begun to offer PET/CT systems as a single unit or as upgrades to existing CT scanners. Although primarily used in diagnostic imaging departments, increasingly major radiation oncology departments have either purchased systems or are in the process of such purchases as an adjunct to radiotherapy planning. Recent advances have even seen micro PET/CT scanners developed for imaging of small animals[7,8,9].

The aim of this article is to provide a review of the current technology and applications of PET/CT as a combined imaging modality. We will review the technology and hardware of a PET/CT scanner and discuss its applications in oncology and potential applications outside of oncology in the current published literature. Extensive literature searches have been undertaken. However, publications included in this review do not include the complete body of literature available, which is now vast. Rather, the aim of the present work was to include a comprehensive selection of articles that are indicative of the technology and the scope of its applications, as well as highlight some of the potential limitations.

Aspects of PET/CT technology

Overview

The following section is a brief overview of the technological and design aspects of combining PET and CT scanners into a single unit. For a detailed description of the physics of either PET or x-ray CT, the reader is referred to current radiology text-books[10,11] and recent reviews such as Muehllehner and Karp[4]. For excellent reviews of multimodality imaging systems focusing specifically on technological advances in scanner design, the reader is referred to Townsend[12] and Zanzonico[13].

Scanner design

The first combined anatomical-functional imaging system to find widespread clinical application was not a PET system, but the GE Hawkeye single photon emission computed tomography (SPECT)/CT scanner (GE Healthcare, Chalfont St. Giles, UK), incorporating a low-power x-ray tube for attenuation correction and localisation with a dual-headed scintillation camera. In the first generation PET/CT scanners there was a minimum level of actual hardware integration with the major vendors incorporating an existing high-end PET scanner with a 2 or 4 slice CT scanner. These essentially separate components were housed inside a single gantry, in the case of the Discovery LS (based on the ADVANCE NXi, GE Healthcare) and Biograph (based on the ECAT ACCEL, Siemens Medical Solutions, Erlangen, Germany), or in two separate gantries, in the case of the Philips Gemini system (based on the Allegro, Philips Medical Systems, Best, the Netherlands). The centres of the scan planes of the two modalities are offset axially by distances of 25 cm (Discovery LS) to 80 cm (Biograph and Gemini. Note: the Gemini allows the user to move the PET gantry to increase this offset, giving the potential to improve access to the patient during the scan). The patient handling system in these configurations is possibly the key mechanical development. The extended tunnel length of the dual gantry system has required a redesign allowing a greater travel distance without a significant increase in patient couch sag.

Recent advances in PET/CT technology have resulted from improvements in the performance of the individual CT and PET components and improving software integration, but the general design concept remains unchanged. The desire for high-speed CT, driven by the cardiology market, has seen the original 2 or 4 slice scanners replaced with 8, 16, 40 and 64 slice models, with the latter capable of high temporal resolution and cardiac gated acquisition. Hardware developments in PET have concentrated on improved detection speed and efficiency. Time-of-flight systems are now on the market for clinical use, made possible because of the development of cerium doped lutetium oxyorthosilicate (LSO) and cerium doped lutetium yttrium oxyorthosilicate (LYSO) scintillator materials, which combine high density, high effective atomic number, good energy resolution (10–11%) and excellent timing resolution (~600 ps)[14]. Time-of-flight reconstruction has been shown to offer improved contrast recovery versus noise for ^{18}F-fluorodeoxy glucose (FDG), with the benefit even greater for larger patients[15], leading to improved image quality and/or higher throughput.

Other potential improvements in PET detector technology that are currently in the research stage include double-layer "phoswich" crystal blocks that allow the depth-of-interaction to be measured[16], thereby improving spatial resolution; and the replacement of photomultipliers for avalanche photodiodes[17], which can be integrated into hybrid PET/Magnetic Resonance Imaging (MRI) systems[18]. Single detector arrays suitable for implementation in an integrated PET/SPECT system have also been proposed[19].

Attenuation correction

One of the physical advantages of hybrid PET/CT scanners is that the intrinsically coregistered CT data can be used for PET attenuation correction. For this reason the PET scanners no longer require separate transmission sources and overall scan times can be markedly reduced by eliminating the need for a separate transmission scan. The option to include a transmission source might still be useful

in special cases where radiation dose to the patient is of particular concern, such as for paediatric patients or volunteers participating in drug trials. However, for the majority of clinical examinations, particularly in oncology, automatic tube current modulation algorithms[20,21] can be used to minimise radiation doses and still provide sufficient statistical quality for robust attenuation correction as well as anatomical correlation. Accordingly, a transmission source is not often required and so most PET/CT scanners are now supplied without one.

When performing a PET attenuation correction using CT data, it is important to take account of the fact that linear attenuation is energy dependent and the CT scan uses a spectrum of x-rays from 40 to 140 keV, whereas PET imaging utilises monoenergetic 511 keV photons. It is therefore necessary to scale the CT derived attenuation to the appropriate energy. At the annihilation photon energy of 511 keV the dominant process is Compton scattering. However, in the CT energy range the main attenuation contribution in bone is from photoelectric absorption. There is no simple function for mapping Hounsfield units to linear attenuation coefficients at 511 keV that is generally valid for all materials.

As Kinahan *et al*[22] suggest, a dual-energy CT scan allows extraction of the individual photoelectric and Compton contributions of the attenuation. However, this unnecessarily increases the patient dose when other, simpler methods of correction are available. One such approach is the segmentation method, which replaces the CT-number in the reconstructed image with an attenuation value at 511 keV corresponding to the type of tissue[22,23]. One drawback of this method is that the density of some tissue types varies considerably and will not be represented accurately by a discrete value. An alternative method is a scaling approach in which the entire CT image is multiplied by the ratio of attenuation coefficients of water (representing soft tissues) at the photon energies of CT and PET. An effective energy for CT is typically selected as 70 keV[23,24]. This method assumes a constant ratio between attenuation coefficients at different energies. However, this is a poor approximation for bone and hence a bilinear or hybrid approach can be adopted[25]. In the bilinear method a different scaling factor is applied to CT-numbers depending on a threshold which is chosen between 0 and 100 Hounsfield units. This method implicitly assumes that all materials in the body can be described as linear mixtures of air and water, or water and bone. The hybrid method integrates both segmentation and scaling by first estimating the attenuation map at 511 keV by separating out the tissue types based on CT-number and then using separate scaling factors for bone and non-bone components. The use of a simple segmentation into bone and non-bone avoids difficulties that may be encountered by tissue misclassification in more complex segmentations.

Scatter correction

Although more sensitive than their 2D counterpart, fully 3D PET scanners (having no interslice septa) are more susceptible to Compton scattered photons, which typically contribute up to 50% of the detected events. Hence, effective and reliable scatter correction is necessary. Modern scanners use sophisticated algorithms to estimate and subtract the single-scatter component in the raw data as part of the reconstruction process. This is done by estimating the activity distribution from a low-quality non-scatter-corrected PET image, estimating the Klein-Nishina cross section from the CT image and calculating the expected Compton scatter distribution[26,27]. A smaller contribution can be attributed to photons that have undergone multiple scattering. These are modelled in some scatter correction methods[28,29], although some of these photons will have lost sufficient energy and will be adequately rejected by energy windowing.

Artefacts

With combined PET/CT imaging, artefacts from the CT-based attenuation correction of the PET image can be encountered and are in addition to those artefacts common to independent PET and CT imaging. A major concern is the propagation of CT artefacts into the corrected PET image. Inaccurate attenuation correction may cause under or over-correction, which is particularly evident as a result of metallic implants in the body. Radiodense spots apparent on the corrected PET image can be mistaken for malignancies or obscure real tumours. A comparison with the uncorrected PET image is necessary for accurate interpretation[30,31] or a metal-artefact reduction method may be used[32,33].

CT contrast material may also contribute similar over-corrections to the PET image. Carney *et al*[34] have suggested a modification in which contrast-enhanced CT pixels can be separated from those containing bone for oral contrast studies and Nehmeh *et al*[35] similarly propose a segmented contrast correction. Antoch *et al*[36] have shown that a negative oral contrast agent, mannitol (2.5%) and locust bean gum (0.2%) dissolved in water (mannitol-LBG), prevents attenuation artefacts due to its water-based nature. In the case of intravenous contrast, Yau *et al*[37] have concluded that it is feasible to incorporate contrast into routine PET/CT protocols and their study demonstrates no clinical or statistical difference from non-contrast imaging. Similarly, Berthelsen *et al*[38] reported no contrast-introduced artefacts or changes in clinical diagnostic interpretation.

Misregistration between the CT and PET images can occur from different motion artefacts. The advantage of PET/CT is that patient movement is considerably limited to translation of the bed through the scanner. Some mechanical misalignment can occur from the sequential data acquisition, however, the primary cause of artefact is due to respiratory motion of the patient[31]. The CT scan is typically acquired during deep inspiration breath-hold, whereas the PET image is obtained during free tidal breathing due to the length of the scan. Different breathing protocols can be implemented to counter this problem[6] although misalignment of the images may still occur. During normal tidal volume breathing more time is spent in end-expiration than end-inspiration and hence the majority of counts arising from organs close to the diaphragm will be acquired in the position of those organs when the lungs are at their smallest volume. However, to obtain better

anatomical detail of the lung parenchyma, most CT acquisition protocols require lung expansion. Accordingly, the position of the diaphragm is generally lower on the CT than the average position of the dome of the liver on the PET images, where true counts are also misrepresented due to the effect of temporal blurring. The combination of this respiration-related undersampling plus the application of attenuation correction coefficients appropriate to lung rather than soft tissue generally leads to under-correction of true counts from the dome of the liver and frequently has the appearance of a relatively photopenic banana-shaped region at the lung base. Motion of internal organs during respiration can cause focal FDG uptake in the dome of the liver to appear to be located in the lower lung field[23,39]. Consequently, accuracy of lesion localisation in the diaphragmatic region may be limited and semi-quantitative assessment of the intensity of lesions in this region is compromised by the combination of respiratory blurring and incorrect attenuation correction.

The transverse field-of-view (FOV) of the PET image is typically larger than that of the CT scan and this can introduce a transaxial truncation artefact[40]. However, Kinahan *et al*[22] state that the effects on the PET emission image are generally smaller than expected, particularly if an iterative transmission reconstruction algorithm is used to reconstruct the missing CT data. Beyer *et al*[40] also discuss the effect of these truncation artefacts for larger patients where PET activity can be underestimated by up to 90% in the truncation area. They propose the use of a retrospective algorithm using an extended field-of-view correction, which considerably improves accuracy of the final image.

Clinical applications and patient management

Overview

The value of PET/CT using FDG for diagnosis and staging is beyond doubt for a wide range of clinical sites. In their systematic review Gambhir and colleagues[41] estimated, across all applications, that 30% of patients undergo a change in management as a result of an FDG PET scan (based on 1565 patients). By far, the most intensive use of FDG PET/CT to date has been as a diagnostic and staging device in oncology. Czernin *et al*[42] have recently provided a valuable review of literature for cancer staging using PET/CT and conclude that there is reliable evidence of its diagnostic advantage for major cancers.

The following section provides a brief overview of a broad range of recent clinical studies in which FDG PET/CT has been employed. Table 1 summarises pertinent data from various studies, indicating the use and efficacy of FDG PET/CT for different tumour sites. In the following sections PET/CT and PET refers to the use of FDG and not other radiotracers unless specified.

Small and non-small cell lung cancer

Lardinois and co-workers[43] compared the diagnostic accuracy of integrated PET/CT with PET alone, CT alone and PET and CT viewed side by side for patients with non-small cell lung cancer (NSCLC). They prospectively compared the results from the four imaging modalities in 50 patients and found that PET/CT provided additional information in 41% of the cases compared with PET and CT viewed side by side[43]. The additional information is useful for more accurate localisation of lymph nodes, chest wall infiltration, atelectasis and peritumoral inflammation. Bar-Shalom *et al*[44] also note that additional information is provided by PET/CT in 49% of cases (64 of 204 patients with lung cancer), although in their study only 14% led to a change in management. A further study by Antoch and co-workers[45] compared contrast enhanced PET/CT with PET and contrast enhanced CT alone in 27 patients with NSCLC. They found that PET/CT resulted in more accurate staging, when using histopathological results as the reference standard, than either PET or CT alone. A study by Keidar and co-workers[46] also looked at NSCLC recurrence. The specificity and positive predictive values of PET/CT, 82% and 89%, were much better than with PET (interpreted with CT reports), which were only 53% and 75% respectively. Stand-alone PET has already proven to be significantly more accurate than CT for staging NSCLC[47] and to have a high impact on patient management[48]. The further improvement in the diagnostic accuracy of PET/CT makes a compelling case for this technology to be used as the primary non-invasive staging tool for evaluation of patients with lung cancer. This is particularly relevant following treatment where distortion of normal anatomy and tissue function as a result of therapeutic intervention can render interpretation of both CT, and to some extent PET, difficult.

In addition to the increasing evidence for the effectiveness of PET/CT for NSCLC, there is emerging data for small cell lung cancer (SCLC). Malamitsi and co-workers[49] examined the role of PET/CT in the successful staging, restaging and management of SCLC and NSCLC in 20 patients (21 studies). Successful diagnosis was achieved in 16 studies and they concluded that in their early experience, PET/CT contributed significantly to correct staging and management. A recent study by Fischer *et al*[50] was concerned with the response evaluation of 20 patients after chemotherapy and attempted to prospectively assess the feasibility of PET/CT for this purpose. They found that PET/CT was indeed feasible for chemotherapy response evaluation, and that FDG uptake significantly correlates with size changes as measured by CT. However, it is unclear as to whether or not there is any considerable benefit of using PET/CT as opposed to CT alone.

Head and neck cancers

PET/CT is of particular relevance to the evaluation of head and neck cancers and recurrent tumours by providing both anatomical and metabolic information. Although a structurally complex region of the body, traditional anatomical imaging modalities such as CT and MRI can result in poor specificity[51]. PET has a distinct advantage in being able to identify metabolic changes in the tumour, which precede morphologic changes after therapy or surgery. However, the PET images are limited by the lack

of anatomical detail[51,52] and the complex patterns of normal physiological uptake.

Schöder *et al*[51] report that in a study group of 68 patients with 157 foci displaying abnormal FDG uptake, there were 53% less equivocal lesions with PET/CT compared with PET alone. Furthermore, six confirmed malignancies were completely missed with PET, compared with only one for PET/CT. Zimmer *et al*[53] discovered recurrence of thyroid carcinoma in four out of eight patients undergoing PET/CT that was otherwise undetectable. In a prospective study, Schöder *et al*[54] studied 31 patients with oral cancer who demonstrated no evidence of lymph node metastases by clinical examination or conventional imaging (CT or MRI). The findings revealed a relatively high number of false-positive findings (6 out of 142) for PET/CT and the authors conclude that despite a reasonably high overall accuracy its clinical application may be limited. Schwartz *et al*[55] investigated the role of PET/CT in pre-radiotherapy staging of head and neck cancers in 20 patients. It was found that PET/CT yielded a sensitivity and specificity of 96% and 98.5% respectively, and that imaging correlation with pathology was far better for PET/CT than for CT alone.

The advantage of PET/CT in evaluation of head and neck cancers is the exact localization of FDG uptake to anatomic and pathologic structures. As Goerres *et al*[56] identified, edema of the neck shortly after treatment can introduce difficulties in clinical evaluation as most imaging modalities are unable to clearly differentiate between scarring and residual cancer. Zimmer *et al*[53], Goerres *et al*[56] and Fukui *et al*[57] all suggest that PET/CT will help in the localization of FDG uptake and therefore facilitate targeted biopsies of treatment sites, allowing earlier diagnosis of recurrence. A recent study found that PET/CT has a high impact on clinical management decisions in both staging and restaging settings[58]. This study also demonstrated that patients with positive and negative scans had significantly different survival suggesting an important role in prognostic stratification and use of PET/CT to select patients for more aggressive salvage therapies.

Gastrointestinal cancers

Rosenbaum *et al*[59] provide a comprehensive overview of the use of PET, CT and PET/CT in relation to gastrointestinal tumours. Schöder *et al*[60] similarly review the field and conclude that PET/CT adds diagnostic benefit in 30-40% of patients compared with PET alone. Wechalekar *et al*[61] also discuss the advantages of PET/CT and review its applications to various cancers, including those of the gastrointestinal tract.

A study conducted by Antoch *et al*[62] demonstrated the response of proven gastrointestinal stromal tumours (GIST) to imatinib (an anti-cancer drug marketed by Novartis™) therapy. The number of lesions detected in 20 patients was 135 for PET, 249 for CT, 279 for side-by-side viewing and 282 for PET/CT. The authors concluded that PET/CT revealed more metastases from GIST than any other modality and correctly characterised the response to imatinib therapy in more patients. Goerres *et al*[63] supported this conclusion and also showed that PET/CT is superior in assessing response to imatinib therapy.

Colorectal cancer

The application of PET/CT in colorectal tumours has seen the staging and restaging accuracy improve from 78% to 89% compared to PET alone and reduced the number of equivocal lesion diagnosis by 50%[64]. In the detection of post-operative recurrence of colorectal cancer in the pelvis, Even-Sapir *et al*[65] have shown the improved diagnostic performance of PET/CT over PET alone. With 62 patients, the accuracy of PET/CT compared to PET alone was 93% and 74% respectively.

Gynaecological tumours

Several studies reveal an increase in metastatic diagnosis for gynaecological tumours, including ovarian, cervical, vulvar, vaginal and endometrial cancer, when using PET/CT compared with PET or CT alone[66,67,68,69]. Makhija *et al*[70] used PET/CT to identify recurrence in eight patients, all with positive histology and seven with negative CT scans. This earlier detection by PET/CT avoided the morbidity and expense of 'second-look' laparotomy. Grisaru and co-workers[72] compared PET/CT with conventional imaging techniques (CT, MRI and ultrasound) in 53 patients with gynaecological malignancies. PET/CT correctly identified all metastatic sites in nine of the 18 patients (50%) undergoing initial staging (with no false positives), while conventional imaging identified metastatic spread in only 39% of patients (two of which were inconclusive). Furthermore, conventional imaging resulted in a 28% false positive rate. In patients studied for recurrence, PET/CT correctly identified recurrence or metastatic disease in 16 patients in whom recurrence had not been detected with conventional imaging techniques. PET/CT was false positive in one case and false negative in another. Wahl[72] identified that PET/CT accurately assessed the presence of recurrent ovarian carcinoma in 81% of patients (N=22) in which a CT scan was negative or equivocal.

Simcock *et al*[73], in a prospective study involving 56 patients with recurrent ovarian cancer, found that PET/CT showed less disease in 9% of cases, more disease in 52% of cases, and ultimately led to a major change of management plan in 58% of patients compared with conventional imaging (predominantly CT). Within this group, PET/CT also found a subset of patients with apparently localised disease or no definite evidence of disease. This result suggests that PET/CT can offer prognostic information along with disease localisation. This group showed improved survival compared with the patients with systematic disease.

Breast cancer

A review of early studies was provided by Zangheri *et al*[74]. In a subsequent retrospective study of 75 patients, PET/CT was found to add incremental diagnostic confidence in more than 50% of patients with FDG uptake abnormality on PET and accurately detected more regions involved by malignancy than did CT[75]. Recent studies have demonstrated that the metabolic characteristics of lytic and

sclerotic bone metastases differ significantly, particularly during therapy[76]. The ability to demonstrate bone architecture on CT and directly correlate this with metabolic signal is likely to improve the sensitivity and specificity of staging and therapeutic response assessment of metastatic bone disease in breast cancer patients and to complement the capability of PET to detect local, nodal and soft tissue disease deposits and evaluate their response to treatment[77]. In a recent study in patients with breast cancer and rising tumour markers, PET/CT had a higher sensitivity (85% vs 70%), specificity (76% vs 47%), and accuracy (81% vs 59%) compared to CT for the diagnosis of tumour recurrence[78]. PET/CT led to changes in the subsequent clinical management of 51% of these patients.

Prostate cancer

The radiopharmaceutical FDG when used in PET/CT has suboptimal sensitivity in the diagnosis of some cancers, i.e. prostate cancer, neuroendocrine tumours and primitive hepatic tumours due to relatively poor FDG avidity in these tumours. These generally slow growing tumours do not show a significant increased FDG uptake and immunohistochemistry studies have demonstrated that these tumours often have relatively low levels of Glut-1, the most important glucose transporter in many other FDG avid cancers. Inflammation and cancer are not clearly distinguishable as both processes are characterised by increased glucose metabolism[79]. Reske and co-workers[80] have investigated the use of ^{11}C-Choline as the radiopharmaceutical for imaging prostate cancer in PET/CT. The results of the study show that ^{11}C-Choline PET/CT identifies substantial tumour volumes within the prostate gland in 100% of patients examined. Similar results were also reported by Kwee[81] using a dual-phase ^{18}F-fluorocholine PET technique. Reske[80] found some overlap of ^{11}C-Choline uptake in areas of the prostate with benign lesions and those with malignancies, leading to an unreliable localisation of the tumour in one of 26 of the patients. It was also found that some small tumour lesions hidden within normal tissue were missed in the study. However, it was suggested that this was due to the resolution of the PET/CT scanner used and that combined with determining the major malignant tumour, this is of small concern[80].

Hodgkin's disease and non-Hodgkin's lymphoma

Hodgkin's disease (HD) and non-Hodgkin's lymphoma (NHL) are malignant neoplasms of the lymphoid tissue. They constitute less than 8% of all malignancies but this has been rising by several percent in the last few years[82]. Studies are beginning to emerge which indicate the usefulness of PET/CT, as opposed to PET or CT alone, in the diagnosis of varying tumours, including the management of lymphomas[44,83,84,85,86]. Rodriguez-Vigil *et al*[87] found that PET/CT improved the overall sensitivity and specificity compared to PET or CT alone, and that PET/CT is more than suitable for staging, assessment of early response to therapy, restaging and follow-up of HD and NHL, ultimately improving the clinical management of patients. Schaefer *et al*[88] retrospectively compared PET/CT with contrast-enhanced CT in 60 patients with either HD or NHL who required staging/restaging. It was found that sensitivity and specificity for staging and restaging with PET/CT were 94% and 100% respectively, compared to 88% and 86% respectively for CT alone. Again it was found that PET/CT was sufficient for staging and restaging lymphomas, however studies are limited and further work is required to confirm these findings. Freudenberg *et al*[89] found for patients with lymphoma a sensitivity of 78% for CT alone, 86% for PET alone, 93% for CT and PET read side by side, and 93% for combined PET/CT imaging. Combined imaging clearly has increased sensitivity compared with either PET or CT alone.

Vertebral metastases

Detection of vertebral metastases is important in clinical practice due to their potential for causing neurological complications. MRI is generally the preferred methodology for this purpose but some patients have either contra-indications or cannot tolerate this type of scan. Metser and co-workers[90] have evaluated the role of PET/CT in the diagnosis of vertebral metastases in 242 lesions in 51 patients. Analysis of the data suggested that PET/CT increased specificity in lesion detection compared with PET or CT alone. PET/CT was more accurate in defining the vertebral level of disease and the part of the vertebra involved. In one third of the patients it was possible to more accurately identify the level of soft tissue involvement. Thus, PET/CT may be a worthwhile alternative for evaluation of suspected vertebral metastases in patients unsuitable for MRI or in whom the MRI findings are equivocal due to prior treatment changes.

Carcinoma of unknown primary

PET/CT is also having more success in detecting occult primary tumours than PET, CT, or PET and CT side by side. Gutzeit *et al*[91] in a study of 45 patients with an unknown primary tumour reported that PET/CT successfully detected more primary tumours than conventional modalities. Although the authors state that the majority of tumours remain occult whichever method is used. The presentation of patients with suspected recurrent disease while showing negative signs from conventional imaging is a common occurrence in oncology. Israel and co-workers[92] have examined 36 patients in this situation using PET/CT and PET alone and found that PET/CT is more accurate than PET alone, but particularly with regard to specificity on a site based analysis, 97% compared to 50%. Sensitivities were similar, suggesting that the main strength of PET/CT in this situation is the avoidance of false-positive interpretations of areas of FDG activity[92].

Patient management

A significant outcome from the majority of studies, independent of the type of cancer assessed, is the change in patient management. The accurate staging of tumours and the early detection of recurrence following therapeutic intervention reduce unnecessary treatment. In addition to the cost reduction, the patient avoids unpleasant and unnecessary side effects associated with prolonged

treatment. Changes to patient management have been discussed in relation to cancer types in the literature. For example, Antoch *et al*[45] and Keidar *et al*[46] both report changes in patient management as a result of PET/CT for lung cancer. King *et al*[93] reports a 30% change in patient management for gynaecological tumours. Schöder *et al*[51] revealed altered patient care in 18% of patients with head and neck cancer.

Bar-Shalom[44] looked at 204 patients with 586 sites suggestive of malignancy. It was found that PET/CT provided additional value in 49% of patients in 30% (178) of sites. The principal benefit was accurate localisation of the PET metabolic information with the anatomical information from CT. The modified interpretation of the 178 sites was found to be accurate in 95% of the cases, with a diagnostic error of 1.4% for all sites evaluated. PET/CT induced six false positive and three false-negative interpretations. The study concluded that PET/CT affected the clinical management of 14% of patients. Changes made included additional diagnostic assessment and decisions for the appropriate treatment and protocol.

Treatment planning

PET/CT has the potential to make a positive impact in radiotherapy treatment planning in three different ways: i) through more accurate staging, ii) through more accurate gross tumour volume (GTV) definition, and iii) by enabling explicitly non-uniform dose prescription with the target volume to maximise probability of local control for a fixed integral dose.

Staging

Improved patient selection and staging for radical radiotherapy using PET/CT will have a significant beneficial effect[94]. It is therefore important to separate the effects of improved patient selection and nodal staging from changes in GTV localisation when reporting the effect of PET on radiotherapy outcomes. Large reported changes in delineated target volume are sometimes the result of inclusion of nodal regions in the GTV and are therefore essentially changes in stage rather then tumour delineation *per se*. It is likely that the largest impact that PET/CT will have on radiotherapy outcomes will be through the provision of more accurate staging information as has already been demonstrated for stand-alone PET[95].

GTV definition

There have been a number of studies showing the effect of PET/CT on GTV and planning target volumes (PTV) definition[96,97,98,99,100,101]. Ciernik and co-workers[96] investigated the use of PET/CT compared with standard CT to conduct treatment planning on 39 patients, 12 of whom were head and neck, 6 were lung cancer and the remaining 21 were cancer of the pelvis. They found that significant changes were suggested by PET/CT in the GTV and PTV definitions. In 56% of all cases, the GTV was changed by more than 25% from PET/CT planning compared to CT based volume definition. Gondi *et al*[100] studied 30 patients, 16 of which had oesophageal cancer and 14 with NSCLC. They employed a conformality index to quantify differences in the GTV definitions obtained by using CT alone and using the combined PET/CT. Their method accounts for size differences as well as three-dimensional overlap of the GTVs. Their results concur with others in suggesting that PET/CT significantly alters the definition of the GTV in radiotherapy planning.

Improvements in identifying primary lesions, lymph node involvement and metastases, along with the accurate definition of these volumes by the use of PET/CT has seen the technique introduced to intensity-modulated radiotherapy (IMRT). The use of PET/CT guided IMRT for the treatment of head and neck tumours has been investigated by Wang *et al*[102] and Paulino *et al*[97]. The benefit of using IMRT is that it allows a high dose of radiation to be delivered to the PTV and high risk disease regions, while irradiation of surrounding critical tissue regions such as the parotid glands, spinal cord, mandible, orbits, optic chiasm and brain is minimised. In the 26 patient study presented by Wang *et al*[102] they found that PET/CT changed initial CT based staging in 57% of cases. Volume analysis revealed that the PET/CT based GTVs were significantly different from those contoured from the CT scans alone in 14 of the 16 cases. Primary tumours in 8 patients were poorly defined or not identified by CT images alone. In addition, 16 of 28 patients who were followed for more than 6 months with a median time of 17 months did not have any evidence of recurrence. In the study by Paulino *et al*[97], a total of 40 patients with squamous cell carcinoma arising in the head and neck were treated using the IMRT technique. A comparison between PET/CT–GTV and CT–GTV was performed resulting in approximately 25% of patients having their PET/CT–GTV underdosed when the CT–GTV was used for IMRT planning. However, these finding are not conclusive, as it is well documented that GTV delineation in the head and neck region can be difficult because certain normal areas can be FDG avid, such as the tonsils, base of tongue, muscles of mastication, thyroid gland and parotid glands[93,98].

One of the key technical questions is exactly how to use PET for GTV delineation. A range of different techniques have been reported for contouring, ranging from a simple visual interpretation in conjunction with an experienced nuclear medicine physician to a threshold method to distinguish between benign and malignant tumour. Gondi *et al*[100] and Heron *et al*[101] normalize PET/CT images using FDG uptake in the liver. Ciernik *et al*[96] and Paulino *et al*[97] advocate an intensity level of 50% of the maximum standardised uptake value (SUV) in the tumour to delineate the borders of the PET/CT GTV. Other groups employed the same threshold method, but with a 40% SUV uptake value[103]. A further method of autocontouring, which uses an SUV threshold value of 2.5 relative to the normal tissue intensity (which is generally regarded as the threshold for the distinction between benign and malignant lesions), has been suggested by Paulino and Johnstone[97]. Ashamalla *et al*[98,99] have refined this method by contouring using a method they termed anatomic biological contouring (ABC). They observed a distinct "halo" around areas of maximum SUV uptake. This method resulted in an SUV of

2.0 ± 0.4, very similar to the original value of 2.5.

A common problem with all these techniques is that the optimum threshold depends on lesion size[104]. Studies are needed comparing histopathology with uptake for each treatment site and each tracer to properly validate any of these delineation methods. Nestle *et al*[105] highlight the fact that all the above delineation methods result in substantially different volumes for non-small-cell lung cancer (NSCLC), concluding that " … *no* method of automatic delineation of FDG positive tissue can be regarded as a reliable *standard* ". Grégoire *et al*[106] come to a similar conclusion: "… fixed threshold-based methods are definitely not adequate for accurately segmenting head and neck tumours and should therefore be avoided". Having pointed out the current limitations, Nestle *et al*[105] do however make a number of sensible pragmatic recommendations, such as the use of well defined protocols for image acquisition, attenuation correction, reconstruction and then windowing and segmentation, emphasising that these should be quality controlled using phantom measurements. Riegel *et al*[107] and Ciernik *et al*[96] also report the need for GTV delineation protocols in treatment planning using PET/CT and highlight the large variations in delineation of the GTV using PET/CT that results if such protocols are not followed. In the absence of objective clinical evidence showing the effect of any particular PET contouring method, the best available method to date is visual contouring by a radiation oncologist in cooperation with a nuclear medicine specialist, following a well-defined protocol[105].

Non-uniform dose prescription

Current radiotherapy practise implicitly assumes uniform spatial radiosensivity and clonogen density distributions throughout the delineated GTV by prescribing a uniform dose. In the absence of further information this is a reasonable assumption and is the basis of clinical experience to date. However, PET provides us with information about the heterogeneity of biochemical function within tumours. To obtain the maximum clinical benefit from this information, explicitly non-uniform dose prescriptions may be beneficial[108] that, for example, boost dose to regions of intense FDG uptake. The feasibility of using IMRT to selectively boost dose to known regions of hypoxia has been demonstrated[109], but significant further research is required before such techniques can be widely clinically implemented. Vanderstraeten *et al*[110] highlight the need for trials, stating that "the hypothesis that tumour regions with the highest FDG uptake are most radioresistant can only be confirmed by clinical results". Predictive radiobiological models of treatment outcome that explicitly include heterogeneity in biochemical function, validated using clinical trial outcomes, would be the ideal tool for assisting treatment planning. These could be built into IMRT optimisation functions, although we are not yet at this stage.

Applications external to the field of oncology

Presently, numerous applications of PET/CT exist that are external to oncology that, particularly with the advent of novel tracers, are predicted to broaden and be of increasingly widespread use[111]. This is reflected in recent literature, incorporating cardiology, neurology, psychiatry, infection and inflammation. The future applications of PET/CT are likely to be quite diverse. A 16 slice (and, less preferably, a 4 or 8 slice) scanner is sufficient for oncology but cardiology, for instance, requires *at least* 16-slice and preferably 64-slice PET/CT. Recent design improvements in PET components allow for 4 mm spatial resolution over a large field of view; 64 section CT scanners are currently being introduced and 128 or 256 section CT is likely to be the next standard – the combination of which would allow for imaging of the entire brain or heart without table movement[112]. Such progress increases the applicability of PET/CT.

There is pronounced accumulation of FDG in activated macrophages and granulocytes associated with inflammation that facilitate imaging with FDG PET/CT. The capacity of FDG PET to identify infection or inflammation has been shown for various diseases such as pneumonia[113], tuberculosis[114], inflammation of mammary glands[115], muscle tissue[116] and sinuses[117], lymph nodes[118] and abscesses[119]. Crymes *et al*[120] provide a review of 273 cases of apparent musculoskeletal infection investigated with FDG PET that show it to be a highly sensitive and specific mode of evaluation – a result reflected recently by Stumpe *et al*[121]. Keider *et al*[122] used FDG PET/CT to investigate inflammation of bone marrow of the foot (that affects 15% of diabetes sufferers) and found that PET/CT allowed precise diagnosis of osteomyelitis versus soft-tissue infection through better anatomic localisation of abnormal PET findings. Schiesser *et al*[123] used PET/CT as part of a study undertaken in 2002, showing that it is a sensitive and specific method for the detection of infectious foci resulting from metallic implants in patients with trauma. PET/CT has also been shown to have advantages in the diagnosis of patients with fever of unknown origin[124].

Labelling of plastic microspheres with gamma emitting isotopes allows study of myocardial blood flow (MBF) via PET. Kaufmann and Camici[125] show that cardiac PET with $^{13}NH_3$ or $H_2{}^{15}O$ is a robust and reproducible technique to obtain measurements of MBF and coronary flow reserve in vivo, and state that it is the "gold standard" against which new modes should be tested. CT has the capacity to complement this information with detailed anatomical data, and indeed Koepfli *et al*[126] employed a hybrid PET/CT scanner to measure MBF with accuracy. Lodge *et al*[127] highlight the advantage of hybrid PET/CT systems in terms of the simultaneous acquisition of anatomical and physiological information, and discuss recent technological developments that allow study of impaired regional coronary blood flow reserve and absolute MBF quantification. Schwaiger *et al*[128] found that PET/CT is a very promising technique for characterisation of coronary artery disease, particularly given the rapid improvement of CT slice technology, with the future use of PET/CT in cardiology largely being determined by cost and product availability, as well as patient referral patterns. In a study of FDG uptake in the thoracic aortic wall, Tatsumi *et al*[129] employed PET/CT and found that FDG uptake is located in

areas of metabolic activity of atherosclerotic changes and is distinct from aortic wall calcification. Wagner *et al*[130] found that there is potential for PET/CT as applied to characterisation of angiogenesis directed molecular intervention in vivo.

Such contemporary use is evidence of the suitability of PET/CT to studies within the areas of cardiology, infection and inflammation, and there are indications that further applications outside the field of oncology are likely to expand in the near future. While the applicability of PET/CT is increasing, it is likely that different configurations may be appropriate for differing PET/CT applications, rather than a single universally applicable design[131].

Conclusions

Despite the introduction of artefacts which are additional to those of PET and CT scanning as single imaging modalities, there are significant advantages associated with the combined PET/CT scanner, including the use of the CT scan for attenuation correction and improved confidence in reporting the fused scans due to more accurate coregistration. The CT data is obtained in a matter of seconds compared with the more time intensive acquisition of a radionuclide transmission scan in conventional PET. This reduces imaging time per patient by up to 40%[23], having a considerable effect on patient throughput. Another advantage of CT attenuation correction is that there is no longer a need for a radioactive transmission source.

PET/CT has distinct benefits compared with other image fusion techniques based on software algorithms or visual co-registration. Misalignment due to patient movement is minimised by acquiring the PET and CT scans in one imaging session. This also overcomes issues associated with the time gap between the different image acquisitions for independent modalities, where pathological changes within the body may occur.

PET/CT is a significant improvement over PET alone in its ability to define accurately the FDG anatomical uptake. Furthermore, the fused image has increased sensitivity compared with either individual scan. Some tumours are not particularly FDG avid and are therefore difficult to differentiate on a PET image. New tracers may address this limitation. However, the CT scan may indicate some abnormality and by combining the two images there is a greater probability that the tumour will be correctly identified and localised. In addition, in some cases there will be some normal physiological uptake of the radiotracer which may lead to false-positives on PET images. However, the CT scan allows identification of the uptake in normal tissue and improves specificity in the combined image. Overall, the combination of PET/CT improves diagnostic confidence and has been shown to have a significant effect on patient management.

Hybrid imaging with PET/CT, SPECT/CT or PET/MRI is likely to become the modality of choice for many disease scenarios and will act as a stimulus for further research and development in radiopharmaceuticals, leveraging the major theoretical advantages of the tracer principle to deliver more sensitive and more specific diagnoses.

Table 1. *The use and efficacy of PET/CT in the treatment of various types of cancers is indicated by the selected studies shown. Only selected results are included to provide an indication of the conclusions from each study. PET+CT is used as an abbreviation for PET and CT viewed side-by-side. Where the accuracy of PET/CT has been independently assessed (without comparison to conventional imaging modalities) the fourth column has been left blank.*

Study	No. of patients	Cancer	Modalities compared with PET/CT	Comments
Small (SCLC) and non-small cell lung cancer (NSCLC)				
Lardinois *et al*[43] 2003	50	NSCLC	PET, CT, PET+CT	PET/CT provided additional information in 41% of patients compared with PET and CT viewed side by side.
Bar-Shalom *et al*[44] 2003	204	lung cancer (n=64) GI tumours (n=34) lymphoma (n=33) breast cancer (n=13) head and neck (n=4) other cancers (n=56)	PET, CT	PET/CT provided additional information in 49% of patients compared with PET or CT.

Study	No. of patients	Cancer	Modalities compared with PET/CT	Comments
Antoch *et al*[45] 2003	27	NSCLC	PET, contrast enhanced CT	PET/CT resulted in a treatment change in 15% of patients compared with PET and in 19% of patients compared with CT.
Keidar *et al*[46] 2004	42	NSCLC	PET+CT	PET/CT changed management in 29% of cases.
Malamitsi *et al*[49] 2006	20	SCLC and NSCLC	CT and bone scan, MRI	PET/CT led to a change in management in 6 patients.
Fischer *et al*[50] 2006	20	SCLC	PET, CT	Response evaluation by PET/CT is feasible, but uncertain as to whether it adds further information.
Brianzoni *et al*[132] 2005	28	NSCLC (n=17) SCLC (n=7) NHL (n=4)	CT	PET/CT images significantly altered volumes in 11 patients (44% as 3 patients were excluded from the study).
Shim *et al*[133] 2005	106	NSCLC	CT	PET/CT correctly staged disease 86% of the time, compared to 79% with stand alone CT. Sensitivity, specificity and accuracy for CT alone were 70%, 69% and 69% respectively, while for PET/CT they were 85%, 84% and 84% respectively.
Kim *et al*[134] 2007	674	NSCLC		On a per-person basis sensitivity, specificity and accuracy of PET/CT were 61%, 96% and 86% respectively. On a per-nodal station basis they were 46%, 98% and 92%.
Head and neck (H&N) cancers				
Schöder *et al*[51] 2004	68	squamous cell carcinoma (n=52) unknown primary neck tumour (n=8) recurrent thyroid carcinoma (n=8)	PET	Accuracy of PET/CT was 96% compared with 90% for PET alone. Six malignancies were missed by PET and one by PET/CT. Patient management changed in 18% of cases with PET/CT.
Zimmer *et al*[53] 2003	8	suspected recurrence of thyroid cancer	MRI, CT	PET/CT identified recurrence in 4 patients who otherwise had undetectable disease.

Study	No. of patients	Cancer	Modalities compared with PET/CT	Comments
Schöder *et al*[54] 2006	31	oral cancer		Relatively high number of false-positive findings (6 out of 142) for PET/CT.
Schwartz *et al*[55] 2005	63	H&N squamous cell carcinoma	Contrast-enhanced CT	PET/CT detected 100% and 96% of heminecks and nodal zones respectively. CT alone only detected 82% and 78%.
Connell *et al*[58] 2007	76	primary H&N mucosal squamous cell carcinoma		PET/CT resulted in tumour classification alternation in 34% of cases, a treatment change in 29% and an altered treatment response assessment in 43%.
Ashamalla *et al*[99] 2007	25	H&N cancers	CT	Significant volume modification (≥25%) was seen in 17 of 25 patients (68%). Interobserver agreement increased with use of anatomic biological contouring (ABC).
Reigel *et al*[107] 2006	16	SCC, NHL, melanoma, B-cell lymphoma	CT	Significant variation occurred across physicians' PET/CT volumes demonstrating the need for delineation protocol. Near-significant variation occurred across physicians' CT volumes.
Ha *et al*[135] 2006	36	H&N squamous cell carcinoma	CT, MRI	Treatment plan confirmed in 69% of cases and altered in 31%. 6 patients in altered group had disease upstaged.
Breen *et al*[136] 2007	10	H&N squamous cell carcinoma	CT, contrast-enhanced CT	No significant differences detected in outlined volumes between modalities.
Murakami *et al*[137] 2007	23	H&N squamous cell carcinoma	Endoscopy, CT, MRI	Using conventional methods coupled with PET/CT improved lymph node staging (74% to 83%) for one observer and including SUV data improved results further (83% to 87%) for two observers.

Study	No. of patients	Cancer	Modalities compared with PET/CT	Comments
Gastrointestinal Cancers				
Antoch *et al*[62] 2004	20	gastrointestinal stromal tumours (Imatinib therapy)	PET, CT, PET+CT	Assessment of correct identification of tumour response at various periods after therapy: 1 mo - PET/CT 95%; PET+CT 90%; PET 85%; CT 44% 3 mo - PET/CT, PET+ CT and PET all 100%; CT 60% 6 mo - PET/CT, PET+CT, PET all 100%; CT 57%.
Goerres *et al*[63] 2004	34	gastrointestinal stromal tumours (Imatinib therapy)	PET, contrast enhanced CT	PET/CT provided additional information to PET or CT alone.
Israel *et al*[138] 2005	34	various tumour types		PET/CT found useful for assessing incidental focal uptake of FDG.
Bar-Shalom *et al*[139] 2005	32	oesophageal cancer	PET+CT	PET/CT changed initial characterisation of lesion in 22% of tumour sites and had better specificity and accuracy than PET and CT compared side-by-side (81% vs 59% and 90% vs 83% respectively).
Colorectal Cancer				
Cohade *et al*[64] 2003	45	colorectal cancer	PET	Frequency of equivocal lesions reduced by 50% with PET/CT and definite lesion characterisation increased by 30%. Overall correct staging increased from 78 to 89%.
Even-Sapir *et al*[65] 2004	62	rectal cancer	PET	The accuracy for differentiating malignant from benign for PET/CT was 93% compard with 74% for PET alone.
Kim *et al*[140] 2005	51	mucinous adenocarcinoma (n=6) non-mucinous adenocarcinoma (n=41) unknown (n=4)	PET, software fusion PET+CT	On a patient basis, accuracy of staging for PET/CT was 88% compared with 71% for PET alone. Image fusion of independently acquired PET and CT images failed in 8 (24%) patients.

Study	No. of patients	Cancer	Modalities compared with PET/CT	Comments
Veit-Haibach *et al*[141] 2006	47	colorectal cancer	CT, PET+CT	Of 50 lesions identified, PET/CT colonography correctly identified 37, PET+CT identified 32 and CT-alone, 26. PET/CT colonography affected therapeutic decisions in 4 cases.
Gynaecological Malignancies				
Makhija *et al*[70] 2002	8	primary ovarian (n=6) fallopian tube (n=2)	CT	62% had recurrent disease based on correlative histology with a positive PET/CT and a negative CT.
Grisaru *et al*[71] 2004	53	gynaecologic malignancies (ovary, cervix, uterus, vagina, vulva, tube, GTN [gestational trophoblastic neoplasia]) staging (n=18) suspected recurrence (n=35)	CT, MRI, US	PET/CT led to a sensitivity of 97% compared with 40% for standard imaging and similarly a specificity of 94% compared with 40%, respectively.
Wahl *et al*[72] 2004	22	epithelial ovarian cancer (n=22)	CT	On a patient basis, PET/CT had 81% accuracy. Failure to detect small tumour foci (<1 cm) was not uncommon.
Simcock *et al*[73] 2006	56	recurrent ovarian cancer	CT	PET/CT altered the known disease distribution in 64% of studies, showing less disease in 9% and more disease in 52%. A major change of patient management plan occurred with 58% of patients.
Choi *et al*[142] 2006	22	cervical carcinoma	MRI	PET/CT shown to be more sensitive than MRI in the detection of lymph node metastases (57.6% compared with 30.3%). No significant differences found with regard to specificity or accuracy.

Study	No. of patients	Cancer	Modalities compared with PET/CT	Comments
Breast cancer				
Tastumi *et al*[86] 2006	75	breast cancer	PET, CT	PET/CT led to improved diagnostic confidence compared with PET in 30 out of 50 patients who exhibited increased FDG uptake. PET/CT accurately staged 59/69 patients, whereas CT staged 53/69.
Radan *et al*[78] 2006	46	breast cancer	Contrast enhanced CT	In 37 patients comparisons of PET/CT and contrast enhanced CT showed higher sensitivity (85% vs 70%), specificity (76% vs 47%) and accuracy (81% vs 59%) for PET/CT.
Veit-Haibach *et al*[143] 2007	44	breast cancer	PET, CT, PET+CT	Overall tumour staging was correctly determined by PET/CT in 91% of cases, 86% for PET+CT, and 82% for PET-alone and CT-alone. PET/CT changed therapy in 2 cases compared to PET+CT, 4 cases compared to PET alone and 5 cases compared to CT alone.
Piperkova *et al*[144] 2007	49	breast cancer	Contrast enhanced CT	PET/CT analysis returned as many true-positive (TP) and true-negative (TN) as PET/CT + CE-CT, while CE-CT alone returned 23 less TP lesions and 16 less TN lesions. PET/CT images had 2 false-positive (FP) and 5 false-negative (FN) findings, significantly better than CE-CT alone (18FP & 28FN). PET-CT + CE-CT returned no FP results and 3 FNs.
Prostate Cancer				
Reske *et al*[80] 2006	26	prostate cancer		PET/CT resulted in 100% true positive based on correlation with histopathologic results.
Schmid *et al*[145] 2005	19	prostate cancer		^{18}F-fluorocholine (FCH) PET/CT determined to be effective in detecting

Study	No. of patients	Cancer	Modalities compared with PET/CT	Comments
				recurrence of disease or metastases based on histopathologic results. Not effective for T-staging of tumour; unable to differentiate between benign and malignant growths.
Lymphoma				
Schaefer *et al*[88] 2004	60	HD and NHL	Contrast enhanced CT	Sensitivity and specificity for staging and restaging with PET/CT were 94% and 100% respectively, compared with 88% and 86% respectively for CT alone.
Raanani *et al*[146] 2006	103	HD (n=35) NHL (n=68)	Contrast enhanced CT	For NHL, 32% of patients changed disease staging and treatment approach was altered in 25% of cases for PET/CT. For HD, 47% of patients changed disease staging and treatment approach was altered in 45% of cases.
Freudenberg *et al*[89] 2004	27	HD and NHL	PET, CT, PET+CT	On a patient basis, sensitivities for CT alone, PET alone, PET+CT and PET/CT respectively were 78%, 86%, 93% and 93%. Patient based accuracies were 67%, 93%, 96% and 96%.
Vertebral metastases				
Metser *et al*[90] 2004	51	spinal lesions	PET, CT	PET/CT identified 242 lesions (90% malignant), PET 220 lesions, and CT 159 lesions. On a patient basis, the sensitivity of PET/CT was 98% and 74% for PET.
Unknown tumours				
Gutzeit *et al*[91] 2005	45	unknown primary tumour	PET, CT, PET+CT	PET/CT successfully detected more primary tumours than the other modalities, although not statistically significant.
Israel *et al*[92] 2004	36	suspected occult recurrence	PET	PET/CT resulted in further management and treatment planning in 33% of patients.

References

1. O'Connor, M. K. and Kemp, B. J., *Single-photon emission computed tomography/computed tomography: basic instrumentation and innovations*, Semin. Nucl. Med., 36: 258-266, 2006.
2. Ambrose, J. and Hounsfield, G. N., *Computerized transverse axial tomography*, BJR., 46: 148-149, 1973.
3. Hounsfield, G. N., *Computerized transverse axial scanning (tomography): Part 1. Description of system*, BJR., 46: 1016-1022, 1973.
4. Muehllehner, G. and Karp, J. S., *Positron emission tomography*, Phys. Med. Biol., 51: R117-R137, 2006.
5. Townsend, D., Beyer, T., Kinahan, P. E., Brun, T., Roddy, R., Nutt, R. and Byars, G., *The SMART Scanner: a Combined PET/CT Tomograph for Clinical Oncology*, IEEE Nucl. Sci. Symp. Conf. Rec., 1170, 1998.
6. Beyer, T., Townsend, D. W., Brun, T., Kinahan, P. E., Charron, M., Roddy, R., Jerin, J., Young, J., Byars, L. and Nutt, R., *A Combined PET/CT Scanner for Clinical Oncology*, J. Nucl. Med., 41: 1369-1379, 2000.
7. Tai, Y.-C., Chatziioannou, A. F., Yang, Y., Silverman, R. W., Meadors, K., Siegel, S., Newport, D. F., Stickel, J. R. and Cherry, S. R., *MicroPET II: design, development and initial performance of an improved microPET scanner for small animal-imaging*, Phys. Med. Biol., 48: 1519-1537, 2003.
8. Yang, Y., Tai, Y.-C., Siegel, S., Newport, D. F., Bai, B., Li, Q., Leahy, R. M. and Cherry, S. R., *Optimization and performance evaluation of the microPETII scanner for in vivo small-animal imaging*, Phys. Med. Biol., 49: 2527-2545, 2004.
9. Liang, H., Yang, Y., Yang, K., Wu, Y., Boone, J. M. and Cherry, S. R., *A microPET/CT system for in vivo small animal imaging*, Phys. Med. Biol., 52: 3881-3894, 2007.
10. Kalender, W. A., *Computed Tomography: Fundamentals, System Technology, Image Quality, Applications*, 2nd Edition, Wiley-VCH, 13: 978-3895782169, 2004.
11. Wernick, M. N. and Aarsvold, J. N., *Emission Tomography: The Fundamentals of PET and SPECT: The Fundamentals of Pet and Spect*, Academic Press, 13: 978-0127444826, 2004.
12. Townsend, D. W., *Multimodality imaging of structure and function*, Phys. Med. Biol., 53: R1-R39, 2008.
13. Zanzonico, P., *Positron emission tomography: a review of basic principles, scanner design and performance, and current systems*, Semin. Nucl. Med., 34: 87-111, 2004.
14. Surti, S., Kuhn, A., Werner, M. E., Perkins, A. E., Kolthammer, J. and Karp, J. S., *Performance of a Philips Gemini TF PET/CT Scanner with Special Consideration for Its Time-of-Flight Imaging Capabilities*, J. Nucl. Med., 48: 471-480, 2007.
15. Karp, J. S., Surti, S., Daube-Witherspoon, M. E. and Muehllehner, G., *Benefit of Time-of-Flight in PET: Experimental and Clinical Results*, J. Nucl. Med., 49: 462-70, 2008.
16. Ohi, J. and Tonami, H., *Investigation of a whole-body DOI-PET system*, NIM A, 571: 223–226, 2007.
17. Pichler, B. J., Swann, B. K., Rochelle, J., Nutt, R. E., Cherry, S. R. and Siegel, S. B., *Lutetium oxyorthosilicate block detector readout by avalanche photodiode arrays for high resolution animal PET*, Phys. Med. Biol., 49: 4305–4319, 2004.
18. Pichler, B. J., Judenhofer, M. S., Catana, C., Walton, J. H., Kneilling, M., Nutt, R. E., Siegel, S. B., Claussen, C. D. and Cherry, S. R., *Performance test of an LSO-APD Detector in a 7-T MRI Scanner for Simultaneous PET/MRI*, J. Nucl. Med., 47: 639–647, 2006.
19. Yamamoto, S., Matsumoto, K. and Senda, M., *Development of a GSO positron / single-photon imaging detector*, Phys. Med. Biol., 51: 457–469, 2006.
20. Gies, M., Kalender, W. A., Wolf, H., Suess, C. and Madsen, M. T., *Dose reduction in CT by anatomically adapted tube current modulation. I. Simulation studies*, Med. Phys., 26: 2235-2247, 1999.
21. Kalender, W. A., Wolf, H. and Suess, C., *Dose reduction in CT by anatomically adapted tube current modulation. II. Phantom measurements*, Med. Phys., 26: 2248-2253, 1999.
22. Kinahan, P. E., Hasegawa, B. H. and Beyer, T., *X-ray-based attenuation correction for positron emission tomography/computed tomography scanners*, Semin. Nucl. Med., 33: 166-179, 2003.
23. Townsend, D. W., Carney, J. P. J., Yap, J. T. and Hall, N. C., *PET/CT today and tomorrow*, J. Nucl. Med. (suppl), 45: 4S-14S, 2004.
24. Beyer, T., Antoch, G., Muller, S., Egelhof, T., Freudenberg, L. S., Debatin, J. and Bockisch, A., *Acquisition protocol considerations for combined PET/CT imaging*, J. Nucl. Med. (suppl), 45: 24S-35S, 2004.
25. Alessio, A. M., Kinahan, P. E., Cheng, P. M., Vesselle, H. and Karp, J. S., *PET/CT scanner instrumentation, challenges and solutions*, Radiologic Clinics of North America, 42: 1017-1032, 2004.
26. Accorsi, R., Adam, L.-E., Werner, M. E. and Karp, J. S., *Optimisation of a fully 3D single scatter simulation algorithm for 3D PET*, Phys. Med. Biol., 49: 2577–2598, 2004.
27. Cheng, C.-C., Rahmim, A., Blinder, A., Camborde, M.-L., Raywood, K. and Sossi, V., *A scatter-corrected list-mode reconstruction and a practical scatter / random approximation technique for dynamic PET imaging*, Phys. Med. Biol., 52: 2089–2106, 2007.
28. Markiewicz, P. J., Tamal, M., Julyan, P. J., Hastings, D. L. and Reader, A. J., *High Accuracy Multiple Scatter Modelling for 3D Whole Body PET*, Phys. Med. Biol., 52: 829-247, 2007.
29. Ollinger, J. M., *Model-based scatter correction for fully 3D PET*, Phys. Med. Biol., 41: 153-176, 1996.
30. Goerres, G. W., Hany, T. F., Kamel, E., von Schulthess, G. K. and Buck, A., *Head and neck imaging with PET and PET/CT: artefacts from dental metallic implants*, Eur. J. Nuc. Med. Mol. Imag., 29: 367-370, 2002.
31. Cook, G. J. R., Wegner, E. A. and Fogelman, I., *Pitfalls and Artifacts in 18FDG PET and PET/CT Oncologic Imaging*, Semin. Nucl. Med., 34: 122-133, 2004.
32. Hamill, J. J., Brunken, R. C., Bybel, B., DiFilippo, F. P. and Faul, D. D., *A knowledge-based method for reducing attenuation artefacts caused by cardiac appliances in myocardial PET/CT*, Phys. Med. Biol. , 51: 2901-2918, 2006.
33. Williamson, J. F., Whiting, B. R., Benac, J., Murphy, R. J., Blaine, G. J., O'Sullivan, A., Politte, D. G. and Snyder, D. L., *Prospects for quantitative computed tomography imaging in the presence of foreign metal bodies using statistical image reconstruction*, Med. Phys., 29: 2404-18, 2002.
34. Carney, J. P., Beyer, T., Brasse, D., Yap, J. T. and Townsend, D. W., *Clinical PET/CT scanning using oral CT contrast agents*, J. Nucl. Med. [abstract], 43: 57P, 2002.
35. Nehmeh, S. A., Erdi, Y. E., Kalaigian, H., Kolbert, K. S., Pan, T., Yeung, H., Squire, O., Sinha, A., Larson, S. M. and Humm, J. L., *Correction for Oral Contrast Artifcats in CT Attenuation-Corrected PET Imagins Obtained by Combined PET/CT*, J. Nucl. Med., 44: 1940-1944, 2003.
36. Antoch, G., Kuehl, H., Kanja, J., Lauenstein, T. C., Schneermann, H., Hauth, E., Jentzen, W., Beyer, T., Goehde,

S. C. and Debatin, J. F., *Dual-Modality PET/CT Scanning with Negative Oral Contrast Agent to Avoid Artifacts: Introduction and Evaulation*, Radiology, 230: 879-885, 2004.
37. Yau, Y.-Y., Chan, W.-Z., Tam, Y.-M., Vernon, P., Wong, S., Coel, M. and Kwok-Fai Chu, S., *Application of Intravenous Contrast in PET/CT: Does It Really Introduce Significant Attenuation Correction Error?*, J. Nucl. Med., 46: 283-291, 2005.
38. Berthelsen, A. K., Holm, S., Klausen, T. L., Andersen, F. and Hojgaard, L., *PET/CT with intravenous contrast can be used for PET attenuation correction in cancer patients*, Eur. J. Nucl. Med. Mol. Imag., 32: 1167-1175, 2005.
39. Schoder, H., Erdi, Y. E., Larson, S. M. and Yeung, H. W. D., *PET/CT: a new imaging technology in nuclear medicine*, Eur. J. Nucl. Med. Mol. Imag., 30: 1419-1437, 2003.
40. Beyer, T., Bockisch, A., Kuhl, H. and Martinez, M.-J., *Whole-Body 18F-FDG PET/CT in the Presence of Truncation Artifacts*, J. Nucl. Med., 47: 91-99, 2006.
41. Gambir, S. S., Czernin, J., Schimmer, J., Silverman, D., Coleman, R. E. and Phelps, M. E., *A Tabulated Summary of the FDG PET Literature*, J. Nucl. Med. (suppl), 42: 1S – 93S, 2001.
42. Czernin, J., Allen-Auerbach, M. and Schelbert, H. R., *Improvements in Cancer Staging with PET/CT: Literature-based evidence as of Septebmer 2006*, J. Nucl. Med., 48: 78S-88S, 2007.
43. Lardinois, D., Weder, W., Hany, T. F., Kamel, E. M., Korom, S., Seifert, B., von Schulthess, G. K. and Steinert, H. C., *Staging of non-small-cell lung cancer with integrated positron-emission tomography and computed tomography*, N. Engl. J. Med., 348: 2500-2507, 2003.
44. Bar-Shalom, R., Yefremov, N., Guralnik, L., Gaitini, D., Frenkel, A., Kuten, A., Altman, H., Keidar, Z. and Israel, O., *Clincal Performance on PET/CT in Evaluation of Cancer: Additional Value for Diagnostic Imaging and Patient Management*, J. Nucl. Med., 44: 1200–1200, 2003.
45. Antoch, G., Stattaus, J., Nemat, A. T., Marnitz, S., Beyer, T., Kuehl, H., Bocklsch, A., Debatin, J. F. and Freudenberg, L. S., *Non-small Cell Lung Cancer: Dual Modality PET/CT in Preoperative Staging*, Radiol, 229: 526, 2003.
46. Keidar, Z., Haim, N., Guralnik, L., Wollner, M., Bar-Shalom, R., Ben-Nun, A. and Israel, O., *PET/CT using 18F-FDG in Suspected Lung Cancer Recurrence: Diagnostic Value and Impact on Patient Management*, J. Nucl. Med., 45: 1640, 2004.
47. Wamena, B. A., Sonnad, S. S., Angobaldo, J. O. and Wahl, R. L., *Metastases from non-small cell lung cancer: mediastinal staging in the 1990s - meta-analytic comparison of PET and CT*, Radiol., 213: 530-536, 1999.
48. Kalff, V., Hicks, R. J., MacManus, M. P., Binns, D. S., McKenzie, A. F., Ware, R. E. H., A. and Ball, D. L., *Clinical impact of (18)F fluorodeoxyglucose positron emission tomography in patients with non-small-cell lung cancer: a prospective study*, J. Clin. Oncol., 19: 111-118, 2007.
49. Malamitsi, J., Valotassiou, B., Iliadis, K., Kosmidis, P., Paspas, F., Vasilaki, M., Pipini, E., Petounis, A., Gogou, L., Pagou, M., Dalianis, K., Efthimiadou, R. and Andreou, J., *Preliminary Results on The Role of PET/CT in Initial Staging, Restaging and Management of Lung Cancer*, Nucl. Instr. Meth. Phys. Res, 569: 319-322, 2006.
50. Fischer, B. M., Mortensen, J., Langer, S. W., Loft, A., Berthelsen, A. K., Daugaard, G., Lassen, U. and Hansen, H. H., *PET/CT imaging in response evaluation of patients with small cell lung cancer*, Lung Cancer, 54: 41-49, 2006.
51. Schoder, H., Yeung, H. W. D., Gonen, M., Kraus, D. and Larson, S. M., *Head and neck cancer: clinical usefulness and accuracy of PET/CT image fusion*, Radiol., 231: 65-72, 2004.
52. Yau, Y.-Y., Samman, N. and Yeung, R. W. K., *Positron emission tomography/computed tomography true fusion imaging in clinical head and neck oncology: Early experience*, J. Oral. Maxillofac. Surg., 63: 479-486, 2005.
53. Zimmer, L. A., McCook, B., Melter, C., Fukui, M., Bascom, D., Synderman, C., Townsend, D. W. and Johnson, J. T., *Combined positron emission tomography/computed tomography imaging of recurrent thyroid cancer*, Otolaryngology – Head and Neck Surgery, 128: 178-184, 2003.
54. Schoder, H., Carlson, D. L., Kraus, D. H., Stambuk, H. E., Gonen, M., Erdi, Y. E., Yeung, H. W. D., Huvos, A. G., Shah, J. P., Larson, S. M. and Wong, R. J., *18F-FDG PET/CT for detecting nodal metastases in patients with oral cancer staged N0 by clinical examination and CT/MRI*, J. Nucl. Med., 47: 755-762, 2006.
55. Schwartz, D. L., Ford, E., Rajendran, J., Yueh, B., Coltera, M. D., Virgin, J., Anzai, Y., Haynor, D., Lewellyn, B., Mattes, D., Meyer, J. and Phillips, M., *FDG-PET CT imaging for preradiotherapy staging of head-and-neck squamous cell carcinoma*, Int. J. Radiat. Oncol. Biol. Phys., 61: 129-136, 2005.
56. Goerres, G. W., von Schulthess, G. K. and Steinert, H. C., *Why most PET of lung and head-and-neck cancer will be PET/CT*, J. Nucl. Med. (suppl), 45: 66S-71S, 2004.
57. Fukui, M. B., Blodgett, T. M. and Meltzer, C. C., *PET/CT imaging in recurrent head and neck cancer*, Semin. Ultrasound CT MRI, 24: 157-163, 2003.
58. Connell, C. A., Corry, J., Milner, A. D., Hogg, A., Hicks, R. J., Rischin, D. and Peters, L. J., *Clinical impact of, and prognostic stratification by, F-18 FDG PET/CT in head and neck mucosal squamous cell carcinoma*, Head & Neck, 29: 986-995, 2007.
59. Rosenbaum, S. J., Stergar, H., Antoch, G., Veit, P., Bockisch, A. and Kühl, H., *Staging and follow-up of gastrointestinal tumours with PET/CT*, Abdom. Imaging, 31: 23-35, 2005.
60. Schoder, H., Larson, S. M. and Yeung, H. W. D., *PET/CT in oncology: integration into clinical management of lymphoma, melanoma, and gastrointestinal malignancies*, J. Nucl. Med. (suppl), 45: 72S-81S, 2004.
61. Wechalekar, K., Sharma, B. and Cook, G., *PET/CT in Oncology – A Major Advance*, Clin. Radiol., 60: 1143-1155, 2005.
62. Antoch, G., Kanja, J., Bauer, S., Kuehl, H., Renzing-Koehler, K., Schuette, J., Bockisch, A., Debatin, J. F. and Freudenberg, L. S., *Comparison of PET, CT, and dual-modality PET/CT imaging for monitoring of imatinib (STI571) therapy in patients with gastrointestinal stromal tumors*, J. Nucl. Med., 45: 357-365, 2004.
63. Goerres, G. W., Stupp, R., Barghouth, G., Hany, T. F., Pestalozzi, B., Dizendorf, E., Schnyder, P., Luthi, F., von Schulthess, G. K. and Leyvraz, S., *The value of PET, CT and in-line PET/CT in patients with gastrointestinal stromal tumours: long-term outcome of treatment with imatinib mesylate*, Eur. J. Nuc. Med. Mol. Imag., 32: 153-162, 2005.
64. Cohade, C., Osman, M., Leal, J. and Wahl, R. L., *Direct Comparison of 18F-FDG PET and PET/CT in Patients with Colorectal Carcinoma*, J. Nucl. Med., 44: 1797, 2003.
65. Even-Sapir, E., Parag, Y., Lerman, H., Gutman, M., Levine, C., Rabau, M., Figer, A. and Metser, U., *Detection of Recurrence in Patients with Rectal Cancer: PET/CT After Abdominoperineal or Anterior Resection*, Radiol., 232: 815-822, 2004.

66. Cohn, D. E., Dehdashti, F., Gibb, R. K., Mutch, D. G., Rader, J. S., Siegel, B. A. and Herzog, T. J., *Prospective Evaluation of Positron Emission Tomography for the Detection of Groin Node Metastases from Vulvar Cancer*, Gynecol. Onc., 85: 179-184, 2002.
67. Nakamoto, Y., Eisbruch, A., Achtyes, E. D., Sugawara, Y., Reynolds, K. R., Johnston, C. M. and Wahl, R. L., *Prognostic Value of Positron Emission Tomography Using F-18-Fluorodeoxyglucose in Patients with Cervical Cancer Undergoing Radiotherapy*, Gynecol. Onc., 84: 289-295, 2002.
68. Horowitz, N. S., Dehdashti, F., Herzog, T. J., Rader, J. S., Powell, M. A., Gibb, R. K., Grigsby, P. W., Siegel, B. A. and Mutch, D. G., *Prospective evaluation of FDG-PET for detecting pelvic and para-aortic lymph node metastasis in uterine corpus cancer*, Gynecol. Onc., 95: 546-551, 2004.
69. Lamoreaux, W. T., Grigsby, P. W., Dehdashti, F., Zoberi, I., Powell, M. A., Gibb, R. K., Rader, J. S., Mutch, D. G. and Siegel, B. A., *FDG-PET evaluation of vaginal carcinoma*, Int. J. Radiat. Oncol. Brit., 62: 733-737, 2005.
70. Makhija, S., Howden, N., Edwards, R., Kelley, J., Townsend, D. W. and Meltzer, C. C., *Positron emission tomography/computed tomography imaging for the detection of recurrent ovarian and fallopian tube carcinoma: a retrospective review*, Gynecol. Onc., 85: 53-58, 2002.
71. Grisaru, D., Almog, B., Levine, C., Metser, U., Fishman, A., Lerman, H., Lessing, J. B. and Even-Sapir, E., *The diagnostic accuracy of 18F-fluorodeoxyglucose PET/CT in patients with gynaecological malignancies*, Gynecol. Onc., 94: 680-684, 2004.
72. Wahl, R., *Why nearly all PET of abdominal and pelvic cancers will be performed as PET/CT*, J. Nucl. Med. (suppl), 45: 82S-95S, 2004.
73. Simcock, B., Neesham, D., Quinn, M., Drummond, E., Milner, A. and Hicks, R. J., *The impact of PET/CT in the management of recurrent ovarian cancer*, Gynecol. Onc., 103: 271-276, 2006.
74. Zangheri, B., Messa, C., Picchio, M., Gianolli, L., Landoni, C. and Fazio, F., *PET/CT and breast cancer*, Eur. J. Nucl. Med. Mol. Imag. (suppl), 31: S135-S142, 2004.
75. Tatsumi, M., Cohade, C., Mourtzikos, K., Fishman, E. K. and Wahl, R., *Initial experience with FDG PET/CT in the evaluation of breast cancer*, Eur. J. Nucl. Med. Mol. Imag., 33: 254–262, 2006.
76. Du, Y., Cullum, I., Illidge, T. M. and Ell, P. J., *Fusion of metabolic function and morphology: sequential [18F]fluorodeoxyglucose positron-emission tomography/computed tomography studies yield new insights into the natural history of bone metastases in breast cancer*, J. Clin. Oncol., 25: 3440-3447, 2007.
77. Cachin, F., Prince, H. M., Hogg, A., Ware, R. E. and Hicks, R. J., *Powerful prognostic stratification by [18F]fluorodeoxyglucose positron emission tomography in patients with metastatic breast cancer treated with high-dose chemotherapy*, J. Clin. Oncol., 24: 3026-3031, 2006.
78. Radan, L., Ben-Haim, S., Bar-Shalom, R., Guralnik, L. and Israel, O., *The role of FDG-PET/CT in suspected recurrence of breast cancer*, Cancer, 107: 2545-2551, 2006.
79. Picchio, M., Messa, C., Landoni, C., Gianolli, L., Sironi, S. and Brioschi, M., *Value of [11C] Choline Positron Emission Tomography for Re-Staging Prostate Cancer: A Comparison with [18F] Fluorodeoxyglucose-Positron Emission Tomography*, J. Urol., 169: 1337-1340, 2003.
80. Reske, S. N., Blumstein, N. M., Neumaier, B., Gottfried, H. W., Finsterbusch, F., Kocot, D., Möller, P., Glatting, G. and Perner, S., *Imaging Prostate Cancer with 11C-Choline PET/CT*, J. Nucl. Med., 47: 1249-1254, 2006.
81. Kwee, S. A., Wei, H., Sesterhenn, I., Yun, D. and Coel, M. N., *Localization of Primary Prostate Cancer with Dual-Phase 18F-fluorocholine PET*, J. Nucl. Med., 47: 262-269, 2006.
82. Segall, G. M., *FDG PET Imaging in Patients with Lymphoma: A Clinical Perspective*, J. Nucl. Med., 42: 609-610, 2001.
83. Hany, T. F., Steinert, H. C., Goerres, G. W., Buck, A. and von Schulthess, G. K., *PET Diagnostic Accuracy: Improvement with In-Line PET-CT System: Initial Results*, Radiol., 225: 575-581, 2002.
84. Israel, O., Mor, M., Gaitini, D., Keidar, Z., Guralnik, L., Engel, A., Frenkel, A., Bar-Shalom, R. and Kuten, A., *Combined Functional and Structural Evaluation of Cancer Patients with a Hybrid Camera-Based PET/CT System Using 18F-FDG*, J. Nucl. Med., 43: 1129-1136, 2002.
85. Charron, M., Beyer, T., Bohnen, N. N., Kinahan, P. E., Dachille, M., Jerin, J., Nutt, R., Meltzer, C. C., Villemagne, V. L. and Townsend, D. W., *Image analysis in oncology patients studied with a combined PET/CT scanner*, Clin. Nucl. Med., 25: 905-910, 2000.
86. Tatsumi, M., Cohade, C., Nakamoto, Y., Fishman, E. K. and Wahl, R. L., *Direct Comparison of FDG PET and CT Findings in Patients with Lymphoma: Initial Experience*, Radiol., 237: 1038-1045, 2005.
87. Rodriguez, V. B., Gomez, L. N., Pinilla, I., Hernandez, M. D., Coya, J. and Martin, C. L., *Positron emission tomography/computed tomography in the management of Hodgkin's disease and non-Hodgkin's lymphoma*, Curr. Probl. Diagn. Radiol., 35: 151-63, 2006.
88. Schaefer, N. G., Hany, T. F., Taverna, C., Seifert, B., Stumpe, K. D. M., von Schulthess, G. K. and Goerres, G. W., *Non-Hodgkin Lymphoma and Hodgkin Disease: Coregistered FDG PET and CT at Staging and Restaging-Do We Need Contrast-enhanced CT?*, Radiol., 232: 823-829, 2004.
89. Freudenberg, L. S., Antoch, G., Schutt, P., Beyer, T., Jentzen, W., Muller, S. P., Gorges, R., Nowrousian, M. R., Bockisch, A. and Debatin, J. F., *FDG-PET/CT in re-staging of patients with lymphoma*, Eur. J. Nucl. Med. Mol. Imag., 31: 325-329, 2004.
90. Metser, U., Lerman, H., Blank, A., Lievshitz, G., Bokstein, F. and Even-Sapir, E., *Malignant Involvement in the Spine: Assessment by 18F-FDG PET/CT*, J. Nucl. Med., 45: 279-284, 2004.
91. Gutzeit, A., Antoch, G., Kühl, H., Egelhof, T., Fischer, M., Hauth, E., Goehde, S., Bockisch, A., Debatin, J. and Freudenberg, L., *Unknown Primary Tumours: Detection with Dual-Modality PET/CT – Initial Experience*, Radiol., 234: 227-234, 2005.
92. Israel, O., Mor, M., Guralnik, L., Hermoni, N., Gaitini, D., Bar-Shalom, R., Keidar, Z. and Epelbaum, R., *Is 18F-FDG PET/CT Useful for Imaging and Management of Patients with Suspected Occult Recurrence of Cancer*, J. Nucl. Med., 45: 2045-2051, 2004.
93. King, G., *PET-CT alters management of patients with gynecologic cancers*, ASCO Proc., May 18-21, Orlando, Florida, 2002.
94. Mac Manus, M., Hicks, R. J. and Everitt, S., *Role of PET-CT in the optimization of thoracic radiotherapy*, J. Thorac. Oncol., 1: 81-84, 2006.
95. Hicks, R. J. and Mac Manus, M. P., *18F-FDG PET in candidates for radiation therapy: is it important and how do we validate its impact?*, J. Nucl. Med., 44: 2003.

96. Ciernik, I. F., Dizendorf, E., Baumert, B. G., Reiner, B., Burger, C., Davis, J. B., Lutolf, U. M., Steinert, H. C. and von Schulthess, G. K., *Radiation Treatment Planning with An Integrated Positron Emission and Computer Tomography (PET/CT): A Feasibility Study*, Int. J. Radiat. Oncol. Biol. Phys., 57: 853–863, 2003.
97. Paulino, A. C., Koshy, M., Howell, R., Schuster, D. and Davis, L. W., *Comparison of CT- and FDG-PET-Defined Gross Tumor Volume in Intensity-Modulated Radiotherapy for Head-and-Neck Cancer*, Int. J. Radiat. Oncol. Biol. Phys., 61: 1385–1392, 2005.
98. Ashamalla, H., Rafla, S., Parikh, K., Mokhtar, B., Goswani, G., Kambam, S., Abdel-Dayem, H., Guirguis, A., Ross, P. and Evola, A., *The contribution of integrated PET/CT to the evolving definition of treatment volumes in radiation treatment planning in lung cancer*, Int. J. Radiat. Oncol. Biol. Phys., 63: 1016-1023, 2005.
99. Ashamalla, H., Guirguis, A., Bieniek, E., Rafla, S., Evola, A., Goswami, G., Oldroyd, R., Mokhtar, B. and Parikh, K., *The Impact of Positron Emission Tomography/Computed Tomography in Edge Delineation of Gross Tumor Volume for Head and Neck Cancers*, Int. J. Radiat. Oncol. Biol. Phys., 68: 388-395, 2007.
100. Gondi, V., Bradley, K., Mehta, M., Howard, A., Khuntia, D., Ritter, M. and Tomé, W., *Impact of Hybrid Fluorodeoxyglucose Positron-Emission Tomography/Computed Tomography on Radiotherapy Planning in Esophageal and Non-Small Cell Lung Cancer*, Int. J. Radiat. Oncol. Biol. Phys., 67: 187–195, 2007.
101. Heron, D. E., Andrade, R. S., Flickinger, J., Johnson, J., Agarwala, S. S., Wu, A., Kalnicki, S. and Avril, N., *Hybrid PET-CT Simulation for Radiation Treatment Planning in Head and Neck Cancers: A Brief Technical Report*, Int. J. Radiat. Oncol. Biol. Phys., 60: 1419–1424, 2004.
102. Wang, D., Schultz, C. J., Jursinic, P. A., Bialkowski, M., Zhu, X. R., Brown, W. D., Rand, S. D., Michel, M. A., Campbell, B. H., Wong, S., Li, X. A. and Wilson, F. W., *Initial Experience of FDG-PET/CT Guided IMRT of Head-and-Neck Carcinoma*, Int. J. Radiat. Oncol. Biol. Phys., 65: 143–151, 2006.
103. Bradley, J., Thorstad, W. L., Mutic, S., Miller, T. R., Dehdashti, F., Siegel, B. A., Bosch, W. and Bertrand, R. J., *Impact of FDG-PET on Radiation Therapy Volume Delineation in Non-Small-Cell Lung Cancer*, Int. J. Radiat. Oncol. Biol. Phys, 59: 78-86, 2004.
104. Biehl, K. J., Kong, F.-M., Dehdashti, F., Jin, J.-Y., Mutic, S., El Naqa, I., Siegel, B. A. and Bradley, J. D., *18F-FDG PET Definition of Gross Tumor Volume for Radiotherapy of Non–Small Cell Lung Cancer: Is a Single Standardized Uptake Value Threshold Approach Appropriate?*, J. Nucl. Med., 47: 1808-1812, 2006.
105. Nestle, U., Kremp, S. and Grosu, A.-L., *Practical integration of [18F]-FDG-PET and PET-CT in the planning of radiotherapy for non-small cell lung cancer (NSCLC): The technical basis, ICRU-target volumes, problems, perspectives*, Rad. Onc., 81: 209–225, 2006.
106. Grégoire, V., Haustermans, K., Geets, X., Roels, S. and Lonneux, M., *PET-Based Treatment Planning in Radiotherapy: A New Standard?*, J. Nucl. Med. (suppl), 48: 68S–77S, 2007.
107. Riegel, A. C., Berson, A. M., Destian, S., Ng, T., Tena, L. B., Mitnick, R. J. and Wong, P. S., *Variability of gross tumour volume delineation in head-and-neck cancer using CT and PET/CT*, Int. J. Radiat. Oncol. Biol. Phys, 65: 726-32, 2006.
108. Ling, C. C., Humm, J., Larson, S., Amols, H., Fuks, Z., Leibel, S. and Koutcher, J. A., *Towards multidimensional radiotherapy (MD-CRT): Biological Imaging and Biological Conformity*, Int. J. Radiat. Oncol. Biol. Phys., 47: 551–560, 2000.
109. Søvik, A., Malinen, E., Skogmo, H. K., Bentzen, S. M., Bruland, O. S. and Olsen, D. R., *Radiotherapy Adapted to Spatial and Temporal Variability in Tumor Hypoxia*, Int. J. Radiat. Oncol. Biol. Phys., 68: 1496-1504, 2007.
110. Vanderstraeten, B., Duthoy, W., De Gersem, W., De Neve, W. and Thierens, H., *[18F] fluoro-deoxy-glucose positron emission tomography ([18F]FDG-PET) voxel intensity-based intensity-modulated radiation therapy (IMRT) for head and neck cancer*, Rad. Onc., 79: 249–258, 2006.
111. Ell, P. J., *The contribution of PET/CT to improved patient management*, BJR., 79: 32-26, 2006.
112. von Schulthess, G. K., Steinert, H. C. and Hany, T. F., *Integrated PET/CT: Current applications and future directions*, Radiobiology, 238: 405-422, 2006.
113. Kapuco, L. O., Meltzer, C. C., Townsend, D. W., Keenan, R. J., Luketich and J.D., *Fluorine-18-fluorodeoxyglucose uptake in pneumonia*, J. Nucl. Med., 39: 1267-1269, 1998.
114. Bakheet, S. M., Powe, J., Ezzat, A. and Roston, A., *F-18-FDG uptake in tuberculosis*, Clin. Nucl. Med., 23: 739-742, 1998.
115. Bakheet, S. M., Powe, J., Kandil, A., Ezzat, A., Rostom, A. and Amartey, J., *F-18-FDG uptake in breast infection and inflammation*, Clin. Nucl. Med., 25: 100-103, 2000.
116. Gysen, M., Stroobants, S. and Mortelmans, L., *Proliferative myositis: a case of a pseudomalignant process*, Clin. Nucl. Med., 23: 836-838, 1998.
117. Yasuda, S., Shohtsu, A., Ide, M., Takagi, S., Kijima, H. and Horiuchi, M., *Elevated F-18 FDG uptake in plasmacyte-rich chronic maxillary sinusitis*, Clin. Nucl. Med., 23: 176-178, 1998.
118. Brudin, L. H., Valind, S.-O., Rhodes, C. G., Panting, C. F., Sweatmang, M., Jones, T. and Hughes, J. M. B., *Fluorine-18 deoxyglucose uptake in sarcoidosis measured with positron emission tomography*, Eur. J. Nucl. Med. Mol. Imag., 21: 297-305, 1994.
119. Tahara, T., Ichiya, Y., Kuwabara, Y., Otsuka, M., Miyake, Y., Gunasekera, R. and Masuda, K., *High [18F]-fluorodeoxyglucose uptake in abdominal abscesses: a PET study*, J. Comput. Assist. Tomogr., 13: 829-831, 1989.
120. Crymes, W. B., Demos, H. and Gordon, L., *Detection of musculoskeletal infection with 18F-FDG PET: Review of the current literature*, J. Nucl. Med. Technol., 32: 12-15, 2004.
121. Stumpe, K. D. M. and Strobel, K., *18F FDG PET imaging in musculoskeletal infection*, Q. J. Nucl. Med. Mol. Imaging., 50: 131-142, 2006.
122. Keidar, Z., Militianu, D., Melamed, E., Bar-Shalom, R. and Israel, O., *The diabetic foot: initial experience with 18F-FDG PET / CT*, J. Nucl. Med., 46: 444-449, 2005.
123. Schiesser, M., Stumpe, K. D. M., Trentz, O., Kossmann, T., Schulthess, v. and G.K., *Detection of metallic implant-associated infections with FDG PET in patients with trauma: correlation with microbiologic results*, Radiol., 226: 391-398, 2003.
124. Meller, J., Sahlmann, C. O. and Scheel, A. K., *18F-FDG PET and PET/CT in fever of unknown origin*, J. Nucl. Med., 48: 35-45, 2007.
125. Kaufmann, P. A. and Camici, P. D., *Myocardial blood flow measurement by PET: Technical aspects and clinical applications*, J. Nucl. Med., 46: 77-88, 2005.
126. Koepfli, P., Hany, T. F., Wyss, C. A., Namdar, M., Burger, C., Konstantinidis, A. V., Berthold, T., von Schulthess, G. K. and Kaufmann, P. A., *CT attenuation correction for*

myocardial perfusion quantification using a hybrid PET / CT scanner, J. Nucl. Med., 45: 537-542, 2004.

127. Lodge, M. A., Braess, H., Mahmoud, F., Suh, J., Englar, N., Geyser-Stoops, S., Jenkins, J., Bacharach, S. L. and Dilsizian, V., *Review: Developments in nuclear cardiology: Transition from single photon emission computed tomography to positron emission tomography/computed tomography*, J. Invasive Cardiol., 17: 491-496, 2005.
128. Schwaiger, M., Ziegler, S. and Nekolla, S. G., *PET / CT: Challenge for nuclear cardiology*, J. Nucl. Med., 46: 1664-1678, 2005.
129. Tatsumi, M., Cohade, C., Nakamoto, Y. and Wahl, R. L., *Fluorodeoxyglucose uptake in the aortic wall at PET/CT: possible finding for active atherosclerosis*, Radiol., 229: 831-839, 2003.
130. Wagner, B., Anton, M., Nekolla, S. G., Reder, S., Henke, J., Seidl, S., Hegenloh, R., Miyagawa, M., Haubner, R., Schwaiger, M. and Bengel, F. M., *Noninvasive Characterization of Myocardial Molecular Interventions by Integrated Positron Emission Tomography and Computed Tomography*, J. Am. Coll. Cardiol., 48: 2107-2115, 2006.
131. Townsend, D. W., Beyer, T. and Blodget, T. M., *PET/CT scanners: A hardware approach to image fusion*, Semin. Nucl. Med., 33: 193-204, 2003.
132. Brianzoni, E., Rossi, G., Ancidei, S., Berbellini, A., Capoccetti, F., Cidda, C., D'Avenia, P., Fattori, S., Montini, G. C., Valentini, G. and Proietti, A., *Radiotherapy planning: PET/CT scanner performances in the definition of gross tumour volume and clinical target volume*, Eur. J. Nucl. Med. Mol. Imag., 32: 1392-1399, 2005.
133. Shim, S. S., Lee, K. S., Kim, B.-T., Chung, M. J., Lee, E. J., Han, J., Choi, J. Y., Kwon, O. J., Shim, Y. M. and Kim, S., *Non–Small Cell Lung Cancer: Prospective Comparison of Integrated FDG PET/CT and CT Alone for Preoperative Staging*, Radiol., 236: 1011-1019, 2005.
134. Kim, Y. K., Lee, K. S., Kim, B.-T., Choi, J. Y., Kim, H., Kwon, O. J., Shim, Y. M., Yi, C. A., Kim, H. Y. and Chung, M. J., *Mediastinal Nodal Staging of Nonsmall Cell Lung Cancer Using Integrated 18F-FDG PET/CT in a Tuberculosis-Endemic Country: Diagnostic Efficacy in 674 Patients*, Cancer, 109: 1068-1077, 2007.
135. Ha, P. K., Hdeib, A., Goldenberg, D., Jacene, H., Patel, P., Koch, W., Califano, J., Cummings, C. W., Flint, P. W., Wahl, R. and Tufano, R. P., *The role of positron emission tomography and computed tomography fusion in the management of early-stage and advanced-stage primary head and neck squamous cell carcinoma,* Arch. Otolaryngol. Head Neck Surg., 132: 12-16, 2006.
136. Breen, S. L., Publicover, J., De Silva, S., Pond, G., Brock, K., O'Sullivan, B., Cummings, B., Dawson, L., Keller, A., Kim, J., Ringash, J., Yu, E., Hendler, A. and Waldron, J., *Intraobserver and interobserver variability in GTV delineation on FDG-PET-CTimages of head and neck cancers*, Int. J. Radiat. Oncol. Biol. Phys., in press.
137. Murakami, R., Uozumi, H., Hirai, T., Nishimura, R., Shiraishi, S., Ota, K., Murakami, D., Tomiguchi, S., Oya, N., Katsuragawa, S. and Yamashita, Y., *Impact of FDG-PET/CT imaging on nodal staging for head-and-neck squamous cell carcinoma*, Int. J. Radiat. Oncol. Biol. Phys., 68: 377-382, 2007.
138. Israel, O., Yefremov, N., Bar-Shalom, R., Kagana, O., Frenkel, A., Keidar, Z. and Fischer, D., *PET/CT Detection of Unexpected Gastrointestinal Foci of 18F-FDG Uptake: Incidence, Localization Patterns, and Clinical Significance*, J. Nucl. Med., 46: 758-762, 2005.
139. Bar-Shalom, R., Guralnik, L., Tsalic, M., Leiderman, M., Frenkel, A., Gaitini, D., Ben-Nun, A., Keidar, Z. and Israel, O., *The additional value of PET/CT over PET in FDG imaging of oesophageal cancer*, Eur. J. Nucl. Med. Mol. Imaging, 32: 918-924, 2005.
140. Kim, J.-H., Czernin, J., Allen-Auerbach, M. S., Halpern, B. S., Fueger, B. J., Hecht, J. R., Ratib, O., Phelps, M. E. and Weber, W. A., *Comparison between 18F-FDG PET, in-line PET/CT, and software fusion for restaging of recurrent colorectal cancer*, J. Nucl. Med., 46: 587-595, 2005.
141. Veit-Haibach, P., Kuehle, C. A., Beyer, T., Stergar, H., Kuehl, H., Schmidt, J., Borsch, G., Dahmen, G., Barkhausen, J., Bockisch, A. and Antoch, G., *Diagnostic Accuracy of Colorectal Cancer Staging With Whole-Body PET/CT Colonography*, JAMA, 296: 2590-2600, 2006.
142. Choi, H. J., Roh, J. W., Seo, S.-S., Lee, S., Kim, J.-Y., Kim, S.-K., Kang, K. W., Lee, J. S., Jeong, J. Y. and Park, S.-Y., *Comparison of the Accuracy of Magnetic Resonance Imaging and Positron Emission Tomography/Computed Tomography in the Presurgical Detection of Lymph Node Metastases in Patients with Uterine Cervical Carcinoma*, Cancer, Cancer, 106: 914-922, 2006.
143. Veit-Haibach, P., Antoch, G., Beyer, T., Stergar, H., Schleucher, R., Hauth, E. A. M. and Bockisch, A., *FDG-PET/CT in restaging of patients with recurrent breast cancer: possible impact on staging and therapy*, BJR, 80: 508-515, 2007.
144. Piperkova, E., Raphael, B., Altinyay, M. E., Castellon, I., Libes, R., Sandella, N., Heiba, S. and Abdel-Dayem, H., *Impact of PET/CT in Comparison With Same Day Contrast Enhanced CT in Breast Cancer Management*, Clin. Nucl. Med., 32: 429-434, 2007.
145. Schmid, D. T., John, H., Zweifel, R., Cservenyak, T., Westera, G., Goerres, G. W., von Schulthess, G. K. and Hany, T. F., *Fluorocholine PET/CT in patients with prostate cancer: initial experience*, Radiol., 235: 623-628, 2005.
146. Raanani, P., Shasha, Y., Perry, C., Metser, U., Naparstek, E., Apter, S., Nagler, A., Polliack, A., Ben-Bassat, I. and Even-Sapir, E., *Is CT scan still necessary for staging in Hodgkin and non-Hodgkin lymphoma patients in the PET/CT era?*, Annals of Oncology, 17: 117-122, 2006.