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Innovations in Imaging

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Innovations in Imaging: An Introduction

BY LAETON J. PANG, MD, MPH

This supplement to *Oncology Issues* introduces four fascinating technologic innovations in diagnostic radiology that hopefully will help advance earlier colon and possibly lung cancer detection, enhance efficiency and patient throughput, improve staging, and ultimately may help direct more effective treatment strategies. But will these improved technologies translate into improved survival for patients or will improvements in survival be artifactual due to stage migration?

Twenty years ago, Feinstein, Sosin, and Wells first published on the "Will Rogers phenomenon."[1] Commenting on geographic migration during the economic depression of the 1930s, American humorist Will Rogers is alleged to have said, "When the Okies left Oklahoma and moved to California, they raised the average intelligence levels in both states." An analogous phenomenon, stage migration, occurs with more careful staging of cancer. If a population of patients is more accurately staged, the survival of all stages is improved because patients with subtle advanced disease will be upstaged.

The Will Rogers phenomenon has been well documented in a variety of settings, including colon, breast, lung, larynx, and prostate cancers.[1-6] In their original study, Feinstein and colleagues found that a cohort of patients with lung cancer first treated in 1977 had higher six-month survival rates for the total group than a cohort treated between 1953 and 1964 at the same institutions. The more recent cohort, however, had undergone many new diagnostic imaging procedures. Many patients who previously would have been classified in a "good" stage were assigned to a "bad" stage. Because the prognosis of those who migrated, although worse than that for other members of the good-stage group, was better than that for other members of the bad-stage group, survival rates rose in each group without any change in individual outcomes.[1]

More recently, Woodward and her colleagues at the M.D. Anderson Cancer Center looked at records of 1,350 women with locally advanced breast cancer who had been followed for a median of 10 years. They used the raw clinical data to stage patients according to each set of guidelines. They found "a surprising difference" in stage-specific mortality between the 1988 and 2003 American Joint Committee on Cancer Guidelines.[3] For example, women diagnosed with stage II breast cancer according to the 1988 guidelines had 5- and 10-year survival rates of 72 percent and 53 percent, respectively. Those same women classified with stage II disease according to the 2003 guidelines, survival rates were 86 percent at 5 years and 75 percent at 10 years.[3]

As a radiation oncologist, I'm not one to argue against advancements in technology. But will these new technologies be reimbursed at a higher rate than standard imaging modalities to encourage modernization? And will the new technologies offer a cost-benefit ratio? Should community cancer centers spend the extra money to acquire these new technologies? More importantly, will patients truly benefit in improved survival?

Clinicians and biostatisticians face significant epidemiologic and logistical hurdles sorting through the differences in staging and treatment to determine whether a true survival advantage has been achieved. Staging systems have yet to incorporate or account for differences in modalities used to stage patients. Most cooperative group clinical trials don't allow use of PET scans for staging patients. Therefore, some patients with more advanced disease who've had PET scans done in the course of evaluation—but who otherwise would have met enrollment criteria—are excluded from participation. Such circumstances make comparison of results to historical controls problematic. The answer to better patient survival probably depends more on finding better treatments for cancer than on better staging, but until then there's always the Will Rogers phenomenon.

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Diagnosis and Staging of Cancer with PET/CT

BY JACQUELINE BRUNETTI, MD

Parallel developments in molecular biology, computer sciences, and imaging technology have paved the way for new paradigms in cancer diagnosis and surveillance. In particular, the capability to image both tumor anatomy and function that is provided by combined positron emission tomography and computed tomography (PET/CT) scanners is changing the way of diagnosing, staging, and monitoring cancer.

HOW IT WORKS

PET/CT scanners perform a CT scan followed by a PET scan, typically imaging from the skull base to the mid-thighs. The newest generation PET/CT scanners can complete the PET and CT acquisitions in less than 30 minutes—a significant improvement over conventional PET scanners that require at least 50 to 60 minutes to complete an exam. With a conventional PET scanner, a 20-minute transmission scan must be performed to obtain attenuation data to correct the PET images.

In a PET/CT scanner, PET attenuation correction is accomplished by using CT data that is acquired in approximately 90 seconds. PET images have low anatomic resolution and, often, areas of abnormality on a PET scan cannot be localized without comparison to a morphologic imaging study such as CT or MRI (see Fig. 1). Even side-to-side comparison of images, at times, is insufficient to allow accurate localization of small abnormalities on PET.

Computer fusion software packages are available that facilitate fusion of PET images with CT images performed on another scanner. However, this approach may be limited in that accurate co-registration of the images may be difficult due to differences in patient position between the two studies; difference in age of the CT versus the PET scan (i.e., the CT may be several weeks older); or, perhaps, an abnormality in the chest is seen on the PET scan and only an abdomen CT is available. In this last circumstance, a delay in the time to diagnosis occurs as the patient then must be referred for an additional CT to investigate the PET scan findings.

PET/CT scanner images are displayed as separate image sets and also as a fused data set with PET and CT slices overlaid according to anatomic location. The fused images allow regions of abnormality seen on PET to be readily identified as pathologic or as areas of normal physiologic activity. The increased sensitivity and specificity of PET/CT has been shown to result in improved detection of areas of normal FDG uptake as opposed to PET alone. The fusion of PET and CT images also provides functional information about unexpected findings on CT that may help distinguish benign from malignant disease. For the cancer patient, the combined PET/CT approach translates into a savings of precious time, as all information is gathered in the same imaging session.

PATIENT PREPARATION

Patient preparation for PET/CT is the same as for conventional PET imaging. The imaging agent for PET is glucose analog, ^{18}F-fluorodeoxyglugose (FDG), and high serum-glucose levels will adversely affect scan results. For this reason, patients are instructed to fast overnight prior to the PET scan. Patients with diabetes pose a particular challenge, and the glucose levels of these patients must be adequately controlled before the PET scan. To avoid increased uptake of FDG in muscles, patients are also instructed to avoid strenuous exercise for at least 72 hours prior to the PET scan.

FDG injection is followed by a 60-minute uptake period to allow distribution of the radiopharmaceutical. Because contracting muscles have increased glucose uptake, patients must remain still during this time to avoid increased glucose uptake in muscles. For patients with breast and pancreatic cancer, a longer uptake period of 90 minutes is advised. This longer period of uptake time has been shown to improve tumor detection for these cancers. [1]

USE OF ORAL CONTRAST REMAINS CONTROVERSIAL

Some PET/CT facilities have the patient drink oral contrast to opacify the intestines to allow better identification of bowel on CT. Studies have evaluated the use and necessity of IV contrast for the CT portion of the PET/CT exam. If a recent contrast CT scan is not available, some benefit may be realized in performing a contrast-enhanced CT to better delineate vascular anatomy, particularly in the neck, or to improve the specificity to the CT portion of the exam. Recent studies have evaluated the effect of contrast on the attenuation correction of the PET and found artifacts only in regions of very high contrast density, such as the subclavian vein.[2]

The use of intravenous contrast in PET/CT remains a controversial topic. It is reasonable to consider the functional PET activity as a contrast agent for CT. A recent study by Shaefer and colleagues reports no advantage of contrast-enhanced CT over PET/CT in the staging and restaging on non-Hodgkin's and Hodgkin's lymphoma.[3] Similar large, patient group studies are needed to determine if contrast-enhanced CT provides a benefit.

For non-small cell lung cancer, colorectal, esophageal, lymphoma, melanoma, head and neck, colorectal, breast, and cervical cancer, PET imaging has been shown

to be more accurate than CT in staging cancer.[4] Supporting data also exist for other cancers such as ovarian, testicular, pancreatic, and soft tissue sarcomas. [4] Cancer staging with PET/CT has been shown to be more accurate than PET alone, and the findings of both PET/CT typically result in changes in patient management.[5-7]

In a recent series of 260 patients with various solid malignancies staged with PET/CT, Antoch and colleagues report 84 percent accuracy with PET/CT for determination of TNM (tumor, node, metatasis) stage. The study found an accuracy of 76 percent for side-by-side comparison of PET and CT; 63 percent for CT alone; and 64 percent for PET alone. PET/CT findings resulted in a change in management in 16 percent, compared with PET alone; 15 percent, compared with CT alone; and 6 percent, when compared to side-by-side interpretation of CT and PET.[8] In a recent article comparing PET with PET/CT to surgical findings in the staging of non-small lung cancer, Cerfolio and colleagues provide similar supportive evidence for PET/CT.[9] The authors found that PET/CT was significantly better than PET alone in predicting stage I and II disease and in determining the tumor and node status of patients.

This incremental improvement in accuracy with PET/CT is the result of the improved sensitivity of PET that is gained from the accurate localization of both benign and pathologic PET activity on fusion imaging, and the contribution that PET imaging makes in characterizing findings found on CT. In approximately one to three percent of patients imaged with PET, unexpected malignancies are discovered.[10] Most frequently, second primary tumors in the GI tract are discovered, but discovery of cancers of the thyroid, breast, and lung are not uncommon (see Fig. 2).

PET/CT USE FOR MONITORING THERAPY

PET/CT is an excellent tool for monitoring therapy. New molecular therapies, targeted at specific cellular functions, require more specific methods of determining effectiveness. As these therapies disrupt molecular processes, monitoring response with imaging techniques that reflect the change in tumor metabolism rather than changes in tumor size is beneficial. Moreover, changes in tumor metabolism will pre-date any change in tumor size. The ability to monitor changes in tumor metabolism may greatly benefit patient care in that response, or lack of response, may be determined early so that appropriate therapeutic changes may be made.

Not infrequently, patients with cancer exhibit a mixed pattern of response with regions of regression, progression, and site of no change identified. The combination of both functional PET information and anatomic CT images is very helpful in a mixed pattern of response as functional changes may be identified in nodes or metastatic foci that have not changed in size.

In particular, PET/CT has been shown to be useful in identification of peritoneal metastatic disease that occurs with ovarian and GI tract malignancies. The fusion of PET and CT images is particularly effective in highlighting small peritoneal lesions that may be missed on even optimally performed CT. Sironi and colleagues evaluated a group of 31 treated ovarian cancer patients and compared the findings of PET/CT to second-look laparotomy findings. They report a sensitivity of 78 percent, an accuracy of 77 percent, and a positive predictive value of 89 percent for PET/CT for identification of persistent ovarian carcinoma.[11]

CHANGES IN TUMOR METABOLISM

Changes in tumor metabolism are expressed as changes in the SUV (standard uptake value) of the lesion. This measure of tumor uptake is calculated by taking into account injected dose, patient body weight, surface area, or lean body mass, as well as time from injection to scan. When using SUV as a measure of tumor response, factors of injected dose, uptake period, and scanning parameters should be similar from scan to scan.

PET/CT'S IMPACT ON RADIATION ONCOLOGY

The improvement in tumor imaging provided by PET/CT is also making a significant impact in the field of radiation oncology. The dose delivered to any tumor is limited by the amount of radiation exposure to the adjacent normal tissues. In the last 10 years advances in both radiotherapy planning computers and delivery systems have resulted in improvements that effectively led to the ability to limit the radiation dose to organs at risk. State-of-the-art radiotherapy facilities are capable of prescribing complex volumetric radiation dose plans that exclude normal tissues and therefore decrease toxicities that may be associated with radiation treatment.

To take full advantage of the technological advances in radiation delivery systems, accurate staging and precise tumor target delineation are critical. As already noted, PET/CT is an excellent tool for staging and restaging cancer. The improved accuracy in staging is invaluable in determining whether a patient is a candidate for curative or palliative radiation or whether chemotherapy and radiation therapy or chemotherapy alone is a more appropriate therapy path.

A key part of the radiation planning process is the determination of the site and local extent of the primary tumor and the creation of a three-dimensional target volume that forms the basis of the treatment plan. The introduction of functional imaging into the radiation therapy treatment process provides a biologic target that is more precise than anatomic targets generated by CT or MRI alone (see Fig. 3). Bradley and colleagues report a change in tumor volumes in 58 percent of patients when fused PET and CT images were used for contouring non-small cell lung cancer compared with contours generated on CT alone.[12] Optimized target delineation provided by PET/CT combined with the ability to administer therapeutic radiation with surgical precision may allow escalation of tumor dose that previously would have been impossible.

STAFFING AND PROGRAMMATIC ISSUES

Implementation of PET/CT into the radiation therapy planning process requires a cooperative effort between the imaging and radiation therapy departments, as well as a dedicated radiation oncology physicist whose job is to ensure that data acquisition and transfer from the imaging device to the planning computers is optimized.

For maximal benefit, PET/CT simulation is performed with the patient in the treatment planning

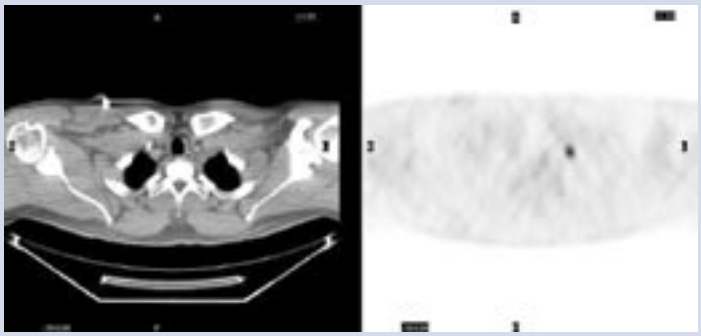


Figure 1a: Axial scans form CT and PET scans of a patient with non-small cell lung cancer (NSLC).

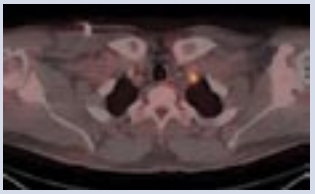


Figure 1b: PET/CT fusion image localizes the PET activity in a small left superior mediastinal lymph node.

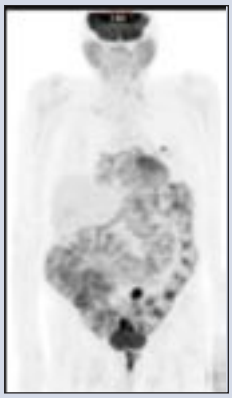


Figure 2a: Whole body PET scan of a 78-year-old male with NSLC shows metabolic activity in a left para-hilar nodule, but also a focus of intense activity in the abdomen.

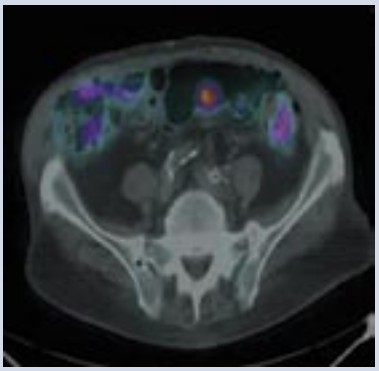
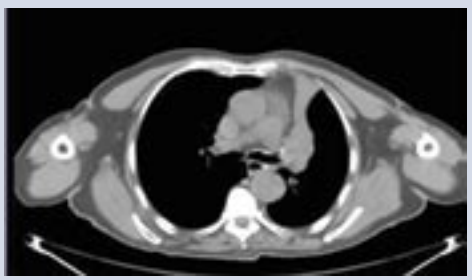
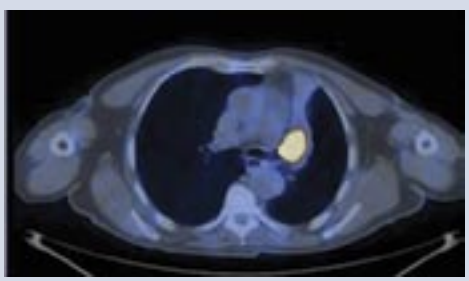


Figure 2b: PET/CT fusion image localizes the abdominal focus in a colonic polypoid mass. Biopsy revealed adenocarcinoma.





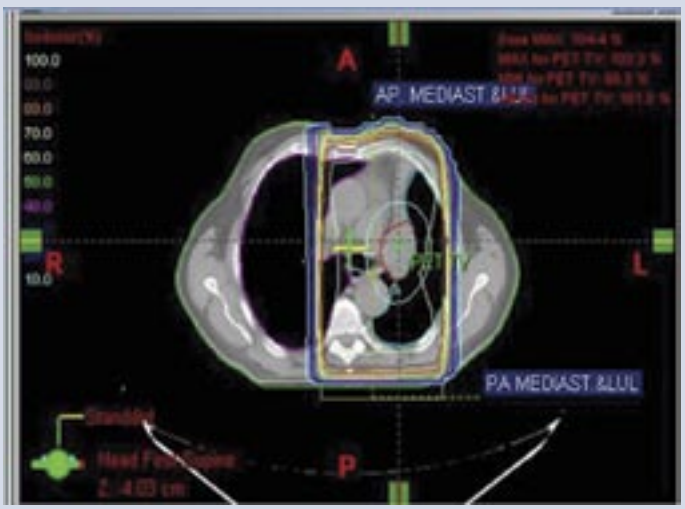


Figure 3b: Radiation therapy plan created using a PET-defined tumor target.

Figure 3a: Axial CT and PET/CT fusion images of a patient with NSLC and left upper lobe collapse. PET activity clearly defines the boundaries of the hilar tumor.

position on a flat table insert. Since planning computers can accept a fixed amount of data, the PET/CT simulation image coverage is limited to the region of the tumor. PET and CT images are exported separately to the planning workstation for generation of treatment contours. It is necessary to set the PET intensity to between 50-60 percent of the maximal intensity to ensure the PET activity approximates the true tumor volume.

A close working relationship between the radiation oncologist and the nuclear physician or radiologist is crucial for the correct identification of primary tumor and local adenopathy. If an institution's radiation therapy and imaging departments are not located at the same site, PET and CT images may be imported to

the planning computers via CD or DVD. Simple visual comparison of PET and CT simulation images also results in more accurate treatment planning over CT alone. In these circumstances, a mechanism for close communication between the radiation oncologist and imaging physician should be established.

ECONOMIC IMPLICATIONS

As of 2005, there are new CPT codes for PET/CT. However, reimbursement criteria may vary from state to state.

According to the Society of Nuclear Medicine (SNM) CMS is in the process of activating the adoption of CPT codes for PET procedures, essentially discontinuing previously used G series HCPCS codes. However, as this supplement goes to publication, the SNM web site reports that "although many of the G-codes will be discontinued in Medicare systems on schedule, the planned implementation and coding instructions for PET CPT codes will be delayed, resulting in a time period during which providers are advised to hold claims until instructions can be issued." The SNM is recommending that PET providers contact their carrier or fiscal intermediary regarding coding for PET procedures in April 2005. For more information, see the SNM web site at *http://www.snm.org/*.

Recently, CMS has expanded coverage for PET imaging. Current reimbursable diagnoses can be found in the box below. In addition to these diagnoses, CMS is currently covering additional diagnoses of brain, ovarian, pancreatic, testicular, small cell lung cancer, and soft tissue sarcoma for patients who are enrolled in approved prospective clinical trials. These are specified as a clinical trial that meets the requirements of the FDA category B investigational device exemption or a clinical study that is designed to collect additional information to assist in patient management.

Select Diagnoses for PET Imaging Currently Reimbursed by Medicare

1. *Breast*: staging of distant metastases, restaging and monitoring response when a therapy change is anticipated.
2. *Cervical*: newly diagnosed staging subsequent to conventional imaging that is negative for extra-pelvic nodes.
3. *Colorectal*: diagnosis, staging, restaging and monitoring when therapy change is anticipated.
4. *Esophagus*: diagnosis, staging, restaging and monitoring when therapy change is anticipated.
5. *Head and Neck*: diagnosis, staging, restaging and monitoring when therapy change is anticipated.
6. *Lymphoma*: diagnosis, staging, restaging and monitoring when therapy change is anticipated.
7. *Melanoma*: diagnosis, staging, restaging and monitoring when therapy change is anticipated.
8. *Non-small cell lung cancer*: diagnosis, staging, restaging and monitoring when therapy change is anticipated.
9. *Thyroid*: staging of follicular cell tumors, restaging of medullary cell tumors and diagnosis, other staging, restaging and monitoring when therapy change is anticipated.
10. Characterization of *solitary pulmonary nodule*, less than or equal to 4 cm in size.

LOOKING FORWARD

PET/CT unites all the benefits of functional imaging combined with all the benefits of high-resolution anatomic imaging performed in a single imaging session. PET/CT benefits patients by providing more accurate cancer diagnosis and staging, thus ensuring appropriate treatment stratification. For monitoring therapeutic effects, PET/CT offers better accuracy than conventional imaging in assessing treatment response. Radiation therapy planning is optimized as PET/CT provides more accurate definition of tumor target making possible the most beneficial delivery of radiation. Finally, it is the patient with cancer who ultimately reaps the full benefits of this new technology in the knowledge that the most advanced and most accurate method of diagnosis, staging, and treatment monitoring is available now.

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Dual Energy-Subtraction Digital Chest Radiography: 01

Oncology Issues speaks with Reginald F. Munden, md, dmd, Associate Professor and Section Chief of Thoracic Imaging at the University of Texas, M.D. Anderson Cancer Center in Houston, Tx. about oncology applications for this new technology

Q *How does dual energy-subtraction digital chest radiography differ from routine chest radiography?*

A: Dual energy-subtraction digital chest radiography takes advantage of the digital ability to produce images quickly. In essence, dual energy-subtraction creates two exposures very quickly—one at a lower kVp and one at a higher kVp. The dual energy-subtraction radiograph is done in a single exposure. Three images are generated: a standard chest radiograph, a soft tissue image, and a bone image. Using dual energy-subtraction digital radiography, the radiologist can view these three separate images. The advantage is that the three images produce a routine chest radiograph, a soft tissue radiograph to look for lung detail, and a third radiograph to look at the bones. For example, with the lung image the radiologist is able to see pulmonary nodules better because the overlying ribs are subtracted from the image and the ribs are better evaluated on the bone image because the soft tissues of the lungs are processed out. A standard radiograph, with all structures visualized, is the third image that is used as a conventional chest radiograph.

Q *How new is this "new" technology?*

A: Dual energy techniques have been around quite a while; however, newer detector and processing technology, as a result of going to digital acquisition of data, makes utilization of dual energy techniques faster and easier compared to conventional film techniques.

When film was used, you had to create two exposures of one image. One exposure was at the higher energy and one was at the lower energy. There was only one image produced on film, which meant no further processing of the image could be performed. This technique also required more radiation exposure for the patient and more time for the radiology technologist.

Now with digital dual energy technology, subtraction radiographs are done in one single exposure with a radiation dosage that is just a little bit higher than that for a routine chest radiograph. The patient takes one breath and the examination is done.

Q *In your opinion, what promise does this technology hold for oncology applications?*

A: In the oncology setting, one of the promising applications for dual energy-subtraction digital radiography is for use in follow-up of patients with cancer. Dual energy-subtraction radiography can be used for routine follow-up radiographs looking for development of pulmonary nodules that would indicate metastatic disease or changes in the lung of lung cancer patients that would indicate recurrent tumor. Dual energy-subtraction examinations are digital studies and are easily incorporated into PACS archives and are easily reviewed on workstations.

The main drawback to dual energy-subtraction is that the radiologist has to review three images instead of the single image of a conventional chest radiograph. This can mean slower patient throughput. On the other hand, with dual energy-subtraction digital radiography, it may be possible for the radiologist to detect pulmonary nodules faster and easier than with routine chest radiographs. So, although there may be more images to look at, it may be possible to read these images more quickly. Another potential benefit may be that dual energy-subtraction examinations will reduce the need for follow-up CT. Dual energy images may also prove to work very well with computed-aided diagnosis (CAD) systems.

Q *Are there any issues in terms of staffing/training to adopt this new technology?*

A: For certified radiology technologists the procedures are similar to those for a routine chest radiograph. For radiologists, the main issue is that there is another image to interpret. The technology can be adapted pretty quickly. Equipment maintenance and certification requires radiology physicist support similar to all digital equipment.

Q *Have you used this technology at M.D. Anderson Cancer Center?*

A: At M.D. Anderson Cancer Center, we have had dual energy-subtraction chest radiography for about six months on one of our units. We have been able to image about 60 patients a day, and to date we have done dual energy-subtraction digital radiography on a between 500 to 600 patients. We are evaluating the process to determine if we want to deploy the system to our 10 other chest units.

Q *What is the reimbursement picture for this new technology?*

A: Currently, dual energy-subtraction DR is reimbursed the same as routine chest radiography. It is important for us to fully validate the system to improve reimbursement for this technique.

Q *In your opinion, should this technology be available in the community hospital setting?*

A: Some considerations would be whether the comunity program was preparing to purchase new digital radiography chest units and whether the technology would benefit their patient population. From an oncology perspective, the big advantage for dual energy is the detection of pulmonary nodules and rib lesions. Other applications of dual energy, such as coronary artery calcium detection, would enter into a center's decision.

Colorectal Cancer Detection: the Role of CT Colonography

BY ABRAHAM H. DACHMAN, MD, FACR

Screening for colorectal cancer is particularly effective because the goal of screening is not only the detection of early carcinoma, but also the detection of pre-malignant adenomas.[1] (More than 80 percent of colorectal carcinomas arise from pre-existing benign adenomas.)[2] CT colonography (also called virtual colonoscopy) is now considered by some to be a viable alternative test for examining the colon for polyps and masses,[3] although some controversy exists as to its role as a screening examination.

SCREENING OPTIONS FOR COLORECTAL CANCER

Several proposed screening choices exist for colorectal cancer, including fecal occult blood testing; flexible sigmoidoscopy; a combination of fecal occult blood testing and flexible sigmoidoscopy; double-contrast barium enema; and colonoscopy.[1] Two additional choices—CT colonography and the testing of stool for genetic markers—are currently being tested.

Colonoscopy is considered the definitive procedure for evaluating the colon because it allows physicians to directly visualize the mucosa. Colonoscopy can also be used for both diagnosis and therapy. Polyps can be biopsied for histologic diagnosis and, if they are small or pedunculated, polyps can be removed. Although the risks of perforation and hemorrhage after colonoscopy are relatively low, they are higher than with any of the other screening alternatives. Unlike sigmoidoscopy, colonoscopy also requires more intensive preparation, which many patients find to be the most difficult aspect of the test. The completion rate for colonoscopy ranges from 75 to 99 percent,[4] with the national average completion rate for colonoscopy at about 90 percent.[5]

COLONOSCOPY VS. CT COLONOGRAPHY

While several professional gastroenterology organizations recommend the use of colonoscopy for colorectal cancer screening, the widespread application of screening with optical colonoscopy is hindered by a long waiting time. In some locations, patients may wait from several months to more than a year to get this test.

Additionally, studies of back-to-back colonoscopies provide evidence that 6 percent of polyps 1 cm in diameter may be missed. In a recent CT colonography multicenter trial, Pickhardt and colleagues[3] used a "segmental unblinding" strategy to test the effectiveness of the colonoscopy. The study found CT colonography to be superior to optical colonoscopy for the detection of 8 to 10 mm polyps.[3] In addition, Pickhardt and colleagues[6] have shown that optical colonoscopy may, in fact, miss 12 percent of polyps measuring 1 cm.

With regards to colon cancer screening, CT colonography has been advocated for: [7,8,9]

- Evaluating the colon proximal to an obstructing colonic mass or stricture
- Completing the colonic examination after an incomplete optical colonoscopy
- Searching for polyps or masses in above-average colorectal cancer-risk patients who refuse optical colonoscopy or whose physician prefers CT colonography because of the risk of sedation or bleeding (e.g., for patients on anticoagulation)
- Screening average-risk patients for colorectal cancer.

The patient who is already prepared and has undergone an incomplete colonoscopy can be accommodated for a same-day, unscheduled CT colonography examination. The patient does not need to make a return visit and repeat preparation. In several large cohorts, patients who underwent both CT colonography and optical

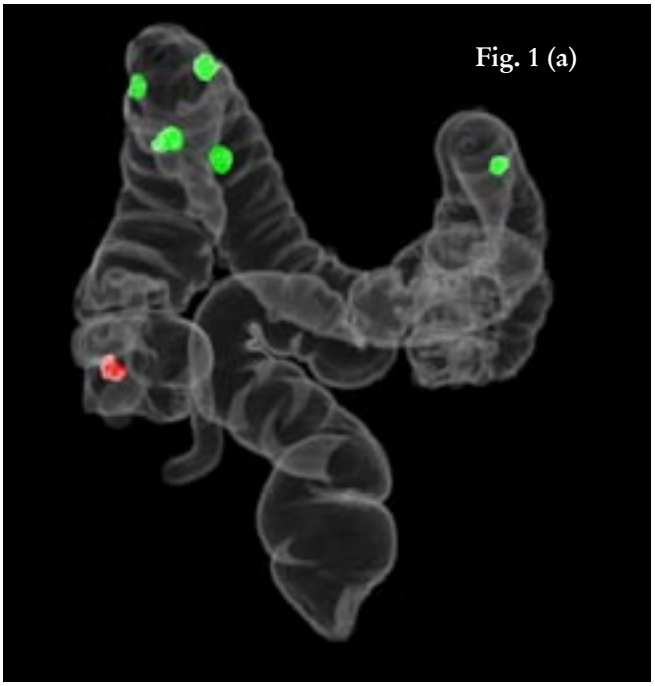


Figure 1: Alternate and novel views. (a) A transparent view indicating the locations of polyps with green and mass with red. (b) A "virtual dissection" view (GE Medical Systems). A polyp is indicated by an arrow.

colonoscopy said they would be more amenable to more frequent colorectal cancer screening with CT colonography.[10]

Morrin and colleagues studied 40 patients who received CT colonography within two hours of an incomplete colonoscopy.[11] The portion of the colon that was not visualized by endoscopy was observed in more than 90 percent of patients and a probable cause for the obstruction was identified in 74 percent of patients.

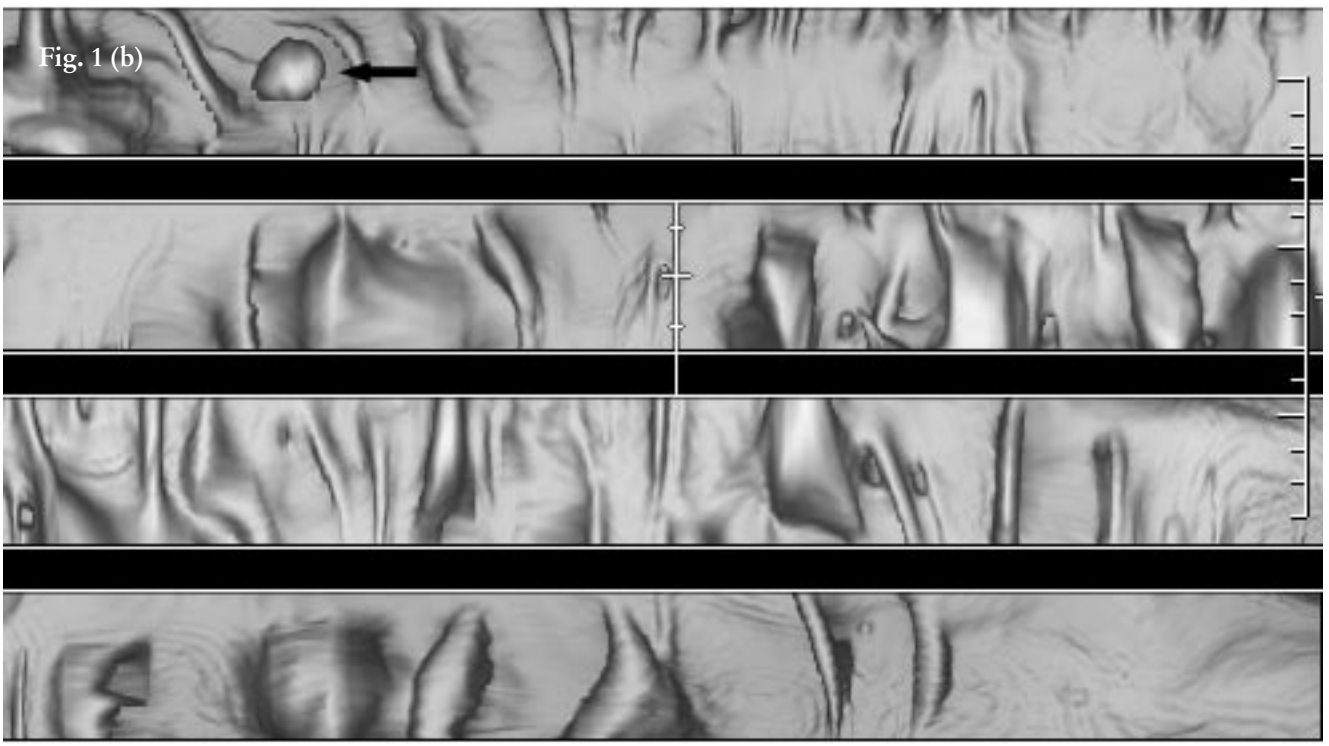
Another study by Fenlon and colleagues showed that CT colonography depicted all 29 occlusive carcinomas, and fully evaluated the proximal colon in 26 out of 29 patients.[12] CT colonography also demonstrated two synchronous cancers and 24 polyps in the proximal colon, many of which were subsequently confirmed by endoscopy, although none could be palpated at surgery. Identification of the synchronous cancers in two patients altered the surgical plan. CT colonography was also more accurate than colonoscopy in localizing the cancers; this may be helpful in preoperative planning.

Neri and colleagues studied 34 patients with CT colonography, pre- and post-intravenous contrast injection.[13] In 29 patients, surgery showed 30 cancers (including 3 synchronous cancers). Colonoscopy missed 10 cancers and 3 synchronous cancers, all of which were detected with CT colonography. The use of intravenous contrast also permitted a definitive search for metastatic disease with a single CT examination.

In addition to colorectal cancer, CT colonography has several other applications. For example, if performed with a sufficient radiation dose, the test will be able to detect and characterize incidental lesions in the kidney as solid (possible renal cell carcinoma) or cystic. Other significant abnormalities such as an abdominal aortic aneurysm, ovarian masses, lung lesions, and adenopathy can also be detected using CT colonography. Many authors report a 12 percent incidence of significant extracolonic findings on CT colonography.[14]

DIAGNOSTIC ACCURACY OF CT COLONOGRAPHY

In discussing diagnostic accuracy it is important to differentiate between by-patient and by-polyp sensitivities.[15] For patient triage to colonoscopy, only the by-patient results are relevant. Likewise, the discerning reader should look at the sensitivity statistic for a particular size threshold and for potentially malignant lesions only, meaning adenomas (excluding hyperplastic polyps and mucosal tags). Due to the varied inclusion criteria (often combining average and above-average-risk patients) and varied methodology in performing and reading CT colonography, it is difficult to give a



single reliable sensitivity for the test. Also, since the technology is rapidly evolving, radiologists currently performing CT colonography will likely use state-of-the-art software; better than that used in many published reports.

To date, the sensitivity of CT colonography is based on cohorts with mixed indications and is often weighted toward above-average risk, increasing the prevalence of polyps in the cohort. In one meta-analysis of 1,324 patients, the pooled per-patient sensitivity for polyps 10 mm or larger was 88 percent, and for 6 to 9 mm polyps, the sensitivity was 84 percent.[16] The specificity remained high. In a recent trial by Pickhardt and colleagues (in which stool tagging and electronic subtraction of stool was employed) the by-patient sensitivity for adenomas 8 mm or larger was 93.9 percent with 92.2 percent specificity, and the by-polyp sensitivity for adenomas 8 mm or larger was 92.6 percent.[3] A large national trial on a screening cohort, the National CT Colonography Trial, sponsored by the American College of Radiology Imaging Network is now being conducted. A panel of experts (The Boston CT Colonography Working Group) has also developed standards for reporting and follow-up recommendations for patients undergoing CTC.[17]

PERFORMING AND INTERPRETING THE PROCEDURE

The complication rate for CT colonography is extremely low, with only rare case reports of colonic perforation. CT colonography should not be done in anyone with an increased risk of perforation, such as patients with peritoneal signs.

CT colonography should be performed with a "dry prep" using magnesium citrate or sodium phosphate,[18] although patients undergoing a same-day CT colonography following an incomplete optical colonoscopy often have had a polyethylene glycol preparation. Stool and fluid opacification is often used, but this practice is still under investigation.[19] Both barium and a water-soluble oral contrast medium can be administered with each meal on the day prior to the examination or on the morning of the examination. The resultant images can be read in 2D or 3D. We use a low-fiber diet (NutraPrep) combined with a very small volume of barium (Tagitol V) at breakfast, lunch, and dinner the day prior to the CT, and a small amount (5cc Gastroview in a cup of water) of water soluble contrast on the evening prior to and day of the exam. This practice may allow use of a mild preparation and potentially eliminates the use of cathartic preparation.[20]

Electronic subtraction of stool and fluid is a further strategy that may help make the exam easier to interpret and more amenable to a primary 3D read. [3,21] When used, glucagon can be administered in a dose of 1 mg subcutaneously about 10 minutes prior to the scan. The entire exam usually takes about 15 minutes of room time. (Note: A rectal examination should be done by the referring physician before proceeding to CT colonography because lesions in the anal canal or near the anal verge may be missed during the procedure.)

A small, thin, rectal tube with or without a retention cuff is introduced. Insufflation can be accomplished with either room air or carbon dioxide. The latter may have the benefit of rapid absorption making the patient more comfortable after the examination.

The supine scan is usually performed first. The patient is then turned to a prone position, and scout scanning repeated before doing the prone scan. With the use of fast 16 to 64 slice CT scanners, respiratory motion is rare, and these scans commonly require a mere 10-second breath hold. A low radiation dose protocol is used and some researchers are using "ultra-low dose" protocols.

Sufficient training and experience in reading colonoscopically-proven cases is critical. Before offering the test to the public for a fee, this author suggests that staff read—under supervision—between 20 and 50 proven cases with the reader achieving a reasonable sensitivity for polyps 10 mm or larger.

Several publications deal with methods and pitfalls of interpretation of CT colonography.[9,22] Software used for the interpretation of CT colonography must permit both 2D and 3D evaluation of the colon.[22] Ideally, both styles of interpretation should be possible: a "primary 2D read with 3D problem solving"[8] and a "primary 3D read with 2D problem solving." Generally, polyps greater than 5 mm or 10 mm are reported. Foci 5 mm or smaller usually represent stool or hyperplastic polyps.

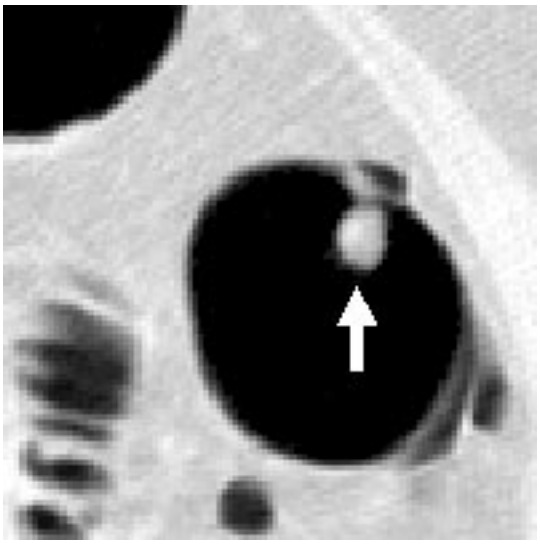
Computer-aided detection (CAD) is expected to become commercially available this year and offers the possibility of a double reading of CT colonography images by a combination of a radiologist and computer.[23] A CAD system automatically detects polyps and masses from CT colonography data and provides the locations of suspicious polyps to radiologists.[24,25]

RELATIVE COST AND REIMBURSEMENT

One of the arguments for the use of CT colonography is the limited availability of optical colonoscopy, suggesting that gastroenterologists' resources should be reserved for a pre-screened cohort with a high prevalence of disease. This practice may be a more cost-effective use of resources, because every positive CT colonography must then be referred for an optical colonoscopy. The cost-effectiveness of CT colonography will depend on the charges and on the interval at which a normal exam needs to be repeated.

In July 2004 category III CPT billing codes were created for CT colonography screening and non-screening. Medicare does not ordinarily reimburse these codes and reimbursement by individual insurance carriers is highly variable, based on location. Many patients seek precertification of insurance reimbursement or, for screening, often self-pay. This poor reimbursement has unfortunately limited the use of CT colonography and "best care" practice of medical management, particularly for non-screening applications. In some locations, radiologists have lobbied successfully for routine reimbursement, even for screening, by local carriers.[26] Radiologists and referring physicians should work together to support appropriate use and reimbursement of CT colonography for the benefit of their patients.

Abraham H. Dachman is director of CT at the University of Chicago and has been involved in virtual



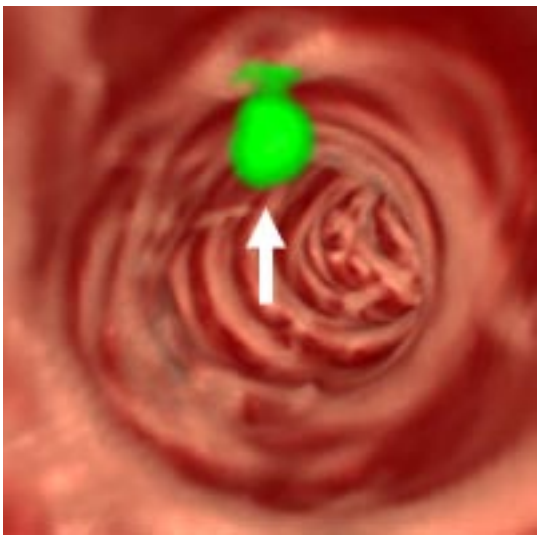


Figure 2: Polyps detected by computer-aided detection (CAD). 10 mm pedunculated polyp in the splenic flexure. (a) axial CT image showing a polyp (arrow) and (b) the 3D endoscopic view of the polyp. The CAD color coding delineates the regions corresponding to the polyp, folds, and colonic wall by green, pink, and brown, respectively. The color coding is based on the shape analysis of the colonic structures performed during the process of automated detection of polyps by CAD.

colonoscopy research since 1993. Editor of The Atlas of Virtual Colonoscopy, *he has published numerous articles on the topic and also teaches courses for radiologists on virtual colonoscopy.*

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3T MR Offering New "Currency" for Oncology Applications?

BY JANIO SZKLARUK, PHD, MD

Since 2002, the Food and Drug Administration (FDA) has approved certain 3T scanners for brain or whole body imaging. These higher field strength scanners offer the potential for reducing imaging acquisition time and improving image quality and resolution. But along with these advances come some caveats. This article provides an overview of current 3T MR technology and discusses some of the promise 3T MR holds for oncology imaging.

Since the introduction of early MRI scanners of lower field strength of 0.1T, there has been a continuous evolution towards higher field strengths. Currently, 1.5T scanners are the most commonly used. A 1.5T scanner has magnetic field strength 30,000 times that of the Earth's. An expected advantage to an increase in field strength is an increased signal to noise ratio (SNR). The improvement in SNR is proportional to the strength of the magnetic field. Thus, the introduction of the 3T scanner should result in an expected SNR of 2 compared to a 1.5T scanner system.

MR CURRENCY

This gain in SNR is considered MRI "currency." The concept of "currency" means that gain in SNR can offer the possibility of reducing imaging acquisition time, which in turn, means reducing motion artifacts, as well as offering the potential for increased patient throughput. Alternatively, improved SNR can be used to increase spatial resolution, which will result in greater spatial localization and visualization of small structures.

TISSUE CONTRAST ISSUES

In addition to SNR and spatial resolution, the quality of MRI images also depends on tissue contrast, which is dependent on tissue relaxation times (T1 and T2). Tissue relaxation times depend on the strength of the magnetic field. In general, T1 values are prolonged at higher fields strength and T2 values are shortened.[1]

The magnitude of the change in relaxation time varies with the type of tissue. Susceptibility effects—known as T2* effects—also increase at higher magnetic fields. Simply put, susceptibility effects can affect the image quality with artifacts or decreased signal to noise. This increase in susceptibility artifacts requires better shimming, and the increase in susceptibility effects may result in limitations of certain sequences (e.g., echo planar imaging, EPI). These changes in relaxation times require a re-examination of sequence parameters to obtain appropriate tissue contrast.

As with MR at 1.5T, with 3T MR the radiologist routinely decides MR pulse sequence parameters with the assistance of the medical physicist.

SAFETY CONSIDERATIONS

The increase in magnetic field strength that offers the promise of 3T MR also brings additional safety issues that must be addressed.

MR images are obtained as a result of the disruption of proton spins by a radio frequency pulse applied to protons in the presence of a magnetic field (i.e., 1.5T). With the introduction of higher magnetic fields, more radio frequency energy deposition is required to achieve the disruption of proton spins. The specific absorption rate (SAR) is a unit of measure of the energy deposited by a RF pulse. The International Electrotechnical Commission (EIC) and FDA have established rules for SAR levels in humans. The FDA guidelines are 0.4W/kg whole body average, 8W/kg peak per any 1 gram of tissue, and 3.2 W/kg in the head. Manipulation of SAR through modification of sequence is one of the challenges of clinical MRI at 3T. Parallel imaging techniques have evolved a means to speed imaging while reducing SAR. One example of parallel imaging technique is ASSET (Array Spatial & Sensitivity Encoding Technique). ASSET uses the unique geometry of phased array coils to spatially encode the image faster.

Another potential biological hazard related to RF energy deposition at higher magnetic fields is the potential to cause skin burns in tissue adjacent to ECG leads or other metallic implants that may act like an antennae.

The force of the magnetic field on paramagnetic material and ferromagnetic material is dependent on field strength. An increase in field strength from 1.5T to 3T will result in a five-fold increase in force for paramagnetic materials and a 2.5-fold increase in force for ferromagnetic material. This increase requires re-evaluation of implants for safety as well as increased precaution to avoid projectile accidents. In the evaluation of 32 aneurysmal clips at 3T, Shellock and colleagues[2] concluded that only clips made from titanium and titanium alloy are entirely safe for patients undergoing MR imaging procedures at 3T because of this total lack of magnetic field interactions. The remaining clips require characterization of magnetic field-induced torque.

Noise levels present another safety issue at higher magnetic fields. When gradient magnets are activated and deactivated during MR image acquisition, a significant amount of acoustic noise is created. With higher magnetic fields strength, gradient amplitudes increase, and

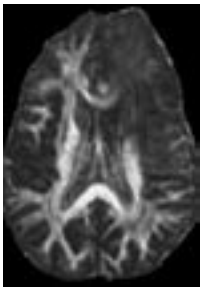

Figure 1a. 40 year old with glioblastoma multiforme with a left frontal lobe tumor. 3T fractional anisotropy diffusion tensor image image of the brain shows abnormal white matter tracts in the left frontal lobe.

acoustic noise becomes even greater. The routine utilization of ears plugs by patients is a necessity at higher magnetic field strengths.

PHYSICAL PLANT/ARCHITECTURAL ISSUES

In regards to room preparation, the FDA requires that an MRI suite have a 5-gauss exclusion zone. A 3T system may be sited within a moderate-sized 1.5T magnet room. However, with a 3T system fringed field spills (between 0.5 gauss and 5 gauss) are farther than with a 1.5T system, which may possibly affect nearby PET, CT, and nuclear medicine equipment.

CLINICAL APPLICATIONS

A number of clinical MR applications may potentially benefit from a higher field strength 3T magnet. For example, the potential applications of 3T MRI to oncologic and non-oncologic imaging in the brain, spine, abdomen, pelvis, and musculoskeletal system are currently being developed.

Diffusion-weighted magnetic resonance (MR) imaging depends on the molecular motion of water that is altered by pathology. Diffusion-weighted MRI has been found useful in the setting of stroke and in distinguishing solid viable tumor from cystic and necrotic regions.[3] At 3T, diffusion-weighted MRI benefits from increased signal to noise ratio, higher B values, and potential thinner section imaging. Imaging techniques utilizing single shot pulse sequences (required of diffusion-weighted imaging) are sensitive to susceptibility effects, and these artifacts increase exponentially with increasing field strength. However, parallel imaging has been implemented in diffusion-weighted imaging at 3T to overcome these artifacts.[4]

Functional MR imaging (fMRI) applications for neuro-oncology include the evaluation of the effects of tumor on white matter fiber tracts and motor cortex function.[5] Diffusion tensor imaging is a modification of diffusion-weighted imaging that is sensitive to the preferential diffusion of water along axonal fibers (see Fig. 1). This modification can result in mapping of white matter tracts, which may, in turn, allow the evaluation of tumor effects on white matter tracts or detection of white matter tracts changes in the presence of pathology. At 3T, fMRI will benefit from the signal to noise ratio.[6] This application has been reported in the detection of occult white matter invasion by gliomas.[6]

Magnetic resonance spectroscopy quantifies the amount of metabolites in a voxel of tissue. The clinical utility of proton MR spectroscopy (1-H-MRS) has been well demonstrated in the brain, prostate, and breast.[7] Increasing magnetic field strengths to 3T increases the signal to noise ratio of metabolites and increases chemical shift between metabolites. These changes may enable the detection of metabolites not detected at lower field strengths magnets and permit the application of magnetic resonance spectroscopy to non-hydrogen nuclei such as sodium MRI.[8] The application of magnetic resonance spectroscopy to other areas such as thorax and abdomen are being explored with 3T magnets.[9]

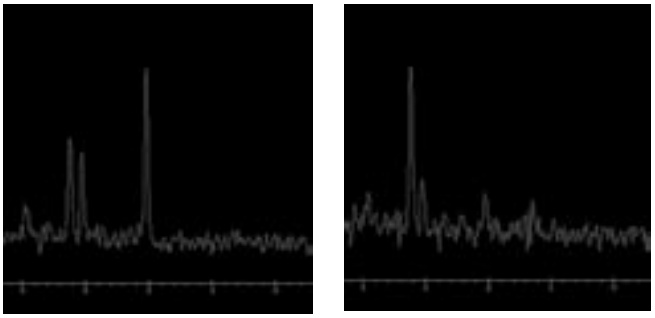

Figure 2a. 70-year-old female with metastatic carcinoid to the liver. Axial fast spin echo T2 weighted image of the liver at 1.5T reveals a hyperintense metastatic mass in segment VIII.

Figure 2b. 70-year-old female with metastatic carcinoid to the liver. Axial fast spin echo T2 weighted image of the liver at 3.0T reveals a metastatic mass in segment VIII. Note the increased SNR and resolution at 3.0T.

The evaluation of prostate cancer has benefited from magnetic resonance spectroscopy. It has been shown that prostate carcinoma is characterized by a decrease in citrate and an increase in choline (phosphocholine) and that tumor can be identified by changes in the choline/citrate signal ratio.[10] The metabolic ratios have also been reported to correlate with the histological grade of prostate cancer and its prognosis.[11]

Dynamic post-contrast imaging has been used to detect and characterize lesions of the liver, breast, and prostate. In the breast, a specific lesion enhancement profile can suggest the diagnosis of malignancy. Similarly, in the prostate a specific dynamic profile will also suggest malignancy. Dynamic post-contrast imaging has also been used to estimate tumor perfusion parameters, such as blood flow and permeability surface. This use may have application in the evaluation of tumor response to anti-angiogenic drugs. These tumor perfusion dynamic post-contrast studies can be performed to evaluate changes due to the paramagnetic effect of Gd (gadolinium) on T1 or T2* values. The shift to higher field strength results in increased temporal resolution, spatial resolution (decreasing volume averaging) and T2* effects on these perfusion studies.

Magnetic resonance angiography can be performed with various techniques including time-of-flight or post-gadolinium enhanced. Magnetic resonance angiography benefits from the 3T magnetic field strength, which reduces motion artifacts, increases spatial resolution, increases vessel detail, and improves background suppression. Time-of-flight images benefit from 3T's increased signal due to prolongation of T1 relaxation

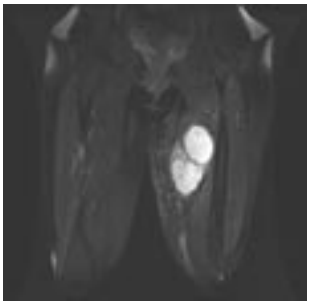

Figure 3. 56-year-old male with malignant fibrous histiocytoma of the left thigh. A coronal T2 weighted fast spin echo image at 3T demonstrates a mass in the medial lower extremity.

times and reduction in background signal. Gadolinium-induced relaxivity at 3T is not significantly different than at 1.5T. The result is greater contrast-to-noise ratio of the enhancing tissue and background. This increased ratio may be applied to neurological, musculoskeletal, or body imaging.[12]

MR imaging application for the abdomen and pelvis have been reported at 3T. Evaluation of the liver, kidneys, and prostate have benefited from the improved signal to noise ratio, spatial resolution, and temporal resolution of 3T systems (see Figure 2). These studies are highly sensitive to radio frequency energy deposition, and the safety requirements in specific absorption rate levels at 3T necessitate changes in imaging protocols. For example, routine use of parallel imaging decreases the concern of higher specific absorption rate levels during an examination at 3T.

The high resolution of the MR images at 3T has permitted the evaluation of microscopic structure. For example, MRI brain microscopy has been used to evaluate cochlear implants.[13] Similarly, abdominal imaging can spend the MR currency at higher fields to either increase the high spatial resolution or temporal resolution. A potential application for higher spatial resolution at 3T is the evaluation of the bile duct in the setting of cholangiocarcinoma. The evaluation of local tumor extension is a great challenge at 1.5T MRI.

Musculoskeletal 3T MRI has shown promise. MR microscopy may be applicable bone structure (see Fig. 3). High-resolution imaging could be applied to the evaluation of injured cartilage, tendons and ligaments due to an increased image quality. As with abdominal imaging, power deposition concerns and changes in T1 relaxation times require changes in imaging parameters. For example, prolongation of the repetition time TR will compensate for the increased T1 values of tissue at higher field.

Cardiac applications for 3T MRI have also been of interest. For example, coronary artery magnetic resonance angiography has been shown to be a valuable tool for non-invasive visualization of coronary arteries.[14,15] Early work of 3T coronary magnetic resonance angiography demonstrated an enhanced signal to noise ratio allowing imaging with small voxel size. This increase allows for visualization of proximal to mid-coronary segments, as well as smaller-diameter branching vessels than at 1.5T.[15]

In conclusion, 3T MRI offers great promise by offering an increase in MR currency of signal to noise ratio. The decision on where to spend this currency—whether in improving spatial or temporal resolution—can be made by on a patient-by-patient basis. However, the changes in T1, T2, and T2* relaxation times and issues of radio frequency deposition at 3T strengths require the re-examination and modification of current imaging protocols.

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