Protocol for MSc. Essay

Title:

Role of Positron Emission Tomography/Computed Tomography (PET/CT) in radiotherapy treatment planning and target definition

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1- Introduction
INTRODUCTION

Many efforts have been made to improve imaging acquisition, the accuracy of target volumes and the delineation of critical organs for the purpose of radiation therapy (RT). In order to perfectly delineate the primary tumor and to optimize radiation doses administered to normal tissues, it is necessary for patients to undergo an imaging study (Bujenovic, 2004).

During the past two decades, many literatures have demonstrated the relative usefulness of computed tomography (CT) and also magnetic resonance imaging (MRI) in diagnosing, staging, and re-staging of cancer, as well as the monitoring and planning of cancer treatment. Spatially accurate medical imaging is an essential tool in three-dimensional conformal radiation therapy (3DCRT) and intensity-modulated radiation therapy (IMRT) treatment planning. CT imaging is the standard imaging modality for image-based radiation treatment planning (RTP). CT images provide anatomical information on the size and location of tumors in the body. They also provide electron density information for heterogeneity-based patient dose calculation. The major limitation of the CT imaging process is soft tissue contrast, which is overcome by using contrast agents or using another anatomical imaging modality like MRI (Bar-Shalom, et al 2003).

One of the disadvantages of anatomical imaging techniques like CT and MRI is its inability to characterize the tumor. Tumors need to be characterized whether they are benign or malignant and if malignant it would be helpful to know whether the proliferation is slow or fast. Necrotic, scar, and inflammatory tissue often cannot be differentiated from malignancy based on
anatomic imaging alone. Anatomical imaging has high sensitivity for detection of structural changes, but a low specificity for further characterization of these abnormalities (Cohade, et al 2003).

The need for better accuracy in definition of the target volume and normal tissues and their subsequent segmentation has led to the use of other imaging modalities for acquisition of functional information (Wahl, et al 1994).

Positron emission tomography (PET), now more than 30 years after its initial development, has become an established nuclear imaging modality that has proved its usefulness in oncology. PET was invented at the Mallinckrodt Institute of Radiology at Washington University in the mid 1970s and was soon adopted into neurology and cardiology as a valuable research tool. However, it took more than a decade for investigators to realize that PET also could be a powerful tool for oncology (Landis, 2005).

Single photon emission computed tomography (SPECT) and positron emission tomography (PET) are imaging techniques that provide information on physiology rather than anatomy. These modalities have been used for evaluation of tumor metabolism, differentiation between tumor recurrence and radiation necrosis, detection of hypoxic areas of the tumor, and distinguish between benign and malignant lesions when CT and MRI cannot. (Daisne, et al 2003)

It has been proved that, compared with CT, PET has higher sensitivity (87% vs. 62%) and specificity (89% vs. 73%) for staging cancer, a higher sensitivity (93% vs. 54%) and specificity (83% vs. 74%) for imaging recurrence, and a higher sensitivity (84% vs. 60%) and specificity (95% vs. 39%) for monitoring the effects of therapy (Gambhir, et al 2001)
Table 1 shows the timing of restaging with PET as well as the role of PET in restaging, differentiation between recurrence and fibrosis, determination of recurrence and its extent and assessment of response to therapy in different type of cancers (Malik and Bruce, 2006).

### Table 1: Timing and Role of Restaging with PET.

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Timing of Restaging with PET</th>
<th>Dominant Contributions of PET</th>
</tr>
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<tbody>
<tr>
<td>Non-small-cell lung cancer</td>
<td>2-6 Mo after completion of chemoradiotherapy; 1-2 mo after surgery</td>
<td>Differentiation between persistent or recurrent tumor and fibrosis in patients with residual chest radiographic abnormalities.</td>
</tr>
<tr>
<td></td>
<td>When recurrence is suspected on the basis of clinical or biochemical findings or by conventional imaging</td>
<td>Selection of biopsy sites for confirmation of suspected recurrence.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Determination of actual extent of recurrence (locoregional and distant).</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>When recurrence is suspected on the basis of clinical or biochemical findings or by conventional imaging</td>
<td>Determination of actual extent of recurrence.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Differentiation between metastatic and benign brolachial plexopathy.</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>When recurrence is suspected on the basis of clinical or biochemical findings or by conventional imaging</td>
<td>Detection of recurrence suspected by elevation of carcino-embryonic antigen by distinguishing of viable tumor from fibrosis after therapy.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Determination of actual extent of recurrent disease (isolated vs. disseminated) and resectability of liver metastases.</td>
</tr>
<tr>
<td>Esophageal cancer</td>
<td>When recurrence is suspected on the basis of clinical or biochemical findings or by conventional imaging</td>
<td>More accurate diagnosis of regional and distant recurrence than with conventional imaging (less accurate for perianastomotic recurrence).</td>
</tr>
<tr>
<td>Head and neck cancer</td>
<td>2-6 Mo after completion of chemoradiotherapy; 1-2 mo after surgery</td>
<td>More accurate assessment of response to therapy and earlier detection of persistent or recurrent disease (locoregional and distant) than with conventional imaging.</td>
</tr>
<tr>
<td></td>
<td>When recurrence is suspected on the basis of clinical or biochemical findings or by conventional imaging</td>
<td>Determination of actual extent of recurrence.</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>3-4 Wk after completion of therapy; 2-3 mo or more after external-beam radiation</td>
<td>Differentiation between viable tumor and necrosis or fibrosis in patients with a residual mass and more accurate differentiation between complete and partial responses than with conventional imaging.</td>
</tr>
<tr>
<td></td>
<td>When recurrence is suspected on the basis of clinical or biochemical findings or by conventional imaging</td>
<td>Determination of actual extent of lymphoma recurrence.</td>
</tr>
<tr>
<td>Melanoma</td>
<td>When recurrence is suspected on the basis of clinical or biochemical findings or by conventional imaging</td>
<td>More accurate diagnosis of locoregional and distant recurrence than with conventional imaging, except for lung metastases (less sensitive than CT).</td>
</tr>
<tr>
<td>Follicular thyroid cancer</td>
<td>When serum thyroglobulin is elevated (&gt;10 ng per milliliter) and whole-body 18F scan is negative</td>
<td>Detection of residual or recurrent disease (locoregional or distant). Identification of patients for potentially curative surgery vs. palliative treatment.</td>
</tr>
</tbody>
</table>
PET has incomparable abilities to determine the metabolic activity of tissues but it needs the assistance of higher-resolution, anatomic information that it cannot provide. CT is the easiest and highest-resolution tomographic modality to integrate into PET imaging. The combination of the two offers the best of both worlds in an integrated data set and thus improves diagnostic accuracy and localization of many lesions (Landis, 2005).

Positron emission tomography/computed tomography (PET/CT) combines two imaging technologies into one, PET provides sensitive information regarding whether a growth within the body is cancerous or not. CT provides detailed information about the location, size and shape of various lesions but cannot differentiate cancerous lesions from normal structures with the same accuracy as PET. The PET/CT scanner (Fig 1) is an open design with two large rings and an open area in between, giving patients the ability to see the area around them and allowing technicians patient access during the exam. Initial attempts at combining PET/CT images involved visual comparison of side-by-side or overlaid PET and CT images; however, exact alignment of the two images is not possible, due to differences in image size or slice thickness between PET and CT and differences in patient positioning between the two separate examinations. There is software programs that now fuse (known as PET/CT fusion) the images. Current PET/CT scanners integrate both scanning techniques into a single device that allows scanning with both techniques in a single session, without moving the patient between examinations. Also, the CT scan involves an external radiation source, functioning as the transmission scan for attenuation correction of PET data, thereby reducing the time required for PET (Hayes, 2004).
PET/CT in Radiotherapy Treatment Planning & Target Definition

PET/CT can image tumor metabolism, proliferation, hypoxia, and apoptosis with precise anatomic image fusion and become an essential tool in the management of patients with cancer by its ability to stage, restage the disease, better localization of the tumor for radiotherapy planning, and assessment of the treatment response (Table 2) (Chang Gung, 2005).

PET-CT exceeds the sensitivity specificity and accuracy of PET alone. In a study by Haney and coworkers in which patients with a wide variety of malignancies were studied, PET-CT demonstrated sensitivity, specificity, and accuracy of 98%, 99%, and 98%, respectively, compared with PET alone, where the sensitivity, specificity, and accuracy were 90%, 93%, and 91% respectively (Haney, et al 2002).

Fig 1: PET/CT scanner
Studies on combined use of CT scan and PET imaging for treatment planning have been performed, with use of interactive co-registration methods so that every voxel of one modality (CT) has its counterpart in the other modality (PET) (Scarfone et al, 2004). Using PET/CT, metabolic tumor mapping, with integration of anatomical and metabolic images, greatly influences the size and shape of both the gross tumor volume (GTV) and the clinical target volume (CTV) (Fig 2) (Perez et al, 2002).

The basis of PET imaging is the labeling of small biologically important molecules such as sugars, amino acids, nucleic acids, receptor-binding ligands or even water and molecular oxygen, with positron emitting radio-nuclides. When these positron emitting tracers undergo radioactive decay, their positions can be detected by the PET scanner. By imaging the temporal distribution of these labeled compounds, we can create “physiologic maps” of the functions or processes relevant to the labeled molecules. Because of this PET offers substantial advantages over anatomic imaging modalities in
PET/CT in Radiotherapy Treatment Planning & Target Definition

Review of Literature

Oncologic imaging and can often distinguish between benign and malignant lesions when CT and MRI cannot. (Kubota, et al 1994 and Landis, 2005)

There are several positron-emitting radioisotopes that have been used for PET imaging. The first four isotopes in table 2 are of particular note with regard to imaging biological systems. Each of them has a pure positron-emitting radioisotope, and none of them has an appropriate single-photon emitting radioisotope. Fluorine, the fourth entry in the table, isn't a normal element in biological systems but fluorine can often replace either a hydrogen atom or hydroxyl moiety. It is also a pure positron-emitter and doesn't have a useful single photon emitting isotope (Jadvar and Parker 2005).

F-18 fluoro-2-deoxy-D-glucose (FDG) is the most frequently used radio-pharmaceuticals today and new F-18 labeled ligands are under development. It has changed dramatically the management of numerous cancers such brain tumors, head and neck cancers, thyroid cancer, parathyroid cancer, lung cancer, esophageal cancer, lymphoma, pancreatic cancer, colorectal cancer, and many others. PET-CT will be used with increasing frequency and will become progressively used as a surrogate marker for disease response. Novel ligands, labeled with F-18, will further increase the clinical utility of this technology (Chang Gung, 2005).
Table 2: Positron-emitting Radioisotopes used in PET

<table>
<thead>
<tr>
<th>Isotope</th>
<th>Half-life</th>
<th>B+ energy (MeV)</th>
<th>Gamma energy (MeV)</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C-11</td>
<td>20.4 m</td>
<td>0.385 (99.8%)</td>
<td></td>
</tr>
<tr>
<td>N-13</td>
<td>9.97 m</td>
<td>0.492 (99.8%)</td>
<td></td>
</tr>
<tr>
<td>O-15</td>
<td>122 s</td>
<td>0.735 (99.9%)</td>
<td></td>
</tr>
<tr>
<td>F-18</td>
<td>110 m</td>
<td>0.250 (100%)</td>
<td></td>
</tr>
<tr>
<td>K-38</td>
<td>7.64 m</td>
<td>1.216 (99.3%)</td>
<td>2.167 (99.8%)</td>
</tr>
<tr>
<td>Cu-62</td>
<td>9.74 m</td>
<td>1.315 (97.6%)</td>
<td></td>
</tr>
<tr>
<td>Cu-64</td>
<td>12.7 h</td>
<td>0.278 (17.9%)</td>
<td></td>
</tr>
<tr>
<td>Ga-68</td>
<td>68.1 h</td>
<td>0.836 (8.79%),</td>
<td>1.077 (3.0%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.352 (1.12%)</td>
<td></td>
</tr>
<tr>
<td>Rb-82</td>
<td>75 s</td>
<td>1.523 (83.3%),</td>
<td>0.776 (13.4%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.157 (10.2%)</td>
<td></td>
</tr>
<tr>
<td>I-124</td>
<td>4.18 d</td>
<td>0.686 (11.3%),</td>
<td>1.691 (10.4%), 7.228 (10.0%), 1.509</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.947 (11.3%)</td>
<td>(3.0%), 1.376 (1.7 %), 1.325 (1.43%)</td>
</tr>
</tbody>
</table>
Table 3: selected tracers used in oncological PET

<table>
<thead>
<tr>
<th>Tracer</th>
<th>Biologic Analogue</th>
<th>Mechanism of Uptake in Tumor Cells</th>
<th>Measured Effect</th>
<th>Application or Potential Application</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{18}$F-Fluorodeoxyglucose</td>
<td>Glucose</td>
<td>Facilitated diffusion by glucose transporters, phosphorylation by hexokinase with subsequent &quot;metabolic trapping&quot;</td>
<td>Aerobic and anaerobic glycolysis, glucose consumption or metabolism</td>
<td>Diagnosis, staging, restaging, monitoring response of various cancer types</td>
</tr>
<tr>
<td>$^{12}$C-thymidine</td>
<td>Thyminde</td>
<td>Facilitated diffusion and active transport by nucleoside transporters, phosphorylation by thymidine kinase with subsequent incorporation into DNA (with $^{14}$C-thymidine) or metabolic trapping (with $^{18}$F-Fluorothymidine)</td>
<td>DNA synthesis, tumor-cell proliferation</td>
<td>Diagnosis, staging, restaging, monitoring response of various cancer types</td>
</tr>
<tr>
<td>$^{11}$C-methionine</td>
<td>Methionine</td>
<td>Active transport by amino acid transport system A with subsequent incorporation into protein</td>
<td>Protein synthesis, tumor-cell proliferation</td>
<td>Diagnosis, staging, restaging, monitoring response of various cancer types</td>
</tr>
<tr>
<td>$^{11}$C-choline</td>
<td>Choline</td>
<td>Active or passive transport with subsequent phosphorylation and synthesis of phosphatidylcholine cell membrane phospholipid</td>
<td>Cell membrane metabolism, tumor-cell proliferation</td>
<td>Staging, restaging, monitoring response of various cancer types</td>
</tr>
<tr>
<td>$^{11}$C-tyrosine</td>
<td>Tyrosine</td>
<td>Active transport by amino acid transport system L</td>
<td>Natural amino acid transport</td>
<td>Staging, restaging, monitoring response of various cancer types</td>
</tr>
<tr>
<td>$^{18}$F-fluorothyrosine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$^{18}$F-fluoromethyltyrosine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$^{18}$F-fluorodihydroxyphenylalanine</td>
<td>Phenylalanine</td>
<td>Active transport by natural amino acid transport system</td>
<td>Dopamine synthesis, natural amino acid transport</td>
<td>Staging, restaging, monitoring response of neuroendocrine and brain tumors</td>
</tr>
<tr>
<td>$^{18}$F-fluoromisonidazole</td>
<td>NA</td>
<td>Diffusion into hypoxic cell reduction and trapping caused by decreased oxygen concentration</td>
<td>Tissue hypoxia</td>
<td>Identification of hypoxic tumor cells</td>
</tr>
<tr>
<td>$^{18}$F-fluoro-17$\beta$-estradiol</td>
<td>Estradiol</td>
<td>Binding to estrogen receptors</td>
<td>Estrogen-receptor status</td>
<td>In vivo assessment of estrogen-receptor density, monitoring response of estrogen-receptor-positive breast cancer</td>
</tr>
<tr>
<td>$^{18}$F-Annexin V</td>
<td>Annexin V</td>
<td>Binding to externalized phosphatididserine on apoptotic cells</td>
<td>Apoptotic cell death</td>
<td>In vivo detection of tumor cell apoptosis, monitoring treatment response of various cancer types</td>
</tr>
<tr>
<td>$^{18}$F-fluorouracil</td>
<td>Uracil</td>
<td>Binding to thymidylate synthetase and hepatic catalysis in liver to $\beta$-fluorouracil with subsequent accumulation in tumor</td>
<td>Accumulation of 5-fluorouracil in tumor</td>
<td>Prediction of tumor response to 5-fluorouracil (e.g., colorectal cancer)</td>
</tr>
<tr>
<td>$^{12}$C-acetate</td>
<td>Acetate</td>
<td>Incorporation into cell membrane lipids</td>
<td>Lipid synthesis</td>
<td>Staging, restaging, monitoring response of various cancer types</td>
</tr>
</tbody>
</table>

Table 3 shows the most common tracers and its labeling agents used in oncologic applications of PET as well as the mechanism of its uptake by tumor cells and its metabolism (Malik and Bruce, 2006).
The PET/CT planning scan

- **Patient positioning**

  Fundamental to the use of images for radiotherapy planning is the requirement to scan the patient in the treatment position. The GE Discovery LS PET/CT scanner has a minimum patient bore of 55 cm. This is significantly less than radiotherapy simulators and large bore CT scanners specifically designed for radiotherapy planning. This restricted bore creates challenges to patient set-up in the treatment position for image data acquisition. However, it should be recognized that use of CT scanners with comparable bore sizes has been common practice in centers where diagnostic CT scanners are used for treatment planning scans. The current generations of PET/CT scanners have increased bore size; however, there will still be some restrictions on treatment position set-up during imaging (Jarritt et al 2006).

  Radiotherapy treatments are performed with patients on a flat couch, whereas diagnostic scans are usually performed using a concave couch, with the patient lying on a thin mattress. For PET/CT data to be used to guide radiotherapy treatment, the scanner must be equipped with a flat-bed insert, which are now routinely available (Fig. 3). It should be noted that addition of this bed attachment reduces the patient port further and again restricts positioning options (Jarritt et al 2006).

- **Immobilization devices**

  The use of immobilization devices in radiotherapy treatment is well established and provides an effective mechanism for the reproducible positioning of patients at each treatment episode. A locally modified Med-TEC thorax immobilization board and a knee rest were used (Med-TEC, Orange City,
IA) in the pilot study. Patients were positioned with both arms above their head to ensure that the arms were outside the treatment fields. The immobilization board was modified with an additional T-bar grip to enable the patient’s arms to be supported above their heads and to reduce the span across the patient’s arms to facilitate positioning within the scanner (Fig. 4) (Jarrit, et al 2005).

Fig 3: Flat-bed insert on scanner couch.

Fig 4: Patient in treatment position passing through scanner.
**Planning scan acquisition**

The principles and practices already established for RTP were transferred to the acquisition of planning data using the PET/CT system. Two therapy radiographers positioned the patient and provided verification that the position during the data acquisition process could be reproduced during treatment. A previous evaluation of staff radiation doses from routine performing of FDG-PET scanning showed that the major component of the accumulated dose is obtained through close proximity to the patient post injection. To minimize dose to the therapy radiographers, the data acquisition process was implemented as a two-stage process. *(Carson, et al 2003)*

**“Cold” set-up session**

Prior to injection of 18F-FDG, the patient was positioned on the couch using the flat-top insert and immobilization devices as previously illustrated. The patient was carefully positioned to ensure that they would be able to maintain the position for the duration of the imaging process. This was of the order of 40 min while a whole-body PET/CT scan was acquired, as the primary purpose of the scan was for diagnosis and staging. In the subsequent study, a diagnostic scan will be performed independently of the treatment planning session. This will reduce the time for the radiotherapy planning PET/CT to 10–15 min. During this session the therapy radiographers used the CT scanner positioning lasers to establish anterior and lateral markers on the patient’s skin, approximately at the position of the xiphisternum. Full details of the patient’s position on the scanner and immobilization board were manually recorded to permit rapid and accurate repositioning of the patient post injection. The patient was then removed from the PET/CT scanner for the injection and uptake phase. Although use of the internal scanner lasers proved acceptable during the pilot study, further experience has shown that their use can be problematic for the
therapy radiographers depending on the shape and size of the patient. This potentially increases the time required to set-up the patient and may lead to increased radiation doses to the radiographers. The use of external room lasers would reduce these problems and is recommended. However, additional quality control testing of these lasers would be required to ensure the external lasers are aligned with the scanner. In addition, the potential effects of sag of the scanner couch during the investigation with the patient being set-up outside the scanner bore and then being moved on the couch into the imaging position must be investigated.

**“Hot” set-up session**

Following the injection and uptake period, the patient was repositioned by the therapy radiographers using the pre-recorded set-up information. Radiopaque markers were attached over the skin marks previously identified and the data acquisition process was completed. After the scan, the radiotherapy radiographers permanently marked the patient’s skin at the position of the radiopaque markers to provide reference points between the CT images and the treatment planning system.

- **Respiratory gating for PET/CT data in Radiotherapy planning**

  In defining a volume on the PET image it is essential to understand the acquisition process, especially in relation to physiological motion. For studies in the head and neck, immobilization techniques should eliminate potential gross movements and the alignment of PET and CT data from a combined PET/CT study should be “exact”. For studies of the chest and abdomen, the use of immobilization devices will help eliminate gross patient movement. However, there remains a significant discrepancy in the way that physiological movement...
due to respiration and heartbeat impacts upon the PET and the CT images. The increasing use of high-speed, multi-slice CT scanners enables images of the chest to be acquired in periods of time which are short compared with the respiratory cycle and effectively provide a “snapshot” of the lungs in time. This technique can be further controlled by the use of breath-hold techniques. However, this situation does not pertain for the acquisition of the PET data. Data are acquired over a number of minutes and represent a time averaged distribution based upon the dwell time of the activity at any point in space during the study. Thus, objects which do not move with time will see no degradation in activity concentration, whereas those objects which move significantly will exhibit a reduced activity concentration due to the distribution of activity throughout a larger apparent volume. It could therefore be argued that these PET images inherently include a margin for physiological motion and that no further allowance should be made in the definition of the PTV (Caldwell CB, et al 2003). Other factors such as gross movement and repositioning errors will remain. This, however, is not the only degrading factor. The presence of respiratory motion introduces inaccuracies into the reconstructed images as a result of mis-registration between PET and CT acquisitions (Visvikis, et al 2003 and Beyer, et al 2004). Since with these hybrid scanners, the CT maps are also used for the correction of the attenuation effects in the emission data, an extra inaccuracy may be introduced by using non-perfectly aligned CT and PET datasets as a result of the respiratory motion (Erdi, et al 2004).

The definition of a PTV clearly remains a complex task and techniques for the definition of a GTV may have a limited impact on the final definition of a PTV, especially where significant physiological motion is known to occur. These uncertainties have led to the investigation of diagnostic and treatment methodologies which measure physiological motion and incorporate the data into the treatment plan and the delivery system. The solutions that have been
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To date for taking into account the effects of respiratory motion concentrate on the acquisition of respiration synchronized PET and CT datasets. The use of breath hold protocols has been used as a means of improving registration between the PET and CT (Goerres, et al 2002). However, these will not aid in the delineation of target volumes as the radiotherapy treatment will be delivered over a few minutes. There is a lot of interest in the use of respiratory gating for both the PET-CT image acquisition and the treatment. Several studies have been carried out to investigate the feasibility of respiratory gating of PET of the upper chest and abdomen (Nehmeh, et al 2004, Boucher, et al 2004 and Wolthaus, et al 2005) and also to quantify the impact of respiratory motion on the underestimation of lesion activity. Different detector systems have been proposed, including a transducer or an impedance electrocardiograph (ECG) monitor measuring changes in abdominal or thoracic circumference, a thermistor measuring the temperature of circulating air during patient respiration, a spirometer measuring respiratory flow (Visvikis, et al 2003), the Varian Real Time position management (RPM, Varian Medical Systems, Palo Alto, CA) (Nehmeh, et al 2004) or the Polaris system tracking the displacement of infrared reflective markers in the patient chest. (Nehmeh, et al 2002) An alternative approach to gating is to use an image derived respiratory signal through the acquisition of dynamic datasets or list mode data (Visvikis, et al 2005). One such respiratory correlated approach used a point source of 18F-FDG attached to the patient’s skin to track respiratory motion. Identifying the frames in which the point source fell within an operator defined region of interest (ROI) allowed PET images corresponding to different points within the respiratory cycle to be created. It was demonstrated that this technique produced similar results to gating. Another approach which uses time activity curves generated from a ROI drawn over a moving object in the image to recover the breathing frequency is currently undergoing clinical validation (Visvikis, et al
The advantage of these techniques is that the data may be retrospectively reconstructed for any breathing phase or amplitude.

Irrespective of the gating methodology implemented, the emission data acquired in each of the temporally gated frames is reasonably free of respiration-produced inaccuracies. However, the resulting individual frame images are of reduced resolution, as well as overall quality, as they contain only a fraction of the counts available throughout a PET acquisition. Some groups have attempted to deal with this problem by acquiring gated data in 3D mode (Boucher, et al 2004). The need, therefore, exists for the development of correction methodologies making use of the gated datasets, in order to obtain respiration free PET images using all available data throughout a standard respiration average PET acquisition. This approach will also remove the need currently existing in terms of significantly increasing the time (over a factor of 3) of gated PET acquisitions in order to compensate for the presence of reduced statistics in the final reconstructed images. Very limited work is currently available in this domain. First, an emission driven solution through the combination of respiratory synchronized emission datasets and an iterative reconstruction algorithm can be envisaged, in a similar fashion to the methodology that has been previously suggested for SPECT cardiac imaging applications (Kyme, et al 2003 and Lee, et al 2005). The second option is based on a realignment methodology to “bring” all of the respiratory synchronized PET datasets to a particular phase in the respiratory cycle. This methodology is potentially applicable to both image and raw data domains, deriving the transformation parameters from the corresponding respiratory motion synchronized CT frames (Nehmeh, et al 2004 and Lamare, et al 2004).
2-Physics of PET/CT
PET/CT is a new diagnostic imaging modality, which proves that adding PET and CT is not merely additive, but highly synergistic. While PET provides high sensitivity for lesion detection, CT provides the anatomic backdrop, which frequently is important in order to make a specific diagnosis (Gustav, 2004).

- **Computed Tomography Imaging**

CT images describe the electronic density distribution of cross sections of the patient anatomy. CT systems provide gray scale display of linear attenuation coefficients that closely relate to the density of the tissue. CT imaging evolved from conventional planar radiographs. In planar X-ray film imaging the three dimensional anatomy of the patient is reduced to a two dimensional attenuation projection image and the depth information of the structures are lost. In CT imaging several attenuation projection images for a volume of tissue are acquired at different angles. These sets of projection images are reconstructed by filtered back projection algorithm to generate two dimensional attenuation cross-section of anatomy of the patient. A CT scanner positions a rotating x-ray tube and detector on opposite sides of the patient to acquire projection images. Early CT scanners used pencil beams of x-rays and a combination of translation and rotation motion to acquire projection images (Bushberg, et al 1994).

Modern CT scanners have a stationary or rotating detector array with a rotating fan beam x-ray tube. There are also two types of scanning: axial and helical CT scanning. In axial scanning the patient is moved step by step acquiring sets of projection images for each slice. In helical scanning (Fig 5) the patient table moves continuously while the x-ray tube acquires a series of
projection images. The projection images are acquired for a helical path around the patient. In helical scanning to reconstruct a cross-sectional planar image, the helical data is interpolated to give axial plane projection data before reconstruction (Fig 6). By removing the time to index the table between slices the total scan time of the patient is reduced. Also reconstruction can be done for any slice thickness after acquiring the data. This helical scanning is available in most of the current CT scanners (Wilting, 2004).

Fig 5: Helical scanning (Continuous scanning while table moves)

Fig 6: Helical interpolation
The reconstructed CT image is a two dimensional matrix of numbers, with each pixel corresponding to a spatial location in the image and in the patient. Usually the matrix is 512 pixels wide and 512 pixels tall covering a 50 cm x 50 cm field of view. The numeric value in each pixel represents the attenuation coefficient as a gray level in the CT image. These numbers are called Hounsfield units or CT numbers. CT number gives an indication of the type of tissue. Water has a CT number of zero. Negative CT numbers are typical for air spaces, lung tissues and fatty tissue. Values of $\mu_{\text{pixel}}$ greater than $\mu_{\text{water}}$ correspond to other soft tissues and bone. Radiologists occasionally make critical diagnostic decisions based on CT number of particular regions of interest. Also attenuation values given by CT numbers are used to calculate the dose delivered to the tumor in RTP. CT number is an important parameter in CT images which must be frequently checked for accuracy (Levin, 2003).

- **Positron Emission Tomography Imaging**

Positron emission tomography (PET) imaging generates images that depict the distribution of positron emitting radionuclide in the patient body. PET imaging often uses the F-18 fluoro-deoxy-glucose (FDG) radioactive tracer to track increased glucose metabolic activity of tumor cells and to provide images of the whole body distribution of FDG. When the positron is emitted by the radioactive tracer it annihilates with an electron to generate two 511 kev photons emitted in nearly opposite directions (Fig 7). These photons interact with the ring of detector elements surrounding the patient (Fig 8). If both the emitted photons are detected then the point of annihilation lies on the line joining the points of detection. This line joining the points of detection is known as the line of response (LOR). The circuit used by the scanner to record the detector interactions occurring at the same time is called coincidence circuitry. This
whole process is called annihilation coincidence detection. Thus a PET scanner uses annihilation coincidence detection instead of mechanical collimation like gamma cameras to acquire projections of activity distribution in the patient. Projections acquired at different angles are reconstructed using iterative algorithms to generate cross-sectional images of activity distribution (Kinahan, 2003).

Fig 7: Annihilation event

Fig 8: Annihilation coincidence circuitry and PET detector geometry
The annihilation coincidence detection process allows many false events to be acquired. Corrections are necessary for these false events before the projections are reconstructed. The total events acquired are classified as trues, random and scatter (Fig 9). A true coincidence is simultaneous interactions occurring in the detectors resulting from emissions occurring in the same nuclear transformation. Random coincidences occur when emissions from different nuclear transformations interact in coincidence with the surrounding detectors. Scatter coincidence occurs when one or both photons from annihilation is scattered in the patient body and interact with the detector to give a false LOR. The acquired annihilation events need to be corrected for random and scatter events. Random coincidence events along any LOR may be directly measured using the delayed coincidence method (Zaidi, et al 2003). The delayed coincidence method uses two coincidence circuits. The first circuit measures both true and random coincidence events. The second circuit has a delay of several hundred microseconds inserted into the coincidence window, so all true coincidences are thrown out of coincidence. The counts measured in the second circuit are subtracted from the first to give true counts. Scatter correction is done for the projection data by model-based scatter estimation. The scatter correction factor is estimated by mathematical models and applied to the projection data before reconstruction (Kinahan, et al 1998).

Annihilation photons emitted by nuclear transformation are attenuated by the patient body. Hence correction for attenuation is also necessary to get an accurate activity distribution. The probability of both photons escaping is the product of the probabilities of each escaping. The probability of photons interacting within the coincidence window is proportional to the probability of photons escaping (Kinahan, et al 2003).
Fig 9: coincidence events

A – True coincidence events
B – Scatter coincidence events
C – Random coincidence events
**PET/CT imaging**

Fused PET and CT images give better diagnostic evaluation than PET or CT images used alone as the greatest limitation in using PET alone for radiotherapy treatment planning (RTP) is its lack of anatomical information. This limitation of PET is overcome by fusing PET and CT images together (Cohade, et al 2003).

The necessity of accurate spatial registration of fused images requires different fusion techniques for different image datasets. Software fusion and hardware fusion are the two different approaches considered by the scientific community (Townsend and Beyer, 2002 & 2003). Software fusion approach use different transformation algorithms to fuse different modality images acquired at different times. The transformation algorithms are classified as rigid and non-rigid transformation algorithms. They are based on whether they fuse images of rigid-body (e.g., head) or non rigid (e.g., abdomen) objects (Patton, 2001 and Yap, 2002).

The hardware approach of image fusion is headed towards designing a single imaging system to acquire simultaneously the different image modalities required. Hardware fusion is partially achieved by construction of a hybrid PET/CT scanner (Beyer et al, 2000 and Townsend et al, 2004) which acquires different modalities sequentially. These hybrid scanners are two separate scanners enabled to operate in sequence one after another to acquire the different image modality datasets in a single imaging session. Although hybrid scanners do not give a true hardware fusion and have not proven to be a better fusion technique scientifically (Kalabbers et al, 2002).
**Dual Modality PET/CT Imaging**

Dual-modality PET/CT was first built at the University of Pittsburgh in collaboration with CTI (Knoxville, TN) and Siemens Medical Solutions (Hoffman Estates, IL), combining separate PET and CT scanning devices into one device (*Beyer, 2000*).

Image fusion was initially achieved by software fusion of anatomical and functional images. Software fusion was generally successful with brain and rigid body volumes. It encountered significant difficulties when fusing images of the rest of the body. Alignment algorithms fail to converge the two image sets due to problems of patient movement or discrepancies in patient positioning between two scans. Also involuntary movements of internal organs arise when patient are imaged on different scanners and at different times.

Dual modality PET/CT imaging is a combination of imaging technologies helping to acquire accurately aligned anatomical and functional images in the same scanning session (*Fig 10*). Also an additional advantage of the combined PET/CT scanner is the use of CT images for attenuation correction. CT images can be scaled in energy and used to correct the PET data for attenuation effects (*Kinahan et al, 2003*)
The PET/CT prototype consisted of a rotating partial ring PET system and a single slice CT scanner mounted on the same rotating support. The CT scanner combined with PET often uses helical scanning CT to enable fast patient throughput, but new scanners with both helical and axial scanning are available now. The CT data is usually acquired first, followed by PET acquisition. There are typically two separate acquisition processing units for CT and PET, and an integrated display workstation. The acquired CT and PET datasets are sent to the reconstruction processing unit for reconstruction. Reconstructed images are fused in the fusion workstation. CT and PET images can also be separately viewed in the workstation.
General PET/CT scan Protocol

The protocol for PET/CT imaging starts with patient preparation. 5 – 15 mCi of FDG is injected into the patient 45 – 60 min before the start of image acquisition. After 45 min, the glucose circulates through the body; the patient gets ready for image acquisition by emptying the bladder. The patient is positioned on the table for an initial topogram. The topogram is used to select the scan range for PET/CT image acquisition. The scan range is selected as a number of bed positions. Once the image acquisition region is selected in the topogram, the helical CT scan is done first; it takes around 30 sec to acquire one bed position. After completion of the CT portion, the scanner bed is moved to the PET starting position and the emission scan is started.

The emission scan duration per bed position varies with the detector technology used. With conventional bismuth germinate oxyorthosilicate (BGO) system, acquisition times will range from 5 to 8 minutes per bed position. The new lutetium oxyorthosilicate (LSO) technology reduces emission scans to 3 to 5 minutes per bed position. The CT data are used to perform attenuation correction. Image reconstruction is completed a few minutes after the PET image acquisition is completed. Since the CT data is used for attenuation correction, the total scan duration for a PET/CT scanner is shorter than that for stand-alone PET scanner, because the CT acquisition is much faster than a conventional PET transmission acquisition (Humm et al, 2003).

For a typical “diagnostic” PET/CT scan using oral and intravenous (IV) contrast for the CT, patients generally are given oral contrast and injected with 18F-fluorodeoxyglucose (FDG) approximately 1 hour before scanning. The
patient subsequently is positioned in the PET/CT scanner and immobilized as indicated (for instance, soft collars may be used to reduce neck movement in patients with head and neck cancer or lymphoma with neck involvement). The first step in a standard PET/CT protocol generally involves the acquisition of a digital scout radiograph, in which the full patient is visualized and the area of interest is selected (Fig. 11 [#1]). Patients then undergo the CT portion of the examination (Fig. 11 [#2]), followed by the PET portion of the examination (Fig. 11 [#3]). A common misconception is that the CT and PET data are acquired simultaneously; however, the data are acquired sequentially, with CT always performed first. Most scanners without a separate transmission rod source will not allow PET acquisition only but will allow dedicated CT acquisition. Because of the sequential data acquisition, there is still a high probability of CT and PET image mis-registration if the patient moves between the CT and PET portions of the examination (Fig. 12). Once attenuation correction (AC) and scatter correction are performed using the attenuation coefficients from the corresponding CT portion of the scan (Fig. 11 [#4]), fused accurately co-registered images are available for interpretation (Fig. 11 [#5]) (Todd et al, 2006).
PET/CT in Radiotherapy Treatment Planning & Target Definition

Review of Literature

Fig 11: Standard PET/CT Protocol. A digital scout radiograph is first acquired, in which the full patient is visualized and the area of interest is selected (1). Patients then undergo the CT portion of the examination (2), followed by the PET portion of the examination (3). Once attenuation correction and scatter correction are performed using the attenuation coefficients from the corresponding CT portion of the scan (4), fused, accurately co-registered images are available for interpretation (5).

Fig 12: Misregistration caused by patient movement. Misregistration of axial CT (A) and PET (B) images are shown on an axial PET/CT image (C). This type of misregistration is due to movement of the patient’s head to the right after the CT acquisition (during the PET acquisition).
**Quality Assurance in PET/CT**

As PET/CT imaging is gaining grounds in RTP, quality assurance (QA) protocols to check the PET and CT as a combined device are needed. QA for PET/CT is not well defined and there is research in progress to define a standard methodology for checking their performance. Some research work has analyzed the artifacts of helical CT and its impact on the attenuation correction of PET images. These studies analyze the problems faced in PET/CT imaging due to breathing and to artifacts from metal and oral contrast agents. Most of the QA currently done in PET/CT scanner facilities are based on stand-alone PET and CT QA protocols (*Bujenovic et al, 2003 and Nehmeh et al, 2003*).

PET scanner quality control includes system corrections such as normalization, calibration and blank scans. Normalization correction compensates for variation in efficiency in each line of response (LOR) in the sinogram. Calibration correction is used to convert the reconstructed image pixel values into activity concentrations. Both normalization and calibration correction are used to compensate for sensitivity variation in the scanner. The blank scan typically is acquired daily using a transmission rod source and it is used with patient transmission data to obtain attenuation correction factor (ACFs). In PET/CT scanners only the normalization and calibration scans need to be done; a blank scan is not needed as CT scans provide ACFs. Blank scans are done during regular CT daily QA instead of the transmission source blank scan used in stand-alone PET scanners. Blank scans give the number of un-attenuated photons (Io) reaching a detector from the x-ray tube. When used with the number of photons detected (I) by a detector during CT imaging it gives the ACF for CT energy photons (*Cohade et al, 2003*).
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Daily and monthly QA for PET imaging in PET/CT scanners is done by scanning a uniform $^{68}$Ge cylindrical phantom for a normalization scan. Both normalization and calibration corrections are checked. The reconstructed PET images are checked for variation in uniformity. This is done by checking the chi-square value of the acquired data. The CT QA is done by checking CT number for an electron density phantom. The CT phantom is a cylindrical hollow acrylic phantom filled with water. Once CT images of the phantom are taken the CT number values of acrylic, water and air are checked and recorded. Thus current QA methods for PET/CT are more oriented to verify the performance as a standalone device rather than as a combined device. Hence validation of the PET/CT dataset has to be done in the scanner and also for the imported PET/CT dataset in the RTP software (Nehmeh et al, 2003).
3- PET/CT & Lung cancers
Radiotherapy is a key treatment modality in the curative treatment of patients with locally advanced non-small cell lung cancer (NSCLC). Recent progress in combined modality treatments incorporating radio-chemotherapy, with or without surgery, as well as the technical advances in radiation delivery, have all led to significant improvements in treatment outcomes (Senan et al, 2005).

Three dimensional conformal radiotherapy (3DCRT) accurately conforms the dose distribution to the planning target volume allowing the radiation dose to the tumor with respect to normal tissue to be optimized. 3D-CRT is widely used in the treatment of thoracic neoplasms, particularly non-small cell lung cancer (NSCLC) (Armstrong et al, 2000). Conformal irradiation techniques have shown advantages in comparison to conventional 2D approach in terms of dose volume histograms of tumor and healthy tissues (Ragazzi et al, 1999, Graham et al, 1999, Kwa et al, 1998 and Rancati et al, 2003).

Careful staging and accurate delineation of target volumes are crucial for preventing geographical misses as it is technically possible to produce radiation dose distributions that tightly conform to the tumor volume. An incorrect definition of the gross target volume (i.e. detectable tumor) or clinical target volume (tumor plus a margin for microscopic extension) is a source of systematic errors, which can lead to under-treatment and reduce the probability of tumor control (Senan et al, 2005).

At present, the standard imaging modality for target volume definition in 3D-CRT is computed tomography (CT), which presents limitation in determining lymph-nodal involvement and in providing information on lesion viability (Wahl et al, 1994).
Positron emission tomography (PET) has been a major innovation in lung cancer imaging that exploits differences in the structure of tissues. Positron emission tomography with 18F fluorodeoxyglucose ([18F] FDG-PET) is showing increasing usefulness in staging and follow-up (Kostakoglu et al, 2003, Follen et al, 2003, Lai et al, 2004).

Clinical studies have mainly focused on the use of 18F-fluorodeoxyglucose (FDG), a glucose analogue that is taken up due to the enhanced glucose metabolism of lung cancer cells, leading to metabolic trapping and accumulation in the cancer cell after phosphorylation by hexokinase (Rempel et al, 1994).

In particular, in lung cancer, [18F]FDG-PET shows a higher accuracy than CT in lymph-node staging, with sensitivity and specificity values of 85% and 90% for positron emission tomography (PET), and 61% and 79% for CT, respectively (Gould et al, 2003).

Data from a randomized trial in surgical patients with Stage I NSCLC found that PET scans changed disease stage in 20% of patients, thereby supporting the recent trend of performing FDG-PET scans in patients who are candidates for curative radiotherapy for the same stage (Viney et al, 2004).

Post-radiotherapy survival has been reported to be superior in patients who have undergone a staging PET scan, a finding that can be explained by the exclusion of up to 30% of patients who have otherwise unsuspected distant metastases (Hicks et al, 2001 and Bradley et al, 2004).
PET scanning may be useful in treatment planning, but only limited prospective data are available from clinical trials. Nevertheless, significant changes in the definition of target volumes have been reported in between 30 and 60% of patients with NSCLC. More recently, PET and CT combined images have been shown to add important information on viable tumor tissue extent and to considerably modify target volumes of 3D-CRT (Fig 13, 14) (Bradley et al, 2004).

Fig: 13 PET-CT scan of a tumor in the right lung. The information contained in separate CT and PET images (left) are better appreciated on co-registered images (upper right), which allow for easier contouring of target volumes (lower right). FDG uptake in the heart is also visible.
Fig: 14 Screen-shot of contoured target volumes on PET and CT images for a peripheral lung tumor.
PET/CT for defining target volumes in NSCLC

- **Nodal target volumes**:

  Accurate identification of nodal metastases is crucial for planning curative radiotherapy, particularly as routine elective nodal irradiation is no longer recommend in NSCLC (Senan et al, 2004). Different meta-analyses have shown FDG-PET to be superior to conventional mediastinal staging using CT scans and esophageal ultrasound (Fischer BM et al 2001, Gould et al, 2003 and Toloza et al, 2003). A planning study reported that treating only FDG positive mediastinal areas decreases radiation exposure of the lungs and the esophagus sufficiently as to allow for radiation dose-escalation (Wel et al, 2005).

  A prospective clinical trial using this approach reported isolated nodal failures in only 1 of 44 patients. (DeRuysscher et al, 2006)

  Although PET-defined mediastinal radiotherapy fields appears a logical step, reported false positive findings occur in up to 39% of patient, depending on the population studied and the equipment used (Graeter et al,2003). As such, findings that can have a major impact on treatment policy should ideally be confirmed by histology. In up to 70% of patients in whom FDG-PET scans indicate nodal metastases, histological confirmation can be obtained using endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) (Annema et al, 2004). As such, the combination of PET and EUS-FNA qualifies as a minimally invasive staging strategy for defining involved-fields in NSCLC.
The issue of whether digital fusion is superior to simple correlative reading for staging lymph nodes is not entirely clear as the available data are conflicting. Some authors report no significant differences in accuracy of establishing either N stage or individual lymph node stations when digital software fusion was used (Magnani et al, 1999). Others have reported comparable sensitivity, but an improved specificity and accuracy, for digital software fusion in identifying correct lymph node stations (Aquino et al, 2002). A recent study reported that nodal staging using hardware fusion (i.e. PET-CT) was significantly more accurate than only visual correlation. However, the latter study has been criticized because of the reported accuracy for PET scans alone (49%) were far below that reported in the meta-analysis. (Lardinois et al, 2003)

A recent retrospective analysis in NSCLC compared a hybrid CT-PET with PET alone with visual matching, with the hybrid CT-PET read first in 129 patients, followed by the PET alone with visual CT matching 2 or more weeks later. Histological verification of nodal stage was obtained in all patients, and both a patient-and TNM-based analysis was performed. Hybrid CT-PET was superior for stages II and III, and was significantly more accurate for both N2 nodes (96% versus 93%) and N1 nodes (90% versus 80%). With regards to specific nodal stations, CT-PET was more sensitive at stations 4R, 5, 7, 10L, 11, while it was more accurate at stations 7, 11 (Fig 15) (Shielda et al, 2000). Overall, the findings of CT-PET were reported to change patient management in 9.3% of these patients (Cerfolio et al, 2004).
Fig: 15 regional lymph node stations. (Ao=aorta, PA=pulmonary artery).
**Target volumes for primary NSCLC:**

Although FDG-PET scanning has an important role to play in the differential diagnosis of pulmonary nodules (Vansteenkiste, 2004), the extent of the primary tumor is usually assessed by thoracic CT scans, occasionally supplemented by magnetic resonance imaging (MRI), e.g. for superior sulcus lesions or when the relationship between the heart or the large vessels is of importance (Bittner et al, 1998).

At present, FDG-PET scans offer little additional advantage over CT or MRI scans for staging of the primary tumor because of its lack of precise anatomical localization. The spatial resolution of modern CT scanners (typically about 1 mm) is far superior to that of current PET scanners (6–8 mm), so that the extra gain with fusion is expected not be large, unless PET scans can reliably address tumor delineation caused by atelectasis or intra-tumor heterogeneity (Jang et al, 2003 and Ciernik et al, 2003).

**Specific issues that have to be addressed in order to clarify the role of PET scans for contouring primary tumors include:**

1. **Low spatial resolution:**

Despite a high contrast resolution, the relatively low spatial resolution of images (presently in the range of 6–8 mm and physically limited to about 2 mm) remains a major drawback of PET scans. Tumor edges on PET scans are indistinct, making contouring difficult and auto-contouring using predefined SUV thresholds has been proposed as a solution. However, criteria for defining tumor thresholds for contouring GTV’s requires data from studies correlating
PET data with pathological specimens. These studies are unfortunately unavailable for NSCLC (Paulino et al, 2004).

2. Significance of hypodense regions:

Some reports have proposed modifying dose distributions to spare ‘hypodense’ regions on FDG-PET scans, and to boost regions showing a high uptake. However, there is little pathological data to support the view that ‘hypodense’ regions represent exclusively sites of necrosis and/or atelactasis. In additions to studies correlating pathology with PET imaging, studies of the molecular characteristics of cancer cells showing different uptake values for PET tracers are needed before the concept of modulating radiation dose-intensity to tumors sub-volumes can rationally be tested in clinical trials (Caldwell et al, 2003).

3. Tumor mobility:

As PET acquisition takes several minutes, tumor motion due to respiration or cardiac action results in PET ‘GTV’s’ that incorporate at least some effects of this motion. As such, PET scans correlate best with imaging techniques that incorporate all mobility, such as slow CT scans (Lagerwaard et al, 2001). Respiration-correlated, or 4D, CT scans are have been shown to be an effective approach for evaluating tumor mobility, and incorporating mobility into treatment planning (Underberg et al, 2004). These modified CT scanning techniques are used almost exclusively in radiotherapy planning, and studies on the fusion of such images with diagnostic PET scans (acquired during free-breathing) are needed. Respiration-gated PET acquisition techniques have been developed (Nehmeh et al, 2003), but their use implies that an appropriate
respiratory phase for radiotherapy (and PET scan) has first to be established. In the near future, availability of respiration correlated PET-CT scans will limit the variations and artifacts due to respiration, and studies investigating the clinical gains from these approaches are awaited.

4. Timing of PET scans:

PET scans are increasingly performed during the initial staging process for NSCLC, without attention to details relevant for radiotherapy planning using for example customized immobilization devices or fiducial markers. Mutual protocols between nuclear medicine specialists and radiation oncologists allow patient positioning with the use of devices in an appropriate way for both diagnostic and therapeutic purposes (Senan et al, 2005).

The assessment of response by conventional imaging is mainly based upon changes in tumor volume. However, these changes do not necessarily correlate with pathological complete remission rates and survival (MacManus et al, 2003). Assessment of tumor response by metabolic parameters is considered to be a promising approach. Studies evaluating the role of FDG-PET scans for response assessment following radiotherapy generally reported a poor agreement between post-radiation CT and PET scans. More patients were judged as complete responders by PET than by CT scan, and PET responses were a better predictor of survival (Hebert et al, 1996).

An evaluation of pre-and post-induction chemo-radiotherapy PET scans in 23 patients with stage N2–3 NSCLC found PET to be of limited value in predicting residual disease at 4–6 weeks after chemo-radiation. (DeYoung et al, 2004) Approximately 80% of patients with a negative post–induction PET at their primary site had in fact residual disease, and approximately 25%
of patients with a negative post-induction PET in the mediastinum had residual tumor. Another report suggested that FDG-PET was better able to predict pathological responses in patients with squamous cell cancer than those with an adenocarcinoma, and found that the technique was less accurate in predicting responses when concurrent chemo-radiotherapy, rather than chemotherapy alone, was used as the induction scheme. Therefore, the utility of PET in predicting pathologic response to chemo-radiotherapy remains presently investigational. Due to concerns about false-negative scans arising from radiation-induced inflammation, the current practice is to defer PET reassessment to between 3 and 4 weeks after completion of chemotherapy, and 3 months post-radiotherapy (Cerfolio et al, 2004).

A large study looked at the pathology of 988 mediastinal lymph nodes and their interpretation on CT and FDG PET-CT. On the basis of CT criteria alone, 75% of the pathologically involved nodes would have been covered by the GTV, whereas 89% of involved nodes would have been covered by the PET-CT planned GTV (Vanuytsel et al, 2000). Conversely, one study showed that irradiation field sizes to the involved mediastinal nodes alone were smaller if PET-CT planning was used (9.9 +/- 4.0 cm3) vs. CT planning alone (13.7 +/- 3.8 cm3) (Wel et al, 2005). DeRuysscher et al 2005 showed that irradiating these PET-positive nodes alone resulted in only a single treatment failure in 44 patients. In a study by Kamel et al 2003, FDG PET scanning changed treatment in 19% (eight) of patients. Three of the patients had their adjuvant radiotherapy cancelled and five patients had their radiation fields changed.

- **New PET/CT tracers:**
Clinical experience with newer tracers is very limited but they may hold promise for the future. A review of this large field is beyond the scope of this article. The most extensive clinical data in lung cancer are available for 3-deoxy-3-$^{18}$fluorothymidine (FLT), a marker for DNA synthesis. A clinical study reported that the uptake of FLT correlated better with proliferation of lung tumors than the uptake of FDG. No FLT uptake was visible in non-proliferating tumors, suggesting that FLT may thus be complementary to FDG in the evaluation of NSCLC (Buck et al, 2003).

**PET/CT for defining target volumes in small cell lung cancer (SCLC)**

Patients with limited-stage lung cancer (LS-SCLC) are candidates for concurrent chemo-radiotherapy, and must be distinguished from the more common presentation of extensive disease. The available literature suggests that that PET has diagnostic value in SCLC (Chin et al, 2002). SCLC is a FDG-avid tumor, with mean SUVmax for primary and mediastinal nodal lesions of SCLC reported to be similar to that seen in NSCLC (Bradley et al, 2004).

In the largest reported series of 120 patients, FDG-PET resulted in a stage migration for 14 patients, correctly upstaging 10 patients to extensive disease and down-staging 3 patients by not confirming metastases of the adrenal glands suspected on the basis of CT scan (Brink et al, 2004) Only 1/120 patient was incorrectly staged by FDG-PET, owing to failure to detect brain metastases. It has been suggested that PET can identify metastases to regional lymph nodes in 25% of patients whose mediastinal CT was negative. At the present time, further evaluation with imaging or biopsy should be
performed to clarify PET results in patients with LD-SCLC whose management is likely to be altered as a result of the scan (Chin et al, 2002).

The benefits of staging FDG-PET scans have clearly been established in NSCLC, and this information is of clinical benefit for selecting candidates for curative radiotherapy. Non-randomized studies suggest that designing radiation fields for the mediastinum with the aid of PET scans may be beneficial. Given the uncertainties arising from image-fusion as well as the low spatial resolution of PET scans, use of PET information for defining target volumes for primary tumors is questionable. It remains to be seen whether the treatment of ‘biological target volumes’ defined using different PET markers will become a clinical reality in the near future (Ling et al, 2000).

PET/CT is changing this role by integrating the information on tumor morphology provided by CT with that on its metabolism and, particularly, on the number of neoplastic viable cells. This is demonstrated by the initial applications of PET and co-registered CT imaging in the evaluation of patients undergoing radical radiotherapy for locally advanced lung cancer. In these cases, the addition of PET to the standard CT protocol appears to significantly change treatment planning (changes of 22%–64% in the planning treatment volume have been reported in 22–100% of patients (Dizendorf EV 2003 and Ciernik IF, et al 2003).
4- PET/CT & Lymphomas
Although the World Health Organization/Revised European–American Classification of Lymphoid Neoplasms (i.e., WHO/REAL) classification has 2 major categories of lymphoid malignancies, i.e., Hodgkin’s lymphoma (HL) and the non-Hodgkin’s lymphomas (NHL) of B-cell or T-cell/natural killer (NK) cell origin, (Harris et al, 1999) within each group there is very significant variability in management and prognosis. Nevertheless, in both HL and NHL, prognosis and treatment depend critically on histological type and disease stage. Biological characteristics, including histologic grade, also may influence outcome and can potentially be assayed by PET (Hasenclever et al, 1998).

Lymphomas represent a diverse range of diseases with manifold presentations, outlook, and therapeutic approaches. Key to the modern management of lymphoma is accurate delineation of the extent of disease. The inability of computed tomography (CT) to identify the involvement of non-enlarged nodes and its relatively poor sensitivity in the detection of extra-nodal sites of involvement limit the performance of noninvasive staging techniques (Hicks et al, 2003).

Functional imaging techniques such as Gallium-67 (Ga-67) scintigraphy have been used for many years to improve the evaluation of patients with lymphoma. Ga-67 scintigraphy was the imaging technique of choice to assess response to treatment in HD and in high-grade NHL. While providing complementary information to CT in many clinical settings, functional imaging has never had sufficient accuracy or localizing ability to seriously challenge conventional primary staging paradigms. However, it suffers from low spatial resolution and a lack of specificity. Its sensitivity is low in infra-diaphragmatic disease because of physiological uptake in the abdomen. Its
limitations in low-grade NHL also are well known. Moreover, a Ga-67 scintigraphy should always be performed before treatment to determine whether the individual patient has a gallium-avid lymphoma (Front et al, 1995). In addition FDG-PET is without any doubt the best noninvasive imaging technique for response assessment in patients suffering from lymphoma (Bar-Shalom et al, 2003 and Fischman et al, 2004).

Despite the important role of Ga-67 scintigraphy in response evaluation, it appears now that FDG-PET is more sensitive for the detection of nodal and extra-nodal sites of disease. Furthermore, FDG-PET also is considered to be more convenient than Ga-67 scintigraphy because a PET study can be performed 1 hour after the injection of 18F-FDG whereas the scintigraphy must be performed several days after the administration of Ga-67. 18F-Fluoro-deoxy-glucose positron emission tomography (FDG-PET), however, has been demonstrated to have both higher sensitivity and specificity than CT in many comparative series. Second, the tumor-to-background ratio is higher for PET than for gallium. Although probably adequate for imaging of the chest, gallium suffers from decreased sensitivity for evaluation of the abdomen due to high physiologic liver and bowel activity. Third, due to its lower anatomic and spatial resolution, gallium imaging has decreased capability to detect small lesions when compared to FDG-PET imaging. As a result of these limitations, up to 36% of lesions seen on PET images may not be visible on gallium exams. Also, negative post-therapy gallium scans are not useful unless a pre-therapy scan demonstrating tumor accumulation of the agent were performed. Post-therapy scans can also suffer from non-specific hilar uptake of gallium that can be confused for recurrent disease (Rohren et al, 2004).

NHL is broadly grouped into low-, intermediate-, and high-grade disease subgroups (Segall, 2001). There is a direct correlation between the
degree of FDG uptake and the histologic grade of lymphoma (Delbeke, 1999). Treatment for NHL is based on several factors, including tumor grade. High-grade tumors demonstrate greater metabolic activity (and greater FDG accumulation) than low grade tumors (Romer et al, 1998). In fact, low-grade lesions (including mucosa-associated lymphoid tissue lesions) may not accumulate sufficient FDG to be visualized (Kostakoglu et al, 2003).

For Hodgkin's disease, the stage at presentation and tumor cell type determine the patients overall prognosis and optimal method for treatment (Guay et al, 2003). Because the anatomic extent of disease is the single most important factor influencing relapse-free duration and overall survival in patients with Hodgkin's disease, accurate staging prior to initiation of therapy is essential for proper patient management (Hoh et al, 1997).

The more-than 35 clinico-pathologic entities described within the spectrum of NHL can be divided into the more clinically useful groups of “indolent” or “aggressive” lymphomas. The most common “indolent” lymphomas are the follicle-center cell (“follicular”) lymphomas, and the most common “aggressive” lymphomas are the diffuse large B-cell lymphomas. For both “indolent” and “aggressive” NHL, stage has a critical role in the selection of treatment. Noncontiguous lymph node involvement and extra-nodal involvement, both uncommon in HD, are more common in patients with NHL and, therefore, sensitive whole-body evaluation is likely to be of major importance in accurately staging these diseases. In particular, bone marrow and hepatic involvement are more common in patients with NHL than HD and may be difficult to detect on conventional imaging. This is important because prognosis is strongly influenced by the number of extra-nodal sites involved (Shipp et al, 1993).
One of the difficulties in staging NHL is detection of focal, as opposed to diffuse, bone marrow involvement because the former can potentially be missed on bone marrow biopsy, particularly if suboptimal samples are obtained for evaluation or if suboptimal evaluation methods used (Campbell et al, 2003). Radionuclide bone scanning is relatively insensitive, and MRI is more sensitive but may require multiple sequences to achieve adequate sensitivity (Yasumoto et al, 2002). PET may have particular advantages for evaluating extra-nodal involvement, including focal bone marrow disease (Fig. 17), splenic (Fig. 16, 18) and small bowel disease (Fig. 19).

Fig 16: on conventional staging this patient with low-grade (follicular) NHL had stage 2A disease. CT demonstrated left lower cervical and mediastinal lymphadenopathy. There was no splenomegaly, and bone marrow biopsy was negative. FDG PET/CT demonstrated abnormal uptake in non-enlarged
axillary and para-aortic nodes and intense splenic uptake, upstaging the patient from stage 1 to stage 3 disease and changing our treatment to chemotherapy.

Fig 17: This patient presented with weight loss and epigastric pain and was found to have an epigastric mass with abdominal para-aortic lymphadenopathy and splenomegaly on CT. Biopsy of the mesenteric mass was inconclusive, and bone marrow biopsy was negative. FDG PET confirmed known sites of abnormality and additional focal liver (horizontal arrows), bone (vertical arrow and other sites not displayed in these coronals).

Fig 18: In addition to its ability to detect diffuse splenic infiltration by virtue of diffusely and, often, intensely increased FDG uptake in the spleen relative to the liver, PET also can detect focal splenic
deposits, even in the absence of structural abnormality. As well as uptake in non-enlarged lesser curve and splenic hilar nodes, several focal splenic nodules are clearly apparent, particularly on fused PET/CT images.

Fig 19: This patient presented with abdominal pain, and bulky para-aortic lymphadenopathy was identified on CT. FDG PET demonstrated high uptake in multiple abdominal nodes as well as several discrete foci with slight elongation, suggesting small bowel involvement. Co-registered PET images and CT with oral contrast obtained contemporaneously on hybrid PET/CT demonstrate intense uptake corresponding to mural thickening of small bowel.

In the primary staging setting, detection of more extensive disease by PET than by conventional imaging would be of major relevance for patients with apparently limited stage HD in whom upstaging could alter management from being radiation-based to chemotherapy alone or combined modality therapy. It also may help to better define radiation treatment volumes in both early and more advanced disease stages by better defining gross tumor volume. If chemotherapy is not used to treat potential systemic microscopic disease in HD, then the accurate tailoring of radiation therapy fields to cover all gross disease becomes even more critical. Demonstration of disease in normal-sized lymph nodes could be of particular importance for planning radiation therapy, given that the quality of radiation therapy delivery has a major impact on overall survival (Duhamke et al, 1996).
There was increasing recognition that wide-field radiation may play an important role, alongside certain chemotherapy agents, in giving rise to second malignancies in this patient population. To reduce this risk most schedules for early Hodgkin’s disease and early non-Hodgkin’s lymphoma use a short course of chemotherapy to contain microscopic regional disease and reduce bulk at the known sites prior to involved field radiotherapy (Moody et al, 2000).

Freudenberg et al 2004 reported that PET/CT imaging with FDG is accurate in restaging lymphoma and offer advantages over separate PET and CT imaging. Data from the present study confirm the high value of PET/CT in patients suffering from lymphoma in both initial staging and restaging. In both situations, FDG PET/CT showed a high sensitivity of 100% and 97%, respectively, as well as a high specificity 100% and 99%, respectively. Freudenberg et al 2004 reported also that combined PET/CT to be superior to PET and CT read side by side. Specifically, combined image reading changed the stage of the disease in 14% of their lymphoma patients (2/14), compared with a separate side-by-side interpretation of the same PET and CT data. The combination of both methods either performed separately or read side by side or performed with a hybrid PET/CT system detected significantly more malignant lesions than did either CT or PET used as a single method. In addition, the combination of PET and CT ruled out false positive findings of PET or CT, which may have an important impact on staging as well as in selecting therapy options.

PET/CT facilitated diagnosis, especially in the differentiation of physiological bowel activity and pathological glucose utilization in the bowel; such differentiation remains challenging without exact anatomical information derived from simultaneously acquired CT, particularly given that bowel displacement may occur between two separate examinations. In addition,
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treatment planning of radiation therapy as well as of surgical biopsy may be facilitated by the exact anatomical correlation of FDG positive findings (Christian la Fougère et al, 2006).

Nevertheless, the value of PET/CT is mostly related to limited CT image quality, as in, for example, CT of the thorax, which compromises the interpretation of sub-centimetre nodules. Normal anatomical structures such as blood vessels may present an ambiguous appearance (Allen-Auerbach et al, 2006). Optimized co-registration requires use of a normal expiration breath-hold protocol for both CT acquisition and the PET portions of the examination. Furthermore, suboptimal image fusion and attenuation correction may result in misinterpretation of PET images (Bockisch et al, 2004).

In HD, bone marrow infiltration by malignant cells in BMB (Bone Marrow Biopsy) occurs in up to 6.5% (Macintyre et al, 1987). Various predictive factors, including B symptoms, peripheral low cellularity, age over 35 and inguinal involvement, have been established to predict possible bone marrow infiltration by HD (Vassilakopoulos et al, 2005). However, BMB in HD has a low yield and BMI (bone marrow involvement) alone does not define a special high-risk group in which a different treatment approach is indicated (Munker R, et al 1995); accordingly, the need for BMB in all HD patients is questionable (Howard et al, 1995).

In NHL, bone marrow involvement occurs in 30%– 50% and is more common in indolent histologies (Foucar et al, 1982 and Conlan et al, 1990). Regarding the focal lymphomatous involvement of bone marrow, the value of unilateral versus bilateral BMB remains controversial. It has been shown that bilateral biopsy of the iliac crest enhances the diagnostic yield of BMB in HD (22 bilateral BMBs were positive, versus 14 unilateral BMBs) and NHL (237
bilateral BMBs were positive, versus 24 unilateral BMBs) (Wang et al, 2002). These data show that focal bone marrow infiltrations in NHL and HD can pass undetected when using unilateral biopsy.

FDG-PET is superior to CT alone or in combination with unilateral BMB in detecting bone marrow involvement in HD and NHL patients and leads to upstaging in a relevant proportion of patients. In patients with FDG-avid bone lesions, direct PET/CT-guided bone biopsy (Fig 20, 21) seems to be more accurate than standard BMB in confirming bone involvement. In the future, the decision to perform a BMB in patients with HD or NHL and the type of biopsy procedure should thus be guided by the results of FDG-PET/CT as the initial staging procedure.

Fig 20: PET/CT images of a 62-year-old woman with recurrence of HD. A) Axial PET/CT image showing increased FDG uptake in an inguinal lymph node (arrowhead) and the left proximal femur (arrow). B) FDG uptake was used for planning the CT-guided percutaneous bone biopsy. The needle tip (arrow) is in the lesion. Histology was positive for lymphomatous infiltration.
Fig 21: PET/CT images for restaging in a 32-year-old woman with recurrence of HD. A) Coronal maximum intensity projection image showing intense FDG uptake in cervical (upper arrow), mediastinal (lower arrow), axillary (arrow at the left axilla) and iliac (lowest arrow) lymph nodes as well as an FDG-avid lesion in the spleen (short arrow). There are multiple lesions with FDG uptake in the bones (arrowheads; left humerus, pelvis, both proximal femora). B) Bone window of the axial CT image at the level of the upper thorax shows enlarge axillary lymph nodes (arrow) but normal bone structure of the scapula (arrowheads). C, D) Corresponding axial PET image (c) and fused PET/CT image (d) demonstrate intense FDG uptake in enlarged axillary lymph nodes (arrow) and the scapula (arrowheads). BMB was negative in this patient.
As regard to gastrointestinal lymphomas PET is superior to morphologic imaging methods in the assessment of lymphoma and PET/CT has already proved to be the most accurate imaging method (Ho CL, et al 2003), even without a full-dose CT scan (Schaefer NG, et al 2004).
5- PET/CT & Head and neck cancers with thyroid malignancies
1-Head and Neck Carcinomas

Most positron emission tomography (PET) imaging studies in head and neck cancer are performed using the radiotracer 18-fluorodeoxyglucose (18FDG). PET with FDG has become a standard clinical imaging modality in patients with head and neck cancer. It contributes valuable information in localizing a primary tumor in patients with neck nodal metastases from an unknown primary, in the staging of primary head and neck cancer, and in the detection of recurrent disease. In addition, FDG-PET provides independent prognostic information in patients with newly diagnosed and recurrent head and neck cancer. PET/CT improves lesion localization and accuracy of FDG-PET and is strongly recommended in patients with head and neck cancer (Schoder and Henry 2004).

Carcinoma of Unknown Primary of Squamous Cell Origin

Cervical nodal metastases from an unknown primary tumor constitute 2% of newly diagnosed head and neck cancers (Grau, et al 2000). Treatment of these patients in most centers includes extensive fields of irradiation to include the entire pharyngeal mucosa, larynx, and bilateral neck. The wide-field irradiation reduces the risk of tumor recurrence; however it causes significant morbidity, particularly in terms of xerostomia. Correct localization of the primary tumor substantially reduces the complication risk of radiotherapy by decreasing the size of the radiation portal (Mendenhall, et al 2001).

The available literature on the accuracy and usefulness of FDG-PET in patients with carcinoma of unknown primary consists of many single-center
small studies with variable diagnostic workup before the PET scan. Rusthoven and coworkers 2004 recently published a detailed review of FDG PET in carcinoma of unknown primary. The overall detection rate, based on 20 studies between 1992 and 2003, was 24.5% in a total of 302 patients. In a subset of studies in which PET was performed after a negative endoscopy and negative CT and/or MRI, the detection rate was similar, 27% in 150 patients (Wong, Saunders 2003 and Fogarty, et al 2003 and Johansen, et al 2002).

PET probably should be performed as the initial test and biopsies under endoscopy should be directed according to PET findings (Schöder and Yeung 2004). FDG-PET also finds additional local and distant metastases in an average of 27% of patients, which certainly changes the radiation field or the objective of treatment from cure to palliation when distant disease is identified (Rusthoven, et al 2004). One of the limitations of PET in this clinical setting is the relatively high false-positive rate related to variable physiologic uptake of FDG in head and neck structures. Since Gutzeit and coworkers 2005 have reported their initial experience using PET-CT for detection of unknown primary tumors that included 18 patients with cervical nodal metastases. The sensitivity of CT, PET, side-by-side PET and CT evaluation, and co-registered PET-CT were 25%, 25%, 29% and 36%, with no statistically significant difference among the modalities in this small patient population.

**PET for Primary Tumor Staging**

At the time the patient is referred for staging (imaging) studies, the primary tumor has already been diagnosed, and a clinical head and neck examination has assessed the status of lymph nodes in the neck. The first goal of imaging studies is therefore to determine the extent of the primary tumor, in
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particular with regard to structures whose involvement may alter the surgical approach (eg, bone invasion, orbital invasion, skull base invasion, tumor “tracking” along nerves and blood vessels). This can be done by either CT or MRI, and PET has little to contribute in this regard. In the few studies that have addressed the ability of PET and CT/MRI to actually visualize a clinically proven primary tumor, PET generally had a higher sensitivity than other imaging studies. This is related to the fact that smaller or submucosal malignancies may be difficult to distinguish from adjacent tissues with anatomic imaging studies alone. For instance, in a recent study from Australia involving 40 patients with head and neck squamous cell carcinoma (HNSCC) (mostly tumors of the oral cavity), FDG-PET detected 35/40 primaries (88%), compared with CT, which only detected 18 of the 35 primaries imaged (51%). Of the 17 primaries not detected by CT, 11 were clearly visualized by FDG-PET (Hannah, et al 2002).

Nodal Staging

The majority of patients with head and neck cancer present with locally and regionally advanced disease with metastatic spread to cervical lymph nodes. Correct staging of the cervical lymph nodes is critical to determine the necessary extent of surgery (type of neck dissection, unilateral versus bilateral) and for precise delineation of the radiotherapy field. Although the usefulness of 18F-fluorodeoxyglucose (FDG)-PET imaging is currently well established for recurrent head and neck cancers, its role in the initial staging of these tumors is less certain. FDG-PET appears to be at least as sensitive or slightly more sensitive than conventional imaging for the detection of nodal metastases in the initial staging of head and neck cancers. Schöder and Yeung 2004 reported an average sensitivity and specificity range of 87%- 90% and 80%- 93% for FDG-PET compared with 61%- 97% and 21%- 100% for CT/MRI in detection of
nodal metastases, respectively. However, the impact on outcome of improved accuracy of PET in pre-therapy staging of cervical nodes is not well established.

The anatomic information with PET is markedly improved with the use of combined PET-CT systems. PET-CT is almost certainly more accurate than PET alone, although few studies have yet been published comparing PET-CT with other modalities. In a recent pilot study, Syed and coworkers 2005 used PET-CT to study 24 patients with head and neck cancer before their treatment. PET-CT down staged the disease and changed the management in 17% of patients, compared with PET alone, by correctly assigning areas of increased uptake to fat or muscle tissue. PET-CT also significantly improved the confidence in anatomic localization and the inter-observer agreement in assigning lesions to specific anatomical territories. PET-CT, MRI, and multislice CT are all changing rapidly and improving. It is not clear which is currently the most accurate, although the combination of metabolic imaging with PET combined with high-resolution CT is likely to be the most powerful technique (Fig 22).

Patients with head and neck cancer and a clinically negative neck (N0 neck) pose another management dilemma to the treating surgeon. Approximately 25% to 30% of these patients are found to have metastatic neck nodes at surgery. This finding means that the majority of patients with N0 necks, who undergo a neck dissection, are unlikely to have a therapeutic effect from this procedure. Several studies have evaluated FDG-PET in this setting, attempting to identify the patients who need radical neck dissection. In 3 studies totaling 48 patients, in which a sentinel node biopsy with immunohistochemistry was used as gold standard, the detection rate of PET was between 0% and 30%, making PET an unreliable modality in this clinical setting (Hyde, et al 2003 and Stoeckli, et al 2003 and Civantos, et al 2002). This is not
unexpected, given that 40% of cervical nodal metastases are less than 1 cm in size and PET detection rate for nodes less than 1 cm is reported at 71%. Kovacs and coworkers 2004 in a recent report, have proposed to use FDG-PET to identify patients who should undergo sentinel node biopsy versus elective node dissection. Given the high specificity of PET in the pre-therapy setting, they suggest patients with a positive PET scan undergo a neck dissection whereas a sentinel node biopsy should be performed in patients with a negative PET scan. In their population of 62 patients with head and neck cancer, this algorithm spared unnecessary neck dissections on 12 neck sides with false-positive CT findings and a negative sentinel node biopsy.
Fig 22: Right tonsillar squamous cell carcinoma. It often is uncertain whether a tonsillar carcinoma arises in the lingual tonsil or palatine tonsil. In reality, these carcinomas frequently arise in the anterior tonsillar fold, which is probably where this carcinoma arose. Tonsillar carcinoma is the most common type of cancer in the neck. These tumors frequently metastasize to ipsi-lateral IIA lymph nodes. PET-CT imaging is worthwhile when there is clinical or CT evidence of metastatic disease. In this setting PET-CT often reveals additional disease, even occasionally contra-lateral, which changes management considerably. Currently, is does not seem to be worthwhile to do PET-CT imaging if there is no evidence of metastatic disease (i.e., the N0 neck) because microscopic disease is frequently present and will not be detected by FDG-PET imaging.
Assessment of Distant Metastases and Synchronous Second Primary Malignancies

Distant metastases are rare in patients with head and neck cancers, but the frequency increases with higher T-stage and size and number of tumor-involved lymph nodes. Patients with nodal metastases in the lower neck or supraclavicular region have a higher chance for distant metastases, too. In general, patients with HNSCC have a higher propensity for synchronous second primaries as compared with many other malignancies (Anzai, et al 2003). For instance, in a smaller series evaluating the role of FDG imaging in head and neck cancer, Stokkel and coworkers 1999 found a synchronous second primary in 12 of 68 patients in their series, although a technically inferior dual-head gamma camera was used. Five of these second primaries were also detected by clinical examination, chest radiograph or CT, so that the PET detection rate was really 7/68, or 10%.

In a recent prospective study of patients with stage II-IV carcinoma of the oral cavity, oropharynx and larynx, FDG-PET detected distant metastases or synchronous second primary tumors in the aerodigestive tract in almost 30% of cases (7 distant metastases and 3 synchronous second primary tumors) (Schwartz, et al 2003). Based on the experience a second primary or distant metastases outside the neck will be detected in 3-8% of cases, depending on the stage and location of the primary tumor. Indeed, this was also reported in a large retrospective analysis, unrelated to PET imaging, where the risk for synchronous second primary tumors also approached 8% (Schwartz, et al 1994).
FDG-PET has good sensitivity and specificity for the detection of primary tumors in the upper aero-digestive tract and a higher accuracy for nodal staging of the neck than any other imaging modality. Distant metastases or synchronous second primary tumors are occasionally detected; therefore, the imaged field of view should extend from the skull base to the floor of the pelvis (Schoder and Yeung, 2004).

**Role of PET in Treatment Planning**

Depending on the stage and location of the disease, treatment options in head and neck cancer include surgery, radiation therapy alone, or radiation therapy in combination with (concurrent) chemotherapy, possibly followed by surgery. If surgery is the primary treatment modality, this may be followed by radiation therapy, depending on the stage and aggressiveness of the primary tumor, status of surgical margins etc. CT and MRI rely on structural changes and are notoriously unreliable in this setting. Because of treatment related edema and inflammation, which may cause alteration of normal tissue planes and nonspecific enhancement after administration of intravenous contrast, these studies frequently can not assess the presence of residual disease with sufficient accuracy. Metabolic PET imaging contributes valuable information in this setting. It allows for the early detection of local and regional disease whose treatment will improve local disease control with the extrapolation that this will also improve survival or at least quality of life (Schoder and Yeung, 2004).

A number of studies have shown that PET can monitor the response to chemo- or radiation therapy in patients with head and neck cancer and may differentiate responders from non-responders; metabolic changes during therapy appear to correlate with tumor growth rate (Reisser, et al 1995 and Kitagawa, et al 2003).
Brun and coworkers 2002 studied 47 patients with head and neck cancer undergoing radical radiation- or combined chemo-radiation therapy. Almost two thirds of these patients had stage IV disease. FDG-PET was performed before and 1 to 3 weeks after the initiation of therapy (i.e., during the course of treatment). PET data were analyzed using SUV and quantitative measurements (metabolic rate of glucose, MRGl). Patients with complete response had, on average, lower post-treatment SUV and MRGl than those without complete response, but there was considerable overlap. Interestingly, the pretreatment SUV was lower in patients who showed a complete response to therapy (median 8.0 versus 12.0). Post-treatment SUV was not different between responders and non-responders (median 4.4 versus 7.7), but quantitative measurements showed lower glucose metabolism in responders as compared with non-responders (MRGl median 14 versus 27 umol/min/100 g).

Goerres and coworkers 2004 studied 26 patients with stage III-IV HNSCC, and PET was performed at 6 weeks after the end of combined chemo- and radiation therapy (median dose 70 Gy). PET correctly detected residual disease in 10 patients (38%) and correctly excluded residual disease in 14 patients; one patient each had a false-positive and false-negative study. Hence, the sensitivity and specificity were 91% and 93%, with an accuracy of 92% for the detection of residual disease, metastases or second primaries. Interestingly, in 2 patients the 6-week PET also revealed a second primary tumor or distant metastases, which had not been detected at the time of initial staging.

In patients with locally advanced disease, chemotherapy or combined chemo- and radiation therapy are also used in the neoadjuvant setting. PET contributes valuable information in this setting. For instance, FDG-PET appeared to distinguish accurately between responders and non-responders to
neoadjuvant chemotherapy in an organ-conservation protocol. All 27 patients enrolled had tissue biopsies taken before and after therapy. At the end of treatment 21 patients were found to be responders and 6 to be non-responders. Using visual analysis and SUV, the study had a sensitivity of 90% and specificity of 83% (Lowe, et al 1997).

In another study in 15 patients undergoing neoadjuvant chemoradiation therapy, lesions with higher pretreatment SUV (>7) showed residual viable tumor cells after treatment in 3 of 8 cases, whereas all lesions with SUV <7 were treated successfully (Kitagawa, et al 1999). All 7 tumors with post-treatment SUV of <4 showed no viable cells on resection, whereas 3/7 tumors with post-treatment SUV >4 did show residual viable tumor cells. In another study in 23 patients the same authors separately analyzed the accuracy of various imaging modalities for the assessment of residual disease after neoadjuvant chemo-radiation therapy (Kitagawa, et al 2003). FDG-PET was more accurate than MRI or CT in detecting residual disease (specificity 89% versus 41%, 59%) in the primary tumor following treatment, although no such difference was noted for nodal metastases.

Greven and coworkers 1994 have repeatedly investigated the role of FDG-PET in the assessment of response to radiation therapy. The authors concluded that imaging at 4 months after radiation therapy was more accurate than at 1 month. However, it needs to be emphasized that no imaging studies were acquired between 1 and 4 months. In our own experience a time interval of 6 to 8 weeks after treatment is usually sufficient to avoid most false positive and false negative findings (Schoder and Yeung, 2004).

FDG-PET has the ability to detect patients with more aggressive disease before therapy and to differentiate between responders and non-
responders to (chemo-) radiation therapy. However, most studies suffer from limitations related to small sample size and the methods of data analysis (data dichotomized based on median SUV in study population, use of arbitrary cut-off values etc.). In addition, quantitative measurements of FDG utilization, as used in some of these studies, are not practical in a clinical routine setting. Larger, prospective studies in a well-defined setting are needed to determine the clinical value of PET in these patients conclusively.

It is now clearly established that FDG-PET has a high sensitivity and specificity for the detection of recurrent disease in patients with head and neck cancer, regardless of the primary treatment modality used (surgery versus radiation therapy) (Wong, et al 2002 and Kunkel, et al 2003). A patient example is shown in (Fig 23). As a rule, clinically detectable recurrent disease is extremely unlikely in the setting of an entirely negative PET scan. FDG uptake, not related to tumor, can sometimes cause false positive (non tumor-related FDG uptake considered to represent tumor; see (Fig 24) or false negative (tumor-related FDG uptake misinterpreted as normal variant, inflammation) interpretations. With adequate patient preparation, certain sources of non tumor-related FDG uptake can be eliminated or at least correctly identified (e.g., laryngeal muscle uptake, radioactive saliva in the throat or vallecula epiglottica, nonspecific FDG uptake in brown fat tissue of the neck) but others cannot (treatment-related inflammation). Nevertheless, some false positive findings may be unavoidable. Accordingly, the sensitivity for the detection of recurrent head and neck cancer is consistently high, but specificity in the treated post-surgical area is lower than elsewhere in the neck or at remote sites, such as lung or bone. Across all studies the negative predictive value is consistently high. Therefore, one can conclude that patients with suspected recurrence but negative PET scan do not require any further evaluation. In contrast, positive predictive value and specificity are somewhat lower for local recurrence at or near the site
of the primary tumor, related to a number of false-positive findings. Nevertheless, if used in a clinical algorithm, a positive PET scan requires a biopsy; if this biopsy is negative for recurrent cancer and does not provide reasons for a false-positive PET scan (inflammation, infection, radiation necrosis etc.), close clinical follow-up and potential repeat biopsy may be required. If the biopsy is negative, a follow-up PET scan is suggested 2 to 3 months later. If the SUV decreases, malignancy is unlikely and no further intervention is needed. If the SUV is unchanged or increases, repeat biopsy is suggested, unless there is another obvious explanation, such as infection, fistula or radio-necrosis (Kunkel, et al 2003).

The first year of follow up notably, 5/16 recurrences were detected by PET only, while the other recurrences were also identified by CT/MR or clinical examination. Early detection of recurrent disease is likely to improve the success rate for any secondary therapy, but it is nevertheless difficult to justify such a surveillance strategy without further supporting data. Moreover, PET studies for the sole purpose of surveillance are currently not reimbursed (Wong and Saunders, 2002).
Fig 23: recurrent disease in a 72-year-old male status post-esophagectomy with gastric pull-up, now presenting with dysphagia and hoarseness. Coronal (A) and Sagittal (B) positron emission tomography images show abnormal fluoro-deoxy-glucose (FDG) uptake in the anterior–superior mediastinum, consistent with malignancy with central necrosis. Additional coronal image (C), in a more anterior position and trans-axial image (D) show FDG uptake in the left hemilarynx. This represents normal tracer uptake in the left vocal cord; the abnormal finding in this study is the lack of FDG uptake in the right hemilarynx due to paralysis of the right recurrent laryngeal nerve, caused by the mediastinal mass (computed tomography image, E).

Fig 24: False-positive study of a 65-year-old male, status post chemo- and radiation therapy, for carcinoma at the base of tongue, now presenting with pain and trismus. Positron emission tomography images show abnormal fluoro-deoxy-glucose uptake in the left mandible (A, coronal; B, Sagittal; C, trans-axial). Physical examination revealed exposed, necrotic appearing bone of the mandible. Debridement and curettage were performed; the specimen showed acute and chronic osteomyelitis.
**Radiotherapy Planning**

PET-CT with FDG is highly accurate in pre-radiotherapy staging of head and neck cancer, with a reported sensitivity of 96% and specificity of 98.5% in nodal level staging (Schwartz, et al 2005). FDG uptake in tumors is also a prognostic indicator, with tumors with high FDG uptake reported to have a high recurrence rate and poor prognosis (Allal, 2004). These tumors may therefore require multimodality treatment and may benefit from high-dose radiation such as obtained with intensity-modulated radiotherapy (IMRT). FDG-PET data can be used in radiation treatment planning by importing the PET data into the treatment planning computer and co-registering with the treatment planning CT scan. For precise co-registration, the same immobilization head mask should be used for the planning CT and the PET or PET-CT scan (Fig 25). In a pilot study by Ciernik and coworkers 2003 the co registration of PET-CT with the planning CT images was highly successful with average deviations of 1.2 +/- 0.8 mm in the x axis, 1.5 +/- 1.2 mm in the y axis and 2.1 +/- 1.1 mm in the z axis. In the clinical setting, Paulino and coworkers 2005 have been able to consistently obtain a co registration error of less than 5 mm. The target volumes (gross tumor volume [GTV]) may be significantly modified when FDG-PET data are incorporated into radiation treatment planning. The target volume may be increased because metabolically active tumor can be detected in normal sized nodes. On the other hand, the PET-based GTV is smaller than CT-based GTV in some patients, because the tumor may be partially necrotic. The radiation dose and volume are modified dramatically, from a curative intent to palliation, if distant metastases are detected on the PET scan. The results of several studies on the use of PET in radiation treatment planning are summarized in (Table 4).
A recent study of 20 patients with mostly locally advanced disease demonstrated an increase in sensitivity with hybrid PET/CT compared with CT alone (Schwartz et al, 2005). The authors showed that PET/CT-based radiation treatment would have significantly changed the dose distribution. These findings need to be confirmed prospectively with larger study populations before this technique can be implemented in routine use.

A number of other studies have compared radiotherapy volumes based on PET-CT vs. CT alone. These studies showed both an increase and a decrease in GTV planned using PET-CT over CT alone (van Baardwijk et al, 2006).

In head and neck cancers, the functional data of the hybrid PET-CT may augment the delivering of radiotherapy. Undoubtedly, the greatest advantage of PET in radiation planning will be in the definition of tumor-bearing tissues. Dwight et al, 2004 demonstrated that PET and CT volumes were different, which resulted in inclusion of additional tumor-bearing areas to the planning target volume. Instead of resulting in the expansion of the PTV, the additional PET information would actually result in a smaller PTV by improving location of the CTV. Furthermore, the PET data are unlikely to change the initial PTV, but, as occurred in our experience, may influence the size and configuration of boost PTV by identifying suspicious areas for inclusion (Fig 26).

Some authors also have demonstrated fused FDG-PET with CT and MRI can be useful in determining radiation target volumes for 3-D conformal radiation therapy (Fig 27) for head and neck (Nowak et al, 1999 and Lenz et al, 2000). These data suggests that PET can be used effectively to select targets for treatment without compromising local control in FDG-negative areas.
Prospective studies are needed to define whether contours for treatment volumes can be based on PET-CT imaging. This application may offer real opportunities for dose escalation schemas and treatment algorithms aimed at improving loco-regional control in advanced cases. Other authors who compared PET with the current diagnostic methods had similar observations (Hannah et al 2002, and Goerres et al, 2003).

Fig 25: Hybrid positron emission tomography-computed tomography (PET-CT) simulation setup. PET-CT table is modified by the addition of a radiation-planning couch planchet. Note head holder secured to planchet. Patient in treatment-planning position in hybrid scanner (inset).
### Table 4: FDG-PET in Radiation Therapy Planning

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Number of Patients</th>
<th>PET or PET/CT for PET imaging</th>
<th>Change in GTV With PET</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nishioka et al</td>
<td>2002</td>
<td>21</td>
<td>PET</td>
<td>increased in 1/21; decreased in 1/21</td>
<td>Sparing of the parotid in 71% of pts with negative PET</td>
</tr>
<tr>
<td>Ciernik et al</td>
<td>2003</td>
<td>12</td>
<td>PET/CT</td>
<td>increased in 2/12; decreased in 4/12</td>
<td></td>
</tr>
<tr>
<td>Scarfone et al</td>
<td>2004</td>
<td>6</td>
<td>PET</td>
<td>Increased in 5/6</td>
<td></td>
</tr>
<tr>
<td>Paulino et al</td>
<td>2005</td>
<td>40</td>
<td>PET/CT</td>
<td>Decreased in 30/40 and increased in 7/40</td>
<td>PET/CT based GTV not included in the high dose IMRT area in 25% patients with CT-only based GTV.</td>
</tr>
<tr>
<td>Schwartz et al</td>
<td>2005</td>
<td>20</td>
<td>PET</td>
<td>Not reported for individual patients; mean PET/CT based GTV not significantly different from CT only based GTV.</td>
<td>Mean contralateral parotid and laryngeal cartilage dose significantly smaller with PET/CT based GTV.</td>
</tr>
</tbody>
</table>
Fig 26: Squamous cell carcinoma involving the right lateral oral tongue. The 3 orthogonal views clearly show the focus of increased uptake is in the lateral tongue. This lesion is a T1 tumor (< 2 cm).
Fig 27: A right posterior nasopharyngeal squamous cell carcinoma. The nasopharynx is the upper part of the pharynx, above the soft palate. Early stage nasopharyngeal cancer, such as the one shown, usually is treated with radiotherapy. PET-CT imaging is used to identify any metastases and to define extent of disease to guide radiotherapy treatment planning.
2- Thyroid Carcinomas

After thyroidectomy, FDG-PET has proven useful in patients with clinical or serological evidence of recurrent or metastatic thyroid carcinoma but negative whole body iodine scan. PET shows metastatic disease in up to 90% of these patients, thereby providing a rational basis for further studies and therapy. In patients with medullary thyroid cancer with elevated calcitonin levels following thyroidectomy, FDG-PET has a sensitivity of 70-75% for localizing metastatic disease. Occasionally incidental intense FDG uptake is observed in the thyroid gland on whole body PET studies performed for other indications. Although diffuse FDG uptake usually indicates thyroiditis, focal uptake has been related to thyroid cancer in 25-50% of cases and should therefore be evaluated further if a proven malignancy would cause a change in patient management (Schoder and Yeung, 2004).

- Differentiated Thyroid Cancer (DTC)

Early studies found a low sensitivity of FDG-PET in the detection of metastases (Joensuu et al, 1988). However, others reported a sensitivity of 50% in 58 unselected patients with DTC, thyroidectomy and prior radioactive iodine (RAI) ablation, (Dietlein et al, 1997) and in a large multi-center study with unselected patients, the sensitivity of FDG-PET for localizing metastatic disease in patients with DTC was 75 % (Grunwald et al, 1999).

Helal and coworkers 2001 prospectively looked at 37 patients with DTC who had undergone resection, RAI ablation and presented with elevated thyroglobulin levels but negative whole body scan (WBS). FDG-PET scan was
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Positive in 28 patients (76%); including 19 of 27 patients with no previously detected metastases by conventional imaging. In a prospective study of 24 patients with DTC, negative WBS and elevated thyroglobulin levels, Frillings and coworkers 2001 reported a sensitivity of 94.6% in the detection of metastases, with specificity of 25%. PET results changed surgical tactics in 9/24 patients.

Schluter et al 2001 studied 118 PET scans in 64 thyroid cancer patients with elevated serum thyroglobulin (n= 48) or clinical suspicion of metastases (n = 16) and negative WBS. The positive predictive value of FDG-PET scan was 83% (34/41) whereas the negative predictive value was 25% (5/20). Treatment was directly changed in 19/24 patients with true positive PET studies (30% of the entire cohort). They also pointed out that true positive FDG-PET findings were correlated positively with increasing serum thyroglobulin levels.

In addition to lesion detectability, there is also evidence that FDG-PET is an independent prognostic indicator in thyroid cancer. In a study by Wang and coworkers 2000, which included 125 patients with negative WBS, positive FDG-PET, elevated thyroglobulin with a clinical follow-up of up to 41 months, multivariate analysis demonstrated that the single strongest predictor of survival was the volume of FDG-avid disease. More recently the same group showed strong inverse correlation between the SUV for FDG uptake in metastatic lesions and survival in thyroid cancer patients.

- Hurthle Cell Carcinoma

Hurthle cell cancer is a histologic subtype of DTC that is clinically more aggressive. The tumor frequently shows little or no iodine uptake, but can
be identified with FDG-PET: a meta-analysis of two studies and 35 patients showed a sensitivity of 92% and specificity of 82% (Plotkin et al, 2002). A sensitivity of 92% (12/13 patients) was also reported in another recent study (Lowe, et al 2003). More importantly, in 7 of these 13 patients PET showed disease not identified by other imaging methods.

- **Anaplastic Thyroid Cancer**

  This is an extremely aggressive tumor and imaging is not required for staging, since all patients are classified as stage IV at diagnosis. As a result FDG-PET scan in anaplastic thyroid cancer has not been studied systemically. However, in some case reports (Joensuu et al, 1988) this malignancy usually shows intense FDG uptake, and in selected cases FDG-PET may be helpful in directing treatment and evaluating the efficacy of therapy (Fig 28).

- **Medullary Thyroid Cancer**

  Medullary thyroid cancer is a rare calcitonin secreting tumor originating from the para-follicular C cells. The primary treatment modality is surgical resection. A PET study may be requested in patients with high serum calcitonin level after surgery. The number of patients studied for this purpose is limited, but it appears that FDG-PET can identify metastatic disease more frequently than other imaging studies. A study of 20 patients reported a sensitivity of 76 %, (Brandt-Mainz et al, 2000) and in a large multi-center study the sensitivity of 78% among 55 patients in whom histologic confirmation was obtained (Diehl et al, 2001). Interestingly, there was no correlation between the calcitonin level and the probability of lesion detection. Indeed it has been suggested that more undifferentiated cancer, which secretes less calcitonin, may show higher FDG uptake, analogous to the situation in DTC. Novel, more
specific PET tracers, such as 6-18F-fluorodopamine or 18F-DOPA may be more appropriate for the detection of recurrent or metastatic medullary thyroid cancer.

Fig 28: Anaplastic thyroid carcinoma. This 52-year-old male patient had local tumor recurrence after a complete thyroidectomy for anaplastic thyroid cancer. Positron emission tomography for staging of recurrent disease (A) showed intense fluorodeoxyglucose uptake in the right thyroid bed and a right supraclavicular lymph node. He was treated with external beam radiation and chemotherapy with good response, both clinically and on follow-up positron emission tomography (B). Three years later he was still alive and disease free.
6- PET/CT & Breast cancer and female genital system
1-Breast cancer

Breast cancer is the most common non-skin cancer and the second leading cause of cancer death in women (Greenlee et al, 2000). The ability to define the extent of disease, to monitor response, and to predict tumor behavior in patients with breast cancer are therefore important public health problems where positron emission tomography (PET) imaging may play a significant role (Hortobagyi, 2000).

Weaker correlation has been reported with micro-vessel density, a surrogate of angiogenesis and tumor cell density (Avril et al, 2001). Established breast cancer prognostic factors that generally do not correlate with primary tumor FDG uptake are steroid receptor status, axillary node status, and tumor size (Crippa et al, 1998).

Detection of primary breast cancer

FDG-PET has been evaluated for diagnosis, staging, restaging and monitoring therapy response in patients with breast cancer. Although the current data suggest that FDG-PET may have limited diagnostic utility in the detection of small primary tumors, in staging the axilla, and in detecting blastic osseous metastatic lesions, but PET has superiority over conventional imaging in detecting distant metastasis and recurrent disease and in monitoring therapy response. FDG localization is significantly higher in ductal carcinoma than in lobular (median SUV 5.6 for infiltrating ductal carcinoma vs. 3.8 for lobular carcinomas). Breast density and hormonal status affect the FGD uptake in breast tissue. Dense breasts demonstrate higher FDG uptake than non dense breasts.
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however the highest SUV observed in dense breasts is relatively low at about 1.4 (Bos et al, 2002).

PET is also useful in the evaluation of patients with augmented breasts in whom the other traditional diagnostic imaging techniques may be inconclusive. For the diagnosis of breast cancer, lesion detectability appears more with delayed scan time of 3 hours more than the usual time of 1-1.5 hours (93% vs. 83% respectively) after intravenous injection of FDG.

Many studies have shown that the level of FDG uptake in primary breast tumors carries clinical and biological information (Buck et al, 2002 and Mankoff et al, 2002). The reason for variable FDG uptake among primary breast tumors is unknown. FDG uptake reflects the culmination of complex and incompletely understood biologic characteristics that affect glycolysis in a specific tumor. Most studies suggest that higher FDG uptake is correlated with more clinically aggressive behavior. This information may help to non-invasively (1) stratify patients according to risk for recurrence or treatment failure and (2) target the aggressiveness of therapy for an individual patient to the aggressiveness of her tumor (Bos et al, 2002).

Most of the large prospective studies using FDG-PET on patients with unconfirmed, suspicious breast abnormalities by clinical or mammographic examinations have shown some of the limitations of FDG-PET in detecting (1) Smaller (<1 cm) tumors, (2) More well-differentiated histologic grade and (3) Tumor histologic subtypes (tubular carcinoma, in situ carcinoma and lobular carcinoma).
Avril et al, 2000, found that the sensitivity for detecting tumors less than 1 cm using sensitive imaging reading criteria (sensitive image reading (SIR) was achieved by including probable (grade 2) and definite (grade 3) malignant lesions.) (PET scans with regional FDG uptake within the background activity of normal breast tissue were considered grade 1 (unlikely), PET scans with diffuse or moderate focally increased FDG uptake were considered grade 2 (probable), and cases with focally marked increased FDG uptake were considered grade 3 (definite) to represent malignant tissue) was 57% (13/22), compared with 91% (155/170) for tumors larger than 1 cm. The sensitivity for detecting carcinoma in situ was even lower at 25% (3/12), and there was a significantly higher false-negative rate with infiltrating lobular carcinoma (65% [15/23]) than infiltrating duct carcinoma (24% [23/97]). The specificity of FDG-PET in differentiating benign from malignant lesions was near 90% in most of these studies with inflammatory conditions accounting for most of the false positive results. Using SUV (STANDERIZED UPTAKE VALUES) threshold values of 2.0 to 2.5) discrimination of benign from malignant lesions can be obtained with about 90% accuracy (Avril et al, 1996 and Hoh et al, 1993). A larger percentage of invasive lobular carcinomas are not detected (65% in one study), possibly due to low tumor cell density, its infiltrative nature, and low metabolic activity (Vranjesevic et al, 2002).

In general, correlative studies have suggested that FDG-PET provides information on tumor behavior that is fairly independent of established breast cancer markers and prognostic factors and may therefore contribute additional information that can be used to infer tumor behavior and help tailor therapy (Eubank and Mankoff, 2004).

Additional insights into tumor biology brought on by the development of newer PET tracers such as 11C-thymidine (marker for cellular proliferation)
and 18F-fluoromisonidazole (marker for tumor hypoxia) will further refine in vivo characterization of individual tumors (Mankoff et al, 2000).

Fig 29: left breast cancer the right photo is FDG-PET image which show intense accumulation of FDG, while the left image is a correlated CT to the same area.
Fig: 30 a multi-focal left breast cancer, the upper image show the CT slides of the lesions, but FDG-PET confirms the nature of these lesions.
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**Fig 31:** IDC in the breast due to better lesion localization. On PET alone, the intense focus of FDG uptake in the right anterior lateral portion of the thorax (black arrow) was difficult to differentiate from axillary lesions, which were observed in the same slice. The FDG uptake was confirmed to be a breast lesion with the help of the CT mapping image (white arrow on CT and fusion images).

**Fig 32:** in the chest wall due to better lesion characterization. The focus of moderate FDG uptake in the left anterior medial portion of the thorax (black arrow) was considered as equivocal on PET alone. The anatomical and morphological information provided by CT (white arrow on CT and fusion images) allowed characterization of the FDG uptake as a malignant lesion in the chest wall.
Axillary Node Staging

FDG PET has limited sensitivity in staging the axilla in patients with early breast cancer, with a false-negative rate that may reach 20%. A recent prospective multi-centre study of axillary nodal staging with FDG PET demonstrated mean sensitivity, specificity, positive and negative predictive values of 61%, 80%, 62% and 79%, respectively. FGD PET appears to be a specific method for staging the axilla such that sentinel lymph node biopsy may be avoided in patients with positive axilla on the PET study. The overall sensitivity and specificity for detection of the axillary metastasis on FDG PET do not appear to be related to the SUV of the primary carcinoma. The differences among studies in the reported diagnostic performances of PET in relation to axillary nodal staging are likely because of several factors, including differences in tumor type, the prevalence of disease in the study population, the imaging methodology, and the image interpretation criteria. However, detection of micro-metastases and small tumor infiltrated lymph nodes is limited to the spatial resolution of the current PET imaging systems. The larger series using FDG-PET for axillary staging in breast cancer patients showed sensitivity in 57% to 100% and specificity in 66 to 100% ranges, (Wahl et al, 2004) shown in Table (5) emphasize the trade-off between sensitivity and specificity in the interpretation of FDG-PET findings.

Lovrics et al, 2004 and Wahl et al, 2004 FDG-PET consistently underestimated the number of tumor-involved nodes compared with pathologic evaluation from conventional axillary dissection. Both of these studies showed that the sensitivity of FDG-PET in detecting axillary metastases is significantly less when only one node is positive versus several positive nodes and when the primary tumor has infiltrating lobular versus ductal histology.
Recent studies comparing preoperative FDG-PET with pathologic results from sentinel L.N. (SLN) biopsy in patients with early-stage breast cancer show sensitivity in range of 20% to 50% (Table 6) with false-negative FDG-PET results occurring predominantly in small-sized (10 mm or less) metastatic sentinel nodes (Barranger et al, 2003).
Table 6: Large Series Comparing Axillary Nodal Staging Using FDG-PET with Pathologic Results of Sentinel Node Lymph Node Biopsy in Breast Cancer

<table>
<thead>
<tr>
<th>Series</th>
<th>Specificity</th>
<th>Sensitivity</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yang, 2001</td>
<td>100%</td>
<td>50%</td>
<td>18</td>
</tr>
<tr>
<td>Kelemen, 2002</td>
<td>90%</td>
<td>20%</td>
<td>15</td>
</tr>
<tr>
<td>Guller, 2002</td>
<td>94%</td>
<td>43%</td>
<td>31</td>
</tr>
<tr>
<td>Van der Hoeven, 2002</td>
<td>97%</td>
<td>25%</td>
<td>70</td>
</tr>
<tr>
<td>Fehr, 2004</td>
<td>93%</td>
<td>20%</td>
<td>24</td>
</tr>
<tr>
<td>Lovrics, 2004</td>
<td>96%</td>
<td>27%</td>
<td>72</td>
</tr>
</tbody>
</table>

Although recent data do not support the routine use of FDG-PET for axillary staging of early breast cancer, FDG-PET may be complementary to SLN mapping and other standard axillary procedures in patients with more advanced tumors and/or equivocally palpable axillary nodes (Schirrmieister et al, 2001).
Detection of Loco regional recurrences and Distant Metastases

FDG-PET can contribute in significant ways to the clinical management of patients with suspected locoregional or distant recurrences. Because it provides functional information, FDG-PET often is complementary to conventional staging methods such as physical examination, cross-sectional imaging (CT or MR) and bone scintigraphy, which rely more on changes in morphology to detect disease recurrence. This is particularly true in the evaluation of anatomic regions that have been previously treated by surgery or radiation where the discrimination between post-treatment scar and recurrent tumor can be problematic. Because of its high sensitivity in the detection of metabolically active tissue, FDG-PET can help define the extent of disease when conventional imaging (CI) is equivocal or negative and recurrence is suspected. Earlier recognition of recurrent disease will hopefully provide more effective treatment options and improve survival in this group of patients (Fig. 34) (Eubank et al, 1998).

Lymphatic spread of tumor to the internal mammary (IM) nodes occurs in up to 25% of patients at the time of initial diagnosis and possibly more commonly in recurrent cancer. Metastases to IM and axillary nodes are usually synchronous and prognosis is significantly worse when IM nodes are involved (Cody et al, 1995). However, IM nodes are not routinely sampled or evaluated in any systematic fashion in current practice because (1) compared with axillary nodes, they are not as accessible and (2) in older studies, radiotherapy of IM nodal disease failed to show improvements in survival and remains controversial in current practice (Sugg et al, 2000). FDG uptake in the IM nodal chain has
been anecdotally reported in some of the studies that have focused on detection of primary tumor or axillary staging. In one study of 85 patients who underwent FDG-PET before axillary node dissection, (14%) had uptake in the IM region but there was no histologic confirmation of these nodes (Bellon et al, 2004). Experience with imaging patients with LABC shows that the prevalence of IM FDG uptake can be as high as 25% and that the presence of IM FDG uptake predicts treatment failure patterns of disease consistent with IM nodal involvement and progression (Fig.33).

Fig 33: IDC in the internal mammary node due to better lesion localization. Positive PET/CT and equivocal CT findings. The smaller focus of intense FDG uptake in the right anterior medial portion of the thorax (black arrow) was difficult to definitely localize on PET alone. CT and fused PET/CT images confirmed that the FDG uptake was localized in the small internal mammary lymph node (white arrow on CT and fusion images), which was diagnosed as equivocal on CT owing to its small size of less than 1 cm.
Fig 34: The patient shown in the case below had a history of breast cancer and had developed left chest pain. She presented for the evaluation of possible metastatic disease. The CT scan revealed extensive soft tissue thickening in the left breast which was felt possibly related to scar from prior surgery and radiation therapy. There was a 2 cm lymph node in the left axilla (not shown) which was concerning for metastatic disease. Axial (center) and coronal (right) images from the patients FDG PET exam demonstrated marked increased FDG accumulation within the left breast corresponding to the soft tissue abnormality on CT. There were also multiple foci of increased uptake within the left axilla. Biopsy revealed recurrent breast cancer.

The skeleton is the most common site of distant metastasis in breast cancer. Bone scintigraphy is considered the most sensitive method of detecting and determining the extent of skeletal metastases. However, purely lytic lesions or metastases confined to the marrow cavity may be difficult to detect on bone scan because of a lack of sufficient osteoblastic response (Nielsen et al, 1991).

In a study of 23 breast cancer patients with known skeletal metastases who underwent both bone scintigraphy and FDG-PET, Cook and coworkers, 1998 showed that FDG-PET detected more lesions than bone scintigraphy
except in a subgroup of patients with osteoblastic metastases. Moreover, the level of FDG uptake in lytic lesions was significantly greater compared with osteoblastic lesions and the prognosis of patients with lytic-predominant disease was significantly worse. These data clearly show a complementary nature of bone scintigraphy and FDG PET in the evaluation of skeletal metastases in breast cancer patients (Fig 35, 36).

Fig 35: IDC in the rib due to better lesion characterization. The focus of intense FDG uptake in the right lateral portion of the thorax (black arrow) was difficult to characterize as axillary, rib, or other lesions on PET alone. CT and fused PET/CT images confirmed this FDG focus to be due to a metastatic rib lesion (white arrow on CT and fusion images)
In a prospective study of 50 women undergoing staging studies for suspected recurrent breast cancer, FDG-PET had a significant impact on defining the extent of disease by changing the clinical stage in 36% of patients and on management by inducing changes in therapy in 58% of the patients.

In retrospective study of 125 patients with advanced breast cancer undergoing conventional imaging and FDG-PET for staging, the extent of disease was changed in 67% (increased in 43% and decreased in 24%) of patients and the therapeutic plan was altered in 32% of patients based on FDG-PET findings. Among different referral categories, FDG-PET altered therapy most frequently in patients suspected of locoregional recurrence, under consideration for aggressive local therapy (44%) and patients with known
metastases being evaluated for response to therapy (33%) (Fig. 37) (Eubank et al, 2004).

The need for a more sensitive staging tool in patients with first-episode locoregional recurrence was recently corroborated by van Oost and coworkers, 2004 their study of 175 patients showed that 16% had distant metastases at the time of locoregional recurrence and 24% developed distant metastases within 18 months of confirmation of recurrence. They estimated that FDG-PET would upstage and likely change the therapeutic plan, in up to 29% of patients with negative conventional staging studies.
Fig 37: Patient treated for breast cancer with recurrence in the left mammary region (arrow in the PET/CT fused image)
**PET/CT and radiotherapy**

Other than the localization per se, the pixel by pixel correspondence of PET and CT may significantly modify our evaluation of tumor extension. So far, the role of PET in oncology has mainly been to assess lymph node (N) and distant metastases (M), rather than to determine tumor extension and its relationship with surrounding tissues (T). PET/CT is changing this role by integrating the information on tumor morphology provided by CT with that on its metabolism and, particularly, on the number of neoplastic viable cells (Ciernik et al, 2003).

During the follow-up of breast cancer, as already reported, the frequency of recurrence or metastatic lesions is high, particularly for large primary tumors (>2 cm) or a tumor stage of >N1. One possible treatment when recurrent/metastatic lesions are limited in number and extension is high-dose radiotherapy, such as stereo-tactic radiotherapy or radio-surgery. We believe that PET/CT can play a major role in these cases by (a) correctly staging the disease and (b) providing an accurate estimate of tumor volumes to be selectively irradiated, characterized for their biological activity (biological target volume). Although PET with co-registered CT via software algorithms can provide similar information on biological target volume, the availability of a dual PET/CT tomography certainly facilitates such application, and will thus hopefully improve the therapeutic effects of radiotherapy procedures (Dizendorf, 2003).
**2-Uterine cancers**

Although FDG PET may significantly improve the management of patients with gynecological cancers, inherent technical and biological limitations have been shown to impair both the sensitivity and specificity of metabolic imaging. Causes of inaccuracies with FDG PET in uterine cancers are summarized in (Table 7) (Nakamoto et al, 2002).

### Table 7: Causes of Inaccuracies with FDG PET in Uterine Cancers: Literature Data

<table>
<thead>
<tr>
<th>Causes of False Negative Results</th>
<th>Causes of False Positive Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Small (&lt; 1cm) or microscopic disease: cervix, nodes.</td>
<td>- Ureteral stasis</td>
</tr>
<tr>
<td>- Stromal invasion</td>
<td>- Bowel retention</td>
</tr>
<tr>
<td>- Parametrial involvement</td>
<td>- Post-radiation changes</td>
</tr>
<tr>
<td>- Indolent malignant disease</td>
<td>- Post-surgery changes</td>
</tr>
<tr>
<td>- Previous radiotherapy</td>
<td>- Recent traumas</td>
</tr>
<tr>
<td>- Low glucose transporter-1 (GLUT-1) expression</td>
<td>- Inflammation / Infection: reactive nodes, granulation tissue, anthracosis, endometriosis, tuberculosis</td>
</tr>
<tr>
<td>- Lack of anatomic landmarks</td>
<td>- Functional ovarian cysts.</td>
</tr>
<tr>
<td></td>
<td>- Ovulatory and menstruating phases.</td>
</tr>
</tbody>
</table>

In cervical and endometrial cancers, initial results highlighted the incremental clinical value of anato-metabolic imaging, especially in terms of diagnostic accuracy. Pilot studies also suggest the potential expected from FDG
PET plus CT in treatment planning and survival prediction (Sugawara et al, 1999).

A. PET/CT software image fusion

1. Diagnosis

A recent study assessed the added-value of side-by-side interpretation of FDG-PET and CT/MRI in gynecological cancers. Their analysis was focused on the imaging discrepancies, which were correlated to pathology results in 32 patients (22 cervical cancers, 7 ovarian cancer, 2 endometrial cancers, and 1 leiomyosarcoma). Among the 24 women with uterine cancers, the software fusion contribution was found significant for localization of biopsy sites (12 patients), treatment planning (5 patients), accurate diagnosis (9 patients: change of FDG PET results in 5 and MRI/CT results in 4), differentiation between pathological and physiological uptake (11 patients). As a conclusion, the authors showed the clinical benefit derived from software image fusion in gynecological cancers based on a more confident and more precise interpretation of FDG-PET findings and MRI/CT results as well (Tsai et al, 2003).

2. Treatment planning and patients’ outcomes

The aspect of intensity modulated irradiation therapy (IMRT) and treatment planning is most evident in patients with cervical cancer with positive para-aortic lymph nodes (Fig. 38). Fused PET/CT images can be imported into current radiation therapy treatment planning systems. Increased doses to positive lymph nodes can be administered while decreasing the doses to normal tissue (Belhocine and Grigsby, 2005).
An interesting area of development has been the use of FDG PET as a guide to the evaluation and planning of intra-cavitary brachy-therapy for patients with cervical cancer. Mutic et al, 2001 have developed a process whereby the brachy-therapy irradiation applicators can be visualized within the metabolic tumor volume isodose distributions can then be generated to demonstrate the irradiation dose distributions to the metabolic tumor volumes. This process has great potential to increase the irradiation dose to the primary cervical tumor while decreasing the dose to normal structures.

In another pilot study, the metabolic volume as determined by FDG PET and CT software image fusion allowed to selecting the patients who may best benefit from radiation therapy; these patients had a tumor volume < 60cm³ and no lymph node disease. Alternatively, patients with other combinations suggestive of poor prognosis (tumor volume >60cm³ and/or nodal involvement) may be treated by more aggressive therapies (Miller and Grigsby, 2002).

B. Hardware PET/CT image fusion

With the advent of combined PET/CT devices, a single multimodality imaging is nowadays feasible in clinical routine. In gynecological cancers, this allows to avoiding many artifacts due to internal organs motion (i.e. abdominal peristalsis, urine stasis) and patients' repositioning between PET and MRI/CT (Wahl, 2004). In a reference study including 285 consecutive female patients, Lerman et al, 2004 also showed the usefulness of PET/CT for differentiating normal from abnormal FDG uptakes within the gynecological sphere; otherwise, benign and physiological endometrial and ovarian patterns may have been falsely interpreted as tumor uptake by using FDG PET alone. Hence, FDG PET may benefit from the anatomic details provided by a concomitant CT; a "one-stop-shop" imaging aimed at increasing the diagnostic accuracy of both
techniques, especially in treatment planning. Additionally, whole-body PET/CT may reduce the number, and then the cost and irradiation, of separated CT and PET studies.

![Fused PET-CT images](image)

Fig. 38: Treatment planning in a patient with FDG-avid para-aortic involvement. Fused PET-CT images can be imported into current radiation therapy treatment planning systems. Increased doses to positive lymph nodes can be administered, while decreasing doses to normal tissues.

In a study, **Israel et al 2003** compared the performances of PET/CT versus PET and/or CT alone in 57 patients with gynecological cancers, including 38 cervical cancers, 6 endometrial cancers, and 13 ovarian cancers. As a main conclusion, PET/CT improved image interpretation over PET and/or CT in 51% of patients. Combined imaging technique led to a change in management of 11
patients with uterine cancers (25%) including 10/38 patients with cervical cancer and 1/6 patients with endometrial cancer. These results are in line with those obtained by Cohade et al 2003, who directly compared PET and PET/CT in a series of 15 patients with endometrial cancer. In this later study, 12 of out 49 tumor sites (24.5%) detected by PET/CT and PET were mis-localized or misdiagnosed by PET alone. In particular, PET/CT helped to correctly reclassify 5 equivocal FDG-avid foci by PET alone as either benign or malignant lesions. The same group also evaluated the added-value of PET/CT over PET in 13 patients with cervical cancer. Similarly, combined imaging was found particularly contributive for a better anatomic localization (physiological versus pathological) and characterization (benign versus malignant) of foci with increased FDG uptake, which were difficult either to localize (>1/3 foci) or to diagnose (~ 1/5 foci) on PET alone (Tatsumi et al, 2003).

Based on the current data, the clinical added-value of PET/CT primarily relies upon its ability to accurately localize FDG-avid sites compared to either PET alone or CT alone. So far, the role of PET/CT remains limited for the detection of non FDG-avid sites, especially normal sized metastatic nodes (i.e. microscopic tumors). Although the size/volume is a key-factor in the lesion detectability by PET and PET/CT, the metabolic activity of tumor is another important parameter to be considered. For instance, < 1cm nodes that are metabolically active may be detected by PET and PET/CT, while > 1cm (nodes) with a low FDG uptake (i.e. metastases with a low metabolic activity, benign nodes, and irradiated nodes) may be missed by metabolic imaging (Belhocine and Grigsby, 2005).
7- PET/CT & Gastrointestinal malignancies
18F-fluorodeoxyglucose positron emission tomography (FDG-PET) imaging is highly accurate in restaging colorectal cancer, esophageal cancer, and gastrointestinal Stromal tumors (GIST). Overall, it compares favorably with anatomical imaging in the evaluation of tumor recurrence because metabolic abnormalities usually precede a structural change. Initial staging of these malignancies with PET is best used in patients with locally advanced disease who may benefit from curative resection if distant metastases are not found. It also appears to have great potential in predicting histopathologic response to neoadjuvant therapy and in monitoring the success of radiofrequency ablation and 90Y microspheres radio-embolization soon after intervention. FDG-PET can be used in other gastrointestinal malignancies as a prognostic tool and to detect distant disease but its role has not yet been well defined (Fabio, et al 2006).

The interpretation of PET abdominal images often is challenging because of the bio-distribution of FDG. Although background FDG activity in the chest usually is negligible, physiologic uptake in a variety of abdominal/pelvic organs can make it difficult to distinguish benign from malignant uptake. FDG is filtered but not reabsorbed in the kidneys, so activity is expected in the urinary system. Stomach wall uptake is common and colonic uptake may be intense, especially in the caecum and recto-sigmoid. The liver has a typical mottled appearance and moderate uptake. The spleen has a more homogeneous pattern, and the degree of uptake is less than the liver. Intense focal ovarian uptake may be physiological in premenopausal women. Para-spinal and peri-nephric fat uptake can be observed. Lymphoid tissue and skeletal muscle often demonstrate increased uptake (Fabio, et al 2006).
1-Colorectal Cancer

Several studies have shown the ability of FDG-PET imaging in the detection of primary carcinomas and pre-malignant lesions of the large bowel (Friedland et al, 2005 and Gutman et al, 2005). Sensitivity is highly dependent on both the size of the lesion, reaching 72% if the tumor is larger than 1 cm, and grade of dysplasia, ranging from 33% in low-grade lesions up to 76% in high-grade lesions and 89% in carcinomas. There is a wide range of nonmalignant conditions in which increased FDG uptake is observed in the colon, such as inflammatory bowel disease, diverticulitis, and physiologic uptake in colonic mucosa, lymphoid tissue, and smooth muscle. Differentiation between benign and malignant uptake is predominantly based on the focal nature of hyper-metabolism. Inflammatory bowel disease and physiologic uptake tend to be diffuse or segmental, whereas the accumulation of FDG in pre-malignant and malignant lesions is focal. Despite a low positive predictive value for malignancy, focally increased uptake of FDG in the large bowel should not be ignored, particularly in light of the high incidence of pre-malignant adenomas and colorectal cancer in the age group that typically undergoes FDG-PET imaging. Focally increased uptake in the colon should lead to further investigation with colonoscopy and, when necessary, biopsy or polypectomy (Van Kouwen et al, 2005).

Few studies have focused on the usefulness of FDG-PET scanning in the initial staging of colorectal carcinomas. Overall, the sensitivity for detection of nodal metastasis is poor and is not significantly different from CT imaging. These results are not surprising because of the inability of FDG-PET to identify micro-metastases and the resolution capabilities of the scanners currently used.
The use of FDG-PET imaging in the preoperative staging of colorectal cancers has been advocated, but a substantial impact on clinical management has not been demonstrated. It is unlikely that initial treatment decision making will be significantly altered on the basis of PET imaging (Kantorova et al, 2003).

Several studies have described the additional value of FDG-PET imaging over anatomical imaging in recurrent colorectal cancer (Bipat et al, 2005). Metabolically active tumors can be detected before a morphologic change is noted on anatomical imaging. A meta-analysis of 11 studies with 577 patients (Huebner et al, 2000) showed an overall sensitivity of 97% and specificity of 76% for FDG-PET detecting recurrent colorectal cancer. A more recent meta-analysis of 61 studies evaluating colorectal liver metastases (Bipat et al, 2005) showed that FDG-PET had a sensitivity of 95% on a per-patient basis, significantly better than CT (65%) and magnetic resonance imaging (MRI) (76%) (Fig 39) (Kantorova et al, 2003).

Few studies have demonstrated the value of FDG-PET in patients with rising CEA levels and no identifiable lesions on conventional imaging. Flanagan and coworkers 1998 reported a positive predictive value of 89% (15/17) and a negative predictive value of 100% (5/5) in patients with CEA measurements of 10 to 45 ng/mL. Valk and coworkers 1999 showed a positive predictive value of 95% (18/19) and a negative predictive value of 85% (11/13). The positive impact of PET on management decision in this clinical scenario is evident. Curative therapy may be attempted for patients with localized disease, whereas unnecessary surgery may be prevented in patients with advanced stage disease.

FDG-PET imaging has been shown to significantly alter patient management when compared with conventional imaging modalities. A
A prospective study by Ruers and coworkers 2002 demonstrated a change in clinical management in 20% of patients being evaluated for resection of colorectal liver metastasis. A change in patient management based on FDG-PET findings was determined to be 29% in a meta-analysis of 11 articles with 577 patients (Huebner et al, 2000). In a prospective study of 102 patients with suspected or confirmed regional recurrence of colorectal cancer, FDG-PET influenced management decision in 59% of cases. The high impact on treatment planning in this particular study was predominantly due to avoiding surgery in patients with widespread disease. In a subset of 20 patients with rising CEA levels but no obvious site of recurrence on conventional imaging, FDG-PET localized recurrence in 13 (65%) (Kalff et al, 2002).

Combined PET/CT imaging is particularly beneficial when interpreting abdominal/pelvic images because focally increased uptake of FDG may be observed in a variety of benign conditions. These include incisions, ostomies, abscesses, fistulas, granulomas, diverticulitis, as well as physiologic uptake in colonic mucosa, lymphoid tissue, and muscle. The anatomic detail provided by CT helps differentiate benign from malignant uptake, increasing the confidence of the reader and yielding a better and more specific report (Rosenbaum et al, 2006).

Lesion characterization on CT also can increase the suspicion for malignancy even in the setting of mild FDG uptake. For example, the sensitivity of FDG-PET to detect mucinous adenocarcinoma is low, presumably because of the hypocellularity of these tumors. The ability to identify cystic changes and calcifications that are characteristic of mucinous lesions on CT scan should increase the index of suspicion of the reader even if the degree of FDG uptake is low (Whiteford et al, 2000).
Precise measurement of small structures is yet another advantage of combined PET/CT imaging. The identification of small lesions (typically less than 1 cm) on CT may help us to prevent excluding malignancy on the basis of low FDG uptake, since the metabolic rate in sub-centimeter lesions is often underestimated because of resolution limitations of the PET scanners (Kantorova et al, 2003).

Finally, the use of integrated PET/CT imaging also improves intensity modulated radiation therapy planning in patients with rectal carcinoma. These patients can be imaged prone on a flat bed to exactly match the position of planned intensity-modulated radiation therapy sessions. Better delineation of target volumes can be accomplished, limiting higher tumoricidal doses to areas of increased FDG uptake and sparing normal adjacent structures (Brunetti et al, 2004).

Because the bowel and other gastrointestinal structures tend to move during a distinctive period, the more or less simultaneous PET and CT investigation by using PET/CT is especially valuable. However, for optimal results, even in PET/CT, the examination should be carried out under optimized preconditions, as many studies on CT colonography have shown. Therefore, tailored PET/CT protocols may be able to enhance the diagnostic accuracy in primary and recurrence staging and in patients with incomplete optical colonoscopy and suspicion of synchronous tumor sites (Fig 38) (Nakamoto et al, 2004).

Cohade et al, 2003 reported that the accuracy of staging in patients with colorectal carcinoma increased from 78% with PET alone to 89% with PET/CT. The number of lesions having an uncertain location was decreased by
55% with PET/CT and the number of equivocal and probable lesion characterization was decreased by 50%.
Fig 38: A, B Patient with incomplete optical colonoscopy and suspicion of synchronous tumor sites received PET/CT, which proved the existence of two tumor sites (arrows).

Fig 39: Whole-body PET MIP (left), trans-axial CT (top left), attenuation-corrected PET (top right), fused image (bottom left), and non-attenuation-corrected PET (bottom right) in a 56-year-old man with recto-sigmoid adenocarcinoma (arrows) and extensive liver metastases (arrowheads)
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2-Esophageal carcinoma

In recent years FDG-PET has been demonstrated to have a higher sensitivity for the detection of primary esophageal tumors than CT (Flamen et al, 2000). Himeno et al, 2002 found that PET can detect primary esophageal cancer with a depth of invasion of T1b or greater and PET to be more accurate than CT or EUS (endoscopic ultrasound) for diagnosing lymph node metastases. Kato et al 2005 found an incremental effect of PET on diagnostic accuracy in the initial staging of esophageal carcinoma including the M stage. Luketich et al 1997 confirmed that PET has a greater sensitivity in detecting distant metastases. In contrast to morphologic imaging methods Jones et al, 1999, FDG-PET has been shown to be a good predictor of response to therapy, because of its ability to differentiate between vital residual tumor tissue and post-therapeutic changes. It is therefore able to distinguish responders from non-responders to neoadjuvant chemotherapy shortly after beginning induction therapy. PET does not depend on structural tissue changes and has been demonstrated to be at least as good as CT in detecting recurrent disease (Fig 41) (Kato et al, 2004).

FDG PET can be used in the planning of esophageal tumors by improving the ability to define cranial and caudal extent, which can be difficult using CT alone. A study of the effect of FDG PET on the CT planning of esophageal tumors showed that FDG PET upstaged eight of 21 patients by revealing metastatic or nodal disease. Radiotherapy planning based on CT alone would have resulted in the exclusion of FDG-avid disease in 11 of the 16 patients eligible, which was mainly due to discordance in the cranial and caudal extent of disease (Leong et al, 2006).
PET/CT can improve the accuracy of PET imaging in distinguishing recurrent disease from benign post-therapy changes, delineating the anatomic location of metastatic disease, and monitoring therapy response by solving a myriad of problems inherent in the post-therapy assessment of cancer. With the use of the pattern of enhanced metabolic activity to facilitate field definition (Fig 40), PET/CT also promises to improve the accuracy of radiation treatment planning (Koshy et al, 2004).

Fig: 40 Utilization of positron emission tomography (PET)/computed tomography (CT) fused images for radiation treatment planning in a patient with moderately differentiated lower esophageal adenocarcinoma. (A) Sagittal view. The blue and orange lines show antero-posterior (AP) and postero-anterior (PA) beams, respectively. The red contour delineates gross target volume (GTV). The green contour encloses region of the esophagus superior to the metabolically active GTV to account for possible microscopic disease. (B) Coronal view. The blue and orange contours represent radiating field by AP and PA beams, respectively. Once again, the red contour represents GTV and the green contour is planned to encompass microscopic disease.
Fig 41: Coronal CT (top left), attenuation-corrected PET (top right), fused image (bottom left), and non-attenuation corrected PET (bottom right) in a 57-year-old man with a large lower esophageal cancer (arrows) and a malignant right para-tracheal lymph node (arrowheads). Uptake resolved in both regions after neoadjuvant chemotherapy and only minimal residual microscopic disease was present in the esophagus after resection.
3-Gastric Carcinomas

The diagnosis of gastric carcinomas is made by endoscopy and tumor biopsies. Local extension of the tumor is typically assessed by endoscopic ultrasound, whereas abdominal ultrasound and CT are used for metastatic workup. The sensitivity of FDG-PET to detect locally advanced gastric carcinomas is dependent on the microscopic growth type of the tumor. Stahl and coworkers 2003 showed that distinct increased uptake of FDG is more commonly seen in the intestinal growth type (15/18, 83% sensitivity) than in non-intestinal type carcinomas (9/22, 41% sensitivity), probably because of the abundance of intra and extra-cellular mucous content and lack of expression of the glucose transporter Glut-1 on the cell membrane of the latter. Both FDG-PET and CT appear insensitive to detect regional lymph node metastasis from gastric carcinomas.

In a retrospective study of 81 patients, Yun and coworkers 2005 showed a sensitivity of 34% for N1 and N2 disease and 50% for N3 disease using FDG-PET. The sensitivity of CT for detection of N1 disease (58%) was significantly better than that of FDG-PET.

A retrospective analysis of 33 patients with suspected recurrence of gastric carcinoma showed a sensitivity of only 70% (14/20) and a specificity of 69% (9/13) for FDG-PET. However, the mean survival for the PET negative group (18.5 months) was significantly higher than the PET positive group (6.9 months), suggesting that PET may serve as a prognostic rather than diagnostic tool in gastric carcinomas (De Potter et al, 2002).
Ott and coworkers 2003 prospectively evaluated patients with locally advanced gastric carcinomas with FDG-PET at baseline and at 2 weeks after initiation of cisplatin-based chemotherapy. Thirty-five of 44 primary tumors (80%) were PET positive. By using a cutoff SUV reduction of 35%, FDG-PET correctly predicted histopathologic response after 3 months of therapy in 10 of 13 responders and in 19/22 non-responders. The identification of non-responders early in the course of chemotherapy will allow optimization of neoadjuvant strategies in locally advanced gastric carcinomas potentially minimizing progression of disease.

Despite the well-known moderately accentuated uptake of FDG in the healthy stomach, FDG-PET is surely helpful in the management of patients with gastric carcinoma. Studies addressing PET/CT in gastric carcinoma are lacking. Therefore it is not known whether the additional information of CT in a combined PET/CT device would further improve diagnostic performance, but it would probably improve local lymph node staging. Further, we assume an improvement in diagnostic accuracy in T and M staging (Rosenbaum et al, 2006).

4-Hepatic Tumors

FDG-PET has a poor sensitivity to detect primary hepatocellular carcinoma because well-differentiated tumors may retain the capacity gluconeogenesis (to convert FDG-6-phosphate to FDG). Lee and coworkers 2005 showed that GLUT1 (glucose transporter 1) concentration is low and HKII (Hexokinase II) is high in hepatocellular carcinoma. In a small series of 12 patients (4 untreated and 8 treated) Lin and coworkers 2005 showed improvement in sensitivity from 56% to 62.5% between images obtained at 1
hour and 2- to 3-hour delay. **Ho and coworkers used 2003** C11 acetate PET in 32 patients and showed a sensitivity of 87% compared with that of 47% with FDG-PET. Hence the importance of FDG-PET in the management of hepatocellular carcinoma is mainly in detecting extra-hepatic spread. In 18 patients **Sugiyama and coworkers 2004** showed that FDG-PET contributed to the management of patients by detecting extra hepatic metastases. In a study by **Khan et al 2000** found that the sensitivity of PET in diagnosis of HCC was 55% compared with 90% for CT scanning, although some tumors were detected by PET only (including distant metastases).

In conclusion, on the basis of the CT finding, the PET signal is suitable to differentiate biological aggressiveness of primary tumors, which stresses the need for combined film reading and therefore the use of PET/CT. It is also reported clinical experience that PET and PET/CT have a high sensitivity to detect extra-hepatic metastases of HCC (**Khan et al, 2000**).

**Bohm et al 2004** investigated the effect of PET in histologically proven intrahepatic lesions and found a sensitivity of 82% for FDG for the detection of primary and secondary liver lesions, with PET being superior to ultrasound (63%) and CT (71%). The sensitivity and specificity of PET and MRI were comparable at approximately 82% and 96%, respectively, for intrahepatic lesions but PET was superior to MRI for detection of extra-hepatic metastases of hepatic primary lesions, with the sensitivity and specificity being 63% and 60% for PET and 40% and 50% for MRI, respectively. In this study the PET results had a direct effect on operative management. Hepatic metastases are quite frequent and the value of PET largely depends on the kind of primary lesion. Liver metastases are likely to be detected only if the PET tracer is frequently accumulated in the respective tumor entity. Further, the
tracer might physiologically accumulate in the liver, which decreased the detection sensitivity in this organ.

This problem may be overcome, at least in part, by employing PET/CT because tracer turnover in the lesion (as depicted by CT) can be analyzed. Thus PET/CT improves sensitivity to detect liver metastases, but only in PET-positive lesions. Moreover, clear discrimination between a superficial but intra-hepatic lesion and a lesion adjacent to the liver requires precise image fusion as available using PET/CT (Fig. 42, 43, 44) (Rosenbaum et al, 2006).

Fig 42: Patient with poorly differentiated HCC and previous hemi-hepatectomy. A) Contrast-enhanced CT shows a new hypodense nodule in the venous phase. B) PET reveals a large area of increased FDG uptake in the remaining right liver lobe. C) PET/CT fusion indicates a tumor beyond the nodule that is visible on CT, thus influencing planned radiofrequency ablation.
Fig 43: Patient with colorectal metastases and previous left hemihepatectomy. A) CT shows two hypodense nodules with contrast enhancement. B) PET/CT fusion indicates a metastatic recurrent tumor beside a scar after operation. C) CT after radiofrequency ablation shows a large area without contrast enhancement (arrow). D) PET/CT fusion after radiofrequency ablation indicates complete ablation of the recurrent metastasis with a photopenic lesion.

Fig 44: A) CT 3 month after radiofrequency ablation shows no sign of local recurrence. B) PET/CT 3 month after radiofrequency ablation demonstrates a local recurrent tumor.
5-Gallbladder carcinoma and Cholangiocarcinoma

The sensitivity of FDG-PET in detecting carcinoma of the gallbladder (GBC) and cholangiocarcinoma (CC) is quite high but seems to be dependant on tumor subtype. Anderson et al. found a sensitivity of 78% for GBC. Sensitivity was 85% for nodular CC but only 18% for infiltrating CC. Sensitivities for extra-hepatic metastases were 50% for GBC and 65% for CC. In the cited study, PET was falsely negative in all three patients with carcinomatosis; 58% of patients had FDG uptake along the tract of a biliary stent (Anderson et al, 2004). Kim et al 2003 showed that peripheral hepatic CCs generally have greater FDG uptake than hilar ones. FDG-PET identified distant metastases of peripheral CC that were not detected with MRI and CT. Similar to gastric mucin-containing carcinomas, Fritscher et al 2001 observed false-negative PET scans in mucinous hilar adenocarcinoma. Kluge et al 2001 demonstrated a high sensitivity for PET in detecting primary CC and its metastases, but regional lymph node metastases were diagnosed with a sensitivity of only 13%. The reason for this poor result is assumed to arise from the difficulty of discriminating between extra-hepatic parts of the tumor itself and FDG-accumulating lymph nodes in the perihilar region.

There have been no previous studies available addressing PET/CT and GBC or CC, but certainly PET/CT is the optimal tool to overcome the limitations of PET and CT alone (Rosenbaum et al, 2006).
6-Pancreatic carcinoma

FDG-PET plays an important role in the differentiation of pancreatic tumors when it is certain that patients have no hyperglycemia or serologic evidence of active inflammation. The sensitivity of PET in detecting pancreatic cancer is similar to that of CT, but PET seems to be more specific. Sperti et al, 2005 found a sensitivity of 94% for both modalities, but PET was significantly more accurate in identifying malignancy. PET can also be helpful in identifying unsuspected distant metastases and suspected recurrent carcinoma when abdominal CT is non-diagnostic (Jadvar et al, 2001). Delbeke et al, 1999 showed that FDG-PET is more accurate than CT in the detection of primary tumors and in the clarification and identification of hepatic and distant metastases. In this study additional FDG-PET investigations altered the management in up to 43% of patients compared with the management of CT alone. Mertz et al 2000 found that EUS and PET improved diagnostic capability in pancreatic adenocarcinoma. Nevertheless, Diederichs et al, 2000 found that PET had sensitivities and specificities of 49% and 63% for lymph node staging and 70% and 95% for detecting hepatic metastases, respectively. The combination of PET and CT in a single scanner overcomes these limitations. The exactly fused anato-metabolic image provides better differentiation of pathologic processes especially in surgically pretreated patients and allows the detection of small metastases, which might be missed by PET alone because they are close to background variations. As Lemke et al, 2004 recently reported, even retrospective image fusion improves the sensitivity of malignancy detection in pancreatic lesions from 77% for CT and 84% for PET to 89%. Because there are greater differences in patient positioning in standalone CT and PET compared with PET/CT, these results are expected to be
even better for the combined device. Further, if optimized breath-holding protocols are used, the frequency of severe artifacts in the area of the diaphragm can be decreased by half (Beyer et al, 2003). Optimization of these factors and the possibility to stage patients in a single examination will increase the use of PET/CT as the main imaging tool in pancreatic cancer in the forthcoming years.
8- PET/CT & Brain tumors
A high sensitivity is reported for primary brain tumor detection with PET. Initial FDG-PET studies can identify elevated FDG uptake in primary brain tumors (Derlon et al, 1989) with good correlation of the grade of malignancy. Thus, low-grade astrocytomas are not easily identified or appear as hypometabolic areas surrounded by normal high FDG uptake within the cerebral cortex hindering a clear definition of exact tumor extension. Many clinical studies have demonstrated that 11C-methionine-PET imaging is highly accurate in defining of tumor boundaries both in primary or recurrent brain tumors, regardless of their histological grading (Patronas et al, 1985).

Ogawa et al, 1993 demonstrated an excellent 97% sensitivity for 11C-methionine-PET in 32 patients with high-grade astrocytomas, but only 61% sensitivity in low-grade astrocytomas. A large study was performed by Herholz et al, 1992 finding 79% accuracy in distinguishing astrocytomas from non-neoplastic lesions in 196 patients with a suspected primary brain tumor.

Mosskin et al, 1986 presented a patient-based sensitivity of 84% using stereotactic biopsies from primary brain tumors and normal brain tissue areas, indicating that tumor specificity of 11C-methionine contains a certain rate of false-positive results. In a large series of astrocytomas, 95% of 37 lesions are clearly visualized in 11C-methionine- PET studies, whereas FDG shows 41% as hyper-metabolic, most of which are high-grade astrocytomas; and 49% as hypometabolic lesions, whereas 10% are difficult to distinguish from surrounding normal brain tissue (Kaschten et al, 1998). The reported advantage of 11C-methionine over FDG in delineating astrocytomas is probably not relevant in CNS lymphoma, where FDG uptake is much higher in tumor than normal brain tissue (Roelcke et al, 1999).
Experience with 18F-tyrosine as radio-labeled ligand for PET studies in primary brain tumors is more limited. Pruim et al, 1995, using 18F-tyrosine PET imaging for both primary and recurrent brain tumors (including metastases and cerebral lymphomas), find 91% of 22 tumors positive for uptake. Wienhard et al, 1991 could demonstrate increased uptake and transport rates of 18F-tyrosine in primary brain tumors (n=15). Such an uptake appears more related to amino acid transport than to protein synthesis.

Nearly all PET studies on tumor detection also addressed the feasibility of tumor characterization and grading, comparing uptake between both benign and malignant processes and between various grades of malignancy. This clinically useful aspect is supported by in vitro proliferation markers (Kole et al, 1999 and Wienhard et al, 1991). Sato et al, 1999 demonstrated a clear positive correlation between proliferation cell nuclear antigen index and 11C-methionine uptake, indicating that 11C-methionine is taken up more rapidly and accumulated in highly proliferative tissue. Somewhat surprising is that this relationship is not confirmed for 18F-tyrosine uptake (n=20) (DeWolde et al, 1997). Different 11C-methionione accumulations in vivo have shown an uptake in low-grade astrocytomas being near background uptake but a high uptake in oligodendrogliomas (Kracht et al, 2003).

FDG-PET, such a better tumor delineation is reported both for 11C-methionine and 18F-tyrosine-PET (Kaschten et al, 1998)11C-Methionine of FDG scanning is combined with activation studies using radio-labeled water (H215O) to depict tumor extension in relation to functional brain areas (Duncan et al, 1997), with the aim to achieve a subsequent more aggressive surgical resection with a reduced risk of neurological impairment. 18F-thymide PET is useful for evaluating the histological grade and cellular proliferation of brain
tumors, as well as for the detection and delineation of brain tumors that show decreased or similar uptake compared with normal gray matter on FDG-PET (Choi et al, 2006). 18F-thymidine PET, however, does not appear sufficiently useful for differentiating tumors from non-tumorous lesions.

Stereotactic biopsies of localizations that are based on either methionine or FDG-PET seem to be more successful to find accurate brain tumor tissue than are biopsy based on CT only. Especially, strong uptake reduction of 11C-methionine in necrotic parts or high uptake in anaplastic parts of the tumor tissue may influence the surgical planning and subsequent results of brain tumor biopsies. In comparison with FDG, methionine is advantageous in offering better detection of non-anaplastic tumor zones and brain tissue with infiltrating neoplastic cells (Goldman et al, 1997). Planning of biopsy trajectories is suggested to be improved by tyrosine, particularly in low-grade astrocytomas (Go et al, 1994).

FDG-PET has been used to differentiate between toxoplasmosis and lymphoma (Costa et al, 1995): high grade uptake of FDG is strongly suggestive of a malignant lymphoma presenting as an extremely metabolically active tumor, whereas a relatively hypometabolic lesion can be demonstrated in toxoplasmosis. The problem of specificity, however, may limit the usefulness of FDG-PET as a routine method, as inflammatory lesions can also accumulate FDG (Wurker et al, 1996).

Luciganini et al, 1997 comprised 16 patients with the diagnosis of primary tumor of the sellar/para-sellar region; the results demonstrated that PET with 18F-FESP is a very specific method for differentiating adenomas from craniopharyngiomas and meningiomas at approximately 70 minutes after tracer injection.
In the early postoperative period, FDG-PET can be used to differentiate residual tumor tissue from postoperative surgical effects (Hanson et al, 1990 and Kim et al, 1992). It seems clear that a decline in tumor tissue uptake of FDG weeks or months after therapy is suggestive of a good response to treatment, indicating either a reduced number of viable cells or reduced metabolism of damaged cells (Haberkorn et al, 1993). After intensive irradiation or chemotherapy for malignant brain tumors, MRI is not able to distinguish tumor progression from radiation damage or necrosis. Some PET methods appear promising as relatively specific indices of therapeutic response. FDG uptake suggest the presence of viable brain tumor tissue (at least when high tumor uptake of FDG was noted before therapy), whereas absence of FDG uptake suggests that necrosis may be present (Fig. 46) (DiChiro et al, 1988 and Ishikawa et al, 1993)

Detection of recurrent or residual viable brain tumor tissue can be troublesome in brain tumors treated by surgery or irradiation. 11C-methionine PET had a sensitivity of 77.8% and specificity of 100% for differentiating recurrence of metastatic brain tumors from post-radiotherapy changes (Tsuguyuguchi et al, 2003). However, 11C-methionine uptake may also be elevated in other conditions where there is a disruption of the blood brain barrier, such as cerebral hematoma or even necrotic areas caused by radiotherapy (Dethy et al, 1994), whereas glucose metabolism may be normal or low in lower grade tumors compared with surrounding cortex. Combined use of 11C-methionine and FDG-PET enhances the accuracy of discrimination between recurrent tumor and post radiotherapy changes. Remarkably, the protein synthesis rate, determined by using 18Ftyrosine-PET, remains unchanged in 80% of patients after radiotherapy (Heesters et al, 1998). Four hours after irradiation, the increase in tumor FDG uptake compared to the pre-
irradiation study is significantly assessed with MRI. For malignant astrocytomas, this relationship has not been assessed yet. Voges et al, 1997 report on a series of 46 patients who underwent serial 11C-methionine and FDG-PET studies after interstitial brachytherapy: 11C-methionine is superior to FDG in delineating residual of recurrent tumor tissue (Fig.47). This finding confirms earlier data on the comparison of FDG and amino acid in visualization of untreated low- and high-grade astrocytomas.

Several PET studies try to establish a relationship between metabolic response and prognosis after initiation of chemotherapy in patients with glioblastoma multiform. The change of FDG uptake induced by chemotherapy can be correlated with survival. Both positive and inverse correlations can be found between metabolic responses and survival, making these data inconclusive so far. In a more recent study, methionine is found to be superior to FDG in monitoring the treatment effects in low-grade astrocytomas (Woesler et al, 1997).
Fig. 46: CNS recurrent glioma: The patient below had a history of a right temporal lobe glioma. The lesion had been treated with surgery and radiation. A follow-up MR exam demonstrated areas of enhancement in the right temporal lobe on post-gadolinium images (black arrows). MR spectroscopy was inconclusive. The FDG PET exam demonstrated a hyper-metabolic focus in the area of MR signal abnormality consistent with recurrent glioma (white arrows).
Fig. 47: Recurrent glioblastoma multiforme. 11C-methionine positron emission tomography shows tumor infiltration in areas (arrows) located outside of the contrast enhancement on computed tomography and T1-magnetic resonance imaging.
9- PET/CT & male genital and bladder cancer
1- Male Genital System

a) Prostate cancer (PC)

Imaging of the prostate is important because of its involvement in many diseases of men. However, a number of problems have prevented success in this area. The size and location of the prostate contribute significantly to this problem.

X-ray computed tomography (CT) lacks soft tissue contrast resolution for the detection of cancer within the prostate and offers no advantages over TRUS (trans-rectal ultrasound) in biopsy guidance (Yu and Hricak, 2000).

Among the currently available nuclear medicine studies only positron emission tomography (PET) has some potential (if any) to detect primary tumor in prostate cancer. The PET tracers used for clinical studies of prostate cancer are 18F-FDG (fluoro-deoxy-glucose), 11C-acetate, 18F-acetate, 11C-methionine, 11C-choline, 18F-choline, and 18F-FDHT (16 beta-18F- fluoro-5alpha-dihydrotestosterone) (Suman and Blaufox, 2006).

Several studies have been conducted using FDG-PET in localized prostate cancer. Most of the results were disappointing (Hoffer et al, 1999 and Schöder and Larson, 2004). Effert and coworkers 1996 studied 48 prostate cancer patients and 16 patients with benign prostatic hyperplasia. They reported a low grade FDG uptake in 81% of these tumors and there was a significant
overlap between benign prostatic hyperplasia and prostate cancer in uptake values. **Hoffer and coworkers 1999** reported similar findings.

In a study of 24 patients **Liu and coworkers 2001** found a sensitivity of 4% for FDG-PET in the diagnosis of primary PC. **Melchior and coworkers 1999** reported higher FDG accumulation in poorly differentiated PC than in low grade PC. **Oyama and coworkers 1999** examined 44 consecutive patients with histologically proven adenocarcinoma of the prostate. In visual analysis, 5 patients with BPH (control group) showed low FDG uptake. On the other hand, 28 of 44 (sensitivity 64%) patients with cancer were visually positive, showing intermediate and high FDG uptake. There was a trend for FDG uptake in PC to correlate Gleason scores. The possible explanations for disappointing results as suggested by **Schöder and Larson 2004** include: (1) a relatively lower metabolic rate in the majority of prostate cancers with lower FDG uptake, (2) older image reconstruction techniques (i.e., use of filtered back projection instead of iterative reconstruction), (3) location of the prostate adjacent to the urinary bladder, and (4) the lack of appropriate patient selection (FDG may be more useful in patients with clinical suspicion of a high-grade cancer).

An in vitro study by **Yoshimoto and coworkers 2001** showed that tumor cell to non-tumor cell ratios were higher for acetate than deoxy-glucose. During the last several years this tracer has been used in prostate cancer. **Oyama and coworkers 2002** studied 22 patients, among who 18 also had an FDG scan. They reported 11C-acetate uptake in all primary tumors with standard uptake values (SUVs) from 3.27 to 9.8, whereas FDG was positive only in 15/18 with SUVs from 1.97 to 6.34.

In another study **Kato and coworkers 2002** found that there was an overlap of SUVs for patients with benign prostatic hyperplasia and those with
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cancer. They also noted that SUVs in normal subjects of below 50 years of age were significantly higher than that of above 50. Except for case reports of Matthies et al, 2004 no significant data are available to evaluate the role of 18F-acetate in prostate cancer.

Similar to FDG, methionine, acetate, and choline are not specific agents. Benign prostatic hyperplasia shows tracer uptake higher than normal but lower than that found in cancer; however, there are no discriminating SUVs to differentiate cancer from hyperplasia (Sutinen et al, 2004). At this time, PET does not play a significant role in the primary diagnosis of prostate cancer. The reasons include a lack of appropriate image acquisition techniques such as zoom mode acquisition (the prostate is a small organ, therefore, zoom mode acquisition may provide better visualization of a small lesion), image fusion (combined PET/CT may provide more confidence to identify a hot area as abnormal in the prostate gland rather than in the prostatic urethra), longer acquisition time to increase sensitivity and possible dual time imaging (proven to be useful in lung lesions to discriminate cancer from an inflammatory lesion; this may help differentiate cancer from benign prostatic hyperplasia) (Fig. 48).

Currently, PET does not play a significant role in directing biopsy. Acetate and choline seem to be better tracers than FDG; however, further studies are needed to decide whether PET can have a significant role in the diagnosis of primary prostate cancer. During routine whole body PET imaging, occasionally, focal intense uptake of tracer in the prostate has been reported during FDG (Fig. 49) and 11C- choline imaging. Further evaluation of these lesions in terms of PSA measurement and TRUS guided biopsy is important. Particularly, intense FDG uptake may indicate presence of a high-grade cancer (Schöder and Larson, 2004).
Fig 48: A 60-year-old African–American man underwent prostate biopsy in September 2001 due to a nodular prostate on rectal examination and an elevated PSA of 11.6. The biopsy showed focal glandular hyperplasia, basal cell hyperplasia, focal inflammation, and no evidence of cancer. In May 2004 the PSA increased to 14.2. Before repeat biopsy the patient underwent FDG-PET scan. A normally acquired PET scan displayed with magnification (A) showed mild asymmetric uptake (arrows) in the prostate, which was thought to be abnormal. The scan of the prostate was also acquired in zoomed mode at 60 min (B) and 120 min (C) after the FDG injection. There were discrete areas of FDG uptake in both images (B and C), which were clearly abnormal. These scans were performed on a PET/CT scanner. The SUV max of the prostate lesion was 1.9 from 60-min images (B) and was 2.2 from 120-min images (C). When PET images (D) were displayed with CT images (E) the focal uptakes were found to be located adjacent to the prostatic calcifications. The prostate biopsy was performed in the next week and the biopsy specimens were obtained from the calcified regions as suggested by PET/CT scan. The pathology was positive for adenocarcinoma (Gleason score 6/10 with minor foci of grade 5 adenocarcinoma).
Fig 49: A 75-year-old man with history of metastatic lung cancer found to have intense uptake of FDG (arrow) in the prostate in the PET/CT scan (A and B). Prostate biopsy revealed adenocarcinoma of the prostate; Gleason score 8/10 (5 +3).
FDG was found to have a low accuracy in primary staging of prostate cancer. FDG is slightly better in detecting metastatic PC than that in primary lymph nodes (Shvart et al, 2002). Heicappell and coworkers 1999 used FDG-PET for preoperative imaging of pelvic lymph nodes in 17 newly diagnosed prostate cancer patients and then compared the findings with postoperative histopathology. FDG was able to diagnose metastatic lymph nodes accurately in 4 of 6 affected patients. The 2 false-negative results were attributed to the small size of the lesions (less than 5mm). There was no false-positive result in this study. Other small studies (Sanz et al, 1999 and Kotzerke et al, 2000) report sensitivities ranging from 0 to 50% and specificities ranging from 72 to 90% for detection of nodal metastases. FDG uptake was noted in pelvic lymph nodes in patients with PET negative primary.

FDG-PET is variable in the detection of bone marrow metastases; however, the general belief is that it is more sensitive for the detection of bone metastases than local disease (Kumar et al, 2004). Shreve and coworkers, 1995 reported a sensitivity of 65% and PPV (positive predictive value) of 98% in 202 bone metastases. Yeh and coworkers, 1996 found that only 18% of bone lesions on the bone scan showed FDG uptake. Kao and coworkers, 2000 reported a high specificity of FDG-PET in detection of bone marrow metastases. Nunez and coworkers, 2002 found better detection of cervical spine metastases by FDG-PET than by bone scan. In another study Morris and coworkers, 2002 evaluated 154 bone lesions in 17 patients. Both FDG and the bone scan were positive in 71% lesions, 23% were seen only on bone scan, and 6% were seen only on PET scan. Schöder and Larson, 2004 suggested that FDG may selectively detect more aggressive tumors, which depend on higher glucose metabolism. In vitro studies in prostate cancer xenografts showed higher FDG uptake in tumors with higher Gleason scores, (Agus et al, 1998) and in clinical
studies FDG uptake correlates with PSA level and PSA velocity as measure of tumor size and progression (Herrmann et al, 2004). It seems that high FDG uptake most likely suggests a relatively high-grade tumor.

**18F-Fluoride PET** The bone scan with 18F is reported to be more sensitive and specific than the conventional bone scan to detect bony metastases, particularly if used in conjunction with CT in a PET/CT scanner. The indications to use this scan are the same as for a conventional bone scan. The major limitation of this test at this time seems to be the cost. A cost-effective study in comparison with conventional bone is needed before this study can be used routinely for detection of bone metastases in prostate cancer (Schöder and Larson 2004).

**PET/CT** This modality is slowly but steadily gaining popularity in oncology. Any of the above-mentioned tracers can be imaged in this device. This can increase the confidence of the interpreter in identifying a hot spot as physiological versus pathological compared with any of the above PET tracers used alone. Preliminary data suggest that this modality may be helpful in the detection of recurrence in the local soft tissue, nodal, or even bone metastases (Even-Sapir et al, 2004 and Schmid et al, 2005).
b) Testicular cancer

Initial Staging

Albers and coworkers, 1999 reported that FDG-PET in 37 patients with stage I and II found FDG-PET had a sensitivity of 70% and specificity 100%, whereas similar values for CT were 40 and 78%, respectively. In this study the 3 false-negative PET results were in 2 small (< 0.5 cm) nodal metastases and a mature teratoma. High sensitivity, specificity, PPV, and NPV of 87%, 94%, 94%, and 94% were reported by Cremerius and coworkers 1999. Hain and coworkers 2000 found similar results in the initial staging of seminoma and non-seminoma. PET also identified additional unsuspected visceral and bone metastases. Most of the studies suggested that PET is superior to CT. However, in a small number (12 patients) of patients with stage I and II non-seminoma, Spermon and coworkers, 2002 reported equivalent results for PET and CT.

Residual/Recurrent Disease

Most patients with bulky nodal disease have residual mass after treatment. In this situation viable tumor cells inside the mass require further treatment, whereas fibrosis or necrosis requires watchful follow-up. Unnecessary radiotherapy or chemotherapy can potentially increase the short-term as well as long-term toxicities. Considering the fact that these individuals are young and most of them will live more than 15 to 20 years when cured, they are more likely to experience the long-term toxicities. Although tumor markers are very useful in this regard, occasionally they may be misleading and not
helpful to locate the site of recurrence/residual (Sant et al, 2001). Imaging plays a significant role in locating the residual/recurrent disease non-invasively. Conventional imaging modalities including CT cannot confirm the presence of viable tumor cells in a residual mass. FDG being a metabolic imaging modality has better results. Stephen and coworkers, 1996 and Sugawara and coworkers, 1999 reported that FDG-PET was able to differentiate viable tumor from fibrosis in the post-treatment residual masses. However, the major limitation of PET is mature teratoma, which is usually negative in the FDG-PET scan but can cause a false-positive result if there are any inflammatory changes associated with it. Hain and coworkers, 2000 reported sensitivity, specificity, PPV, and NPV of 88%, 95%, 96%, and 90%, respectively, for FDG in differentiating viable tumor from fibrosis or necrosis or mature teratoma. Sanchez and coworkers 2002 found that FDG-PET can detect relapse earlier than CT. Several other studies conducted in patients with seminomas or non-seminomas have shown that FDG-PET is superior to CT in this regard (Cremerius et al, 1998 and De Santis et al, 2001).

**Monitoring Treatment Response**

FDG-PET has been shown to predict response to chemotherapy, similar to high-grade lymphomas (Fig. 50). Bokemeyer and coworkers, 2002 reported that FDG-PET accurately predicts the outcome of high-dose chemotherapy in 91%; in comparison CT accurately predicted outcome in 59% cases and tumor markers predicted the correct response in only 48% of cases.
Fig. 50: A 24-year-old man with a history of testicular cancer [mixture of teratoma (80%) and germ cell tumor], status post-surgical resection and chemotherapy. PET/CT was performed 4 weeks after chemotherapy; CT continues to show a large para-aortic mass; however, FDG-PET showed a photopenic lesion with very mild uptake at the periphery of the lesion. Subsequent excision biopsy of the lesion showed only necrotic tissue with surrounding inflammation; no tumor cells were found in the specimen.
2-Bladder cancer

The role of FDG-PET in the detection of localized bladder cancer is limited because of the difficulty in differentiating radiotracer activity excreted into the urine from tumor activity in the bladder or adjacent lymph nodes (Suman and Blaufox, 2006).

However, FDG-PET has demonstrated some utility in identifying distant lymph node involvement and distant disease. Kosuda and coworkers 1997 reported that PET imaging identified 17 of 17 patients with metastatic disease (lung, bone, and remote lymph nodes) as well as 2 of 3 patients (67%) with localized lymph node involvement. Similarly, Heicappell and coworkers reported a 67% detection rate for local nodal disease. Investigators have attempted to improve the sensitivity of PET by using tracers that are not excreted in the urine. Ahlstrom and coworkers, 1996 found 11C-methionine is superior to FDG; however, tumor was identified with a sensitivity of 78% (18/23) only with methionine PET. They also reported that tracer uptake was proportional to tumor stage. 11CCholine, another tracer minimally excreted in the urine, was studied by de Jong and coworkers, 2002 in 18 patients with bladder cancer before cystectomy and 5 volunteers. Normal bladder showed little uptake. The primary tumor was visualized in 10 patients with residual invasive diseases in the cystectomy specimen (mean SUV, 4.7 +/- 3.6, range, 1.5-13.0). Utility of FDG-PET in the evaluation of bladder cancer seems to be limited to the evolution of distant metastases.
10- Summary and conclusion
In the rapidly changing world of health technology, PET/CT has now gained a place of prominence. The clarity of the data achieved, the routine implementation of image fusion in a multimodality setting, and the apparent ease with which labeled fluoro-2-deoxy-D-glucose (FDG) can be used to depict and follow up cancer are clearly the causes of the rapid acceptance of this technological development within the community of cancer caregivers.

The Holy Grail of oncologic imaging would be a device that is able to see both the anatomic and physiologic details of tissue. We are getting closer to define the combined PET/CT scanners. With precision, functional images of PET can be superimposed on the corresponding anatomic images and essentially the PET tracer can be considered a metabolic contrast agent.

After performing many oncology studies using an integrated PET/CT system, the investigators concluded that combined PET/CT images offer significant advantages, including 1) more accurate localization of foci of uptake, 2) distinction of pathologic from physiologic uptake, and 3) improvement in guiding and evaluating therapy.

PET/CT is possibly the superior imaging modality for the initial staging and diagnosis of primary and recurrent head and neck cancers, NSCLC, lymphomas, colorectal, hepatic and pancreatic carcinomas. PET/CT is best at N staging and M staging in these patients, and it is clearly superior to CT and MR in this context.

For brain tumors PET/CT is not a first tool for the investigation of a patient suspected to have it. Most of the time, referrals arise from a series of
failed initial investigations. Perhaps the most direct referral for a suspected brain tumor arises from those patients suspected to have para-neoplastic syndrome where PET/CT is used to localize a tumor.

This was as regard to disease assessment and staging and restaging of these cancers and others which can affect the treatment strategies. Recently PET/CT is used as a powerful tool for better localization of the tumor for radiotherapy target volumes and so better dose escalation for these targets.

The use of PET/CT for determining radiation target volumes for 3-D conformal radiation therapy made GTV significantly modified than CT-based GTV in some patients may be smaller because the tumor may be partially necrotic, or larger because of the extend of biological tumor margin which can't be seen by the anatomical imaging alone.

Many studies confirmed the efficacy of the use of PET/CT radiotherapy treatment planning especially with HNSCC, NSCLC, brain tumors, bulky lymphomas, melanomas. Other tumors are still investigational.

In general terms PET/CT is still not a first-line investigation for the diagnosis of cancer. In most institutions, PET/CT is being used after the patient has presented to a hospital and been submitted to a whole battery of clinical, laboratory-based and conventional imaging-based studies. But in radiotherapy it is going to be the first choice for precise treatment planning and good target definition.
11-References


64. Cohade, C.; Osman, M.; Nakamoto, Y.; Marshal, T.L; Links, M.J; Fishman, K.E; Wahl, L.R. Initial Experience with Oral Contrast in PET/CT: Phantom and Clinical Studies. Journal of Nuclear Medicine, 2003; Vol (44): 412-416


98. Eberl, S. Evaluation of PET scanners, Acceptance Testing and QC, AAPM Meeting, (2003), San Diego


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& Target Definition

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Review of Literature & Target Definition


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182. Kalabbers, B.M; De Munck, J.C.; Slotman, B.J; Bree, R.D; Hoekstra, O.S; Boellaard, R.; Lammertsma, A.A. Matching PET and CT scans of
PET/CT in Radiotherapy Treatment Planning

Review of Literature & Target Definition

the head and neck area: Development of method and validation. Medical Physics, (2002); Vol (29), 2230-2238.


200. Kitagawa Y, Nishizawa S, Sano K, et al: Prospective comparison of 18F-FDG-PET with conventional imaging modalities (MRI, CT, and 67Ga scintigraphy) in assessment of combined intraarterial chemotherapy and


225. Lee TS, Segars PW, Tsui BW. Application of 4D MAP-RBIEM with space time Gibbs priors to gated myocardial SPECT. J Nucl Med (2005); 46:162P.
PET/CT in Radiotherapy Treatment Planning & Target Definition


243. MacManus MP, Hicks RJ, Matthews JP, et al. Positron emission tomography is superior to computed tomography scanning for response-
PET/CT in Radiotherapy Treatment Planning & Target Definition


349. Townsend, D.W; Carney, J.P.J; Yap, J.T; Hall, N.C. PET/CT today and tomorrow. Journal of Nuclear Medicine, (2004); Vol (45): 4S-14S


379. Wilting, J.T. Technical aspects of spiral CT. www.medical.philips.com


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The first step in the process is the device. This distance becomes a place. The device is more important. It is not because. The device becomes a more extensive area. Areas where the target can be moved. The device is moved by the ultrasound depiction. The device becomes a device. It is not an opportunity. The device is moved and it is used in the use. It is not because the target is set. The device is different. The target is an important area. The device is not because it is large. The device is moved and the target is moved and the device is important. The device is not because it is large.

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بروتوكول توطئة للحصول على درجة الماجستير

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