Advances in Oncologic Imaging
Update on 5 Common Cancers

Oguz Akin, MD; Sandra B. Brennan, MBBCh, FRCR; D. David Dershaw, MD, FACS; Michelle S. Ginsberg, MD; Marc J. Gollub, MD, FACR; Heiko Schöder, MD; David M. Panicek, MD, FACS; Hedvig Hricak, MD, PhD

Imaging has become a pivotal component throughout a patient’s encounter with cancer, from initial disease detection and characterization through treatment response assessment and posttreatment follow-up. Recent progress in imaging technology has presented new opportunities for improving clinical care. This article provides updates on the latest approaches to imaging of 5 common cancers: breast, lung, prostate, and colorectal cancers, and lymphoma. CA Cancer J Clin 2012;62:364-393.

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Keywords: breast neoplasms, colon and rectum neoplasms, lung neoplasms, prostate neoplasms, non-Hodgkin lymphoma

Introduction
Imaging has become essential in all aspects of cancer care, from disease detection and characterization, to treatment response assessment and posttreatment surveillance. Recent progress in imaging technology has presented new opportunities for improving clinical care. In this article, we chose to highlight 5 common cancers (breast, lung, prostate, and colorectal cancers, and lymphoma) for which notable advances in imaging have occurred. Interventional oncology, employing minimally invasive, image-guided techniques, is assuming an increasingly large role in treating cancer and its complications but is beyond the scope of this review.

Breast Cancer Imaging
Breast cancer is the second leading cause of cancer death in women in the United States. The National Cancer Institute estimates a woman’s lifetime risk of developing breast cancer at 12%. Early detection of breast cancer through mammographic screening and advances in treatment have been credited with a 30% decrease in breast cancer mortality since 1989, and it has been estimated that the reduction in mortality may reach 50% by 2015. From 1999 to 2008, cancer death rates have declined by more than 1% per year, with breast cancer accounting for 34% of the total decline in women. In 2012, approximately 226,870 cases of breast cancer and 63,300 cases of breast carcinoma in situ are expected to be newly diagnosed, and breast cancer is expected to account for an estimated 39,510 deaths (14% of all female cancer deaths).

Despite these statistics, screening mammography continues to be a contentious issue. In this journal in 2007, the American Cancer Society (ACS) published guidelines for breast cancer screening. In 2009 the US Preventive Services Task Force concluded that the benefit of routine mammographic screening of women in their 40s was too low to offset the harms and recommended against routine screening mammography in women aged 40 to 49. They recommended biennial screening for women aged 50 to 74 and concluded there was insufficient evidence to recommend mammographic screening for women 75 years or older. These recommendations met with wide criticism and were overridden. In 2010, the Society of Breast Imaging and the Breast Imaging Commission of the ACS issued recommendations for breast cancer screening to

1 Associate Professor of Radiology, Weill Medical College of Cornell University, and Associate Attending Radiologist, Memorial Hospital for Cancer and Allied Diseases, New York, NY; 2 Assistant Professor of Radiology, Weill Medical College of Cornell University, and Assistant Attending Radiologist, Memorial Hospital for Cancer and Allied Diseases, New York, NY; 3 Professor of Radiology, Weill Medical College of Cornell University, and Attending Radiologist, Memorial Hospital for Cancer and Allied Diseases, New York, NY; 4 Associate Professor of Radiology, Weill Medical College of Cornell University, and Associate Attending Radiologist, Memorial Hospital for Cancer and Allied Diseases, New York, NY; 5 Associate Professor of Radiology, Weill Medical College of Cornell University and Attending Physician, Nuclear Medicine Service, Department of Radiology, Memorial Hospital for Cancer and Allied Diseases, New York, NY; 6 Associate Professor of Radiology, Weill Medical College of Cornell University, and Attending Radiologist, Memorial Hospital for Cancer and Allied Diseases, New York, NY; 7 Professor of Radiology, Weill Medical College of Cornell University, and Attending Radiologist, Memorial Hospital for Cancer and Allied Diseases, New York, NY; 8 Professor of Radiology, Weill Medical College of Cornell University, Attending Radiologist, Memorial Hospital for Cancer and Allied Diseases, and Chair, Department of Radiology, Memorial Sloan-Kettering Cancer Center, New York, NY.

Corresponding author: Hedvig Hricak, MD, PhD, Dr(hc), Chair, Department of Radiology, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, room G-278, New York, NY 10065; Fax: (212) 794-4010; muelle@a@mskcc.org

DISCLOSURES: The authors reported no conflicts of interest.

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TABLE 1. Breast Cancer Screening Guidelines⁵,⁶

| Risk Level | Screening Recommendations |
|-----------|---------------------------|
| All women/normal risk | Annual mammogram starting at age 40 y |
| Intermediate risk: Atypia, lobular carcinoma in situ, personal history of breast cancer | Annual mammogram from time of diagnosis. Uncertain if annual magnetic resonance imaging is appropriate |
| High risk: Strong family history of breast/ovarian cancer, genetic mutation conveying high risk for breast cancer, mediastinal radiation (e.g., Hodgkin disease) | Annual mammography and magnetic resonance imaging starting at age 30 (8 y after treatment of Hodgkin disease); these tests may be done alternately at 6-mo intervals to provide for more frequent screening |

provide guidance in light of the controversies and emerging technologies.⁵ These recommendations (Table 1)⁵,⁶ were based on multiple prospective randomized trials as well as population-based experience showing that mammographic screening reduces breast cancer mortality in all women screened starting at age 40. Screening is most effective, especially for premenopausal women, when conducted annually. The upper age limit at which the benefit of mammographic screening is lost is unknown.

Recommendations for screening with nonmammographic imaging are based not on evidence showing mortality reduction but largely on surrogate indicators, ie, tumor size and nodal status, suggesting improved survival compared with women who are not screened. Magnetic resonance imaging (MRI) has a higher sensitivity than mammography or ultrasound (US) for breast cancer detection. In its 2007 guideline revision, the ACS advocated the use of MRI in women who have a 20% to 25% or greater lifetime risk of breast cancer, including women with a strong family history of breast or ovarian cancer and women who were treated for Hodgkin disease. For women with an intermediate (15%-20%) lifetime risk and for women with a personal history of breast cancer, atypia, lobular carcinoma in situ, or dense breasts, the ACS concluded there was insufficient evidence to make recommendations for or against the use of MRI screening.

Studies comparing mammography, US, and MRI for the detection of breast cancer in high-risk women have shown MRI to have greater sensitivity than the other 2 modalities, with the combination of mammography and US achieving sensitivity of 52% and the combination of mammography and MRI achieving sensitivity of 93%.⁶-⁹ As a supplement to MRI, screening US offers no benefit, but US may have a role in high-risk women who have contraindications to MRI. Because of the limitations of mammography in women with dense breasts, additional screening with sonography in such women may be beneficial, although it results in a large number of false positives (in the largest, multi-institutional study, 1 in 9 women screened underwent biopsy).⁹ The addition of screening US or MRI to mammography in women at elevated risk of breast cancer increases the cancer detection yield but also increases false-positive findings.⁹ One study found that the use of US as a supplement to annual screening mammography increased cancer detection by 5.3 cancers per 1000 women in the first year, and 3.7 women per 1000 per year in each of the second and third years; the addition of MRI screening to mammography and US resulted in a supplemental cancer detection yield of 14.7 per 1000 women.¹⁰

Detection and Characterization

The most important imaging criterion for the identification of breast cancer is lesion morphology. Due to their uncontrolled growth pattern, cancers are usually irregular masses, whereas benign lesions are more frequently smooth. Further characterization of lesions is possible based on cancers being more inhomogeneous and hypervascular compared to benign entities. In addition, cancer often has necrotic sites that undergo calcification. Identification of such calcification makes it possible for mammography to detect small and noninvasive cancers.

The imaging characteristics of malignant lesions are nonspecific and usually do not allow a definitive diagnosis. When a biopsy is recommended based on mammography, it has a 25% to 45% likelihood of resulting in a diagnosis of carcinoma.¹¹ Similar positive predictive values are reported for biopsies recommended based on MRI.

For probably benign lesions, short-term follow-up may be recommended to assess for interval growth over time. These lesions have a < 2% likelihood of malignancy.¹²

All imaging techniques have false negatives. For screening mammography for the general population, this rate is approximately 20%, increasing as breast density increases. With MRI, about 90% of cases of invasive cancer are discovered; the ability of MRI to identify ductal carcinoma in situ is less well established, with reported sensitivities in the 40% to 80% range.¹³,¹⁴ The sensitivity of sonography is less well established.

Role of Imaging in Treatment Decisions and Treatment Planning

In most cases after breast core biopsy is done, a benign result is obtained that explains the imaging finding and the patient is spared surgery. In about 20% to 40% of cases, breast core biopsy yields a diagnosis of cancer and the patient has definitive surgery. In a minority of cases, however, cancer is not diagnosed but the biopsy findings warrant rebiopsy or surgical excision. The most common reasons for rebiopsy are discordance or specific unusual histologies, sometimes referred to as high-risk or complex lesions.¹⁵ These complex histologies include atypical ductal hyperplasia, lobular carcinoma in situ, and atypical lobular hyperplasia, histologies which often have carcinoma near
the site of biopsy. With these histologies, the likelihood of carcinoma, usually in situ, being discovered at surgical excision can range from 10% to 50%, depending on the amount of tissue excised at needle core biopsy. Lesions for which there is not uniform consensus on the need for surgical excision include papillomas, radial scars, and mucin-containing lesions. In some women in whom ductal carcinoma in situ is found at needle biopsy, invasive carcinoma will be discovered when a larger volume of tissue is removed at surgery.

In women with diagnosed cancer for whom breast-conserving surgery is being considered, imaging is important in determining whether tumors can be managed without mastectomy. Additional sites of tumor near the index cancer may result in wider surgical excision, whereas distant ones require mastectomy. The identification of the extent of the presenting cancer also increases the likelihood that cancer can be resected with negative margins, obviating the need for reexcision to remove all detectable cancer. Preoperatively, mammography should be used to determine the extent of tumor, including suspicious microcalcifications. The role of MRI in preoperative staging is controversial. Although additional foci of tumor are found with MRI in as many as one-third of women, no improvement in patient outcome has been demonstrated in studies published to date. However, in patients with tumors whose extent is difficult to determine, such as invasive lobular carcinoma, routine use of MRI may be considered appropriate. MRI can also be highly accurate in determining whether chest wall invasion has occurred.

In women presenting with breast cancer, screening of the contralateral breast with MRI has been demonstrated to reveal otherwise undetected contralateral cancers in about 5% of cases. Because of this, patients undergoing MRI staging at the time of their diagnosis of breast cancer should routinely have the opposite breast imaged. There is no agreement that routine MRI screening of the contralateral breast should be done in women who would not otherwise undergo MRI.

Sonography can be useful in detecting additional cancers in women with dense breasts. There are no recommendations for routine staging sonography for these women.

For women with locally advanced breast cancer who undergo neoadjuvant therapy before breast cancer surgery, assessing the extent of tumor remaining in the breast after treatment is difficult, at best. Mammography, sonography, and physical examination can overestimate disease due to posttreatment inflammatory mass. The absence of evidence of malignant disease on these examinations does not exclude residual, often microscopic, tumor. Posttreatment staging is best accomplished with MRI, which has been found to predict complete response with sensitivity above 60% and specificity as high as 90%.

In women who have undergone breast conservation, a mammogram after surgery and before radiation is recommended to exclude residual tumoral calcifications. If margins are positive at excision, MRI can be helpful in assessing the extent of residual disease. After the completion of breast conservation therapy, a new baseline mammogram of the treated breast is recommended.
Thereafter, annual mammography should be performed. One study suggests that annual screening MRI can also be helpful in detecting otherwise occult recurrences.\textsuperscript{28}

**Emerging Technologies**

Mammographic tomosynthesis uses mammographic imaging to obtain sectional, tomographic images through the breast. This improves the ability to visualize masses that might be obscured by overlying tissue. Compared with conventional screening mammography, screening with mammographic tomosynthesis has been reported to decrease call-backs for additional imaging by 30\% without changing sensitivity.\textsuperscript{29,30} Criticisms of mammographic tomosynthesis have included the fact that it is less able to detect tumor calcifications than conventional mammography and that it entails additional radiation exposure for women in whom additional imaging would not be recommended after conventional screening mammography.

Contrast-enhanced digital mammography involves the injection of iodinated contrast material, as is done for computed tomography (CT); this enables hypervascular lesions to be seen with modified mammography technology, potentially providing the same information obtained

\textbf{FIGURE 2.} A 27-year-old female with locally advanced poorly differentiated invasive ductal carcinoma underwent evaluation of extent of disease before starting neoadjuvant chemotherapy. Sagittal fat-suppressed T1-weighted postcontrast MR images demonstrate an almost 6-cm heterogeneously enhancing mass (A) involving the skin of the lower breast (arrow) with (B) right axillary (arrow) and (C) right internal mammary adenopathy (arrow).
through MRI. Little has been published on the clinical application of this technology, but diagnostic accuracy better than that of mammography and approaching that of MRI has been reported.\(^3^1,3^2\)

At breast MRI, the addition of functional imaging techniques to improve specificity has also been studied. MR spectroscopy allows the detection of cellular metabolites in vivo and can be used to measure choline concentrations in defined volumes of the breast. Because choline is elevated in carcinomas, as well as some benign states, its presence increases the likelihood that a lesion is malignant. MR choline spectroscopy has been shown to improve the positive predictive value of breast MRI and may be useful in reducing the number of lesions that require biopsy (Fig. 4).\(^3^3\) Studies of spectroscopy have reported sensitivities of 70% to 100% and specificities of 67% to 100% in the detection of breast cancer. Decreasing choline concentrations may also be a useful indication of tumor response to treatment.

**FIGURE 3.** Sagittal fat-suppressed (A) T2-weighted and (B) T1-postcontrast subtraction MR images are shown of the left breast in a 61-year-old female who was status post–left lumpectomy for invasive ductal carcinoma (IDC) and ductal carcinoma in situ (DCIS) with close histological margins. The images demonstrate a seroma cavity (long arrow) in the lower inner quadrant from recent lumpectomy with thin rim enhancement. In the left upper inner quadrant almost 2 cm superior and anterior to the seroma cavity, a spiculated mass 1.3 × 1.0 cm in size was noted (short arrow). This was subsequently seen on ultrasound, biopsied, and found to be invasive carcinoma with mixed mucinous and papillary features.

**FIGURE 4.** Sagittal fat-suppressed T1-weighted postcontrast MR image is shown (A) of the right breast of a 48-year-old female who was status post-contralateral mastectomy for DCIS with the spectroscopy voxel placed over an enhancing mass (arrow). The magnified spectrum (B) demonstrated no choline peak. Biopsy yielded fibroadenoma.
before any change in tumor volume can be detected.\textsuperscript{34,35} Technical factors have limited the use of spectroscopy to lesions 1 cm in size or larger.

Diffusion-weighted MRI (DW-MRI) measures the random movement of water molecules in tissue. Using DW-MRI data, apparent diffusion coefficients (ADCs) can be calculated for individual pixels and then displayed as an image. These ADC maps allow quantitative assessment of diffusion characteristics. In cancers, where cells are tightly and randomly packed together and where active transport mechanisms do not function properly, water diffusion is lower than in normal tissues. Thus, ADCs measured by DW-MRI are commonly lower for cancers than for benign entities (Figs. 5 and 6).\textsuperscript{36,37} As with spectroscopy, adding DW-MRI data to other imaging characteristics of lesions on breast MRI may increase the positive predictive value of the examination, in turn decreasing the number of benign lesions requiring biopsy for diagnosis.

Ultrasound elastography measures tissue stiffness by calculating, after the imparting of force, the displacement of each pixel relative to the surrounding tissue in real time.\textsuperscript{38}
Cancers are characteristically more firm and less elastic than other tissues. Ultrasound elastography has been reported to differentiate benign from malignant breast lesions with sensitivities of 78% to 100% and specificities of 21% to 98%.\textsuperscript{39} When added to other US techniques, it may improve radiologists’ performance in distinguishing malignant breast lesions.\textsuperscript{39}

Positron emission tomography (PET), alone or combined with CT, allows noninvasive, quantitative assessment of biochemical and functional processes at the molecular level in the body. It is most often performed with the radiolabeled glucose analogue \([^{18}\text{F}]\text{fluorodeoxyglucose} ([^{18}\text{F}]\text{FDG})\) to detect the elevated glucose metabolism that is a hallmark of cancer. In breast cancer, its utility depends on the pretest probability for advanced disease, and thus the clinical stage. For instance, the diagnostic yield of \([^{18}\text{F}]\text{FDG PET}\) is limited in patients with stage I and II disease; in particular, \([^{18}\text{F}]\text{FDG PET}\) is not sufficiently accurate for axillary nodal staging in this subset of patients.\textsuperscript{40} In contrast, it provides meaningful information in patients with advanced disease, where it accurately defines disease extent,\textsuperscript{41} frequently eliminates the need for other imaging tests, and provides an early readout of treatment response as well as prognostic information. For instance, a decline in the intensity of \([^{18}\text{F}]\text{FDG uptake during neoadjuvant therapy, as determined by the standardized uptake value (SUV)},\) is a strong predictor of clinical or pathologic response.\textsuperscript{42,43} Some studies have suggested that the assessment of changes in both \([^{18}\text{F}]\text{FDG uptake and blood flow (as measured with \([^{15}\text{O}]\text{water})\) provides more accurate response prediction than \([^{18}\text{F}]\text{FDG alone}\) and also predicts for disease-free and overall survival (OS) after subsequent surgery.\textsuperscript{45} Despite the heterogeneity of the published data (in terms of the types of chemotherapy used, tumor histologies, receptor status, and criteria for histopathologic response), it seems clear that early response assessment by PET provides predictive and prognostic information; however, standardization of imaging protocols and prospective validation are needed before it can become part of routine clinical practice.

Conceivably, combined PET/MRI (eg, using DW-MRI or perfusion imaging) may be more accurate for response prediction and assessment than either test alone, but this remains to be proven. In patients with metastatic disease, a decline in the maximum SUV (SUVmax) indicates response to therapy; nonresponders can be identified early and may potentially benefit from alternate treatment regimens. In patients with osseous metastases, SUVmax is inversely related to OS.\textsuperscript{46}

Positron emission mammography (PEM) adapts full-body PET imaging to the breast. In a multicenter study, the interpretation of PEM in conjunction with mammographic and clinical findings yielded a sensitivity of 91% and a specificity of 93% for breast cancer.\textsuperscript{47} However, PEM is rarely the only modality to detect cancer (or multifocality), and its use in healthy women has been criticized because of the need to administer a radioactive tracer. Besides \([^{18}\text{F}]\text{FDG}, other radiotracers are being studied in breast cancer; for example, imaging with \([^{18}\text{F}]\text{fluoroestradiol may be helpful in selecting patients who are likely to benefit from antihormonal therapy.}

**Lung Cancer Imaging**

Lung cancer remains the most common cause of death from cancer worldwide, having resulted in 1.38 million deaths (18.2% of all cancer deaths) in 2008.\textsuperscript{48} It also represents the leading cause of death in smokers and the leading cause of cancer mortality in men and women in the United States. In 2012, it was estimated that 226,160 new cases of lung cancer would be diagnosed (accounting for about 14% of cancer diagnoses) and that lung cancer would cause 160,340 deaths (about 29% of cancer deaths in men and 26% of cancer deaths in women) in the United States.\textsuperscript{1} The 1-year relative survival rate for the disease increased from 35% to 43% from 1975 through 1979 to 2003 through 2006.\textsuperscript{49} The 5-year survival rate is 53% for disease that is localized when first detected, but only 15% of lung cancers are diagnosed at this early stage.

For the purposes of treatment, lung cancer is classified as non–small cell lung cancer (NSCLC), representing 85% of cases, and small-cell lung cancer (SCLC), representing 14%. The 5-year survival rate for SCLC (6%) is lower than that for NSCLC (17%).\textsuperscript{49}

**New Histologic Classification**

The International Association for the Study of Lung Cancer (IASLC), the American Thoracic Society (ATS), and the European Respiratory Society (ERS) have jointly introduced a new classification of lung adenocarcinoma that makes correct image interpretation essential. The new classification is based on the 2004 World Health Organization (WHO) classification but eliminates the terms bronchioloalveolar carcinoma and mixed subtype adenocarcinoma. For resection specimens, the terms adenocarcinoma in situ (AIS) and minimally invasive adenocarcinoma (MIA) were introduced to define patients who, if they undergo complete resection, will have 100% or near 100% disease–specific survival, respectively. AIS refers to small solitary adenocarcinomas with pure lepidic growth (noninvasive growth along alveolar structures), whereas MIA refers to small solitary adenocarcinomas with predominantly lepidic growth with \(\leq 5\)-mm invasion (Fig. 7). AIS and MIA are usually nonmucinous but rarely may be mucinous. AIS and MIA generally appear as a single peripheral ground-glass nodule on CT. A small solid component may be present if areas of alveolar collapse or fibroblastic proliferation are present,\textsuperscript{50,51} but any solid
component should raise concern for a more invasive lesion (Fig. 8). Growth over time on imaging can often be difficult to assess due to the long doubling time of these AIS and MIA, which can exceed 2 years. However, indicators other than growth, such as air bronchograms, increasing density, and pleural retraction within a ground-glass nodule are suggestive of AIS or MIA.

Most Common Lung Cancers: Typical Radiologic Features

Adenocarcinoma accounts for 38.5% of all lung cancers and is the most prevalent histologic type of lung cancer in both smokers and nonsmokers in the United States, having replaced squamous cell carcinoma as the most common cell type. The typical radiologic appearance is that of a solitary pulmonary nodule or mass, the border of which may be well-marginated, lobulated, irregular, or poorly defined (Fig. 9). Air bronchograms can also be associated with this subtype. Peripheral adenocarcinomas may directly invade the pleura and grow circumferentially around the lung, mimicking diffuse malignant mesotheliomas.

Once the most common cell type of lung cancer in the United States, squamous cell carcinoma has declined in incidence and is now the second most common histologic type of lung cancer, occurring in 23.8% of cases. Squamous cell carcinoma is highly associated with smoking, because tobacco smoke causes chronic inflammation and injury to the bronchial epithelium. Over time, this injury can progress to squamous metaplasia and eventually invasive carcinoma. This pathogenesis helps to explain why approximately two-thirds of squamous cell carcinomas arise in the central to mid-lung zones where the larger airways, such as the main, lobar, and segmental bronchi, are located; the appearance of these endoluminal lesions may reflect the obstruction they produce (eg, postobstructive atelectasis or pneumonia). The remaining third of squamous cell carcinomas are peripheral and may present as solitary nodules or masses. Squamous cell carcinoma is the cell type most likely to result in cavitation.
Large cell carcinoma is an uncommon histologic subtype of NSCLC, accounting for approximately 2.9% of all cases. It is strongly associated with smoking and generally presents as a large, peripheral tumor.

SCLC incidence has decreased over the past few decades, and SCLC now accounts for 14% of all lung cancers in the United States. Most SCLC tumors arise centrally and are large and lobulated, invading the mediastinum and hilum. SCLC is an aggressive tumor that is frequently metastasized at the time of diagnosis and is generally considered a disseminated disease treated with chemotherapy.

Screening for Lung Cancer

Chest CT screening for lung cancer has always held promise, but concerns regarding the potential for false positive results and a lack of evidence that CT screening prevents death from lung cancer have limited its use. On November 5, 2010, the National Lung Screening Trial results were released. The National Cancer Institute (NCI) funded the National Lung Screening Trial, a randomized trial, to determine if screening with low-dose CT, as compared to chest radiographs, would reduce mortality from lung cancer among high-risk persons. The results showed that with low-dose CT screening, there was a significant reduction of 20% in the mortality rate from lung cancer in the CT arm of the randomized controlled trial. With low-dose CT screening, there was also a significant reduction of 6.7% in the rate of death from any cause. The trial was launched in September 2002 and had enrolled 53,456 participants when recruitment goals were reached in April 2004. Eligible participants were between 55 and 74 years of age at the time of randomization, had a history of cigarette smoking of at least 30 pack-years, and, if former smokers, had quit within the previous 15 years. Screening for lung cancer with CT could potentially change lung cancer from a disease that is predominantly diagnosed in late stages to one that is diagnosed at an earlier stage with a greater chance of cure. Implementation of lung cancer screening will add $1.3 billion to $2.0 billion in annual national health care expenditures depending on adherence. However, screening has the potential to prevent more than 8000 premature lung cancer deaths per year. This benefit comes at an additional annual cost of $240,000 per death avoided. The true value of this intervention awaits the results of a formal cost-effectiveness analysis of long-term costs and outcomes compared with no lung cancer screening.

Detection and Characterization Algorithms

Accurate staging in lung cancer is crucial for determining appropriate management. Conventional NSCLC staging includes the patient’s medical history, physical examination, pathology review, blood tests, and a CT scan (preferably contrast-enhanced) including the chest and upper abdomen. When [18F]FDG PET findings suggest mediastinal nodal metastases, guidelines generally recommend histologic confirmation, and when [18F]FDG PET findings suggest distant metastatic disease, histologic or correlative imaging confirmation is recommended. Guidelines suggest that an absence of nodal involvement on PET scans can, in a clinical T1N0 patient with a peripheral tumor, reliably obviate the need for invasive, histologic mediastinal nodal staging. Integrated PET/CT has been found to be more accurate than PET alone, CT alone, or visual correlation of PET and CT for staging NSCLC. The high concentration of [18F]FDG found in the normal brain limits the sensitivity of PET for detection of brain metastases. MRI is the preferred modality for brain imaging, when indicated.

CT is often not accurate at assessing invasion of the chest wall or mediastinum for T staging. MRI currently has a limited role in the staging of lung cancer but may be used to evaluate for vascular or vertebral body invasion with suspected T4 tumors, and to assess the integrity of the brachial plexus in patients with Pancoast tumors.

Active Surveillance

The standard treatment of choice for localized stage I through stage IIIA remains surgical resection with or without chemoradiation therapy. Unfortunately, the 5-year survival rate for all stages of lung cancer remains 16%. Careful follow-up may lead to earlier detection of recurrences or earlier detection of a second primary bronchogenic carcinoma. The risk of developing a second lung cancer in patients who survived resection of NSCLC is approximately 1% to 2% per patient per year, and for SCLC survivors it is approximately 6%. Ten years after the initial treatment for SCLC, the risk increases to >10% per patient per year. This cumulative risk can make death from a second lung cancer common in lung cancer survivors. The current
recommendations for routine follow-up after complete resection of NSCLC are as follows: for 2 years following surgery a contrast-enhanced chest CT scan every 4 to 6 months and then yearly noncontrast chest CT scans. Detection of recurrence on CT is the primary goal in the initial years, and therefore, optimally, a contrast-enhanced scan should be obtained to evaluate the mediastinum. In subsequent years, when identifying an early second primary lung cancer becomes of more clinical importance, a noncontrast CT chest scan suffices to evaluate the lung parenchyma (Fig. 10).

**Assessment of Response to Standard Chemotherapies and Targeted Therapies**

In patients undergoing induction chemotherapy, the [18F]FDG PET response correlates with histologic response. [18F]FDG PET scan data can provide an early readout of response to chemotherapy in patients with advanced-stage lung cancer. A prospective study of 57 patients found that the median times to progression and OS were significantly longer for metabolic responders than for metabolic nonresponders (163 vs 54 days and 252 days vs 151 days). These data (confirmed by several other studies) suggest that second-line therapies, including tyrosine kinase inhibitors, should be initiated early because continuous treatment with the same drug regimen is unlikely to succeed in metabolic nonresponders. Kinase inhibitors targeting the epidermal growth factor receptor can improve progression-free survival (PFS) and OS in some patients with advanced-stage NSCLC. However, in unselected patients, the response rates are only in the 10% to 20% range. Response rates are generally higher in patients with specific epidermal growth factor receptor mutations, but even some patients without such mutations show clearly improved PFS and OS. Recent studies have shown that [18F]FDG PET can separate metabolic responders from nonresponders as early as 2 weeks after initiation of targeted therapy. Early identification of nonresponders could potentially avoid drug side effects and reduce the considerable costs associated with continued unsuccessful therapy.

**Treatment by Radiofrequency Ablation**

Current advances in both surgical techniques and diagnostic imaging have spawned a resurgence of interest in sublobar resection and other local therapies as alternatives to lobectomy in patients who are not candidates for anatomic lobectomy. Radiofrequency ablation (RFA) is one such local treatment modality and functions by imparting frictional energy to a tissue, causing destruction through heat. Currently recognized uses of RFA for primary tumors include treatment of early-stage tumors in patients who are not surgical candidates and adjacent salvage therapy. Most patients treated with pulmonary ablation will have had a preprocedure CT or a fusion PET/CT scan, which allows more precise anatomic localization of abnormalities seen on PET. Generally, either CT or PET/CT is performed within a few weeks of the procedure to provide a new baseline to which future images can be compared to assess for changes in size, degree of enhancement or [18F]FDG avidity. In evaluating posttreatment imaging, it is important to understand expected changes that are attributable to the treatment itself. Immediately after ablation, a region of ground glass opacity surrounding the treated lesion is usually seen, which resolves in about 1 month. A small percentage of lesions may cavitate, and the vast majority of these cavities will decrease in size. On posttreatment PET/CT, a normal rim of uniform [18F]FDG activity may be seen surrounding the treated lesion, corresponding to inflamed tissue, which may persist months after therapy. However, increasing [18F]FDG uptake over time after RFA is suggestive of tumor regrowth rather than posttreatment inflammation. A retrospective study of 68 patients who underwent RFA of lung lesions found that certain patterns of FDG uptake on post-RFA PET/CT scans could be classified as favorable (eg, mild homogeneous rim uptake) or unfavorable (eg, hypermetabolic nodule in the rim of the postablation cavity). In addition to changes in [18F]FDG avidity, an increase in the size of the treated lesion and changes in enhancement patterns are suspicious for local tumor progression (Fig. 11). A nodular enhancement pattern or a rim of enhancement 3 months after ablation suggests recurrence.
Prostate Cancer Imaging

Prostate cancer remains the most frequently diagnosed cancer in men as well as the second leading cause of cancer-related death in men in the United States, with an estimated 241,740 newly diagnosed cases and 28,170 deaths from the disease expected in 2012. The prevalence of prostate cancer increases with age, and about 1 in 6 men (16%) are diagnosed with the disease during their lifetime.

Prostate cancer is highly heterogeneous, with variable clinical outcomes that are difficult to predict both before and after treatment. Although several predictive methods have been developed, the treatment decision-making process is complex and requires balancing clinical benefits, life expectancy, comorbidities and potential treatment-related side effects. The Gleason score and the disease stage at diagnosis are the most important prognostic factors in prostate cancer. Although prostate-specific antigen (PSA) screening has resulted in the diagnosis of prostate cancer at earlier stages and with lower Gleason scores, it has also contributed to concerns about overdiagnosis, overtreatment of clinically insignificant disease, associated treatment-related toxicity, and escalating costs.

An imaging modality that could reliably assess prostate cancer would be of great help in selecting from the wide range of management options now available. These options include radical therapies (those directed at the entire organ), such as radiotherapy and surgery; less aggressive focal therapies that are garnering increasing interest; and, for selected patients with low-risk prostate cancer, active surveillance. In this clinical context, there is a pressing need to improve not only anatomical imaging for tumor detection, localization and staging, but also functional and metabolic imaging for characterization of tumor biology. This section summarizes the latest advances in MRI and PET imaging methods for functional and metabolic assessment of prostate cancer.

Advances in MRI of Prostate Cancer

MRI is potentially an ideal imaging modality for the local staging of prostate cancer, given its ability to depict the prostate and surrounding structures in exquisite detail. Recently, morphologic imaging with conventional MR imaging sequences has been supplemented by a multiparametric imaging approach using new functional and metabolic methods, namely DW-MRI; dynamic contrast-enhanced MRI (DCE-MRI), which probes tissue microvascular and perfusion properties; and MR spectroscopy (Fig. 12). Although all of these newer techniques are currently available for clinical use in tumor localization and staging, there is an ongoing research effort to improve and standardize the acquisition methods for these imaging techniques as well as the methods for quantifying the data they yield. At the same
time, MRI technology is continuously advancing, providing better hardware (eg, 3-T magnets), improved imaging coils, and improved imaging sequences.

**Diffusion-Weighted MRI**

As noted earlier, because the diffusion of water molecules within tumors is more restricted than in normal tissue, ADCs calculated with DW-MRI tend to be lower in cancer than in normal tissue. A number of studies, using various image acquisition methods and reference standards, have reported the utility of DW-MRI in prostate cancer detection.74-79 More importantly, studies have indicated that the greatest value of DW-MRI as an addition to conventional MRI might lie in its potential to assess prostate cancer aggressiveness noninvasively, because ADC values have been shown to correlate significantly with tumor Gleason scores.77-79 For instance, in a study using whole-mount step-section pathologic analysis as the reference standard, Vargas et al found a significant inverse correlation between ADC values and Gleason scores: mean ADCs were (1.21, 1.10, 0.87 and 0.69) \times 10^{-3} \text{ mm}^2/\text{second} for prostate cancers with Gleason scores of 3+3, 3+4, 4+3, and 8 or higher, respectively \( (P = .017) \).79 However, the clinical value of DW-MRI in predicting the surgical Gleason score needs to be further studied.

**Dynamic Contrast-Enhanced MRI**

DCE-MRI is based on the repeated acquisition of images of a region of interest during the passage of an intravenously administered contrast agent. DCE-MRI allows malignant tissue to be distinguished from benign tissue by exploiting differences in the distribution of the contrast agent between vascular and extravascular spaces over time. Among various models for quantitative analysis of DCE-MRI data, the Tofts model is commonly used in clinical practice for estimating pharmacokinetic parameters.80 DCE-MRI allows quantitative measurement of several parameters related to tissue microvascular and perfusion...
properties, such as the volume transfer constant ($K^\text{trans}$) from vascular space (VS) to the extravascular–extracellular space (EES); the rate constant ($k_{ep}$) from EES to VS; the fractional volume of EES ($v_E$); and, to assess global tumor perfusion, the area under the contrast concentration curve (AUC) from the start of contrast enhancement to specific time points. In addition, quantitative DCE-MRI parameters can be displayed as color-coded parametric maps for visual interpretation.

Prostate cancer usually shows early, rapid, and intense enhancement with quick washout of contrast compared to noncancerous prostate tissue. Several studies have highlighted the incremental value of DCE-MRI to standard MRI techniques in prostate cancer detection, staging, and assessment of recurrence. For example, Ocak et al found that $K^\text{trans}$, $k_{ep}$, and AUC were significantly higher ($P < .001$) in prostate cancer than in the normal peripheral zone of the prostate. Although DCE-MRI has shown potential in assessing prostate cancer in preliminary studies, further research is necessary to establish its clinical value and indications and address technical challenges, such as standardization of acquisition and analysis methods.

**MR Spectroscopy**

Commercially available acquisition and analysis software packages for MR spectroscopic imaging of the prostate produce 3-dimensional spectral data showing the relative concentrations of tissue metabolites within specified volumes of tissue. In the prostate, the metabolites of interest on in vivo MR spectroscopic imaging are citrate, creatine, choline, and polyamines. Whereas healthy tissue in the peripheral zone of the prostate produces large amounts of citrate, choline is elevated in prostate cancer as a result of increased cell membrane turnover and increased cell surface relative to healthy tissue. Therefore, the (choline + creatine)/citrate ratio has traditionally been used to identify prostate cancer on MR spectroscopy. The polyamine peak is reduced in prostate cancer. Shukla-Dave et al showed that prostate cancer detection with MR spectroscopic imaging could be improved through the use of a statistically based voxel classification procedure that incorporates both the polyamine level and the (choline + creatine)/citrate ratio.

A prospective multi-institutional study reported that in patients with relatively low-risk, low-volume disease who underwent radical prostatectomy, the addition of MR spectroscopy to MRI did not significantly improve the accuracy of prostate cancer localization. Yet, other studies have indicated that MR spectroscopy might have potential for aiding cancer localization, estimating tumor volume, noninvasively assessing prostate cancer aggressiveness and predicting the probability of insignificant cancer.

**Advances in PET Imaging of Prostate Cancer**

Integration with CT has enhanced the clinical value of PET, and $[^{18}\text{F}]$FDG PET/CT is now one of the most accurate, routinely used imaging tools for detecting, staging, and assessing treatment response in several cancers. Yet some cancers, including prostate cancer, often cannot be distinguished by their $[^{18}\text{F}]$FDG avidity on PET/CT. The degrees of $[^{18}\text{F}]$FDG uptake in prostate cancer and some benign conditions, such as benign prostatic hyperplasia and chronic inflammation, show some overlap. Furthermore, $[^{18}\text{F}]$FDG is normally excreted in urine, and the physiologic activity in the urinary bladder can mask pathologic uptake in the prostate. High $[^{18}\text{F}]$FDG uptake is noted in more aggressive prostate cancers that are poorly differentiated or of high Gleason score ($> 7$) (Fig. 13); however, the main application for $[^{18}\text{F}]$FDG PET is in patients with aggressive, castrate-resistant metastatic prostate cancer, where it determines disease activity of metastatic sites, provides prognostic information, and is a meaningful adjunct in response assessment.

Other tracers more promising than $[^{18}\text{F}]$FDG for prostate cancer assessment have recently been evaluated in clinical studies. Choline is a class of phospholipid and a major component of biologic membranes. As prostate cancer shows up-regulated choline kinase activity and increased choline uptake, radiolabeled choline ($[^{18}\text{F}]$- and $[^{11}\text{C}]$choline) has been used for PET imaging in prostate cancer. $[^{18}\text{F}]$FDG PET can identify lymph node metastases. Occasionally, this may lead to a change in the surgical approach, when the scan shows unexpected lymph node involvement outside the standard field for nodal dissection. In contrast, lack of choline uptake in lymph nodes cannot reliably exclude small metastases; therefore, the planned extent of nodal dissection should not be restricted to a smaller than standard field based on a negative presurgical choline scan. Currently, the major indication for choline PET/CT is the early localization of recurrence in patients with PSA relapse after primary radical treatment. Potentially, this test may also be useful in radiotherapy planning. Acetate participates in cytoplasmic lipid synthesis, and an increased fatty acid synthesis is thought to occur in prostate cancer. Similarly to $[^{11}\text{C}]$choline, radiolabeled acetate ($[^{11}\text{C}]$acetate) appears to be more useful than $[^{18}\text{F}]$FDG in the assessment of prostate cancer before and after treatment. Other novel PET tracers that have been investigated in prostate cancer include anti-1-amino-3-$[^{18}\text{F}]$ fluorocyclobutane-1-carboxylic acid ($[^{18}\text{F}]$FACBC), which enables imaging of amino acid transport; and 16$\beta$-$[^{18}\text{F}]$ fluoro-5α-dihydrotestosterone ($[^{18}\text{F}]$FDHT) for androgen receptor imaging. Although further studies are needed for their clinical development, these novel tracers are very promising.
For instance, given the important role of the androgen receptor in the pathogenesis of prostate cancer, \(^{18}\text{F}\)FDHT PET may be of potential use in monitoring treatment response.

In summary, the role of PET imaging in prostate cancer is still evolving, as new and promising tracers are under investigation. Rigorous clinical trials using these new tracers in specific clinical scenarios will be needed before they can be employed routinely.

**Evolving Roles of Imaging in Prostate Cancer Management**

Traditionally, the role of imaging in cancer management has been restricted to morphologic assessment for detection, localization, staging, and posttreatment follow-up. Recent advances in imaging techniques as summarized above have markedly expanded the role of imaging beyond anatomical assessment. Modern concepts in prostate cancer imaging embrace multiparametric and multimodality techniques that integrate tumor morphology with information on physiological and biological tumor characteristics.

**Prostate Cancer Detection and Diagnosis**

Prostate cancer is typically diagnosed by digital rectal examination, testing for serum PSA level, and transrectal US (TRUS)-guided biopsy. MRI, especially when acquired with multiparametric techniques (DW-MRI, DCE-MRI, and/or MR spectroscopy), reportedly has the potential to add value in prostate cancer diagnosis, eg, by guiding biopsy to the most suspicious areas and reducing the number of systematic/random biopsies. However, it should be noted that the diagnostic performance of MRI in prostate cancer detection depends on tumor volume and grade, with accuracy being higher for tumors of higher volumes and grades.

Systematic TRUS-guided biopsy remains the main method for diagnosing prostate cancer, although it is prone to sampling errors, ie, a negative TRUS-guided biopsy does not necessarily rule out prostate cancer. Therefore, in men with elevated PSA and negative TRUS-guided biopsy, the use of MRI has been investigated, most often for locating suspicious areas for targeted biopsies; this process can be facilitated by TRUS-MRI fusion techniques.

**Prostate Cancer Characterization and Treatment Selection**

Early detection of prostate cancer through PSA screening has made precise risk stratification a necessity for minimizing harms resulting from overdiagnosis and overtreatment. Treatment decisions are usually made based on clinical information such as PSA level and histopathology findings at biopsy. Although predictive tools such as nomograms are widely used in routine practice, integration of modern imaging methods such as MRI into clinical decision algorithms could potentially improve prostate cancer management. In a study of 612 consecutive men with prostate cancer, Wang et al
showed that MRI findings provided statistically significant incremental value to nomograms for predicting organ-confined disease in all risk groups, but especially in the intermediate- and high-risk groups.112

Currently, about 50% of men with newly diagnosed prostate cancer in the United States are considered to have clinically low-risk disease (clinical stage T1-T2a, biopsy Gleason score ≤ 6, PSA < 10 ng/mL).113 Some clinically low-risk prostate cancers prove to be of higher grade, stage and/or volume than expected at surgery, whereas others are insignificant or indolent cancers that may never require treatment.114

Given the risks of morbidity associated with radical treatment (eg, radical prostatectomy or radiation therapy), active surveillance (monitoring of PSA levels, periodic imaging and repeat biopsies) is gaining acceptance as an alternative initial management strategy for carefully selected men with low-risk prostate cancer.115 Active surveillance could be a considerably more cost-effective approach than immediate treatment for prostate cancer, as suggested in a theoretical cohort.116 Furthermore, by preserving quality of life and minimizing the harms from radical treatment of low-risk prostate cancer, active surveillance could mitigate the concerns regarding extensive screening, overdiagnosis, and overtreatment of prostate cancer. Ultimately questions about how to best practice active surveillance will need to be addressed in prospective studies. Currently, the main challenges in active surveillance of prostate cancer are adequate characterization of disease at diagnosis and determination of the risk of progression.

Focal therapy, another emerging management option in prostate cancer, offers preservation of healthy tissue along with local cancer control by treating only areas of cancer.117 Although prostate cancer is often multifocal, it has been proposed that focal therapy directed only at clinically significant tumors [tumor volume > 0.5 mL and Gleason score (≥ 7)] might suffice for disease control.118 Optimal methods of selecting patients suitable for focal therapies and precisely localizing tumor foci within the prostate are the subject of ongoing research. Advanced multiparametric MRI techniques and prostate mapping biopsy are promising tools for these purposes. Other emerging roles of imaging in focal therapy are real-time guidance of focal therapy and assessment of the adequacy of necrosis following treatment.119

In summary, active surveillance, focal therapy, radical prostatectomy, and radiation therapy represent a range of treatments with varying degrees of invasiveness for men with different disease grades and stages. Active surveillance and focal therapy, which are relatively new options, are promising but are complicated by uncertainties in risk stratification that affect treatment decision-making, as well as by uncertainties regarding the definition of appropriate outcome measures. Biopsy, which leaves the possibility of under sampling, is not sufficient to resolve these uncertainties. Novel biomarkers and modern imaging are expected to play increasingly important roles in facilitating broader acceptance of both active surveillance and focal therapy. Further research, particularly involving prospective validation, is needed to facilitate standardization and establish the roles of advanced imaging tools in routine prostate cancer management.

Colorectal Cancer Imaging

Colorectal cancer (CRC) is the third most common cancer worldwide and the second most frequent cause of cancer death in the United States. The American Cancer Society estimates that 143,460 new cases of CRC will be diagnosed and 51,690 deaths from CRC will occur in the United States in 2012.120 Because of screening and removal of premalignant polyps, incidence rates have declined over the last 3 decades. When CRC is diagnosed at an early stage, the 5-year survival rate is 90%.1 Due to important differences between CRC and other cancers, imaging plays a comparatively pivotal role in CRC detection and management. For example, a precursor lesion, the adenoma, accounts for 80% of CRCs, and thus screening has been shown to be very effective.121 Although colonoscopy with biopsy will confirm most cancers, increased use of CT colonography due to its proven efficacy has greatly affected the demand for radiologists to become trained, and may lower the cost and perforation risk associated with screening.122 In addition, improved outcomes after tailored locoregional CRC liver metastasis treatment, with contributions from interventional imaging, have underscored the importance of accurate pretreatment staging of liver metastases.123 Additions such as diffusion-weighted imaging and hepatocyte-specific contrast agents have improved detection rates substantially, allowing more appropriate treatment.124 Finally, MRI for staging of rectal cancer has become standard practice and, in some instances, is performed in lieu of surgeon-performed endorectal US (ERUS), providing the radiologist with an even greater role in the management of patients with CRC.125 In this section, we will review current and developing radiologic practices in CRC with respect to screening, preoperative evaluation, surveillance, and posttreatment restaging.

Screening

CRC is a largely preventable disease, as the progression of the adenoma-carcinoma sequence of mutations is slow and leaves ample time to intervene. Nonetheless, approximately 41% of the population eligible for screening remains unscreened.126 Most screening is performed using nonimaging tests (Table 2). Any of these screening strategies will reduce...
mortality from CRC. Recent modifications to recommendations from some researchers and/or organizations include a preference for the immunochemical fecal occult blood test (iFOBT), which provides a higher sensitivity for high-risk adenomas and cancers in lieu of the older Hemoccult II FOBT; screening African Americans beginning at 45 years of age; and inclusion of fecal DNA testing with reported sensitivity and specificity of 81% and 82%, respectively.

Among imaging tests used for screening, barium enema has seen a continual decline in usage, at least in part due to the landmark study showing that this test detected only 39% of polyps identified at colonoscopy, including only 48% of those >1 cm in size. The recent (and largest, with >2500 patients) multicenter CT colonography (CTC, also known as virtual colonoscopy) screening study, performed by the American College of Radiology Imaging Network, found that CTC had sensitivity of 90% and similar specificity for polyps >9 mm, and the number of centers using CTC has increased. Widespread deployment of CTC remains hindered, in part, by the 2009 decision of the Center for Medicare and Medicaid Service (CMS) to deny reimbursement based on 1) potential radiation risk, 2) impact of detection of extracolonic findings, and 3) efficacy in the 65 years and older age group of concern to CMS. Data from studies reported after this decision put CTC in a good position to be reconsidered for reimbursement. The median estimated effective dose is currently 5 to 6 mSv, a dose far less than that received from cosmic radiation in a 1-year period. Extracolonic findings occur in 7% to 11% of cases and lead to extra examinations in about 6% with a relevant new diagnosis made in 2.5%, according to the experience of the largest screening center in the United States. Furthermore, when detection of extracolonic cancers and aortoiliac aneurysms is included along with CRC screening, CT colonography has been shown to be more clinically effective and more cost-effective than optical colonoscopy. In an observational study, CTC accuracy was maintained in patients aged 65 to 79 years, who were compared to the overall general population sample. In the older patients, CT colonography remained a safe and effective modality and program outcome measures, such as colonoscopy referral and extracolonic work-up rates, remained similar to those in other screened groups.

Detection and Characterization

Diagnosis and clinical staging of primary colon adenocarcinoma is most often accomplished by combining colonoscopy with biopsy and performing cross-sectional imaging to detect metastatic disease. The classic role of tumor identification historically played by the single or double-contrast barium enema (DCBE) began to diminish significantly with the rapid development of CTC. Increasing reimbursement for colonoscopy and the rapid development of CTC have likely further attenuated its widespread use. Although most tumors are detected on DCBE and are either semiannular or annular (Fig. 14), a recent large Canadian study found that 22.4% of cancers were missed at DCBE. Single-contrast BE is inferior to DCBE and requires compression of the whole colon to overcome its decreased sensitivity.

| TEST                        | MULTISOCIETY JOINT GUIDELINES* | USPSTF                  | ACG                                      |
|-----------------------------|--------------------------------|-------------------------|------------------------------------------|
| **TESTS THAT DETECT POLYPS AND CANCER** |                                 |                         |                                          |
| Colonoscopy                 | Every 10 y beginning at age 50 | Every 10 y beginning at age 50 | Every 10 y beginning at age 50; preferred strategy: Begin at age 45 in African Americans |
| Flexible sigmoidoscopy      | Every 5 y                       | Every 5 y with high-sensitivity FOBT every 3 y | Every 5-10 y                             |
| Computed tomography colonography | Every 5 y                   | Insufficient evidence to recommend | Every 5 y                                |
| Double-contrast barium enema | Every 5 y                      | Not recommended          | Not recommended                          |
| **TESTS THAT DETECT CANCER** |                                 |                         |                                          |
| High-sensitivity FOBT       | Every year                     | Every year              | Every year                               |
| Fecal DNA test              | Interval uncertain              | Insufficient evidence to recommend | Every 3 y                                |
| FIT                         |                                | Every year              | Every year                               |

ACG indicates American College of Gastroenterology; FIT, fecal immunochemical test; FOBT, fecal occult blood test; USPSTF, US Preventive Services Task Force.

*US Multisociety Task Force on Colorectal Cancer, American Cancer Society, and American College of Radiology.
Although CT and MRI are widely used for preoperative whole-body staging, they are not recommended first-line methods for detection of primary lesions (Fig. 15). In contradistinction, CTC has matured into an excellent diagnostic method for detection of CRC. Data drawn largely from screening studies tell us that its sensitivity for polyps >10 mm is 90% or greater, and that it will detect nearly every cancer. In fact, a recent meta-analysis of more than 11,000 patients indicated that CTC had sensitivity of 96.1% (398 of 414) for CRC, and when cathartic cleansing and fecal tagging were used, no cancers were missed (Fig. 16). Detection of flat cancers remains a challenge with CTC as compared with endoscopic methods in which mucosal surface details are better appreciated. CTC not only detects CRC, but with its cross-sectional depiction also allows characterization of tumors using the TNM staging system with reasonable T- and N-stage accuracies of 83% and 80%, respectively. CTC is an operator-dependent technique that has shown great variability between radiologists with different degrees of training. Computer-aided detection (CAD) was developed for this reason and because 10,000 to 15,000 images must be scrutinized for each large adenoma detected. In a screening cohort of 3077 consecutive asymptomatic adults, stand-alone CAD had sensitivities of 97% and 100% for advanced neoplasia and cancer, respectively.

With magnetic resonance colonography (MRC), detection of masses is limited because techniques employing air cause susceptibility artifacts, and those employing dark-lumen techniques with water-filling and intravenous gadolinium are under scrutiny because of concerns about the potential risk of nephrogenic systemic fibrosis. In addition, in the largest screening study, the sensitivity of MRC was only 70% in patients with colorectal lesions more than 10 mm in size.

Imaging plays a critical role in detecting liver metastases in order to properly stage and treat the patient with colorectal cancer. NCCN guidelines recommend contrast-enhanced CT or MRI. Contrast-enhanced multidetector CT (MDCT) offers the highest spatial resolution. Metastases are usually hypovascular and best seen during the portal phase of imaging. Detection of smaller lesions or
those in a fatty liver can be problematic. In these cases, MRI can be helpful but also potentially limited in small lesions.\textsuperscript{143} MRI advances in the last decade include faster imaging; DW-MRI, interrogating the motion of water molecules; and hepatocyte-specific contrast agents such as gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid (Gd-EOB-DTPA) and gadobenate dimeglumine (Gd-BOPTA), which are excreted into the biliary system. Delayed imaging after injection of one of these agents may improve the detection of very small metastases, revealing them as hypointense to liver on T1-weighted images.\textsuperscript{144} In our experience, the combination of DW-MRI and Gd EOB-DTPA MRI yields the highest sensitivity for small liver metastases (Fig. 17). PET imaging, although useful for whole-body imaging, has inherently low resolution, thus limiting the detection of small liver metastases.\textsuperscript{145} The addition of perfluorobutane microbubbles (taken up by Kupffer cells) has improved the sensitivity of US for the detection of smaller lesions.\textsuperscript{146}

Imaging of rectal cancer has advanced on a faster track with MRI than has imaging of extrapelvic colon cancer, due in part to the relatively immobile pelvic location of rectal cancer and in part to its distinct treatment considerations. Staging is primarily accomplished with ERUS, typically performed by surgeons, as well as with MRI using phased-array coils to completely visualize the pelvic anatomy and, especially, the circumferential resection margin, an important landmark for the standard total mesorectal excision (Fig. 18). The MERCURY study\textsuperscript{125} established the near equivalence of MRI to histopathology for identification of this margin, an important advantage of MRI over ERUS, with which the margin is not routinely visualized.\textsuperscript{147} T- and N-stage accuracies of MRI (87\% and 74\%, respectively) were similar to those of ERUS (82\% and 74\%, respectively).\textsuperscript{148} Accurate lymph node identification remains a problem for MRI. Toward this end, a new albumin-bound gadolinium agent has shown some promise, and further results are awaited.\textsuperscript{149}

FIGURE 17. Liver metastasis segment 8 is shown. (A) T2-weighted fat saturation image showing mildly hyperintense metastasis. (B) T1-weighted fat-saturated, gadolinium-enhanced image showing peripheral ring-like enhancement of metastasis. (C) Diffusion-weighted image showing hyperintense signal due to restricted water diffusion in tumor metastasis. (D) Enhanced image, 20 minutes after injection of gadoxetate disodium (Eovist), hepatocyte phase. T1-weighted image shows hypointense metastasis.
Role of Imaging in Assessing Treatment Response

Imaging plays a critical role in 1) determining response to systemic and locoregional treatment of liver metastases, 2) assessing response to local treatment and restaging rectal cancer primary lesions, and 3) detecting and assessing the treatment response of extrahepatic metastatic disease. Systemic treatment (and in some centers, hepatic artery infusion) of nonresectable liver metastases with chemotherapy aims at reduction of the metastatic burden, which, occasionally may allow attempts at curative liver resection. Using MDCT and MRI, RECIST 1.1 criteria will determine the need for further therapy. Typically, response will be seen as a decrease in the size and enhancement of heterogeneously or ring-enhanced hypodense metastases at portal phase imaging. As mentioned above, due to the limitations of CT with regard to soft tissue contrast and fatty liver, MRI has greater sensitivity for remaining (or new) lesions \(< 1.0\) cm due to its superior soft tissue contrast. In a recent meta-analysis of 25 eligible studies, MRI showed higher sensitivity than CT on a per-patient basis \((P = .05)\) and on a per-lesion basis as well \((P = .0001)\). With its 81.1% sensitivity and 97.2% specificity, MRI is thus the preferred modality. Nonetheless, under the current NCCN guidelines, CT remains the preferred modality.

Locoregional (“liver-directed”) therapies have proliferated and now include radiofrequency, microwave ablation, transarterial chemo- or particle embolization and irreversible electroporation. With these treatments, responding lesions can actually increase in size, and simple size criteria are no longer sufficient to determine response. The European Association for the Study of the Liver has issued new criteria to assess viability of remaining tumor based on enhancing residual volume by multiphase CT or MRI. However, the field is rapidly changing and there is no consensus on the optimal imaging strategy following locoregional therapy. Although larger studies are needed, a small study from Germany recently showed equivalence between functional and morphologic imaging in this setting, with accuracy and sensitivity of 91% and 83%, respectively, for PET/CT and 92% and 75%, respectively, for MRI.

Restaging of primary rectal cancer tumors after standard treatment with chemoradiotherapy is fraught with inaccuracies, probably due to edema, fibrosis and the inherent limitations of morphologic imaging. ERUS has only a 20% to 35% positive predictive value for residual tumor. CT and MRI are likewise limited, with MRI showing 43% accuracy in TNM downstaging in one study. Even functional methods such as PET are limited by over- and understaging. One important challenge for imaging is to identify the approximately 25% of patients that achieve a pathological complete response so that they may avoid radical surgery. In a study of 68 patients, PET indicated that 28 patients had a complete metabolic response, yet only 8 of these truly had a pathological complete response \((pCR)\). Reducing the size of the primary tumor is an important goal in rectal cancer, unlike other colon cancers, to avoid removal of the anal sphincters and the need for a colostomy. RECIST criteria are limited when applied to measuring gastrointestinal luminal tumors. MRI volumetric studies have recently been shown to allow some assessment of successful downstaging and can be predictive of sphincter preservation if the decrease in volume is \(> 75\). TNM downstaging at MRI just 2 weeks after treatment has a PPV of 94% for the presence of disease confined to the rectal wall. Furthermore, a total volume reduction of 45% was found to be a statistically useful cutoff \((P < .001)\), independently predicting longer disease-free survival, longer OS, and a reduced rate of recurrence in a study of 405 patients. Nonetheless, volumetry has not been reliable for predicting pCR.

Advanced MRI techniques have recently been applied to treatment response prediction in rectal cancer in the hopes of achieving more accurate results. DW-MRI using specially added motion-probing gradients showed 87% accuracy for determining pCR when the apparent diffusion coefficient \((ADC)\) cutoff of \(1.3 \times 10^{-3}\) was used in a study of 76 patients; even after just 1 week of radiochemotherapy, ADC differences were apparent between eventual responders and nonresponders. DCE-MRI was recently used in a pilot study of 23 patients undergoing chemotherapy for locally advanced rectal cancer; the permeability transfer coefficient \((K^{trans})\) was found to be statistically significantly lower in the 6 patients who achieved pCR than in the rest of the patients.

PET has been shown to be more sensitive than conventional imaging for detecting extrahepatic metastatic disease in patients considered for liver metastasectomy, with the
potential to alter treatment in up to 27% of patients. In addition, it is well established that [18F]FDG PET offers incremental value in restaging due to its ability to identify unsuspected metastases cost-effectively. However, routine PET scanning at baseline staging is probably not justified, and the NCCN “strongly discourages” it. The use of PET for treatment response assessment is less well established. By showing variations in SUVs, PET has the potential to capture metabolic changes that occur before anatomic changes, especially with the use of newer targeted therapies aimed at growth factor receptors (e.g., vascular endothelial growth factor [VEGF]). However, multiple small studies have mainly shown limitations in lesion detection after chemotherapy due to either shrinkage to a size below the limits of PET resolution, or, more commonly, down-regulation of hexokinase and glycolysis by chemotherapy. Therefore, apparent complete metabolic responses may be misleading. New developments in imaging of treatment response draw on advances in technology, such as integrated PET/MRI, that combine functional and anatomic imaging, as well as advances in our understanding of tumor physiology, e.g., through the use of hypoxia markers such as [18F]fluoromisonidazole (FMISO) and [60Cu]-ATSM (a copper radiotracer). For example in early studies, hypoxic rectal tumors showing avidity for these tracers had a worse prognosis than other rectal tumors. Whole-body DW-MRI scanning for metastatic disease has come into use as a new strategy that does not involve ionizing radiation; it has shown promising results in multiple tumors and had 81% sensitivity for colorectal cancer lesion detection in an early pilot study.

Surveillance

Recent meta-analyses of randomized controlled trials comparing low-intensity and high-intensity surveillance programs have shown advantages for more intense follow-up in Stages I-III disease, however, controversies remain regarding the optimal surveillance strategy. Version 3.2012 of the NCCN guidelines recommends CT scans of the chest, abdomen, and pelvis annually for 3 to 5 years to monitor for the presence of potentially resectable metastatic lesions, primarily in the lung and the liver. In addition, other consensus guidelines recommend colonoscopy 1 year after resection and then at 3 years and every 5 years thereafter to detect and remove metachronous polyps. PET/CT is not recommended for surveillance. Trials such as the Scandinavian COLFOL trial are still ongoing to determine whether frequent imaging (e.g., every 6 months for 36 months) or low-intensity imaging (at 12 and 36 months) is the best strategy. In the colorectal imaging community, interest has been sparked in the potential to combine CT scanning surveillance for metastatic disease with colonoscopic surveillance for luminal disease through the use of contrast-enhanced CT colonography in lieu of more invasive, frequent colonoscopy.

At least 1 NCI-sponsored trial will attempt to address whether this strategy is viable (personal communication, Perry Pickhardt). In a retrospective study of 742 patients, findings at CTC suggested that the need for surveillance colonoscopy could potentially be reduced. Also under investigation is the validity of the CT Colonography Reporting and Data System (C-RADS) created in 2005. Similar to the validated Breast Imaging-Reporting and Data System (BI-RADS), this system makes specific recommendations for CTC follow-up intervals based on initial colonic and extracolonic findings. Validation of C-RADS and results of cost-effectiveness studies of the system are eagerly awaited.

Imaging of Lymphoma

The malignant lymphomas are broadly divided into Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL); they account for approximately 8% to 9% of all malignancies in the United States, where 70,000 new cases of NHL and 9000 new cases of HL are expected to be diagnosed in 2012. The most recent WHO classification scheme defined more than 30 histologic entities of NHL, broadly divided into B cell versus T cell and NK cell lymphomas. In the United States, diffuse large B cell lymphoma (DLBCL) is the most common subgroup (31%), followed by follicular lymphoma (FL, 22%). HL is now divided into 2 major subcategories: classical (including nodular sclerosis, mixed-cellularity, lymphocyte-rich, and lymphocyte-depleted entities) and nodular lymphocyte predominant.

The traditional tasks of imaging studies in the management of lymphoma include accurate staging, confirming complete response at the end of therapy, and characterizing clinically suspected recurrence. Imaging of lymphoma has undergone tremendous changes and continues to evolve quickly. PET/CT now plays an integral role in managing lymphoma.

Over the last few decades the clinical outcome of lymphoma patients has improved significantly. For instance, in patients with early-stage HL, freedom from treatment failure and survival rates well above 90% can now be achieved, and even in patients with DLBCL, OS and PFS as high as 90% and 79%, respectively, have been reported at a median follow-up of 44 months. The improvement in prognosis is largely related to advances in molecular pathology leading to better disease characterization and identification of prognostic markers, improved staging with cross-sectional imaging, the widespread use of functional imaging for staging and response assessment, and improved treatment regimens. Most of the recent progress in imaging in lymphoma occurred after the widespread introduction of [18F]FDG PET and PET/CT. Accordingly, [18F]FDG PET is now part of the revised lymphoma response criteria. This section will therefore emphasize the major contributions of [18F]FDG PET in the management of lymphoma.
One of the most important tasks for PET, beyond staging and restaging, is now the early assessment of treatment response after a few cycles of chemotherapy (Fig. 19), both for prognostication and as a tool to guide changes in the treatment regimen (response-adapted therapy).

Clinical Utility of \([^{18}F]FDG\) PET in Lymphoma
The clinical utility of \([^{18}F]FDG\) PET in lymphoma depends on the intensity of radiotracer uptake in disease sites, which will affect the test accuracy for staging and characterizing residual masses after completion of therapy, as well as the role of the test in response assessment. The intensity of \([^{18}F]FDG\) uptake in lymphoma is determined by tumor histology, grade (eg, indolent versus aggressive NHL),\(^{181,182}\) viable tumor cell fraction, rate of tumor cell proliferation, up-regulation of glucose metabolism and transporters, salvage pathways and tumor-specific pathways, local perfusion (which determines substrate delivery to the cancer cell) and the presence of hypoxia. Most sites of HL show clearly abnormal \([^{18}F]FDG\) uptake.\(^{183}\) On the other hand, the \([^{18}F]FDG\) avidity among NHL subtypes varies widely\(^{182,184}\): indolent lymphomas tend to show lower \([^{18}F]FDG\) uptake than aggressive disease entities. This finding can be helpful in guiding biopsies to the sites of most aggressive disease and in diagnosing transformation from previously indolent to aggressive disease.\(^{181,182}\) Most disease sites of indolent NHL, such as FL, are still well recognized.\(^{185,186}\) However, only 55% of extranodal marginal zone lymphomas and 83% of small lymphocytic lymphomas show \([^{18}F]FDG\) uptake.\(^{187}\) For practical purposes, we recommend that PET be used in all cases of HL and most cases of NHL where the information may influence staging, aid response assessment, or guide radiotherapy planning.

What Constitutes Abnormal \([^{18}F]FDG\) Uptake?
The intensity of \([^{18}F]FDG\) uptake is graded on a 5-point scale (according to the Deauville criteria\(^{188}\)). In interim scans done after a few cycles of chemotherapy, only residual \([^{18}F]FDG\) uptake higher than mean activity in the liver in the same scan is usually considered abnormal. For response assessment at the end of chemotherapy, the revised criteria from 2007\(^{180}\) apply.

FIGURE 19. A 46-year-old male with diffuse large B cell lymphoma, stage IV was studied. Baseline maximum intensity projection (MIP) positron emission tomography (PET) image with \([^{18}F]fluorodeoxyglucose ([^{18}F]FDG) (A) shows widespread disease, which is essentially resolved on interim scan after 4 cycles of chemotherapy (B). The interim scan also shows increased \([^{18}F]FDG\) uptake in bone marrow related to administration of granulocyte colony-stimulating factor (GCSF). (C,D) Transaxial CT and PET/CT fusion images at baseline show abnormal \([^{18}F]FDG\) uptake in extensive mediastinal and hilar lymphadenopathy as well as in bone lesions in a right rib and the right scapula. On interim scan (E,F) abnormal \([^{18}F]FDG\) uptake at all of these sites has resolved although residual enlarged lymph nodes remain. The sites are better seen on a contrast-enhanced CT (G) and measure up to 5.3 cm × 3.6 cm. Chemotherapy was continued for a total of 8 cycles. At the time of writing, the patient remained disease-free after 9 years of follow-up.
Staging

The modified Ann Arbor staging system remains in use for both HL and NHL. Accurate staging is a prerequisite for appropriate therapy. Use of [18F]FDG PET as well as, more recently, PET/CT, improves staging accuracy in both HL and NHL, over use of CT alone, in particular with regard to extranodal involvement. Depending on the clinical setting and disease entity, PET may upstage 15% to 30% of patients. Upstaging by PET is often associated with a change in clinical management, has implications for radiotherapy planning, and probably also improves outcome. Most sites of lymph node involvement are reliably identified on both CT and PET. PET (but not CT) also reliably identifies splenic involvement. Ideally, lymphoma staging should be done with the combination of contrast-enhanced CT and PET, folded into a single examination and covering the range from skull base to upper thighs. This approach will provide the highest diagnostic yield for disease sites and thereby avoid understaging and undertreatment. Neither test is well suited for the assessment of bone marrow. However, in patients with a low pretest likelihood of bone marrow involvement, such as those with early stage HL, a lack of abnormal [18F]FDG uptake in marrow can provide reassurance. Bone marrow biopsy remains essential in all other lymphoma settings. Of note, PET may identify bone marrow involvement in approximately 10% of cases with negative biopsy findings.

Response Assessment at Completion of Therapy

The major goal of imaging in this setting is the identification of patients with residual disease (“residual mass”) who may benefit from additional treatment, such as autologous stem cell transplant. [18F]FDG PET scan data can be used to exclude residual disease with high certainty: the specificity is in the range of 85% to 100%, and the negative predictive value is in the range of 90% to 100% for most cases of HL and NHL, perhaps with the exception of bulky (> 5.0 cm) residual disease. In contrast, positive predictive values as low as 50% to 75% have been reported; therefore, positive PET findings should be confirmed with biopsy before embarking on additional therapy. Alternatively, one might opt to repeat the PET scan in 6 to 12 weeks. The interpretation of end-of-treatment PET scans is based on visual assessment; SUV measurements do not provide any additional benefit.

Early Response Assessment Using Interim [18F]FDG PET Scans

The rapidity of decline in FDG uptake between baseline and interim scans (after a few cycles of chemotherapy) provides an insight into the kinetics of tumor cell kill; i.e., the earlier PET becomes negative, the greater the chemotherapy responsiveness of the tumor cell clone, and the greater the chance for a complete response at the end of treatment and for cure. However, treatment-induced inflammation may lead to false-positive scans. This is more likely when patients are treated with accelerated chemotherapy regimens (“dose-dense approach”), or when rituximab is part of the regimen. The major studies on interim PET in lymphoma have been summarized in a review and a meta-analysis. A few recent studies will be discussed in brief here.

Advanced Stage Hodgkin Lymphoma

For advanced stage HL, impressive results were reported by Gallamini et al in 260 patients. After 2 cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) chemotherapy, 81% of patients had a negative PET scan, indicating rapid response to therapy. These patients’ 2-year PFS was 95%, as compared to only 13% in patients with positive PET scans showing residual disease. PET after 2 cycles of chemotherapy had positive and negative predictive values of 92% and 95%, respectively, provided more accurate prognostic information than the clinical international prognostic score, and was the only prognostic marker in a multivariate analysis. A study by Cercl et al in 104 patients confirmed the high negative predictive value (92%) of early interim [18F]FDG PET; the 3-year event-free survival (EFS) was 90% for patients with PET–2–negative scans and 53% for those with PET–2–positive scans. Thus, the positive predictive value was lower than in the aforementioned study by Gallamini et al, possibly because larger percentages of patients had stage IV and bulky disease. ([18F]FDG uptake resolves more slowly in advanced-stage disease and larger tumor masses; in addition, response in larger masses induces more inflammation, leading to false-positive [18F]FDG uptake. Another site of slow response and common false-positive [18F]FDG uptake on interim scans is the skeleton.) In contrast to the promising data mentioned above, a recent study in patients with early-stage HL reported that only end-of-therapy, but not interim, PET predicted patient outcome. Based on interim PET after cycle 2, the 4-year PFS was 87% in patients with, and 91% in those without residual abnormal [18F]FDG uptake; in contrast, the corresponding PFS rates for end-of-therapy scans were 54% and 94%, respectively. The study suggested that many patients with early-stage disease may still achieve cure even if their disease responds slowly to therapy.

Diffuse Large B Cell Lymphoma

In DLBCL, the value of interim [18F]FDG PET after 2 or 4 cycles of chemotherapy has also been investigated. The negative predictive value was high, with a 2-year EFS...
of about 80% in patients with negative interim scan results. This value is lower than the negative predictive value in HL, probably because of the more aggressive nature and worse prognosis of DLBCL. In contrast, positive predictive values were only 32% to 50% with the use of visual analysis or SUV ratios. At least in part, this may have been due to the use of rituximab, leading to frequent false-positive \(^{18}\text{F}\)FDG uptake related to treatment-induced inflammation.\(^{210}\)

To overcome the limitations of visual scan interpretation (subjectivity, interobserver variability), some investigators have suggested a semiquantitative measure (ASUV), which can be derived by calculating the ratio of \(^{18}\text{F}\)FDG SUV in disease sites at interim scan to the \(^{18}\text{F}\)FDG SUV at baseline. In some studies, a decline in SUV of 66% (after 2 cycles of therapy) or 70% (after 4 cycles of therapy) was more accurate for predicting complete response at the end of treatment and PFS than was visual analysis in post hoc analysis.\(^{217,219}\) A greater (or steeper) percentage of decline in \(^{18}\text{F}\)FDG SUV from baseline to interim scan indicates a better chance for complete response and cure, assuming that treatment-induced inflammation is negligible. Measuring SUV (rather than estimating FDG intensity visually) may also be more objective and potentially improve interobserver agreement.\(^{216,218}\)

**Response-Adapted Therapy**

Interim PET imaging may influence treatment decisions. For instance, if a negative interim scan could reliably indicate absence of, or minimal microscopic, residual disease, then the planned chemotherapy regimen could potentially be shortened (de-escalated). This might pertain to low-risk patients with early stage HL, patients with advanced-stage HL treated with the more aggressive and more toxic bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP) regimen, or selected young patients with DLBCL. These hypotheses are now being tested in clinical trials.

For instance in advanced-stage HL, the German Hodgkin Study Group has recommended a regimen of 8 cycles of escalated BEACOPP as a new treatment paradigm.\(^{220}\) Although excellent outcomes can be achieved with this regimen, it is also associated with significant toxicity, prompting efforts to de-escalate treatment (and thus reduce toxicity) in patients with early favorable response by PET.\(^{221}\)

Compared to the implications of an early negative PET scan, the implications of a positive interim \(^{18}\text{F}\)FDG PET scan are less clear. Two alternative strategies are conceivable: either intensification of therapy to overcome resistance, or (particularly in light of high false-positive rates on interim scans) continuation with standard therapy but closer surveillance and follow-up after the end of therapy, with salvage therapy for relapsed disease. Several current clinical trials are using early interim \(^{18}\text{F}\)FDG PET for treatment decisions. Examples in early-stage HL include Cancer and Leukemia Group B (CALGB) study 50604 (clinicaltrials.gov; NCT01132807), in which patients with nonbulky stage I/II disease receive 2 cycles of ABVD followed by \(^{18}\text{F}\)FDG PET. Interim PET-negative patients receive 2 additional cycles of ABVD chemotherapy, whereas interim PET-positive patients proceed with 4 cycles of escalated BEACOPP chemotherapy followed by involved field radiotherapy. Examples in advanced stage HL include trials that emphasize escalation of therapy in early PET nonresponders and those that emphasize de-escalation. These approaches are chosen based on differing treatment philosophies: An escalation strategy is pursued if one believes that standard chemotherapy will provide cure and/or high OS rates except in some patients who may need more aggressive treatment. In contrast, a de-escalation strategy is pursued if one believes that patients with negative interim PET scan require less chemotherapy or can be treated with different, less toxic regimens. An example of an escalation strategy is Southwest Oncology Group S0816 (ClinicalTrials.gov identifier NCT00822120). Here, all patients are initially treated with 2 cycles of ABVD therapy, followed by interim \(^{18}\text{F}\)FDG PET. Patients with positive interim PET proceed to 6 cycles of escalated BEACOPP, whereas those with negative interim PET continue treatment with another 4 cycles of ABVD. Endpoints include 2-year PFS and OS. In contrast, de-escalation from primary aggressive chemotherapy is under investigation in the German trial of HD18 for Advanced Stages in Hodgkin Lymphoma (clinicaltrials.gov/ct2/show/NCT00515554). Here, investigators will compare standard treatment with 8 cycles of escalated BEACOPP to experimental arms in which patients with negative interim PET scans after cycle 2 only receive 2 more cycles of the same regimen, whereas rituximab is added to 6 more cycles of escalated BEACOPP in patients with positive results on interim PET. The primary endpoint is PFS. De-escalation (from escalated BEACOPP to ABVD) is also under investigation in a trial (Study of a Treatment Driven by Early PET Response to a Treatment Not Monitored by Early PET in Patients With AA Stage 3-4 or 2B HL; ClinicalTrials.gov identifier NCT01358747) conducted in France.

In DLBCL, the role of interim \(^{18}\text{F}\)FDG PET for response-adapted therapy is also under investigation. For instance, a study sponsored by the Lymphoma Academic Research Organisation (ClinicalTrials.gov identifier NCT01285765), conducted in France, compares standard treatment with 6 cycles of R-CHOP in patients with localized disease and good prognostic features to de-escalated therapy consisting of only 4 cycles of R-CHOP in patients with negative \(^{18}\text{F}\)FDG PET after the initial 2 cycles of therapy. Complete early response is to be confirmed by
the end-of-therapy scan, and 3-year PFS will serve as the endpoint. In patients with advanced disease and 2 or 3 adverse features, NCT 00498043 (GELA LNH07-3B) compares induction therapy with R-CHOP or R-ACVBP, and the subsequent consolidation treatment is chosen based on PET findings after therapy cycles 2 and 4.219

**Imaging Prior to Stem Cell Transplant**

High-dose chemotherapy with autologous stem cell transplantation (ASCT) can improve the outcome of selected patients with relapsed or primary refractory lymphoma. Residual $^{18}$F-FDG-avid disease after first-line chemotherapy, prior to transplant, indicates suboptimal chemosensitivity and a high risk for subsequent relapse.222-226 A meta-analysis including 12 studies in 630 patients with HL or DLBCL confirmed that residual abnormal $^{18}$F-FDG uptake after chemotherapy predicts relapse after subsequent ASCT with overall sensitivity of 69% and specificity of 81%, and the predictive accuracy of PET is higher than that of cross-sectional imaging.226 Eradicating PET-positive disease before ASCT should therefore be a major goal of modern therapy. This notion was confirmed in a recent study in 97 patients with primary refractory or relapsed HL.224 Patients with negative PET after 2 cycles of ifosfamide, carboplatin, and etoposide (ICE) therapy proceeded to high-dose chemotherapy and stem cell transplant. Patients with persistent positive PET after ICE continued treatment with the second-line, non–cross-resistant gemcitabine, vinorelbine, and doxorubicin (GVD) chemotherapy regimen and proceeded to transplant when their PET had turned negative. At a median follow-up of 51 months, patients with negative pretransplant PET (after 1 or 2 chemotherapy regimens) had an EFS of >80% as compared to 29% for patients with persistent positive PET ($P$ < .001).

**Surveillance Imaging After Completed Therapy**

Surveillance imaging aims to detect recurrent disease early, before clinical signs or symptoms might prompt an investigation, enabling early therapeutic intervention; the hope is that such early intervention will lead to better outcomes than therapy initiated after patients become symptomatic. Most recurrences in lymphoma occur in the first 2 years after completion of therapy. Frequent imaging follow-up for at least 2 years is therefore widely practiced. The clinical utility of this approach obviously depends on the sensitivity and specificity of the imaging test, on the rate of natural progression of the disease, and on the availability of potentially curative treatment regimens. Although follow-up imaging after first-line therapy is usually done with CT, this test is ineffective for detecting early recurrence in normal-sized nodes as well as bone marrow or spleen, or reactivation of disease in residual masses whose size remains stable. In 2003, it was suggested that, at the expense of a high rate of false positive findings, $^{18}$F-FDG-PET could detect recurrence before it became apparent clinically or on CT imaging.227 In 2009, a study in 421 patients prospectively tested the value of routine follow-up imaging with CT and $^{18}$F-FDG PET.228 Among patients with HL, 32% had recurrence detected by PET as compared to 23% by CT and 22% by clinical examination. The same tests showed recurrence in 31%, 25%, and 22% of aggressive NHL cases, and 60%, 49%, and 38% of FL cases, respectively. As expected, false positive findings occurred secondary to $^{18}$F-FDG uptake in reactive lymph node and sarcoid granuloma.

Subsequent dedicated studies in HL showed that the majority of surveillance PET scans are true negative, that the overall diagnostic yield is low, and that the positive predictive value is only in the range of 25%.229,230 A recent analysis in patients with early-stage nonbulky HL showed that no imaging follow-up test is needed at all in those with a negative $^{18}$F-FDG PET at the end of ABVD chemotherapy.231

In DLBCL, surveillance imaging is widely practiced in the United States,232 but an overall benefit (earlier detection of recurrence leading to earlier treatment initiation and improved outcome at a reasonable cost) has not been proven. Interestingly, patients in whom recurrence was detected first by surveillance imaging (ie, when they were asymptomatic) were 4 times more likely to have low-risk disease than patients in whom the clinical examination and symptoms prompted imaging studies, which questions the value of the surveillance program.233 Because of these data, earlier enthusiasm for surveillance PET imaging in both HL and DLBCL is now subsiding.

**New Approaches**

Limited data suggest that high uptake of the proliferation marker $^{18}$F-FLT is an indicator of poor response to R-CHOP chemotherapy and poor patient outcome in DLBCL.234 It may potentially also be helpful in differentiating indolent from aggressive lymphoma (by showing higher uptake values in the latter), as well as for early response assessment.

Although CT will likely remain the main structural imaging test for staging and follow-up of lymphoma patients, there has recently been interest in using MRI for staging and restaging (mainly in pediatric patients in order to reduce lifetime radiation exposure). Moreover, DW-MRI may improve lesion conspicuity as compared to standard MR sequences, and early changes in ADC may potentially separate (functional) responders from nonresponders before a decrease in lesion size occurs235-237; however, a clear benefit for staging or patient management remains to be shown. Of note, normal spleen usually shows
high signal intensity on DW-MRI, which limits its value for detecting splenic involvement by lymphoma. This and similar limitations of either technique could probably be circumvented with combined PET/MRI imaging, the impact of which may prove to be greatest in pediatric lymphoma patients.

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