The development of PET/CT imaging has improved diagnostic accuracy for staging of cancer and is increasing the accessibility of PET for radiation treatment planning. Integration of PET imaging into radiation treatment planning requires close collaboration between radiation oncologists and nuclear physicians, together with detailed understanding of unique patient and data workflow.

In this article, we review the literature on the use of PET in radiation treatment planning, its potential benefits, and some of the clinical, economic and technical challenges. We also address the specific radiation oncology workflow requirements and PET/CT system design considerations.

The final section discusses future applications that may allow the use of PET imaging as a true marker of the tumor biology.

## Clinical drivers

### Diagnosis & staging

$^{18}$F-FDG PET/CT has become an essential tool for staging and restaging of various types of malignant tumors. For example, it can improve the accuracy of preoperative staging for ovarian cancer, especially for detection of metastatic disease outside of the pelvis (Figure 1). It has also been shown to have a significant impact on patient management [1, 2]. For example, Hillner et al. [3] showed that FDG imaging on patients scheduled to undergo biopsy rendered the interventional procedure unnecessary in approximately 70% of the cases.

Furthermore, Czernin et al. [4] demonstrated that the staging accuracy of PET/CT is significantly higher than that of PET or CT alone for a multitude of malignancies studied. PET/CT also shows exciting potential in predicting the response to treatment for several types of cancer, including metastatic breast cancer [5], lung cancer [6] and lymphomas [7, 8].

### Radiation therapy

In radiation oncology, PET imaging offers the ability to incorporate biologic information into radiation therapy workflow. To date, most of the work in this arena has involved patients with non-small cell lung cancer (NSCLC). The literature suggests that biologic targeting with PET alters the radiation treatment volume significantly in 30% - 60% of NSCLC patients for whom definitive therapy is planned. This is mostly the result of the incorporation of regional nodes with 18F-FDG avidity that had previously been judged to be uninvolved on the basis of CT criteria (Figure 2). In some cases, areas of increased 18F-FDG uptake may help in
Implementing FDG-PET in radiation therapy treatment planning has been demonstrated to have a major impact on accurate target definition and the prediction of treatment outcome. For high precision radiation therapy, target definition based on CT alone results in too great a variability between radiation oncologists [9]. With the addition of FDG-PET, radiation therapy can be delivered more accurately, allowing safe dose escalation (Figure 4.)

**Clinical and technical challenges**

Today, the modern combined PET/CT scanner provides the best means for determining the biological tumor volume and for planning radiation therapy in those cancers that are well imaged by PET. Radiation therapy planning systems enable seamless transfer of PET/CT data into the contouring workspace, and provide a wide range of options for display of fused PET and CT images.

For treatment planning, the PET/CT scanner should be fitted with a rigid tabletop, and the imaging suite should be equipped with a laser positioning system identical to that used for simulation and radiation therapy treatment. The details of PET/CT simulation workflow are described in the section on Workflow below.

After the PET/CT data are imported into the planning computer, the radiation oncologist is faced with a series of new challenges:
- How do I define the gross tumor volume using PET and CT?
- What nodes should I regard as positive?
- How do I define the edge of a tumor when it imperceptibly fades into normal tissues?

There has been little guidance from the literature on how best to use PET/CT information in contouring tumor and target volumes. Some problems are relatively easy to deal with. For example, a lymph node that is negative for tumor by CT criteria, but is unequivocally involved on PET, can easily be incorporated into the target volume. Similarly, enlarged nodes that are not metabolically active on PET may be omitted from the gross tumor volume if considered unlikely to contain tumor.

Because of the potential for interobserver variation in using PET to determine target volumes, several methods have evolved that attempt to make the results as uniform as possible. These are essentially either visual methods using the skill...
of the human observer, or automated methods using a mathematical algorithm to contour the edge of the tumor in a reproducible and unbiased way.

These challenges are being addressed today by specific radiation oncology imaging and image processing protocols designed for improved accuracy and reproducibility.

**Workflow**

Radiation therapy planning requires specific imaging protocols that may be different from conventional diagnostic procedures. This section describes the CT simulation workflow in radiation oncology, and how PET can be integrated into it. Patient/tumor motion management is discussed in the context of radiation oncology planning. The requirements for patient positioning are presented, as well as a review of the requirements published in the AAPM Radiation Therapy Committee Task Group No. 66 report by Mutic et al. [10].

**CT simulation**

CT-based therapy simulation has become an essential part of the radiation therapy procedure, enhancing the workflow in radiation oncology departments. The CT simulation process utilizes the CT scanner and components of the treatment planning system to provide the information needed for dose calculation.

CT simulation is often referred to as virtual simulation. In general, virtual simulation is defined as any simulation based on a software-created “virtual simulator” and a volumetric patient size. The scan does not necessarily have to be CT, and other imaging modalities can be used. It is important for the virtual simulator to recreate the treatment machine and to allow import, manipulation, and display of images from CT and/or other imaging modalities. The simulation process is dependent on available resources, patient workload, physical layout and location of system components, and proximity of team members.

**General CT and CT/PET simulation workflow**

The CT simulation process has been previously described in detail by Mutic et al. [10].

A graphical representation of the CT simulation workflow is shown in Figure 5. PET/CT systems can also be used for CT simulation or CT/PET simulation. Figure 6 illustrates a typical workflow for a PET/CT simulation scan.

The simulation scan workflow involving CT or PET/CT systems typically includes the following steps:

- Patient positioning on a flat tabletop
- Immobilization using devices in conformance with TG-66 for positioning accuracy (many immobilization devices require a larger bore size than that of conventional radiology CT & PET/CT systems, which could be as much as 85 cm)
- Initial patient marking (Figure 7).
- CT or CT/PET scanning
- Transfer to virtual simulation workstation (requires DICOM export of CT and PET data as well as 3D contours – DICOM RT Structure Set)
- Localization of initial coordinate system
- Localization of targets and placement of isocenter

[Figure 5. CT simulation workflow.]

[Figure 6. PET/CT simulation workflow.]
Scan limits
Scan limits should be specified by the physician and should encompass area at least 5 cm beyond the anticipated treatment volumes. Slice thickness and spacing do not have to be constant throughout the entire scanned volume. Areas of interest can be scanned with narrow (1 mm - 3 mm) thickness and spacing, while large slices (5 mm) can be used for scanning surrounding volumes. This will maintain good image quality while minimizing tube load. The typical scan length for the CT simulation scan is less than 20 cm. Consequently, a corresponding PET scan will be a single bed position scan or a two bed position scan.

CT images
CT images not only provide information about target volumes but also about critical (normal) organs in the vicinity. Using CT images for radiation therapy treatment planning enables improved dose delivery to target volumes while reducing the dose to critical organs. CT images also provide density information for heterogeneity-based dose calculations.

A major weakness of CT images is the relatively limited soft tissue contrast. For several treatment sites, contrast can be used to help differentiate between tumors and surrounding healthy tissue. This is the rationale for adding a diagnostic, contrast-enhanced CT examination to the CT SIM scan.

In addition, the limited soft tissue contrast limitation can be overcome by using CT images in conjunction with magnetic resonance (MR) studies for treatment planning. PET images can play a similar role by adding metabolic information to complement the anatomic details of the CT image.

Respiratory correlated CT simulation
Patient breathing significantly impacts the way lung cancers and upper abdominal malignancies are treated. As the lungs expand and contract while inhaling and exhalung, lung tumors move and even change shape, making precise targeting of radiation beams difficult. Therefore, there is...
a need to characterize tumor motion in the therapy simulation process.

The American Association of Physicists in Medicine (AAPM) Report No. 91 [11] recommends that respiratory management techniques be considered if either of the following conditions occur:

- A greater than 5 mm range of tumor motion is observed in any direction
- A significant normal tissue sparing as determined by the clinic can be gained through the use of a respiration management technique.

The recommended 5 mm motion-limit criterion value may be further reduced for special procedures, such as stereotactic body radiation therapy. This value may be also reduced in the future as other errors affecting radiation therapy, such as errors in target delineation and setup, are reduced, so that respiratory motion then becomes the factor limiting accuracy.

The lungs, esophagus, liver, pancreas, breast, prostate, and kidneys, among other organs, are known to move with breathing. Therefore, respiratory correlated imaging should be recommended for all examinations, particularly examinations of the lung and upper abdominal cancers. Since respiratory induced tumor motion will be present during radiation delivery, it is important to estimate the mean position and range of motion during CT simulation imaging (Figure 8).

The techniques available for CT imaging that can include the entire range of tumor motion for respiration at the time of CT acquisition are:

- Slow CT (Non-Gated CT SIM)
- Inhalation (Inspiration CT SIM) and exhalation (Expiration CT SIM) breath-hold CT
- Four-dimensional or respiration-correlated CT (Multiphase Respiratory Gated CT SIM)

One solution for obtaining representative CT scans for peripheral lung tumors is slow scanning. The CT scanner is operated very slowly, such that, on average, multiple respiration phases are recorded per slice. Hence, the image of the tumor at least in the high-contrast areas should show the full extent of respiratory motion, provided that the scanner operates at a particular table position for longer than the respiratory cycle. This technique yields a volume that encompasses the tumor. In addition to anatomic delineation, slow scanning is more advantageous than standard scanning, because the dose calculation is performed on a geometry that is more representative of that during the entire respiratory cycle, as occurs during treatment. The disadvantage is the loss of resolution due to motion blurring, which potentially leads to larger observer errors in tumor and normal organ delineation. Due to motion blurring, this method is only recommended for lung tumors that are not involved with either the mediastinum or the chest wall. This method is also not recommended for other tumor sites e.g. the liver, pancreas, kidney, etc.

A solution to obtaining a tumor-encompassing volume that can be implemented in most clinics is to acquire both inhalation and exhalation gated or breath-hold CT scans of the patient during the CT simulation session. Taking both inhalation and exhalation CT scans will more than double the CT scanning time and relies on the patient’s ability to hold his or her breath reproducibly. The two scans require image fusion and extra contouring. For lung tumors, the maximum intensity projection available in most visualization systems can be used to obtain the tumor-motion encompassing volume, provided there is no mediastinal tumor involvement. The advantage of this approach over the slow scanning method mentioned above is that the blurring caused by the motion present during free breathing is significantly reduced.

Another solution for obtaining high-quality CT data in the presence of respiratory motion is 4D CT or respiration-correlated CT [12] (Figures 9, 10).

Four-dimensional data can be analyzed to determine the mean tumor position, tumor range of motion for treatment planning, and the relation of tumor trajectory to other organs and to a respiration monitor. A limitation of 4D CT is that it is affected by variations in respiratory patterns during acquisition. A 4D CT scan can be obtained in approximately a minute of scanning time with a 16-slice CT
simulation is to match the PET image(s) to the CT image(s). It needs to be pointed out that if a MIP CT image is used to define the range of tumor motion (the most typical case) this image should be also used for the purpose of attenuation correction and localization of PET data.

Future applications

The cancer imaging paradigm is moving beyond detection of the tumor cells. In addition to the currently available combination of CT and FDG PET imaging, new tracers may enable the use of PET to measure cell hypoxia and proliferation, which are the key factors affecting tumor response to therapy, and may enable the use of biological information for therapy planning.

In this section of the article we will review the biological rationale for utilization of FLT ($^{18}$F-3-deoxy-3-fluorothymidine) and FMISO ($^{18}$F-fluoromisonidazole) in radiation treatment planning and discuss some of the challenges facing these techniques. FLT and FMISO are currently available for use in the USA by holders of an Investigational New Drug (IND) Exemption.

Background

In recent years, image guided external beam radiation therapy has led to significant improvements in successful dose delivery. A combination of accurate tumor delineation with CT pre-treatment imaging, organ deformation and motion tracking with respiratory correlated data collection is now possible. FDG PET imaging plays a role in better differentiation of tumor from normal tissue.

The logical progression from physical improvements in treatment planning and dose delivery is to incorporate biological information from different imaging modalities to better delineate treatment volumes and dose delivered within the tumor while sparing the normal tissues.

In addition, further improvements in treatment outcomes may be gained from biological imaging to study treatment response providing the opportunity for real time adaptation of therapy and the development of new therapeutic strategies.

Biological rationale

As we learn more about tumor biology and about the response to radiation therapy, radiation oncologists have been challenged by two basic radiobiological issues:

- Hypoxic tumors are not effectively eradicated with conventional doses of radiation [12, 13]
Enabling technology: PET/CT
A dedicated PET/CT system, available to or accessible by a radiation oncology department, may be an ideal solution to the development of adaptive image-based radiation dose guidance. PET/CT delivers a spatially registered combination of the anatomical and biological information. Locating the imaging system in radiation oncology would provide several clinical and practical benefits:
- Validation of the techniques in defined clinical models
- Demonstration of improvements in a radiation oncology department
- Development of tools to aid the interpretation and assimilation of the information
- Increasing awareness of the potential of this integrated approach.

Biological treatment planning
Traditionally, radiation treatment planning is based on tumor volume information obtained from therapy simulation imaging studies. CT imaging provides images of excellent spatial resolution, but they do not always provide sufficient contrast to identify tumor extent or regions of high cellular activity that might be targeted with boost doses.

As the tumor volume and biology changes with continuing treatment it is important that the process of target delineation and treatment modification should also be a continuing process. As described above, PET imaging has the potential to provide complementary, biological information regarding cell hypoxia and proliferation.

Enabling technology: biological image guided therapy
Biological image-guided therapy goes beyond geometry, providing patient-specific quantitative information on functional cell properties before, during and after treatment. That it improves the knowledge on the functional properties of a tumor is a logical result of the quality and accuracy of current imaging equipment, potentially enabling the radiation therapist to monitor, model and predict tumor response to the treatment, as well as offering the opportunity to adapt therapy to response measurement.

Pharmacokinetic modeling based on Pinnacle 3 treatment planning software provides

• Radiosensitivity varies as a function of the proliferative status and cell cycle phase of tumor cells [14].

Due to the lack of biological imaging in routine clinical treatment planning, there is limited knowledge regarding the spatial location of hypoxic cells and no methodology to identify proliferation patterns within the tumor.

This situation may change due to the recent developments of advanced PET imaging markers. The PET radiopharmaceutical FLT is taken up and retained by cells as a function of their proliferative activity and it has been validated as an indicator of cell proliferation in experimental models and correlation studies in human tumors [15].

FMISO PET can image tumor hypoxia by increased tumor uptake, because FMISO metabolites are trapped exclusively in hypoxic cells. In tumor hypoxia, the FMISO tumor concentration measured by PET typically exceeds plasma concentration [16].

One could hypothesize that using biology-based dose planning in the initial radiation treatments, dose could be boosted to the hypoxic and proliferating sub-regions of the tumor. These areas are likely to be the most resistant cells of the tumor. As treatment progresses and the tumor changes, the interplay between angiogenesis, proliferation and hypoxia will signify regions of active repopulation, resistant regions and regressing tumor. It would be reasonable to postulate that FLT-retaining regions should continue to receive a radiation boost as should any hypoxic areas that could be identified by PET FMISO imaging.

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Currently, there is no reimbursement in the USA for non-FDG PET oncology applications. FLT and FMISO PET imaging has been studied for many years but clinical trials have not yet led to implementation in routine clinical practice.

The National Cancer Institute’s Cancer Imaging Program has created Investigational New Drug Applications (IND) for new imaging agents in order to engage in multi-center clinical trials of these materials. The first two of these application sets are for FLT and FMISO.

We believe that ongoing efforts of physicians, professional societies and industry will provide evidence that PET imaging is an effective tool in incorporating tumor biology in therapy planning and monitoring. Such evidence will in turn lead to reimbursement and widespread clinical use.

**Conclusion**

As discussed in this article, the ability to measure cell hypoxia (using FMISO) and proliferation (using FLT) may enable the prediction of tumor response to therapy and may lead to the use of this specific biological information for therapy planning. Philips has developed specific products and research tools to facilitate further clinical research into these applications.
Figure 14. The images show a dynamic PET study in which FMISO was used to localize hypoxic regions. On the left, the “conventional” late time image, on the right, the quantitative oxygen concentration (red is low $[O_2]$) given by Bioguide. Data: Memorial Sloan Kettering Cancer Center, New York, NY.

Figure 15. Individualized therapy: Plans adapted to the actual instead of the average or expected functional characteristics will have improved cure rates. In both images, the red curve delineates the prostate and the green curve a hypoxic region. Both IMRT plans consist of 5 beams, the only difference is the dose prescription. On the left side a uniform dose is prescribed to the prostate. On the right side, the dose is adapted to the hypoxic region. Data: University of Washington, Seattle.

References


