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# Tumor Biology-Guided Radiotherapy Treatment Planning: Gross Tumor Volume Versus Functional Tumor Volume

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**This issue of *Seminars in Nuclear Medicine* deals with a watershed event in cancer treatment—the combined use of functional and anatomical information to guide therapeutic interventions. The use of positron emission tomography/computed tomography (PET/CT) in radiation treatment planning and tumor response evaluation brings a paradigm change in the development of image-guided therapies into routine clinical practice. The implications, as seen in the following articles, are not only promising but also groundbreaking. And, as in every new scientific breakthrough, each step forward generates a myriad of additional important clinical and research questions. Functional imaging takes advantage of the subtle differences between normal and malignant tissues at the cellular level to reveal in vivo unique functional characteristics of neoplasms. The ultimate goal of the partnership between nuclear medicine physicians and radiation oncologists is to use this information with absolute clarity in target definition for radiation treatment planning and therapy, as well as response evaluation. Functional imaging can provide metabolic information and behavioral correlation along with the anatomical imaging for correlative target delineation. Additionally, as a purely diagnostic instrument, PET/CT provides a tool for oncologists to make critical decisions regarding radiation treatment planning modifications secondary to changes in tumor staging (up or down), treatment field modifications, localized control, sites of residual and/or metastatic disease and post therapy response evaluation. The articles in this issue of the seminars provide insights into the current state-of-the-art of functional imaging techniques, mostly centered on the use of $^{18}$F-fluorodeoxyglucose PET/CT in image guided oncologic therapies. Because it is a novel science, the future of image-guided functional treatment planning is bright with technologic and biologic innovations, translational research and new clinical applications.**

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Mah and coworkers[1] have shown how recent increases in computed tomography (CT) bore size (from 70 to 85 cm), the decrease in slice thickness, and scanning speed have significantly improved both the spatial and contrast resolution of CT for soft-tissue targets, allowing the use of pixel-size information in radiation treatment planning. It is now routine clinical practice to obtain axial images in radiation treatment positions (prone and supine). Low-contrast resolution has improved the ability to differentiate between adjacent tissues with similar attenuation coefficients, thereby improving the definition of tumor edges, while allowing for separation, differential, and subtraction analysis as it pertains to radiation planning registration.

The baseline image for coregistration of additional imaging modalities such as magnetic resonance (MR), single-photon emission computed tomography (SPECT), and angiography, has now been clearly set as positron emission tomography (PET)/CT. Fast multislice CT scanners and 4D-CT provide further aid in overcoming motion issues associated with conventional scanners and anatomical regions, such as edge definition, target deformation and correlation between time and

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position for moving targets. Brunetti and coworkers[2] demonstrate the importance of adding the time dimension, exploring the innovative utilization of coregistered 4D-CT/PET as a tool to handle target motion in radiation oncology planning.

Mah and coworkers[1] also describe how treatment planning techniques and the ability to fuse image data sets has changed the delivery of radiation treatments. The importance of precise coregistration when radiation dose is calculated on a pixel-by-pixel basis cannot be over emphasized; with image guided intensity modulated radiation therapy, regions outside target volumes will not receive therapeutic doses of radiation. The sophistication and precision of modern radiation planning and delivery techniques are greatly enhanced by image fused data sets which take into account functional information. Brunetti and coworkers[2] point how detailed technique and careful coregistration are crucial for optimal results.

## PET/CT for Target Validation

The hybrid or fusion-imaging of PET/CT will continue to improve both the sensitivity and specificity of clinical imaging. PET/CT presently represents the fastest growth area of medical imaging, with many applications coming from extensions of immunohistochemistry and SPECT, which are finding applications in differentiating malignant from benign disease, grading and staging of malignancy by TNM classifications, evaluating tumor response to therapies, recurrences detection, and the possibilities of discerning solid tumor with different sensitivities (based on physical status) for effective radiation treatment.[3-12]

Although pioneering investigators are accumulating experience and data compilation, the primary assessment to date has been target volume and staging modifications (approximately one-third of all patients) and dose distribution changes (adding another 25-30% of patients) with the addition of PET imaging to CT. Ahn and coworkers[13] demonstrated the importance of incorporation of nodal disease not viewed on CT in head and neck cancer, whereas Macapinlac and coworkers[14] showed the reduction in treatment volumes in nonsmall cell lung cancer caused by nonactive actelectasis that appeared as mass volume on CT alone.

The articles by Ahn,[13] Schöder,[15] and Macapinlac[14] and coworkers in this issue provide a comprehensive review of the current status of PET/CT in treatment planning, with clinical data, which shows a very significant effect of $^{18}$F-fluorodeoxyglucose (FDG) functional imaging both in changing target volumes and changing doses to areas previously thought to harbor only microscopic disease. As an aggregate, it seems reasonable to estimate that between 55% and 60% of patients submitted to functional imaging have potential changes in target volumes and/or dose distribution parameters.[3-9,11,12]

## Tumor Versus Normal Tissue Expression Patterns

Molecular imaging has become one of the main areas of interest in drug discovery and the preclinical market place. From a drug-development perspective, molecular imaging provides information on the pharmacological effects on in vivo biochemistry and physiology. It can also provide pharmacokinetic information regarding absorption, distribution, metabolism, and excretion/elimination of a labeled agent, pointing toward tumor burden and functional activity. Equally definitive in the search for differences between tumor and normal tissues has been the study of patterns of DNA changes (*genomics*), which are likely to prove more useful than looking for single DNA changes in tumor cell populations. The imaging of radiolabeled genetic markers may yield a wealth of information in the cancer genomics arena.

A significant portion of the recent explosion in potential tumor targets has been generated by automated gene sequencing profiles, proteonomics, and high-throughput screening of these targets in preclinical animal (tumor xenograft) modeling. Although there are a significant number of molecular imaging agents available to investigators, a consensus exists that additional tracers that target more physiologic functions are essential to drive new molecular imaging techniques into the clinic. There is also a significant need for increasing specificity. Many tumor markers also are increased in infection and inflammation.

As the Mah[1] and Schöder[15] articles point out, biomarkers for tumor sensitivity and resistance will emerge to help guide personalized therapies and radiation "dose-painting" because radiation planning computer algorithms are ready for this challenge. Homogeneous doses of radiation covering tumor targets of different functional and genetic parameters may soon be an abandoned paradigm of the past. The expression patterns that can discriminate viable tumor from normal or inflammatory material, summarized in Table 1, will have their basis in the tumor microenvironment, genetic fingerprints, tumor aggressiveness, and post-treatment response characteristics. As Schöder points out, FDG-PET has, as its basis, a level of increased tumor uptake in regions of high metabolic/glycolytic activity. As such, FDG-PET as we know it produces maps of increased FDG glycolysis and uptake, which are relatively nonspecific imaging tools, and which may soon be replaced by more unambiguous images that deal with the above mentioned parameters. Table 1 describes just a few, highly studied examples. Many more are in various stages of development.

## Novel PET and Other Radionuclides for Dynamic Conjugations

On the basis of various criteria such as imaging photons, particle emission, dosimetry, and feasibility of production, a number of radioactive metals are considered suitable for labeling antibodies for radioimmunoimaging and/or radioimmunotherapy. Examples of suitable radiometals for both PET and general nuclear medicine include:

- For imaging: $^{55}$Co,$^{64}$Cu,$^{66}$Ga, $^{68}$Ga, $^{82}$Ru, $^{99m}$Tc,$^{111}$In, and $^{203}$Pb

**Table 1** Tumor Expression Parameters Suitable for Imaging

| Tumor Expression Parameter | Marker | Clinical Application | References |
|---|---|---|---|
| Glucose metabolism | $^{18}$F-FDG | General tumor imaging | 64,65 |
| Proteins/amino acids | $^{11}$C-methionine | Brain tumors | 16,17 |
| | $^{11}$C-choline | Prostate tumors | 18-24 |
| | $^{18}$F-DOPA | Carcinoid | 27-31 |
| | $^{18}$F-methyltyrosine | Musculoskeletal tumors | 32 |
| Proliferation (DNA) | $^{18}$F-thymidine | Radiation response | 33-39 |
| Apoptosis | $^{18}$F-annexin V | Treatment response | 63 |
| Hypoxia | $^{18}$F-misonidazole | Radiation planning | 40-47 |
| Receptor binding (avidity) | $^{18}$F-estradiol | Breast cancer imaging | 48-56 |
| Angiogenesis/blood flow/perfusion | $^{18}$F-galacto-RDG | Integrin $\alpha v\beta 3$ binding | 57-59 |
| Membrane/lipid synthesis | $^{18}$F-acetate | Proliferation | 24-26 |
| Bone turnover | $^{18}$F | Skeletal disease | 60-62 |

- For therapy: $^{47}$Sc, $^{67}$Cu, $^{90}$Y, $^{105}$Rh, $^{109}$Pd, $^{153}$Sm, $^{177}$Lu, $^{186}$Re, $^{188}$Re, $^{199}$Au, $^{210}$At, $^{18}$F, and $^{212}$Bi

Depending on the success of chelating agents and covalent linkage patterns for certain ligands and peptides to produce more stable complexes with most of the radioactive markers mentioned previously, $^{55}$Co, $^{64}$Cu, $^{67}$Cu, $^{111}$In, $^{203}$Pb, $^{90}$Y, $^{124}$I, and $^{153}$Sm appear to be the most promising agents because their coordination geometries and because they are suitable for bifunctional chelating agents, which bind radiometals with a higher density (number of coordination sites) and/or incorporate greater structural rigidity to produce immunoconjugates with better in vivo kinetic stability. From a practical standpoint, however, the usefulness of a radionuclide is still based on production capabilities, convenience of delivery for imaging, and half-life parameters (Table 2).

## Quantitation and Standardization

A critical feature of great quantitative value for both delineation and prediction of treatment response is whether we will be able to standardize the uptake volume (voxel) as standard uptake volumes (SUVs) or any other valid reproducible parameter within the regions of interest in a similar fashion to magnetic resonance spectroscopy (MRS)/magnetic resonance imaging (MRI). Different authors in this issue outline several methods of standardization and comparison of FDG uptakes.[11] The current reproducibility of SUVs in clinical practice is highly controversial, because interobserver and device variability still exists. When SUVs and other methods are applied for determination of target volumes rather than simple staging or tumor identification, variability becomes a critical issue, well outlined in the Macapinlac,[14] Schöder,[15] and Brunetti[2] articles. In this regard, newer fusion and coregistration methods based on novel computer algorithms may reduce the considerable variability in visual interpretations and subjective inaccuracies that they now offer.

**Table 2** Some Typical Pet Radionuclides and Selected Applications

| Radionuclide | Half Life (min) | Application |
|---|---|---|
| Iodine-124 ($^{124}$I) | 6048 | Apoptosis imaging, thyroid cancer |
| Yttrium-86 ($^{86}$Y) | 884 | Response to targeted agents, Antibody labeling |
| Copper-64 ($^{64}$Cu) | 768 | Hypoxia marker, blood flow |
| Fluorine-18 ($^{18}$F) | 110 | Multiple applications |
| Gallium-68 ($^{68}$Ga) | 68.3 | Somtostatin receptors |
| Carbon-11 ($^{11}$C) | 20 | Prostate, gliomas |
| Nitrogen-13 ($^{13}$N) | 10 | Drug development |
| Oxygen-15 ($^{15}$O) | 2 | Vascularity marker |
| Rubidium-82 ($^{82}$Ru) | 1.25 | Cardiac imaging |

## Nonspecific Versus Specific Uptake for Tumor Expression Parameters

Through advanced radiochemical processes, a plethora of radioactive ligands can be conjugated to functional binding agents. The capability of localizing selectively to a tumor is crucial. Metal chelating agents may be conjugated with various functional binding agents for localization and may include antibodies (polyclonal and monoclonal); antibody fragments, eg, the F(ab′)$_2$, Fab', or Fc portions of an immunoglobulin; other proteins; and fragments or peptides. [66] A newer approach is the use of genetically engineered proteins, peptides, and antibodies and a number of other functionally active compounds.

Tracers that are more specific to physiologic properties and biochemical parameters with the greatest tumor avidity will play an increasing role in differentiating disease and evaluating therapeutic responses. A summary review of the lead compounds that are finding their way out of the preclinical modeling is presented in Table 3. Many of these agents also can be used in combinational algorithms for further delineation of tumor expression parameters beyond FDG.

In this regard, fluoro-misonidazole has demonstrated selective binding to hypoxic compartments within tumor. However, the high lipophilicity and slow clearance kinetics

**Table 3** Examples of Lead Novel PET Imaging Compounds That Are Under Development

| | References |
|---|---|
| **Glucose metabolism** | |
| 2-[$^{18}$F]-fluoro-2-deoxy-D-glucose | 64,65 |
| **Proliferation** | |
| $^{124}$I iododeoxyuridine, thymidine | 33-39,69,70,75,86 |
| **Protein metabolism** | |
| CEA | 99,100 |
| $^{11}$C methionine, $^{18}$F-ethyltyrosine | 16,17,67,68 |
| $^{11}$C-tryptophan | 76-78,84 |
| $^{18}$F-DOPA | 28-31,82 |
| Intestinal peptide, MIBG, somatostatin analogs | 79-83,95-97 |
| $\alpha$-melanocyte receptors, $^{18}$F-galacto-RGD | 58,59,98 |
| **Membrane synthesis** | |
| $^{11}$C, $^{18}$F choline | 18-24 |
| **Hormone receptors** | |
| Androgens, estradiol, progesterone | 74,87-91 |
| **Reporter genes** | |
| $^{18}$F-FEAU, FIAU, FMAU | 72 |
| **Apoptosis** | |
| Annexin-V, phosphatidyl serine (PS) | 63,92 |
| **Hypoxia** | |
| $^{18}$F-misonidazole, $^{18}$F-fluorazamycin arabinoside | 40-47,93 |
| **Angiogenesis** | |
| Fibronectin, vascular endothelial growth factor (VEGF), integrin $\alpha v\beta 3$ | 57-59,69,85 |
| **Receptor avidity** | |
| Herceptin-2, EGF, dopamine | 66,71,73,94,96,101,102 |
| **Vascularity, blood flow** | |
| VEGF | 85 |

of this radiotracer necessitate imaging for longer durations, with appropriately matched radionuclides with longer half lives. Similarly, several other analogs such as fluoroerythronitroimidazole, fluoroetanidazole, and 1-(5-Fluoro-5-deoxy-$\alpha$-D-arabinofuranosyl)-2-nitroimidazole are under development[43,45,46] because of more favorable hydrophilicities, pharmacokinetics, and lower toxicities.

# Imaging of Future Genetic Markers With No Contemporary PET Correlates

Molecular-genetic studies of cancer and our understanding of the multiple and converging pathways that are involved in tumor progression have rapidly expanded. More specific therapy requires the ability to measure the level of target expression in the tumor ultimately to pursue "biomarker imaging" that reflects the endogenous molecular-genetic processes. Future biomarker imaging maybe be at the same level as immunohistochemistry is today in its ability to use cellular markers for clearer definition of disease whether for staging or assessment of involvement and treatment response. In this regard, biomarker imaging maybe the target expression of a particular protein or measuring the activity of particular "up/downstream" pathways.

Taking advantage of the differential expression patterns between normal and abnormal tissues based on unique epitopes and surface markers by labeled antibodies continues to be a pragmatic and feasible approach. Many of the tumor expression parameters are Class 1 and 2, that are restricted antigens recognized only by lymphocytes ie, melanoma–melanocyte differentiating antigens. Other antigens can be either mutated or the shared antigens commonly overexpressed in cancers as in P53, CEA, etc. Of concern is whether any of these genetic markers are unique enough to be imaging or treatment responsiveness applied or have the universality of FDG. An overview of some of the more common tumor expression parameter possibilities is provided for the benefit of understanding the potentials of imaging biologic tumor volumes.[68,103-105] While the predominate emphasis has been placed on therapeutic agents tethered as "guided missiles" to the specific antibodies, the improved approach has seen the recent developments of humanized (chimeric) antibodies with highly specific reporter molecules to preferential cell surface receptors that exist in malignant tissue.

## Cytokeratins

The presence of cytokeratins indicates epithelial cells, so this marker is a reasonably effective "epithelial screen" to search for epithelial differentiation in poorly differentiated malignant tumors. A negative cytokeratin AE1/AE3 could help rule out or rule in carcinoma. The most common carcinoma that is negative for cytokeratin AE1/AE3 is hepatocellular carcinoma. Cytokeratin 5/6 (CK 5/6) is a marker for squamous cells and squamous carcinomas, as well as other variants of squamous carcinoma, including basaloid squamous carcinomas. This marker is important for lymphoepitheleomas-like thymic carcinomas.

## DNA Methylation and Phosphorylation

Human tumor cells often demonstrate abnormal patterns of DNA methylation. DNA methylation provides an epigenetic mechanism for altering gene expression by silencing genes. Hypermethylation frequently underlies the silencing of tumor suppressor genes. The opposite condition, in which DNA is hypomethylated, has been observed in a spectrum of human tumors. DNA methylation and the rate-limiting step in glycolysis, hexokinase, are generally increased or overexpressed in many human cancers.

Quiescent cells versus growth and differentiation can be understood in terms of progression through the cell cycle, for which the retinoblastoma (Rb) gene product is critical. Rb plays a key role in cell cycle progression and differentiation in a number of tissues. Rb hypophosphorylation forces cells to leave active cycling and enter $G_o$; therefore, regulation of this

protein has more than a casual interaction with the Rb/p53 cell cycle pathway.

## Oncogenes and Tumor-Associated Proteins

The most common tumor associated proteins subject to imaging are CA 125, CA 15-3, CA 19-9, MART-1 (Melanin-A), MDM2, NY-ESO-1, and Rb gene product. Additionally, RAR beta2 (retinoic acid receptor beta2), a tumor suppressor gene, is frequently hypermethylated in several malignant tumors. The Ras oncogene has been identified in the tissues of a wide variety of cancers, although it has not been identified as specific for any single cancer.

Other peptides that have been associated with disease that are actively being pursued include cystatin C, a marker of glomerular function in children with cancer; serum homocysteine (Hcy), a potentially useful tumor marker to monitor tumor activity; and the intestinal trefoil factor, a marker of intestinal differentiation that also may play a role in cancer cell biology by inhibiting cell adhesion, promoting cell invasion, and blocking apoptosis. Finally, PKM2 tumor marker plays a general role in caspase-independent cell death of tumor cells and thereby defines this glycolytic enzyme as a novel target for cancer therapeutics and diagnostics, whereas PP11 (placental protein 11) can act as a tumor marker because of its specific association with various forms of cancer.

## Common Cancers and Associated Tumor Markers

The CA 19-9 marker is the most useful marker for pancreatic cancer. Approximately 85% of people with pancreatic cancer have increased levels of this marker in their blood. This marker also has been used to follow the effects of treatment on more advanced disease.

Prostate-specific membrane antigen (PSMA), a transmembrane protein expressed in all types of prostatic tissue, remains a useful diagnostic and possibly therapeutic target. The radioimmunoconjugate form of the anti-PSMA monoclonal antibody 7E11 is used in the commercially available and US Food and Drug Administration-approved diagnostic tool, ProstaScint (Cytogen Corporation, Princeton, NJ) immunoscintography scans. PSMA is a very sensitive marker, but so far it has not proven to be better than serum PSA, and its use in detecting or monitoring cancer is still being studied. There are expectations that the introduction of SPECT/CT will improve its accuracy and use. Alpha-methylacyl-CoA racemase is potentially an important tumor marker for several cancers and their precursor lesions, especially those linked to high-fat diets (ie, breast, prostate and colon cancer). Additionally, CD133, mRNA expression is increased in cancer patients with metastatic disease, specifically with bone metastasis.

Most colorectal cancers contain changes in genes such as p53, APC, and k-ras. New studies have found abnormal DNA molecules in the stool of patients with early colorectal cancer. Imaging stool samples for these DNA changes may prove to be an effective way to screen for this disease. Imaging the number of repeated sequences in DNA (microsatellite instability) may give physicians the ability to assess treatment efficacy.

CA19-9, a nonspecific tumor-associated antigen, allows supportive correlation of malignancies of the gastrointestinal tract, breast, and lung. Carcinoembryonic antigen (CEA), a member of a family of cell surface glycoproteins that are produced in excess in essentially all human colon carcinomas and in a high proportion of carcinomas at many other sites, can currently be imaged. If the CEA is not elevated in patients with advanced or recurrent cancer, sometimes the CA 19-9 will be and can be used to follow the disease.

At the time of diagnosis, breast cancer tissue is often tested for estrogen and progesterone receptors, as well as the HER-2/neu antigen. These markers provide some information on tumor aggressiveness and prediction of therapeutic response. The markers most commonly used to follow patients with advanced cancer or to detect tumor recurrence are CA15-3 and CEA and the CA 27.29. These have been the most useful in measuring the results of treatment for patients with advanced disease and can be potentially valuable as imaging agents for recurrent disease, although early trials have been disappointing.

There are large numbers of antibodies specifically of use in breast cancer detection that could be targeted for imaging and therapy: CA15-3, estrogen/progesterone receptor, HER2, HER4 (c-erbB-4), and Ki-67, Rb gene product, Smad3, STAT3, TAG-72, uPAR, S-phase kinase-associated protein 2, EGF, MAP kinase (ERK1+ERK2), metallothionein, MTA1, MUC1 (Mucin 1), MUC2 (Mucin 2), NY-ESO-1, and syndecan-1 (Sdc-1), known as CD138, a cell surface heparin sulfate proteoglycan. Additionally, MCK-2 has been proposed as a potential tumor marker in breast cancer.

Metallopanstimulin, a 9.5-kDa subunit "zinc finger" protein, is expressed in a wide variety of actively proliferating cells and tumor tissues, including recurrent breast cancer. Mig-7 may be a potential early marker of migrating and circulating carcinoma cells. MUC1 overexpression is considered to be the most sensitive and specific marker of invasive carcinoma. Tumor M2-PK and circulating tumor M2-pyruvate kinase are more commonly increased in esophageal, gastric, and colorectal cancer patients. Cytokeratin 19, cytokeratin 8, cytokeratin 8/18, galectin-3, MUC1 (Mucin 1), MUC2 (Mucin 2), MUC5AC, and Smad3 are all in the earliest phases of development for diagnostics and therapy.

Although no tumor markers are universally elevated in lung cancer, neuron-specific enolase could prove useful in the imaging of small cell lung cancer for diagnosis and staging, as well as for recurrence. It may be noteworthy that small cell carcinoma usually have a very high uptake of FDG. Tissue polypeptide antigen, a protein marker present in high levels in many rapidly dividing cells along with other tumor markers, has had some usefulness to evaluate patients being treated for lung and bladder cancers.

Melanoma-associated restricted tumor antigens have been used to test tissue samples to help diagnose melanoma in suspicious areas, as has the S-100 protein, which is found in most melanoma cells. Tissue samples of suspected melano-

mas often are tested for this marker to help in diagnosis. TA-90, a protein found on the outer surface of melanoma cells, can be used to look for the spread of melanoma. Its value in charting the progress of melanoma, however, is still being evaluated along with other cancers such as colon and breast. A trial with antimelanin antibody is currently underway. Histidine decarboxylase also has been suggested as a new marker for neuroendocrine differentiation, inflammatory pathologies, and several leukemia and highly malignant forms of cancer, such as melanoma and small cell lung carcinoma.

Epithelial ovarian cancer, the most common form of ovarian cancer, is linked with elevated levels of CA 125. Other markers that are sometimes measured are CA 72-4 and the LASA-P. CA 125, which is increased in 90% of women with advanced disease, is the standard marker used. Ovarian cancer, even when advanced, is often confined to the abdomen and pelvis and hard to locate through x-ray imaging. Because of this, the CA 125 is often the most effective way to measure the response to treatment, or to find recurrence. There is preliminary evidence that FDG-PET imaging of patients with serum CA 125 elevation and normal CT scans reveals the presence of abnormal uptake, especially in the peritoneal cavity and retroperitoneum. The potential of targeted CA 125 imaging is thus ready to be explored.

## MRS and MRI/PET

Although functional imaging (based on in vivo functional characteristics) has the capacity to take advantage of differential tissue characteristic at the cellular level, the dynamics of molecular and biochemical assessment may not be fully achieved until it is integrated as MRS and PET. Although the goal of absolute clarity in target definition for radiation treatment planning is the same, the information, relative to co registration and slice thickness, is infinitely more detailed at the microscopic level. Slice thicknesses at 7.4 Tesla are already approaching 50 $\mu$m for delineation of axial and coronal slice thickness. Functional images will provide spatial registration along with the anatomical imaging for better correlative target delineation.

As a purely diagnostic instrument, MR/PET will be capable of using both protons and the phosphorous atom and their evaluation capacities. Other MR markers are on the way, but their practical use is unclear at this time. In a manner similar to the voxel image registration of CT, the use of MRS will provide biochemical information related to energy correlates of membrane activity. Examples are phosphomonoesters, phosphatidyl choline and ethanolamine, the energy pathways of lactic acid spectrum phosphates, inorganic phosphates, citrate, etc, in the region of interest. Phosphatidylserine, an abundant and accessible marker of tumor vasculature and cell membranes, has value as a potential marker of therapeutic response (ie, apoptosis and necrosis). Dynamic imaging of blood flow and proton imaging provide additional tools to be studied.

## Conclusion

After a major review of the literature, the Food and Drug Administration has been convinced of the justification for the approval of radiopharmaceuticals and moving forward toward the rapid incorporation of PET into both the practice of nuclear medicine and oncology. The growth of applications in oncology has additionally been enhanced by the decision of Medicare to support the National Oncologic PET Registry that will assess the utility of currently available tumor imaging agents in all cancers without restriction on indication. The potential utility of radiopharmaceuticals labeled for PET/CT will continue to depend on both design and development in addition to regulatory compliances with safety and efficacy by various investigational users. The innovative approaches outlined in this seminar place us at the time when the incorporation of functional data into cancer treatment has become a reality. Radiation oncology has partnered with nuclear medicine, and both are engaged in the search for newer functional paradigms for image-guided oncologic diagnostics and therapies. The future depends on our ability to engage into quality and speedy translational research in radiochemistry, and mechanism(s) of tumor cell uptake and localization of radiotracers for new markers and more precise guidance.

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