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BY LISA FRATT

PET/CT & Next-Generation Radiation Therapy

Radiation therapy is a balancing act that is growing more precarious every year. In the early days, radiation therapy was a relatively inexact science, with radiation oncologists using a handful of crude x-rays to guide treatment. Typically, they added fairly large margins to the target region, harming normal tissue in the process, or they erred on the side of caution and missed cancerous tissue.

The past decade, however, has delivered tremendous advances on both sides of the radiation therapy process. On the imaging side, sophisticated acquisition techniques more clearly delineate tumors and margins. Plus, advances in treatment such as intensity-modulated radiation therapy (IMRT) and respiratory gating translate into ultra-precise treatments, sparing normal tissue and more accurately bombarding malignancies. 2008 brings new advances to further fine-tune radiation therapy protocols.

For example, sites around the world are turning to Siemens Medical Solutions molecular imaging suite as the cornerstone of next-generation radiation therapy. Enabling technologies include Siemens Biograph 16 and 64 PET•CT scanners and Siemens Multimodality workstation with *syngo* TrueD software.

The forefront of clinical research

The Department of Radiation Oncology at University of Maastricht (MAASTRO) in Maastricht, The Netherlands, stands at the forefront of clinical research detailing the advantages of PET/CT in radiation oncology. The clinic deployed Siemens Medical Solutions Biograph 16 PET•CT scanner in 2002, becoming the first global site to use a hybrid system for radiation therapy simulation. Since August 2007, the department has used Biograph 40 TruePoint PET•CT; the higher resolution system allows respiratory correlated PET/CT. It is also on the cutting edge of research in the use of *syngo* TrueD software to improve tumor delineation, which, in turn, allows physicians to more tightly refine treatment margins and radiation dose within the tumor.

The clinic's first research project was designed to answer a basic question in functional imaging, says Professor Philippe Lambin, MD, PhD. That is, does PET/CT provide better visualization of lung tumors than standard CT simulation? Researchers found that PET/CT did provide better visualization. "We found that tumor volume is generally smaller on PET/CT than on CT, and, in many cases, there are discrepancies between CT findings and PET/CT results. Either CT misses some areas that light up on the PET study, or PET/CT detects cancerous activity missed by the conventional CT scan," explains Lambin. The findings enabled researchers to improve treatment for lung cancer patients by irradiating more accurately the macroscopic tumor and reducing the amount of normal tissue irradiated during the radiation therapy treatment course (de Ruysscher et al, 2005).

The next study, a prospective trial, analyzed outcomes of patients with discrepancies between PET/CT and CT findings. It's not uncommon for PET/CT results to contradict CT findings. For example, CT often indicates cancerous activity in a patient's lymph nodes, but the nodes do not light up as cancerous on the PET/CT study. That's because CT may detect inflammations or scar tissue, which are not uncommon in patients with compromised lungs. PET/CT, however, analyzes functional content of tissue to more accurately identify cancerous areas.

Conventional protocols treat CT-positive lymph nodes with radiation. Maastro Clinic designed a multi-year trial to determine if bypassing treatment of these nodes presented a risk of recurrence to patients and recently reported that it is safe to forego treatment on lymph nodes identified as positive on CT and negative on PET/CT.

Another trial, recently completed, built on this finding and treated patients, not with a fixed dose ("the same radiation dose for all the patients"), but at an isotoxic level ("the same risk of complications for all the patients, but a different tumor dose for each"). This approach allows physicians to take advantage of PET/CT to determine small treatment volumes and escalate the tumor dose, in some patients until 80 Gy without increasing the risk of complications. This trial using sequential chemo-radiotherapy shows promising results with survival at two years above 47 percent in nonsmall cell lung cancer stage III, a result that compares very favorably to results of randomized trials with concurrent chemo-radiotherapy.

The enabling technologies for Maastro Clinic's advances include Siemens' hardware and software, says Lambin. Biograph 40 TruePoint PET•CT allows the clinic to provide respiratory gating as the standard of care for lung cancer patients. "Respiratory gating allows us to individualize, based on tumor movement, the safety margin around the tumor (Bosmans et al, 2006). Acquiring respiratory gated PET/CT images, then auto-contouring based on Standard Uptake Values (SUV) on the gated studies in *syngo* TrueD and sending structures to our planning system allows us to define more accurately the area to irradiate, decrease the volume of irradiated area and escalate the dose to improve outcome," says Lambin.

Siemens' software overcomes another major challenge in radiation therapy workflow. Conventional programs are plagued by variability in tumor delineation among various physicians. That is, tumor delineation is a human process prone to human error. Maastro Clinic uses Siemens TrueD treatment planning software to automate measurements, minimizing temporal discrepancies and variability among physicians. "The gold standard—pathological findings—show that this software is doing very well, but next to that it also shows that consistency among physicians is much better with autodelineation software, such as TrueD [van Baardwijck et al, 2007]. It provides a more homogeneous delineation, which is useful in clinical practice and for clinical trials. We use autodelineation routinely for lung cancer and we are currently investigating its value for rectal, cervical, and head and neck cancer," sums Lambin.

Collaborative pioneers

Copenhagen University Hospital in Denmark pioneered the use of PET for radiation therapy treatment planning in 2001. Geography facilitated the approach with a PET scanner located adjacent to the radiation oncology department. The program first focused on head and neck cancers and then began using the hybrid scanner for cervical cancers. "We decided to use whole-body PET/CT rather than abdominal PET scans and found that 30 percent of cervical cases had more cancer than we thought," reports Anne Kill Berthelsen, MD, chief physician,

[Lung Cancer: Primary tumor in left lung with deposit in contralateral lung attached to chest wall. PET/CT performed on Siemens Biograph 40 for metastatic evaluation and RT planning. TrueD visualization of FDG PET/CT datasets with region of interest (ROI) drawn on FDG avid tumor in right lung adjacent to chest wall. Note central hypointensity of FDG uptake within tumor suggesting tumor necrosis. 3D volume ROI drawn on TrueD incorporates FDG avid tumor and excluded necrotic tissue. ROI saved as DICOM RT Structure sets for export to Radiation Treatment Planning system for simulation. Courtesy of MD Anderson Cancer Center, Orlando, Fla.]

PET and Cyclotron Unit and Department of Radiotherapy.

Today, the hospital uses whole-body PET/CT as the standard of care for radiation therapy planning for head and neck, cervical, lymphoma and lung patients. In addition, the approach drives more precise treatment. "Before we implemented PET/CT for radiotherapy planning, we used RECIST criteria for malignant lymph nodes, which is 1 cm. Now, we include all PET positive lymph nodes in the radiation field despite their size," explains Berthelsen. *syngo* TrueD software streamlines the treatment planning process by allowing users to fuse and compare PET/CT images. TrueD automates processes, so physicians can monitor functional and anatomical changes and adjust treatment as needed.

"Although we have two PET/CT scanners and a dedicated PET scanner, we use Siemens Biograph 16 exclusively for radiation therapy planning because tumor delineation on the *syngo* workstation with TrueD software is very precise," explains Berthelsen. State-of-the-art imaging equipment is only part of the equation for a successful PET/CT program in radiation oncology.

Copenhagen University Hospital employs a collaborative approach that optimizes the expertise of multiple specialties. Nuclear medicine physicians tackle tumor delineation on the PET part of the hybrid scan. Next, CT images including the tumor delineation regions are sent from TrueD to the Varian Medical Systems Eclipse workstation, where radiation oncologists and radiologists partners to delineate margins on CT images. The process becomes slightly more complex with head and neck cases as PET/CT studies are fused with MRI results to create a more comprehensive picture of the disease and normal anatomy.

Berthelsen credits the success of the program to close proximity of the PET/CT scanner and radiation therapy department. "Everyone and everything we need are in the same two departments, making it easy to coordinate among radiation oncologists, radiologists and nuclear medicine physicians," Berthelsen says. Other factors in the success of the program include a dedicated IT staff that manages integration of the various scanners and workstations, and a sound working partnership with Siemens. The hospital also focused on training technical staff, so technologists understood how to acquire hybrid images for radiation therapy.

Transforming treatment

MD Anderson Cancer Center at Orlando Regional Healthcare in Orlando, Fla., is a multidisciplinary cancer care center committed to leading-edge treatment and superior patient care. The site installed a Siemens Medical Solutions Biograph 64 TruePoint PET/CT scanner a year ago, and since then it has revamped its protocols for treatment of a number of cancers including early and stage three lung cancers and esophageal cancers. "Siemens Biograph 64 TruePoint PET•CT has dramatically changed the way we treat patients," says Alan R. Forbes, MD, PhD, radiation section leader for thoracic/head and neck and lymphoma/myeloma specialty sections.

It's difficult to balance the equation for effective radiation therapy of lung nodules. "The problem in treating lung cancer," says Forbes, "is that the lung's tolerance to radiation is low, but tumor requirements are high." For example, in conventional arrangements, a tumor might require a 70 Gy dose, while the lung's radiation tolerance is 15 Gy.

"We've seen excellent advances in early stage lung cancer," says Forbes. The new regimen calls for a four-day cycle of ablative radiation therapy; the very high cauterizing radiation dose destroys everything at the center of the beam. Results hover close to lobectomy, making the treatment a good option for borderline and nonsurgical candidates; however, there are downsides to ablative treatment. "There is no normal tissue sparing. If we were to hit a bronchus with the beam, it's likely that it would be destroyed, which closes off the lung supplied by that bronchus. We have to be very accurate; volume and positioning are critical," explains Forbes.

The new protocol centers on the Biograph 64 TruePoint PET•CT. The team places fiducial markers in the lung and gates the tumor's position to the respiratory cycle. The ability to gate the tumor is essential, enabling the team to narrow the beam and focus treatment on the nodule while avoiding the surrounding volume throughout the treatment.

Consider as an example a typical early stage patient with a 1 cm nodule. The tumor might move 4 cm during respiration. With conventional imaging and planning, the radiation therapy team includes respiratory motion in the treatment volume to ensure a full dose reaches the tumor. Respiratory gating allows the team to trim the treatment volume and minimize the dose to normal tissue. "Biograph 64 TruePoint PET•CT provides an ideal imaging platform. 4D CT provides a crisp, clear view of the nodule and its movement during the respiratory cycle. The scanner makes it possible to offer ablative radiation therapy as a treatment option for many early stage lung cancer patients," says Forbes.

The site also uses the Biograph 64 TruePoint for 4D PET imaging. It's not uncommon for lung cancer patients to present with inflammatory tissue around the malignant nodule. "It's a challenge to determine which tissue is malignant and which is inflamed. 4D PET outlines the tumor very well, and 4D CT outlines the tumor very well, allowing us to discriminate malignant and benign tissue and appropriately focus the dose."

PET/CT has proven useful in the treatment of locally advanced lung cancer. "It's difficult to image these patients with conventional PET scans. But PET/CT images reveal the metabolic activity in highly active lymph modes and the precise movement of the primary lung mass," says Forbes. The scanner delivers a new level of diagnostic accuracy, which, in turn, provides physicians the data needed to more appropriately inform treatment decisions. That is, some patients who initially appeared to be surgical or radiation candidates may be spared from treatments that are not likely to be effective.

Another patient population that benefits from PET/CT imaging is esophageal cancer patients.

Despite the advances of the last year, Forbes anticipates further improvements over the next year. Siemens new High-Definition PET•CT will improve resolution to 2 mm, providing a means to analyze tiny nodules detected on screening CT studies. "The new [corresponding] software should improve treatment as well by allowing us to better correlate the physiologic uptake of the tumor and its geometric shape on CT studies," explains Forbes.

Other advances could take the form of new tracers. Hypoxic indicators could point to regions where cancer is likely to recur.

Looking ahead

Maastro Clinic aims to use the Biograph 40 TruePoint PET•CT scanner and TrueD software as a springboard to deliver further improvements in radiation therapy. It plans a host of new trials and protocols this year.

Radiation oncologists have known that tumors are heterogeneous for decades; however, until recently, they did not have a tool to differentiate various regions of a tumor. Now, Maastro Clinic intends to tap into the Biograph 40 TruePoint PET•CT and TrueD software to redefine radiation therapy and monitor response to treatment. The latest version of *syngo* TrueD incorporates deformable registration. "Deformable registration is an amazing technology for advancing assessment of therapy response. It enables us to identify patterns of recurrence within the tumor. Long term, this information will allow us to predict before treatment the risk of tumor relapse for each voxel and give a higher radiation dose to the tumor voxel having a higher risk of local relapse. The concept of 'pattern of relapse within the tumor' will revolutionize the approach evaluating tumor response," explains Lambin. Similarly, Maastro Clinic is using Biograph 40 TruePoint PET•CT during treatment and three months post-treatment in lung and head and neck cancer patients to look at the "metabolic response," a surrogate endpoint highly correlated to survival and to look at the pattern of relapse within the tumor (van Baardwijck et al, 2007).

Finally, Maastro Clinic and Siemens are collaborating on the development of new biomarkers that could answer sophisticated questions about the phenotype of the tumors, or the "tumor passport." "New agents could determine whether or not a tumor is hypoxic, rapidly proliferating or susceptible to specific receptors. Ultimately, information provided by PET/CT could help physicians adapt treatment, the type of radiation and the type of drug, to each specific patient," sums Lambin. This will increase the complexity of the decision process dramatically. It will be crucial to have decision support systems to facilitate decision-making based on rational arguments and on patient wishes about the best treatment for each patient. An example of such initiative is "Remind CS," a decision support software for lung cancer, under development in the Image Knowledge Management division of Siemens. Stay tuned. MII

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