Time Spent by Breast Imaging Radiologists to Perform Value-Added Activities at an Academic Cancer Center
Fernando Collado-Mesa, MD, Geetika Klevos, MD, Kristopher Arheart, PhD, et al

Imaging Management of Breast Density, a Controversial Risk Factor for Breast Cancer
Shannon Falcon, MD, Angela Williams, MD, R. Jared Weinfurtner, MD, et al

Skeletal Scintigraphy
Jaime L. Montilla-Soler, MD, and Rikesh Makanji, MD

Cardiac Magnetic Resonance Imaging in Oncology
Daniel Jeong, MD, Aarti Patel, MD, Christopher J. François, MD, et al

Conventional Modalities and Novel, Emerging Imaging Techniques for Musculoskeletal Tumors
Meera Raghavan, MD

Multimodal Imaging of Head and Neck Squamous Cell Carcinoma
Kenneth L. Gage, MD, PhD, Kerry Thomas, MD, Daniel Jeong, MD, et al

Assessing Response of High-Grade Gliomas to Immune Checkpoint Inhibitors
Solmaz Sahebjam, MD, Dexter G. Stallworth, MD, Sepideh Mokhtari, MD, et al
Editorials

Innovations in Diagnostic Imaging and the Transformation of the Clinical Practice of Radiology in Collaborative, Multidisciplinary Cancer Care
John A. Arrington, MD, Donald L. Klippenstein, MD, and Robert A. Gatenby, MD, PhD

Finally, a Practical Approach to Value-Based Medicine
Lodovico Balducci, MD

Articles

Time Spent by Breast Imaging Radiologists to Perform Value-Added Activities at an Academic Cancer Center
Fernando Collado-Mesa, MD, Geetika Klevos, MD, Kristopher Arheart, PhD, James Banks, MD, Monica Yepes, MD, and Jose Net, MD

Imaging Management of Breast Density, a Controversial Risk Factor for Breast Cancer
Shannon Falcon, MD, Angela Williams, MD, R. Jared Weinfurtner, MD, and Jennifer S. Drukteinis, MD

Skeletal Scintigraphy
Jaime L. Montilla-Soler, MD, and Rikesh Makanji, MD

Cardiac Magnetic Resonance Imaging in Oncology
Daniel Jeong, MD, Aarti Patel, MD, Christopher J. François, MD, Kenneth L. Gage, MD, PhD, and Michael G. Fradley, MD

Conventional Modalities and Novel, Emerging Imaging Techniques for Musculoskeletal Tumors
Meera Raghavan, MD

Multimodal Imaging of Head and Neck Squamous Cell Carcinoma
Kenneth L. Gage, MD, PhD, Kerry Thomas, MD, Daniel Jeong, MD, Dexter G. Stallworth, MD, and John A. Arrington, MD
Assessing Response of High-Grade Gliomas to Immune Checkpoint Inhibitors
Solmaz Sahebjam, MD, Dexter G. Stallworth, MD, Sepideh Mokhtari, MD, Nam D. Tran, MD, PhD, and John A. Arrington, MD

Departments

Original Research: Cost-Effectiveness Analysis of Interventions to Reduce Risk of Aspiration in Elderly Cancer Survivors Residing in Skilled Nursing Facilities
S. Mantravadi, PhD

Pharmacy Report: Fever in Patients With Cancer
Yanina Pasikhova, PharmD, Steven Ludlow, PharmD, and Aliyah Baluch, MD

Case Report: Primary Adrenal Angiosarcoma: A Rare and Potentially Misdiagnosed Tumor
Ariel Grajales-Cruz, MD, Francis Baco-Viera, MD, Ernesto Rivé-Mora, MD, Carlos Ramírez-Tanchez, MD, David Tasso, MD, Norma Arroyo-Portela, MD, Elizabeth Calderón, MD, Ilean Joan Padua-Octaviani, MD, and William Cáceres-Perkins, MD

Case Report: NUT Midline Carcinoma: A Rare Malignancy
Sameer Al Diffalha, MD, Nidal Al Aukla, MD, Saleh Hasan, Shohreh Dickinson, MD, and Farah Khalil, MD

Case Report: CD4-Positive T-Cell Large Granular Lymphocytosis Mimicking Sézary Syndrome in a Patient With Mycosis Fungoides
Ling Zhang, MD, Magali Van den Bergh, MD, and Lubomir Sokol, MD, PhD

About the art in this issue:
Irena Orlov, an innovative, contemporary fine artist, architect, designer, illustrator, and photographer known for creating captivating works that are full of energy. Extraordinarily versatile in her mediums, Irena could never imagine life without art. She is an artist whose path in the fine arts has led her to a unique expression of mood and color. The combination of antique and a very clean, crisp, modern design sense creates a highly prized, individual art style. Her images begin spontaneously and give expression to personal creativity and insight. Each piece is unique in design. Irena often prefers to think of herself as a craftsman, constructing or interpreting imagery and messages from her conscious and subconscious mind. In addition to galleries, her art has appeared in major retail stores and catalogs, online shopping sites, fundraising catalogs, and has been licensed for wall art, calendars, home accessories, and bedding. Irena has lived in Ukraine, Russia, Israel, Canada, and now lives and works in Los Angeles, CA. For more information about Irena and to view additional artwork, please visit http://www.irenaorlov.com/.

Cover:
Industrial feel 5694 (detail)

Articles:
Industrial feel 5693
World around you
Tiny asteroids
Inspiring moments 3
Industrial feel 5687
Industrial feel 5673
Industrial feel 21

Industrial feel 5694
Innovations in Diagnostic Imaging and the Transformation of the Clinical Practice of Radiology in Collaborative, Multidisciplinary Cancer Care

This issue of Cancer Control highlights innovations in diagnostic imaging as well as the evolving role of the radiologist in cancer care. Although significant advances have been made in imaging technology during the past decade, an even greater evolution has taken place in the role of diagnostic imaging and the radiologist in multidisciplinary cancer care. As we continue the transformation to patient-centered care, delivering the best quality and most efficient care possible, the clinical practice of diagnostic imaging has evolved. Radiologists spend less time in the reading room and more time interacting with patients and collaborating with clinical colleagues. Supervising and accurately interpreting imaging studies while being available for consultations primarily by phone but unseen and disconnected from patients is no longer adequate.

A hallmark of a patient-centered, integrated clinical care model is multidisciplinary care. Radiologists can add significant value and help provide the most efficient care possible when they participate in multidisciplinary discussions about treatment plans and actively engage with patients and clinicians. Tumor boards held weekly can help facilitate collaboration and clinical decision-making among medical and radiation oncologists, surgeons, radiologists, and pathologists. True, multidisciplinary clinics should give patients the opportunity to be evaluated by medical, surgical, and radiation oncologists in a comprehensive, single appointment setting. Doing so helps keep patients actively engaged in their care while also minimizing the time between diagnosis and treatment. Thus, radiologists should be active participants on multidisciplinary teams and fully embrace and support patient-centered care. We must keep our focus centered on our patients while providing the best personalized cancer care in a multidisciplinary setting.

The articles in this issue of Cancer Control highlight exciting advances in diagnostic imaging and address controversies and challenges in breast, musculoskeletal, head and neck, and brain tumor imaging. The first 2 articles are dedicated to breast imaging and describe important contributions specialists in breast imaging are making to patient-centered care. The next 3 articles discuss advances in skeletal scintigraphy, cardiac magnetic resonance imaging (MRI), and imaging of musculoskeletal tumors. The last 2 articles review the role of diagnostic imaging in the management of head and neck squamous cell carcinomas and high-grade glial tumors.

Dr Collado-Mesa and colleagues at the Sylvester Comprehensive Cancer Center of the University of Miami in Florida quantify value-added activities provided by their breast imaging radiologists, who spend, on average, more than 90 minutes every day on value-added, patient care activities as they continue to evolve toward a more patient-centered practice. The article describes the important value-added activities provided by their radiologists as members of a multidisciplinary breast care team, as well as the challenges faced by specialists in breast imaging, who spend more of their work day in direct contact with patients and clinical colleagues.

Dr Falcon and coauthors discuss the challenges and controversies of the imaging management of breast density. Although breast density is a recognized independent risk factor for the development of breast cancer, the risk is controversial and no consensus exists on the need for supplemental screening in such patients.

Drs Montilla-Soler and Makanji present an overview of the use of skeletal scintigraphy in oncology and discuss how advances in the field directly impact disease management and patient care.
outcomes, including how the coupling of diagnostic and therapeutic nuclear medicine agents has become a valuable tool in treating osteoblastic skeletal metastases.

Dr Jeong and colleagues review the expanding role of cardiac MRI in oncology and the emerging field of cardio-oncology to help evaluate and preserve the cardiovascular health of patients with cancer. These authors review the advances and wide range of clinical applications of cardiac MRI, including the diagnosis and evaluation of cardiac masses. With an increasing emphasis on cardiac safety during cancer therapy, cardiac MRI also plays an important role in the evaluation of cardiac dysfunction in patients with cancer.

Dr Raghavan provides a review of musculoskeletal tumor imaging, describing the strengths, weaknesses, and appropriate utilization of different imaging modalities. Advanced imaging and novel techniques, including habitat imaging and chemical shift and diffusion-weighted MRI, are discussed. Each imaging modality provides unique diagnostic information, and the imaging technique and modality selected must be tailored and personalized for each patient.

Dr Gage and coauthors provide an overview of imaging modalities in patients with head and neck squamous cell carcinomas. Use of imaging for the staging, treatment planning, and surveillance of head and neck squamous cell carcinomas as well as the strengths and weaknesses of MRI, computed tomography (CT), and combined positron emission tomography (PET)/CT are discussed. Because of the technological advances in PET/CT, the modality is playing an increasingly important role in the diagnosis and management of head and neck cancers.

Dr Sahebjam and colleagues highlight the role of diagnostic imaging in assessing the response of high-grade gliomas to immunotherapy and checkpoint inhibitors. With the unique challenges encountered in distinguishing an immune-mediated inflammatory response from tumor progression in these patients, the authors stress the critical role of diagnostic imaging in response assessment of glioblastomas to immunotherapy. The article highlights the need for radiologists to actively participate on a multidisciplinary neuro-oncology team to prevent the premature discontinuation of potentially beneficial immunotherapy in patients with glioblastoma but doing so without compromising safety in clinical trials.

Innovations and technological advances in diagnostic imaging and its equipment will certainly continue. We must not allow the transformation and evolution of the role of diagnostic imaging and the radiologist in patient-centered cancer care to stagnate. We must continue to innovate and enhance the role of diagnostic imaging in the multidisciplinary approach to personalized cancer care. We hope you enjoy this issue of Cancer Control.

“There’s a way to do it better — find it.”
— Thomas Edison

John A. Arrington, MD
Senior Member and Co-Vice Chair, Diagnostic Imaging and Interventional Radiology
H. Lee Moffitt Cancer Center & Research Institute
Tampa, Florida
John.Arrington@Moffitt.org

Donald L. Klippenstein, MD
Senior Member and Co-Vice Chair, Diagnostic Imaging and Interventional Radiology
H. Lee Moffitt Cancer Center & Research Institute
Tampa, Florida
Donald.Klippenstein@Moffitt.org

Robert A. Gatenby, MD, PhD
Senior Member and Department Chair, Diagnostic Imaging and Interventional Radiology
Chief, Diagnostic Imaging Services
Co-Director, Cancer Imaging and Technology Center of Excellence
Program Leader, Cancer Biology & Evolution
H. Lee Moffitt Cancer Center & Research Institute
Tampa, Florida
Robert.Gatenby@Moffitt.org
The Department of Diagnostic Imaging and Interventional Radiology at the H. Lee Moffitt Cancer Center & Research Institute provides comprehensive screening, diagnostic, interventional imaging, and surveillance services for all clinical programs. The department's mission is to contribute to the prevention and cure of cancer through clinical imaging services, education, and research. The department is composed of a team of radiologists, nurses, technologists, and ancillary staff members who specialize in all subspecialties of cancer imaging, including neuroimaging, thoracic body imaging, musculoskeletal imaging, nuclear imaging, breast imaging, and vascular imaging. All of our radiologists are board certified and have undergone fellowship training.

Interventional radiology is a medical subspecialty of radiology that utilizes minimally invasive, image-guided procedures to diagnose and treat diseases in nearly every organ system. The concept behind interventional radiology is to diagnose and treat patients using the least-invasive techniques available to minimize risk and improve health outcomes. Compared with open surgery, these procedures have decreased risk, less pain, and less recovery time.

The Department of Diagnostic Imaging and Interventional Radiology offers the most advanced imaging equipment and provides state-of-the-art services that include conventional radiography, mammography, fluoroscopy, ultrasonography, computed tomography, magnetic resonance imaging, nuclear medicine imaging (radioisotope studies), positron emission tomography, single photon emission computed tomography, image-guided therapies and biopsies, and both vascular and nonvascular interventional services.

### DEPARTMENT CHAIR
Robert Gatenby, MD

### VICE CHAIR (BUSINESS)
John Arrington, MD

### VICE CHAIR (ADMINISTRATION)
Donald Klippenstein, MD

### NEURO RADIOLOGY
John Arrington, MD  
Gregory Carney, MD  
Reed Murtagh, MD  
Dexter Stallworth, MD

### INTERVENTIONAL RADIOLOGY
Benjamin Biebel, MD  
Junsung Choi, MD  
Ghassan El-Haddad, MD  
Bela Kis, MD, PhD  
Nainesh Parikh, MD  
Jennifer Sweeney, MD

### BODY IMAGING
Jamie Caracciolo, MD  
David Carroll, MD (PRN)  
Jung Choi, MD, PhD  
Sebastian Feuerlein, MD  
Kenneth Gage, MD, PhD  
Robert Gatenby, MD  
Daniel Jeong, MD  
Donald Klippenstein, MD  
Cesar Lam, MD  
Rikesh Makanji, MD  
Melissa McGettigan, MD  
Brian Morse, MD  
Eric Outwater, MD (PRN)  
Trevor Rose, MD  
Kerry Thomas, MD  
Kim Wilson, MD

### NUCLEAR MEDICINE
Claudia Berman, MD  
Kenneth Gage, MD, PhD  
Jamie Montilla-Soler, MD

### BREAST IMAGING
Alec Chau, MD  
Shannon Falcon, MD  
Blaise Mooney, MD  
Bethany Niell, MD, PhD  
Jared Weinfurtner, MD  
Angela Williams, MD

### ADMINISTRATIVE/TECHNOLOGY SUPPORT
Division Administrator  
Terry Clark, MS  
Imaging Practice and Business Manager  
Kevin Fields, MBA  
Diagnostic Imaging Managers  
Anita Burch-Volpe  
Christy Smallwood  
Patient Care Manager, Interventional Radiology  
Grace Cabral, RN  
Management Assistants  
Data Analyst

### CLINICAL SUPPORT
Imaging Technologists  
Certified Physician Assistants  
Advanced Registered Nurse Practitioners  
Registered Nurses  
Licensed Practical Nurses  
Patient Service Specialists

### EDUCATION AND TRAINING
Imaging Technologists  
Radiology Residents  
Radiology Fellows

### RESEARCH/TRANSLATION
Clinical Researchers  
Research Assistants  
Research Associate  
Data Managers  
Applied Research Scientists  
Research Scientists (PhDs)  
Postdoc Fellows  
Grants Administrator
**Research**

Departmental staff members participate in ongoing clinical trials, retrospective and prospective studies, and translational research projects in an effort to improve patient outcomes.

Selected, active research related to diagnostic imaging and interventional radiology at Moffitt Cancer Center includes:

<table>
<thead>
<tr>
<th>MCC ID No.</th>
<th>Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>14841</td>
<td>Automated Quantitative Measures of Breast Density</td>
</tr>
<tr>
<td>15264</td>
<td>Commonly Asked Questions About DCIS</td>
</tr>
<tr>
<td>16069</td>
<td>Radiomics of Solid Tumors</td>
</tr>
<tr>
<td>17173</td>
<td>Chemotherapy Induced Neural Deficits Related to Cognitive Control Among Hematopoietic Cell Transplantation (HCT) Patients: A Pilot Study</td>
</tr>
<tr>
<td>17268</td>
<td>Investigation of Serial Studies to Predict Your Therapeutic Response With Imaging and Molecular Analysis 2 (I-SPY 2 TRIAL)</td>
</tr>
<tr>
<td>17423</td>
<td>Lesion Composition and Quantitative Imaging Analysis on Breast Cancer Diagnosis</td>
</tr>
<tr>
<td>17590</td>
<td>Breast Cancer Heterogeneity: Quantitative Analysis of MRI Features of Breast Cancer</td>
</tr>
<tr>
<td>17816</td>
<td>A Phase 1 Study of TPI 287 Concurrent With Fractionated Stereotactic Radiotherapy (FSRT) in Treatment of Brain Metastases From Advanced Breast and Non-Small Cell Lung (NSCL) Cancer</td>
</tr>
<tr>
<td>17837</td>
<td>Pilot Radiomics &amp; Radiogenomics of Cancer</td>
</tr>
<tr>
<td>17978</td>
<td>A Phase I Trial of Hypofractionated Stereotactic Irradiation (HFSRT) With MK-3475 and Bevacizumab in Patients With Recurrent High Grade Gliomas</td>
</tr>
<tr>
<td>18110</td>
<td>Pre-Referral MRI for Bone and Soft Tissue Masses (Benign and Malignant) in the Extremity: Are They Ever Adequate and What's the Cost? A Retrospective Review of Time and Money Wasted</td>
</tr>
<tr>
<td>18134</td>
<td>Breast Lesion Location Correlation on MRI and Mammography Using Geometric Localization</td>
</tr>
<tr>
<td>18300</td>
<td>Rendering Second Opinion Interpretations on Outside Breast Imaging: Impact on Additional Workup and Management</td>
</tr>
<tr>
<td>18613</td>
<td>Phase II Study of nab-Paclitaxel in Combination With Gemcitabine for Treatment of Recurrent/Refractory Sarcoma in Teenagers and Young Adults</td>
</tr>
<tr>
<td>18640</td>
<td>Correlation of Pathologic and Radiographic Tumor Size Dimensions and Impact of Discrepancies on Final Pathologic Staging in Breast Cancer Patients</td>
</tr>
<tr>
<td>18660</td>
<td>Phase II Trial of SMO/AKT/NF2 Inhibitors in Progressive Meningiomas With SMO/AKT/NF2 Mutations</td>
</tr>
<tr>
<td>18661</td>
<td>Phase I Trial of Hypofractionated Stereotactic Irradiation (HFSRT) Combined With Nivolumab in Patients With Recurrent High Grade Gliomas</td>
</tr>
<tr>
<td>18824</td>
<td>Breast Cancer Risk and Background Parenchymal Enhancement on Breast MRI</td>
</tr>
<tr>
<td>50056</td>
<td>Is HPV-Related Oropharyngeal Cancer a Communicable Disease?</td>
</tr>
<tr>
<td>50095</td>
<td>Evolutionary Score Predicts Chemotherapy Resistance of Breast Cancer</td>
</tr>
</tbody>
</table>

To schedule a patient appointment with a physician in the Department of Diagnostic Imaging and Interventional Radiology, call the New Patient Appointment Center at 813-745-3980 or 1-888-860-2778 (during normal business hours). For information about clinical trials, call 813-745-4106.

[www.MOFFITT.org](http://www.MOFFITT.org)
Finally, a Practical Approach to Value-Based Medicine

Value-based medical care has been the mantra of the Affordable Care Act.\(^1\) Value-based — as opposed to volume-based — reimbursement has gained universal consensus — at least in theory. Indeed, it is impossible to argue against holding treatment outcomes and rates of patient satisfaction as the ultimate determinants of compensation for a medical intervention.

Value is usually defined as quality/cost.\(^2,3\) In the last 20 years, health care providers and administrators have struggled to operationalize this definition in order to assess value in clinical practice. Such difficulties include evaluating quality and cost. A large component of quality is based on patient preferences at the time of personalized or patient-centered care.\(^4\) The estimate of value could be improved when a “value team” comprised of health care administrators and providers of different specialties (eg, physicians, nurses, physical therapists, nutritionists) assessed the benefits and costs of a specific intervention such as hip replacement. The team approach led to shorter hospital stays, decreased rates of readmissions and complications, better rates of patient satisfaction, and reduced cost.\(^5\)

Much progress has been achieved in the determination of value. A study by Lee et al\(^6\) demonstrated that value could be improved when a “value team” comprised of health care administrators and providers of different specialties (eg, physicians, nurses, physical therapists, nutritionists) assessed the benefits and costs of a specific intervention such as hip replacement. The team approach led to shorter hospital stays, decreased rates of readmissions and complications, better rates of patient satisfaction, and reduced cost.\(^6\)

In general, health care systems are adopting evidence-based clinical pathways for the management of specific conditions;\(^7\) however, more time is needed to establish whether this reasonable approach focused on the process of care will be translated into value-based care.

In this issue of Cancer Control, Collado-Mesa and colleagues describe a novel and important contribution to the assessment of value. At a large academic center, the Sylvester Cancer Center of Miami, Florida, 3 fellowship-trained breast radiologists calculated over 20 days the time they spent engaging in professional activities beyond the actual reading of a mammogram — their only reimbursable task. These activities included preparing for tumor boards (which is an essential function of a comprehensive cancer center), describing findings to patients — the majority of whom requested to see the actual imaging — and performing physical examinations of breasts when indicated. To execute these pertinent, unreimbursed tasks, they committed, on average, 92.1 minutes of their time every day. Because interpreting the findings on a mammogram requires an average of 3 minutes and is reimbursed as 0.7 working work-relative-value units, they concluded that they completed a combined average of uncompensated 52 work-relative-value units every day!

The implications of this study go well beyond the specialty of radiology and involve health care professionals across all specialties in the new health care environment that is properly “patient centered.” To spend time talking to patients, especially to a patient with a serious condition, is an ethical duty of the clinician, because this conversation allows the patient to exercise his or her autonomy — the first pillar of medical ethics.\(^8\) It is also good practice because clear, convincing information improves treatment adherence and patient satisfaction.\(^9\) Oftentimes, especially for patients who are older, the conversation is not limited to the office visit but includes other contact points by phone or e-mail. The provision of this essential service is hindered by the current medical economic reality. To maintain an adequate income, physicians may feel compelled to transform their clinics into “factory-assembly lines” and reserve 15 minutes or less to each patient. Responsible practitioners may decide to take an income cut and dedicate more time to each patient visit or, alternatively, to extend their working hours by taking patient and family calls after the clinic is closed. The Centers for Medicare & Medicaid Services now compensates physicians for the time they spend with the patient, but the compensation is lower than that for procedures that could have been performed during the same time period and is probably inadequate to support a practice without such procedures.

Although it was not mentioned by Collado-Mesa and coauthors, several new administrative mandates require additional, substantial investment in time. Of these, the completion of electronic health records occupies most of the professional time in any given patient visit. Implementing this electronic tool has increased the strain on physician time, further restricting the time available to interact with patients.\(^10\) Nagging and harassment by health care insurance companies, including prior authorization for common procedures and adherence to a very restrict drug formulary, represent common causes of strain and time diversion.

Collado-Mesa and others also describe the radiology value-added matrix proposed as a platform to as-
sess value in clinical practice. This matrix, which could be considered germane to other specialties, involves quality, service, utilization management, and professional development. It could very well complement and complete the assessment of value based on adherence to clinical pathways.

Perhaps the main limitation of the article by Collado-Mesa and colleagues is the unilateral assessment of value from the viewpoint of the health care professional. The perspective of the patient should be included to establish the value of some activities, such as interpretation and discussion of the findings on mammography. How much would the patient like to pay for these additional services? Also, how much is an institution willing to pay for these activities if they improve patient satisfaction and increase the demand for the services and the income of the institution?

Collado-Mesa and coauthors highlight and document an aspect of value-based care that has been largely ignored, ie, the time invested by physicians in activities pertinent to their practices but unrelated to the direct delivery of care. These activities are essential for quality and include interacting with patients and participating in multidisciplinary meetings. Although they are recognized as essential, these activities are hindered in the current practice environment, which limits our ability to spend time with patients. Collado-Mesa and colleagues explain that value-based care can only be obtained by accommodating these activities into the busy, daily schedule of the provider. To do so, the perspectives of the clinician, the patient, and the institution should be integrated.

Lodovico Balducci, MD
Editor, Cancer Control
Senior Member
Program Leader, Senior Adult Oncology Program
Moffitt Cancer Center
Tampa, FL

References
Value-added activities performed by breast imaging radiologists can help improve the patient experience across the continuity of care.

Time Spent by Breast Imaging Radiologists to Perform Value-Added Activities at an Academic Cancer Center

Fernando Collado-Mesa, MD, Geetika Klevos, MD, Kristopher Arheart, PhD, James Banks, MD, Monica Yepes, MD, and Jose Net, MD

Background: Health care reform in the United States has generated a paradigm shift in the practice of radiology aimed at increasing the degree of patient-centered care. We conducted a study to quantify the amount of time breast imaging radiologists spend on value-added activities at an academic comprehensive cancer center located in Miami, Florida, and accredited by the American College of Radiology as a Breast Imaging Center of Excellence.

Methods: A prospective, observational study was conducted during a period of 20 consecutive workdays. Three participating breast imaging radiologists maintained a real-time log of each activity performed. A generalized linear model was used to perform a 1-way analysis of variance. An α level of .05 was used to determine statistical significance.

Results: The average daily time dedicated to these activities was 92.1 minutes (range, 56.4–132.2). The amount of time significantly differed among breast imaging radiologists and correlated with their assigned daily role (P < .001 for both) but was independent of their years of experience. The daily role that required the most time was the interpretation of diagnostic imaging studies, which is when most interactions with patients, their relatives, and referring physicians occurred. The specific activity that required the most time was preparing for and participating in tumor boards.

Conclusions: Our findings suggest that the breast imaging radiologists who participated in this study dedicated a significant amount of their time to value-added activities to help improve patients’ experience across the continuity of their care. We propose that similar studies be conducted at other institutions to better assess the magnitude of this finding across different breast imaging care settings.

Introduction

Health care reform in the United States has generated a paradigm shift in the practice of radiology...
which value-added activities are categorized and synthesized. The categories in this matrix include quality, service, utilization management, and professional development. Because of the nature of their subspecialty, breast imaging radiologists have personal interactions with their patients and their patient’s loved ones, as well as with referring physicians and specialists within the breast health care team (eg, surgical oncologists, plastic surgeons, hematologic oncologists, radiation oncologists, pathologists). At the Sylvester Comprehensive Cancer Center of the University of Miami Miller School of Medicine (Miami, FL), which is accredited by the American College of Radiology as a Breast Imaging Center of Excellence, breast imaging services are provided by dedicated, fellowship-trained breast imaging radiologists in a clinic-type setting. Many of the patients who receive care at the Sylvester Comprehensive Cancer Center present with complicated clinical and surgical concerns. As members of a multidisciplinary breast care team, the breast imaging radiologists perform value-added patient care activities, many of which take place in direct contact with the patient. The goal of this study was to quantify the time that breast imaging radiologists at the Sylvester Comprehensive Cancer Center dedicate to these activities.

**Methods**

A prospective, observational study was conducted at the Sylvester Comprehensive Cancer Center. No patient data were accessed or recorded and the study received exception from our Institutional Review Board.

The study was performed during a period of 20 consecutive workdays during the months of November and December 2015. The study participants were 3 fellowship-trained, dedicated breast imaging radiologists, with 3.5, 5.5, and 6.5 years of experience in breast imaging. The work schedules of the breast imaging radiologists are based on staff availability and organized by shift and role, including interpreting findings on screening mammography and performing image-guided breast procedures; interpreting findings on diagnostic mammography, ultrasonography of the breast, and magnetic resonance imaging (MRI; both screening and diagnostic) of the breast; or a combination of both roles.

A list of value-added patient care activities performed by the breast imaging radiologists at the Sylvester Comprehensive Cancer Center was created by a consensus of all breast imaging radiologists (Table). For the purpose of this study, value-added activities included those that breast imaging radiologists perform; those that were critical to the success of the enterprise; and those that required the investment of time not reflected or only partially reflected in the traditional volume-based metrics such as the number of studies interpreted, the number of work-relative-value units generated, and reimbursements on the basis of billings. The list allowed for tracking activities that took place but which were not initially included.

During the data-gathering period, the participating breast imaging radiologists maintained a log in which they concurrently recorded the duration of each activity in real-time as they were performed. Time was rounded to the nearest minute. The day of the week and the specific role of the breast imaging radiologist on that day were also recorded. The day of the week was included because it was deemed to be indicative of the concurrent surgical clinics that would impact patient volume.

At the Sylvester Comprehensive Cancer Center, technologists perform ultrasonography. However, breast imaging radiologists will perform a targeted examination themselves when patients or referring physicians report a palpable abnormality; or if, upon review of other imaging studies (mammography, computed tomography, MRI), the breast imaging radiologist suspects an abnormality may be present but was not observed by the technologist.

For the purpose of this study, value-added activities not directly relating to patient care were excluded (ie, medical education, research, administrative activities).

**Statistical Analysis**

Data were collected on time spent on various activities by breast imaging radiologists, days of the week, and specific roles. The data followed a Poisson distribution; therefore, a generalized linear model was used to perform a 1-way analysis of variance, with time in minutes as the outcome and groups defined by activity, person, day of the week, and specific role. Multiple comparisons were made among categories for each group. An α level of .05 was used to determine statistical significance. SAS 9.3 (SAS Institute, Cary, NC) was used for all analyses.

**Results**

The average daily time that each breast imaging radiologist dedicated to value-added activities was 92.1 minutes (range, 56.4–132.2). The amount of time dedicated to these activities was significantly different between breast imaging radiologists (P < .001), but this difference was independent of their years of experience (Table).

The activity requiring the most time was preparation and participation in tumor boards followed by patient discussions of the results from same-day breast imaging studies and recommendations based on those findings. Breast imaging radiologists spent the least amount of time on performing focused physical examinations of the breast, axilla, or both (see Table).

The amount of time dedicated to these activities
significantly differed depending on the specific role of the breast imaging radiologist on that day \( (P < .001) \); being in the role of interpreting the diagnostic breast imaging studies had the most significant effect (see Table). No significant difference was observed between time spent on these activities and day of the week. However,

<table>
<thead>
<tr>
<th>Variable</th>
<th>Minutes, Mean (SE)</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perform focused physical examination of the breast, axilla, or both</td>
<td>5.5 (1.3)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Perform focused ultrasonography of the breast, axilla, or both</td>
<td>21.3 (2.3)</td>
<td></td>
</tr>
<tr>
<td>Issue clearance for procedure(s)</td>
<td>12.3 (1.9)</td>
<td></td>
</tr>
<tr>
<td>Discuss stopping medication(s) before procedure(s)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Help with scheduling additional studies/procedure(s)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discuss and obtain signed informed consent form with patient or legal guardian</td>
<td>14.7 (1.9)</td>
<td></td>
</tr>
<tr>
<td>Perform radiology-pathology correlation</td>
<td>12.7 (1.7)</td>
<td></td>
</tr>
<tr>
<td>Discuss results from biopsy and recommendations from radiology-pathology correlation</td>
<td>9.5 (1.5)</td>
<td></td>
</tr>
<tr>
<td>Workup/protocol for breast imaging and intervention (ie, additional clinical notation, pathology review)</td>
<td>18.1 (3.6)</td>
<td></td>
</tr>
<tr>
<td>Discuss results of breast imaging studies and recommendations</td>
<td>28.7 (3.3)</td>
<td></td>
</tr>
<tr>
<td>Help breast imaging technologists with questions regarding study, views, patients, and physician orders, among other questions</td>
<td>7.5 (1.0)</td>
<td></td>
</tr>
<tr>
<td>Help obtaining and uploading prior or outside breast imaging or reports</td>
<td>5.3 (1.6)</td>
<td></td>
</tr>
<tr>
<td>Review outside studies and issue outside consultation report</td>
<td>17.8 (2.4)</td>
<td></td>
</tr>
<tr>
<td>Review imaging, reports, and results, among others, with the surgeon, hematologic-oncologist, radiation oncologist, or other members of the health care team</td>
<td>9.2 (1.4)</td>
<td></td>
</tr>
<tr>
<td>Prepare and present case(s) and participate in tumor boards</td>
<td>35.0 (17.8)</td>
<td></td>
</tr>
<tr>
<td>Discuss family history and other risk factors for breast cancer to establish screening recommendations and possible need for genetic counseling or risk assessment</td>
<td>19.3 (7.1)</td>
<td></td>
</tr>
<tr>
<td>Consult in person or via phone with patient, her relatives, or both on the day prior to or on the day of or after breast imaging examination</td>
<td>11.2 (1.7)</td>
<td></td>
</tr>
<tr>
<td>Issue clearance for and provide oral sedation for MRI of the breast</td>
<td>10.8 (4.1)</td>
<td></td>
</tr>
<tr>
<td>Respond to and manage emergencies at the breast imaging center</td>
<td>10.0 (7.7)</td>
<td></td>
</tr>
<tr>
<td>Other(^a)</td>
<td>18.4 (4.3)</td>
<td></td>
</tr>
</tbody>
</table>

**Experience as a Breast Imaging Radiologist, y**

<table>
<thead>
<tr>
<th>Experience as a Breast Imaging Radiologist, y</th>
<th>Minutes, Mean (SE)</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participant A (6.5)</td>
<td>56.4 (7.7)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Participant B (5.5)</td>
<td>132.2 (17.8)</td>
<td></td>
</tr>
<tr>
<td>Participant C (3.5)</td>
<td>87.9 (11.9)</td>
<td></td>
</tr>
</tbody>
</table>

**Week Day**

<table>
<thead>
<tr>
<th>Week Day</th>
<th>Minutes, Mean (SE)</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monday</td>
<td>79.9 (14.2)</td>
<td>.381</td>
</tr>
<tr>
<td>Tuesday</td>
<td>105.0 (21.0)</td>
<td></td>
</tr>
<tr>
<td>Wednesday</td>
<td>67.4 (12.0)</td>
<td></td>
</tr>
<tr>
<td>Thursday</td>
<td>99.3 (17.6)</td>
<td></td>
</tr>
<tr>
<td>Friday</td>
<td>124.7 (33.8)</td>
<td></td>
</tr>
</tbody>
</table>

**Role of Breast Imaging Radiologist**

<table>
<thead>
<tr>
<th>Role of Breast Imaging Radiologist</th>
<th>Minutes, Mean (SE)</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interpret findings on diagnostic mammography</td>
<td>109.0 (10.9)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Interpret findings on ultrasonography and MRI of breast (screening and diagnostic)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interpret findings on screening mammography</td>
<td>43.4 (6.6)</td>
<td></td>
</tr>
<tr>
<td>Perform image-guided breast procedures</td>
<td>78.2 (12.9)</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\)Includes peer review, appropriateness criteria, attending daily conferences to discuss screening mammography results assigned as Breast Imaging Reporting and Data System category 0.

MRI = magnetic resonance imaging, SE = standard error.
Discussion

Radiology in the United States is undergoing a paradigm shift toward patient-centered practice aimed at dedicating more time in a radiologist’s work day toward direct and meaningful engagement in patient experience and improved communication (doctor–patient relationship and among the health care team). In the health care setting, value is defined as the sum of health outcomes and patient experience per capita. In a modern breast imaging practice, generating reports or performing biopsies alone is insufficient to meet this definition of value. Value-added services are duties beyond billable activities that improve outcomes, increase patient satisfaction rates, or reduce costs. On average across all radiology specialties, these activities occupy 15% of a radiologist’s work day and may be freely provided under the relative value, unit-based repayment model.

A study by Koney et al showed that 81% of surveyed patients have an interest in reviewing imaging results with an expert, and 88% anticipate that reviewing imaging results with an expert would be beneficial. An example of transformations taking place in the practice of radiology comes from Massachusetts General Hospital (Boston, MA), where a radiology consultation clinic allows patients to meet with radiologists to review imaging and ask questions.

The results from the present study demonstrate that breast imaging radiologists at the Sylvester Comprehensive Cancer Center dedicate a significant amount of time to patient care activities. Although doing so is in line with recommended best practices, these activities had no associated productivity measurement. In spite of this, the rate of productivity of the participating breast imaging radiologists in this study, measured in work-relative-value units generated through interpretative activities and image-guided procedures, was above the 75th percentile of their benchmark during the study period.

Working in an academic setting, the breast imaging radiologists at the Sylvester Comprehensive Cancer Center dedicate time to prepare for and participate in tumor boards. Even though this contribution has been shown to significantly impact patient care, no productivity unit is awarded for this activity. In patient requests, breast imaging radiologists are asked to communicate with patients’ loved ones or caregivers, who on occasions, might not be physically present, thus requiring conversations to occur after the patient has left the facility.

Breast imaging radiologists also care for patients before, during, and after image-guided breast procedures. This care can include obtaining clearance for holding anticoagulation, obtaining a history of allergies to local anesthetic, and managing local anesthetic options. Once the results of image-guided breast biopsies are available from the pathology department, breast imaging radiologists dedicate time to correlate imaging features with the histology findings — a function that radiologists who perform image-guided biopsies of other organs are not ordinarily expected to do. Breast imaging radiologists personally communicate the results of biopsies and discuss with patients management recommendations, which must be done in a prompt and effective manner. They also dedicate time to explain the specific clinical and surgical management — as necessary — for both benign and malignant breast disease. They may also refer patients to oncology, plastic surgery, hematology-oncology, and radiation oncology services.

The busiest days at the surgical oncology clinic likely explain the observed trend that the participating breast imaging radiologists dedicate more time to value-added activities on Tuesdays and Fridays (see Table). For patient convenience, as well as more efficient care, patients are scheduled on those days for imaging studies immediately prior to their outpatient visits with the surgical oncologists. In keeping with the practices of Imaging 3.0, these reports are finalized and available before the referring physician needs the information for patient care decisions. In addition,
on surgical oncology clinic days, greater numbers of breast imaging studies and image-guided breast procedures are added to the schedule.

The amount of time dedicated to managing emergencies also reflects the fact that breast imaging radiologists at the Sylvester Comprehensive Cancer Center respond to all cases of reactions and extravasation from intravenous contrast. They also respond to any interrupted MRI of the breast due to patient-related concerns or issues. Within the center, breast imaging radiologists are also involved in the management of episodes, such as vasovagal reactions and image-guided biopsy–related bleeding, and manage them until they resolve.

Although the time invested to perform an activity is but a single factor involved in measuring a physician’s level of productivity in volume-based outcomes (namely in work-relative-value units), if the time dedicated to these value-added activities was instead fully dedicated to activities accruing work-relative-value units, such as interpreting digital screening mammography, then a significant number of work-relative-value units could have been generated. For example, 0.7 work-relative-value units is assigned to interpret the findings from digital screening mammography, and reported times to perform such an interpretation range from 1.1 to 3.0 minutes; thus, based on this information, the average of 92.1 minutes/day dedicated to noninterpretable activities in our study would have resulted in an additional 21.5 to 58.6 work-relative-value units per breast imaging radiologist every day.

Limitations

The results of the present study cannot be generalized to all breast imaging practices, because patient populations and the organization of daily work activities involving patient interactions likely differ from that of the Sylvester Comprehensive Cancer Center. Although recall bias is not likely to have occurred because the data were recorded in real-time, our results may have been affected by self-report bias. Not all activities considered by some to be value-added — such as teaching, research, and administrative tasks — were included in the study, so this may have resulted in an underestimation of the true time commitment to all value-added activities. Value metrics such as the impact of value-added services on treatment strategy, change in diagnosis, customer satisfaction, cost containment, and complication rates were also not examined.

Conclusions

The daily work of breast imaging radiologists involves a combination of clinical care, including the treatment and counseling of patients; interactions with breast imaging technologists, referring physicians, and other specialists of the breast health care team; interpreting the findings from breast imaging studies; and performing image-guided breast procedures. The amount of time that breast imaging radiologists at the Sylvester Comprehensive Cancer Center dedicate to value-added activities is in line with the paradigm shift underway in the practice of radiology in the United States, whereby radiologists are moving toward a more patient-centered approach. It is important to note that time dedicated to the value-added activities in this study is for the most part, not reflected by the usual measurement of volume-based productivity. We propose for similar studies to be conducted at other institutions to better assess the magnitude of this finding across different breast imaging care settings.

References

Women are becoming more aware of breast density, its implications on their risk for developing breast cancer, and its influence on detecting cancer.

Imaging Management of Breast Density, a Controversial Risk Factor for Breast Cancer

Shannon Falcon, MD, Angela Williams, MD, R. Jared Weinfurtner, MD, and Jennifer S. Drukeininis, MD

**Background:** Breast density is well recognized as an independent risk factor for the development of breast cancer. However, the magnitude of risk is controversial. As the public becomes increasingly aware of breast density as a risk factor, legislation and notification laws in relation to breast density have become common throughout the United States. Awareness of breast density as a risk factor for breast cancer presents new challenges for the clinician in the approach to the management and screening of women with dense breasts.

**Methods:** The evidence and controversy surrounding breast density as a risk factor for the development of breast cancer are discussed. Common supplemental screening modalities for breast cancer are also discussed, including tomosynthesis, ultrasonography, and magnetic resonance imaging. A management strategy for screening women with dense breasts is also presented.

**Results:** The American College of Radiology recognizes breast density as a controversial risk factor for breast cancer, whereas the American Congress of Obstetricians and Gynecologists recognizes breast density as a modest risk factor. Neither organization recommends the routine use of supplemental screening in women with dense breasts without considering additional patient-related risk factors.

**Conclusions:** Breast density is a poorly understood and controversial risk factor for the development of breast cancer. Mammography is a screening modality proven to reduce breast cancer–related mortality rates and is the single most appropriate tool for population-based screening. Use of supplemental screening modalities should be tailored to individual risk assessment.

**Introduction**

Breast density is an independent risk factor for the development of breast cancer, although the magnitude of this risk is controversial. Breast density is a visual assessment of the ratio of parenchyma to fat as seen on mammography. Fibroglandular tissue is radiodense or white on mammography, whereas fat is radiolucent or black. Four categories of breast density have been defined by the criteria of the American College of Radiology’s (ACR) Breast Imaging Reporting and Data System, 5th ed. (BI-RADS; Fig 1):

- Almost entirely fatty
- Scattered fibroglandular densities
- Heterogeneously dense
- Extremely dense

The sensitivity of mammography for noncalcified lesions decreases as breast density increases due to a “masking” of the lesion by overlying normal tissue. Approximately 50% of women have breast tissue clas-
sified as either heterogeneously dense or extremely dense, thus reducing the sensitivity rate of mammography. However, almost entirely fatty breasts may have coalescent areas of dense tissue that can obscure lesions. Therefore, the BI-RADS criteria allow for the overall assessment of breast density to convey the likelihood of having an obscured lesion or “masking” effect. Dense tissue is most often seen in the breasts of younger premenopausal women, but it has also been observed in older postmenopausal women.

Reduced sensitivity rates of mammography due to masking alone do not explain the increased risk of breast cancer associated with increased breast density. First described in 1976, Wolfe identified breast density as a risk factor for breast cancer, qualitatively evaluating the mammographic appearance of the breast. A direct relationship was reported between progressively dense breast tissue and increasing risk of breast cancer. McCormack et al performed a meta-analysis of 42 studies and found that increased breast density was a strong risk factor for breast cancer independent of other known risk factors but was confounded by age and body mass index. The risk of breast malignancy associated with dense breasts has been reported to be 4- to 6-fold, making it second only to age and BRCA carrier status for highest risk. However, critics argue that this assessment of risk is an overestimation. The studies compared extremes (ie, dense breasts to fatty breasts) rather than comparing dense breasts to average-density breasts (between scattered fibroglandular and heterogeneously dense tissue). When the risk for breast cancer is expressed relative to average breast density, the risk decreases to 1.2 to 2.1 times higher than the average for heterogeneously dense or extremely dense breasts, respectively. Thus, breast density may more accurately represent a modest risk factor similar to that for a woman with 1 first-degree relative with unilateral postmenopausal breast cancer.

Awareness is increasing among public and medical communities alike regarding breast density as a risk factor for breast cancer as well as the limitations of mammography in women with dense breasts. Thus, in 2009, Connecticut became the first state to mandate patient and referring physician notification of dense breasts, as determined by the interpreting radiologist. Since then, 26 states have enacted similar notification laws, and legislation has been introduced in several other states. Controversy surrounds these notification laws, particularly with regard to how notification relates to additional imaging and reimbursement.

Price et al identified the efficacy, benefits, and
harms of supplemental screening tests as key issues. Although notification increases patient awareness, it also increases patient anxiety.9,10 Conversely, notification may give a false sense of security to women with fatty breasts who receive a negative finding on mammography.10 Critics also raise concerns that notification will increase demand for additional screening beyond mammography, which could result in additional false-positive findings and increased health care costs.10 Five states have mandatory insurance coverage for supplemental screening, suggesting that disparities could develop between women who can afford additional screening and those who cannot.8,10,11 In a study performed in New Jersey after the implementation of legislation directed at notifying women of their breast density — which also mandated health insurance coverage — an increase was seen in patients utilizing screening ultrasonography, thus resulting in an expansion of the ultrasonography department at the New Jersey institution as well as increasing the direct cost for health care insurers of approximately $4.9 million to $9.8 million for a given month.7

Thus, as notification laws gain momentum, clinicians may be faced with new challenges in their approach to breast cancer screening in women with dense breasts. In this review, we address the available types of supplemental screening studies, the risks and benefits of each modality, and suggest an imaging approach to managing the imaging of dense breasts.

Screening Mammography and Tomosynthesis

Mammography has long been the mainstay of detecting breast cancer and is the only screening test proven to reduce breast cancer–related mortality.12 Early detection by mammography has reduced breast cancer–related mortality by up to 30% — a rate based on several large, randomized controlled trials with 10 to 20 years of follow-up time.12,13 The overall sensitivity rate of digital mammography is between 81% and 87% for the detection of breast cancer in women aged 40 to 79 years; the detection rate of cancer via mammography is 4 to 5 per 1,000 people in the average population.14

However, mammography is an imperfect screening tool. Although it remains the gold standard for breast cancer screening, awareness is increasing that mammography has reduced sensitivity in certain subpopulations of women. In particular, among women with dense breasts, tissue superimposition can occur to a greater degree,14 and 50% of cancers will be visible in extremely dense breast tissue.15 Among women with heterogeneously dense or extremely dense breast parenchyma, full-field digital mammography (FFDM) has been shown to be more sensitive than film-screen mammography.16 The sensitivity rates of both digital and analog mammography remain low in women with dense breast parenchyma, thus limiting its usefulness in younger women at high risk.7,18

Digital breast tomosynthesis is an emerging technology utilized by many breast imaging centers, both domestically and internationally. Digital breast tomosynthesis was approved in February 2011 as an adjunct screening tool.19 It is an FFDM system capable of producing standard 2-dimensional (2D) and 3-dimensional (3D) tomosynthesis imaging. Digital breast tomosynthesis can help improve the detection and characterization of lesions by minimizing the influence of tissue overlap in women with nonfatty breasts. To acquire the image, the tube moves in an arc across the breast, and a series of low-dose scans are obtained from different angles. Typically, the imaging is then reconstructed into thin, 1-mm slices that can be scrolled through slice by slice — similar to that seen in computed tomography. Thin-slice imaging allows the clinician to better detect lesions, particularly masses, architectural distortions, and asymmetries (Fig 2).20 Increased lesion conspicuity is beneficial when imaging dense breast tissue because it can be difficult for the clinician to detect lesions in extremely dense breast tissue.

The addition of tomosynthesis to digital mammography has been shown to reduce recall rates and increase cancer-detection rates in the general population.21 Several studies have reported a 40% rate increase or more in invasive cancer detection when compared with digital mammography alone and a simultaneous 15% reduction in the rate of false-positive results.21-25 Two prospective European studies evaluated the efficacy of FFDM in combination with digital breast tomosynthesis for breast cancer screening.22,23 Skaane et al22 reported a 40% increase in the detection rate of invasive cancers with a simultaneous 15% rate reduction in false-positive results in 12,621 screening examinations when using FFDM in combination with digital breast tomosynthesis compared with FFDM alone. In an analysis of 7,292 screening examinations, Ciatto et al23 demonstrated an increased cancer-detection rate from 5.3 to 8.1 cancers per 1,000 women screened, with a simultaneous 17% reduction in recall rate. Two single-site observational studies performed by Rose et al24 and Haas et al25 also demonstrated statistically significant reductions in recall rates of 37% and 30%, respectively, although both groups demonstrated an increase in cancer detection, and neither reached statistical significance — possibly due to small sample sizes.

In a retrospective, multisite study evaluating the use of digital breast tomosynthesis in combination with FFDM among 173,663 patients, Friedewald et al21 demonstrated an increase in the rate of invasive cancer detection from 2.9 to 4.1 per 1,000 cases after add-
ing digital breast tomosynthesis to FFDM. This was a relative increase of 41%. Although an increase was also observed in the rate of biopsy among patients screened with FFDM in combination with digital breast tomosynthesis (19.3 vs 18.1 per 1,000 cases for the digital mammography cohort), a concomitant 21% relative increase was seen in positive predictive values for biopsy, thus reflecting the higher yield of malignancy in women undergoing biopsy from the group undergoing FFDM in combination with digital breast tomosynthesis. The association with fewer unnecessary tests and biopsies, with a simultaneous increase in cancer-detection rates, would support the potential benefits of tomosynthesis as a tool for screening. This would, in theory, be particularly useful as an adjunct to FFDM screening in women with dense breasts by eliminating confounding, overlapping breast tissue, thereby helping to better detect masses and decrease recall rates.

In a study by Lee et al., simulation models of breast cancer were utilized. Compared with biennial FFDM alone, the researchers showed that combined biennial FFDM and digital breast tomosynthesis for US women aged 50 to 74 years with dense breasts would avert 1 additional breast cancer–related death per 2,000 women screened as well as 405 false-positive findings on screening examinations per 1,000 women. They concluded that adding tomosynthesis to biennial FFDM for women aged 50 to 74 years with dense breasts was likely to improve health outcomes at a reasonable cost.

Thus, the evidence supports the finding that digital breast tomosynthesis improves detection rates of breast cancer with both increased sensitivity and specificity. However, its potential drawbacks include increased interpretation time and higher doses of radiation. Thus, further studies are needed to demonstrate whether screening with digital breast tomosynthesis in combination with FFDM results in a greater decrease in breast cancer–related mortality rates compared with FFDM alone.

**Ultrasonography**

The reduced sensitivity rate of mammography in women with dense breasts prompted the search for a widely available, reproducible, and cost-effective adjunct screening tool. Ultrasonography offers an affordable option for the detection of small masses without additional ionizing radiation or intravenous contrast. Robust support for ultrasonography as a supplementary imaging modality for the screening of dense breasts.

![Fig 2A-D. — Screening of a woman aged 58 years. (A) Craniocaudal and (B) mediolateral mammographic views of the left breast show heterogeneously dense breasts without any obvious mammographic abnormality. Tomographic slices in the (C) craniocaudal and (D) mediolateral projections demonstrate a 9-mm spiculated mass in the left upper inner quadrant (arrows). Subsequent ultrasonography-guided core biopsy revealed grade 1 invasive ductal carcinoma.](image)
comes from data collected by Berg et al. They conducted a multicenter, randomized trial involving 2,809 women with dense breasts who were at increased risk for breast cancer. The authors compared the performance of 2-view mammography alone to 2-view mammography combined with hand-held survey ultrasonography performed by a radiologist. Mammography in combination with ultrasonography yielded 11.8 breast cancers per 1,000 women compared with 7.6 breast cancers per 1,000 women screened with mammography alone. In a sub-study of the data from Berg et al., annual screening examinations or incident rounds were analyzed from 2,659 eligible women. The data revealed an increase in the rate of cancer detection each year when supplemental ultrasonography was utilized. A total of 32 additional cancers were detected by ultrasonography alone, 30 of which were invasive cancers. The median size of the invasive tumors was 10 mm, and 96% of these had node-negative disease. Overall, the data for the second and third years revealed greater rates of sensitivity for cancer detection when supplemental screening ultrasonography was combined with mammography. Thus, data from these incremental studies suggest a possible benefit in continuing annual screening with supplemental ultrasonography in conjunction with mammography.

A retrospective study was performed by Hooley et al. in Connecticut after implementation of the Connecticut Public Act 09-41, which requires that increased breast density be directly communicated to the patient. Hand-held, whole-breast ultrasonography was performed by technologists in 935 women with dense breasts in both the diagnostic and screening populations. An additional 3.2 cancers were detected per 1,000 women screened in the first year of implementation. Similarly, Weigert et al. retrospectively evaluated the utility of ultrasonography for screening among women with dense breasts from 6 Connecticut practices by compiling 8,647 screening ultrasonography sessions during the first year of test availability following the legislation. The addition of hand-held ultrasonography performed by certified technologists resulted in an additional 3.25 cancers detected per 1,000 women with dense breast and normal findings on mammography. The data from these studies support that hand-held ultrasonography — whether performed by a radiologist or trained technologist — could increase the sensitivity rate for detecting breast cancer in women with dense breasts.

A multicenter study by Tagliafico et al. evaluated the cancer-detection rate of tomosynthesis and hand-held screening ultrasonography after a negative finding was obtained on 2D diagnostic mammography among 3,231 self-referred women with heterogeneously dense or extremely dense breasts. Adding tomosynthesis detected an additional 13 breast cancers (12 of which were also identified on ultrasonography, whereas 1 was seen on tomosynthesis alone). Hand-held screening ultrasonography performed by a dedicated breast imaging radiologist detected an additional 23 breast cancers. These cancers were detected with low false-positive recall and biopsy rates. The false-positive recall rates for tomosynthesis and ultrasonography were 1.7% and 2.0%, respectively; the false-positive biopsy rate was 0.7% for both groups. The lower false-positive rate could have contributed to operator experience (ultrasonography was performed by a dedicated breast imaging radiologist) as well as lack of recall for what was likely a benign finding in the clinical practice setting.

Hesitation still exists in implementing routine, supplemental ultrasonography screening despite the data from the aforementioned studies. Using hand-held 2D ultrasonography to detect small masses is labor intensive. Operator variability, shortages of trained personnel, and reductions in radiologist efficiency for image acquisition all contribute to the widespread discouragement for whole-breast surveys. To combat some of these challenges, 3D automated whole-breast ultrasonography has been introduced as an alternative modality. Three-dimensional automated breast ultrasonography received premarket approval by the US Food and Drug Administration (FDA) in September 2012. It is approved for use in combination with mammography for breast cancer screening in women who are asymptomatic who have normal or benign findings on mammography, have had no prior clinical breast intervention, and have dense breast parenchyma (Fig 3). Its automated algorithms give the clinician the ability to obtain reproducible imaging data from volumes of the breast within a short time interval.

Brem et al. conducted a multicenter, prospective study of 15,318 participants with dense breasts, comparing the results of screening mammography combined with automated breast ultrasonography with screening mammography alone. Adding automated breast ultrasonography yielded an additional 1.9 cancers detected per 1,000 women screened. In a study that included data from 6,425 sessions of automated whole-breast ultrasonography and mammography performed in asymptomatic women, Kelly et al. concluded that automated whole-breast ultrasonography improved callback rates, confidence in callbacks among women with dense breasts, and improved the accuracy rate for detecting breast cancer. In women with dense breasts, automated whole-breast ultrasonography alone detected 65% of the cancers compared with 39% of cancers using mammography alone — an overall 2-fold increase in the rate of cancer detection. Multiple studies substantiate that supplemental breast ultrasonography — whether 2D hand-held or 3D automated whole-breast ultrasonography — can
improve rates of cancer detection. However, the limitations of ultrasonography must be considered. Low positive predictive values are generalizable to nearly all of the studies. Results from the trial conducted by Berg et al showed a reasonable recall rate for ultrasonography of 5.4%, but the positive predictive value for recall was 6.5% and the positive predictive value for engendered biopsies was 8.9%. Hooley et al and Weigert et al also reported low positive predictive values of 6.5% and 6.7%, respectively. Brem et al showed a decreased positive predictive value with ultrasonography (performed with automated whole-breast ultrasonography) as compared with mammography alone, which had a specificity rate of 13.4%. As comparison studies become available over years of sequential screening, it has been suggested that the number of biopsies prompted by false-positive findings on ultrasonography may improve.

Ultrasonography is a workhorse for diagnostic breast imaging, but its role in screening remains unclear. Studies utilizing screening ultrasonography demonstrate its capability for detecting invasive malignancies in dense breasts at small sizes and localized stages that could potentiate an increase in breast cancer survival rate; however, more studies are needed to determine the impact on mortality. The best indications for screening ultrasonography in dense breasts may be for women with intermediate risk or in those women at high risk but with a contraindication to magnetic resonance imaging (MRI).

**Magnetic Resonance Imaging**

MRI is a cross-sectional imaging modality that provides soft-tissue contrast between fat, fibroglandular tissue, and lesions. MRI of the breast was approved by the FDA as an adjunct to mammography for the detection of breast cancer in 1991. Since that time, MRI of the breast has been further refined and is now considered the most sensitive imaging tool available for the diagnosis of invasive breast cancer. Limitations of MRI of the breast must be weighed against the potential benefits when selecting candidates for screening MRI. As such, the role of screening MRI in patients with dense breasts has not been well defined.

Fibroglandular tissue does not mask lesions on MRI, unlike mammography. Administration of intravascular contrast (gadolinium) helps distinguish suspicious lesions from normal breast tissue due to preferential contrast uptake by malignant tumors (Fig 4). However, normal fibroglandular tissue is enhanced to varying degrees, which is an imaging characteristic termed *background parenchymal enhancement*. Similar to breast density, 4 categories of background parenchymal enhancement are included in the BI-RADS criteria (Fig 5):

- Minimal
- Mild
- Moderate
- Marked

Hypothetically, background parenchymal enhancement may obscure malignancies or yield false-positive results, but studies have shown that background pa-
parenchymal enhancement does not appear to negatively impact the diagnostic accuracy of MRI. Furthermore, no clear link exists between background parenchymal enhancement and breast density. For example, a woman with extremely dense breasts may have minimal background parenchymal enhancement, whereas a woman with scattered fibroglandular tissue may have marked background parenchymal enhancement.

Use of screening breast MRI in patients with dense breasts may sound appealing, but data on its efficacy are limited. In 2007, the American Cancer Society released recommendations for screening MRI of the breast as an adjunct to mammography based on evidence and expert opinion. According to its guidelines for screening MRI, heterogeneously or extremely dense breasts on mammography are considered equivocal, with insufficient evidence to recommend for or against MRI screening (Table). Dutch researchers Emaus et al launched a trial to study dense tissue and early screening for breast neoplasms, which is currently ongoing (NCT01315015), to evaluate the cost and effectiveness of MRI screening in patients with dense breasts and negative findings on mammography. At this time, implementation of MRI screening in patients with dense breasts and no known additional risk factors is not supported by sufficient data.

The evidence supporting MRI screening of the breast continues to evolve. Many studies have shown benefit in high-risk populations (> 20% lifetime risk). In 2008, Warner et al performed a meta-analysis of 11 prospective studies that compared the sensitivity rates of annual screening mammography performed in conjunction with MRI and annual screening mammography alone. Their meta-analysis found an increase in sensitivity rate of 94% when mammography was combined with MRI as compared with a rate of 32% for mammography alone. These findings are similar to other studies, including a multicenter trial by Sardanelli et al, in which MRI was determined to be more sensitive (91%) than clinical breast examination (18%), mammography (50%), ultrasonography (52%), or mammography plus ultrasonography (63%). In addition, 31% of cancers were detected by MRI alone. In 2015, Riedl et al screened a high-risk patient population with mammography, sonography, and MRI, and they found that a higher percentage of cancer was detected by MRI alone (45%) vs mammography alone (5%) and ultrasonography alone (0%). The authors also found an added cancer detection rate of 1.3% with MRI alone, which translates to 13 additional cancers detected per 1,000 screening MRI examinations performed. A 2015 report by Raikhlin et al documented detecting an additional 10 cancers per 1,000 patients screened with MRI and mammography together vs mammography alone.

In addition to studies of high-risk populations, the data from other studies support use of screening MRI of the breast in populations for which ACS guidelines in 2007 suggested insufficient data were presented, including patients with high-risk lesions and those with...
a personal history of breast cancer.48,49 For example, in a retrospective study of 1,699 patients with a personal history of breast cancer and no other risk factors, Brennan et al50 observed a cancer-detection rate of 12%, of which 59% were detected by MRI alone. MRI screening in this study yielded a positive predictive value of 39%, and the authors concluded that a definite benefit to its use exists in this population.50

Benefits of MRI screening should be weighed against risks and limitations such as cost. Saadatmand et al51 performed a large, prospective study evaluating use of MRI screening in patients with familial risk factors and an estimated lifetime risk of breast cancer that was higher than 15%. The benefit of including annual screening MRI resulted in an estimated mortality rate reduction of 25% vs 17% in those who did not undergo MRI; however, Saadatmand et al51 found that adding MRI to the annual screening regimen was 2.5 times more expensive per life-year gained.

By addressing the costs and time limitations of acquisition, active research in abbreviated protocol screening MRI of the breast shows promising results. In 2014, Kuhl et al52 conducted a prospective, observational reader study on an abbreviated protocol screening MRI of the breast based on a maximum intensity projection analysis of early, postcontrast, T1-weighted imaging. Compared with the full protocol, which had an acquisition time of 17 minutes, the abbreviated protocol took 3 minutes to perform and, on average, 28 seconds to interpret; in addition, the abbreviated protocol had equivalent diagnostic accuracy.52 Since then, additional studies have lent further evidence supporting the abbreviated screening protocols, suggesting that they may replace full protocols in the future without sacrificing diagnostic accuracy.53-55

Another important limitation of MRI is its rate of specificity. The increased sensitivity rate associated with MRI comes at a cost in terms of reduced specificity, thus resulting in increased callback rates and
benign findings on biopsies. When MRI was added to mammography, Warner et al.\(^56\) and Sardanelli et al.\(^44\) found that the specificity rates decreased from 99% to 95% and 96%, respectively. Raikhlin et al.\(^47\) reported a specificity rate of 86% for MRI of the breast with associated callback rates nearly 10 times higher and biopsy rates nearly 5 times higher than with mammography alone. Schwartz et al.\(^48\) concluded that the positive predictive value of 20% and the increased callback rate of 24% may not justify MRI screening in the population they studied for the added cancer detection rate of 2%. 

Contraindications to MRI of the breast are generally related to gadolinium contrast, including those with gadolinium allergy, compromised renal function, and those who are pregnant. Other contraindications include the presence of a pacemaker/defibrillator, presence of some types of metallic foreign bodies, and claustrophobia.

Screening MRI of the breast is the most sensitive imaging modality for detecting breast cancer, but the limitations of MRI prevent its use as a population-based screening tool. The results from studies show that the benefits of MRI typically outweigh the limitations among patients with an estimated lifetime risk of breast cancer of higher than 20%.\(^28,40-47\) As new data become available, additional indications may emerge. In the meantime, no clear indication exists for performing screening MRI in patients with dense breasts, and the recommended use of screening MRI in this population should be the same as that for the general population based on personal risk.

### Molecular-Based Imaging

Molecular-based imaging technology uses a physiological approach to identify lesions in the breast and can detect mammographically occult cancers.\(^57,58\) Gamma detectors are used to image the breast after injection of a radiotracer, technetium sestamibi, which has preferential uptake in highly proliferating tumor cells, thereby identifying functional differences in tumors from normal breast tissue.\(^58-60\) Breast-specific \(\gamma\) imaging uses a dedicated, single-head, scintillating sodium iodide detector. Molecular breast imaging is the latest generation of systems and uses cadmium zinc telluride detectors in a dual-head configuration. Although the technologies differ between these 2 systems, the terms are often interchangeably used.\(^58,59\) Compared with breast-specific \(\gamma\) imaging, molecular breast imaging has improved rates of count sensitivity, energy resolution, spatial resolution, and lesion detection. In addition, molecular breast imaging requires fewer amounts of injected radiotracer.\(^59\) Positron emission mammography is another nuclear medicine system in practice; however, radiotracer uptake increases with breast density, resulting in background parenchymal activity that could obscure underlying malignancies.\(^61\)

Rechtman et al.\(^57\) investigated the sensitivity of breast-specific \(\gamma\) imaging for the detection of breast cancer in women with dense vs nondense breasts in 347 biopsy-proven breast cancers, and they determined that the sensitivity rate was similar in women with dense (94.7%) and nondense breasts (96.5%). In addition, mammographically occult breast cancers were equally detected in both groups. The authors concluded that breast-specific \(\gamma\) imaging detected breast cancer regardless of the pathological subtype, nuclear grade, or tumor size.\(^57\)

Shermis et al.\(^59\) retrospectively assessed the clinical performance of molecular breast imaging as a supplementary screening tool for dense breasts in 1,696 women not at high risk and detected 13 mammographically occult malignancies, 11 of which were invasive. The authors reported that the incremental cancer detection rate (7.7%) and positive predictive value for biopsy (19.4%) were higher than that seen with screening ultrasonography.\(^59\) They concluded that molecular breast imaging is an acceptable alternative for supplemental screening in women with dense

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recommend annual screening MRI</td>
<td>BRCA mutation</td>
</tr>
<tr>
<td></td>
<td>First-degree relative of BRCA carrier but untested</td>
</tr>
<tr>
<td></td>
<td>Lifetime risk ≥ 20%</td>
</tr>
<tr>
<td></td>
<td>Received radiation to the chest aged 10–30 y</td>
</tr>
<tr>
<td></td>
<td>Li-Fraumeni syndrome and first-degree relatives</td>
</tr>
<tr>
<td></td>
<td>Cowden and Bannayan-Riley-Ruvalcaba syndromes and first-degree relatives</td>
</tr>
<tr>
<td>Insufficient evidence to recommend for or against screening MRI</td>
<td>Lifetime risk 15%–20%</td>
</tr>
<tr>
<td></td>
<td>Lobular carcinoma in situ</td>
</tr>
<tr>
<td></td>
<td>Atypical lobular hyperplasia</td>
</tr>
<tr>
<td></td>
<td>Atypical ductal hyperplasia</td>
</tr>
<tr>
<td></td>
<td>Heterogeneously or extremely dense breast on mammography</td>
</tr>
<tr>
<td></td>
<td>Women with a personal history of breast cancer</td>
</tr>
<tr>
<td>Recommend against screening MRI</td>
<td>Women &lt; 15% lifetime risk</td>
</tr>
</tbody>
</table>

MRI = magnetic resonance imaging.

Data from reference 38.

---

*b* Cancer Control 133

April 2017, Vol. 24, No. 2
breasts. These findings are in line with earlier prospective studies: Data have shown that molecular breast imaging can detect mammographically occult cancers that are primarily invasive and range in size from 2 mm to 5.1 cm.

Although studies have shown that molecular-based imaging has a high rate of sensitivity for detecting cancer in dense breasts, as well as a high positive predictive value, its availability and use as a supplemental imaging tool has been limited secondary to concerns of radiation exposure.

The injected radiotracer delivers radiation throughout the body, including radiosensitive organs beyond the breast. The radiation dose for breast-specific γ imaging has been reported to be more than 5 times that of standard mammography and twice that of standard mammography plus tomosynthesis. The radiation dose of molecular-based imaging is 2 to 5 times greater than the dose of mammography, but research has shown promising results using lower doses of radiotracer, which may be more acceptable. However, future studies are needed to ensure adequate image quality at this dose.

The total dose of mammography and molecular-based imaging is low (< 10 mSv) compared with the dose associated with adverse-event risk (> 50 mSv), so the benefit may outweigh the risk for some women. The only commercially available, FDA-approved biopsy unit is a breast-specific γ imaging system. However, biopsy units guided by molecular breast imaging are in development. Advantages of molecular-based imaging over MRI include its lower cost and fewer contraindications.

**Automated Breast Density**

Reporting of breast density has implications on the assessment of patient care and risk of breast cancer. However, intraobserver and interobserver variability exist in the visual assessment of the BI-RADS density category selected by the clinician on mammography. In response to this challenge, several automated software programs have been developed that measure volumetric breast density. However, quartiles of breast density have been eliminated in the BI-RADS criteria, so the assessment is no longer quantitative and brings into question the utility of quantitative software in the BI-RADS reporting. In a retrospective study of 1,185 mammography examinations, Youk et al compared the visual assessment of breast density based on the BI-RADS criteria with that of 2 commercially available software programs. They found that more findings on mammography were classified as being nondense with one program and as dense with another program when compared with the findings from the visual assessment. By contrast, Ekpo et al evaluated one of the programs previously determined to be underestimating. In their study, they compared automated vs visual breast density assessment in 234 women undergoing digital breast tomosynthesis. The authors found a moderate to substantial agreement in breast density assessment between the BI-RADS criteria and the automated software. Active research is being conducted to incorporate both automated and visual density assessments into patient risk models, and volumetric breast density measurements may prove to be beneficial in developing algorithms for automated risk assessment.

**Conclusions**

Approximately 50% of women have breasts that are at least heterogeneously dense — a figure that amounts to...
27.6 million women aged 40 to 75 years in the United States.11 The American College of Radiology identifies breast density as a controversial risk factor for breast cancer with no consensus that it confers sufficient risk to warrant supplemental screening.10 In a position statement from the American Congress of Obstetricians and Gynecologists, dense breasts are identified as a modest risk factor for breast cancer.66 The organization does not recommend routine use of adjunctive studies to screening mammography in asymptomatic women with dense breasts who are without additional risk factors.66

Understanding breast cancer risk conferred by density in the setting of a patient’s history, as well as an appreciation of the imaging tools available, will help aid clinicians in developing the most appropriate screening plan for each of their patients. Mammography remains the most appropriate modality for population-based screening.2,66 One suggested approach for screening women with dense breasts is to use tomosynthesis for all levels of risk, supplemental whole-breast ultrasonography for women with average risk, and supplemental magnetic resonance imaging for women with intermediate and high risk (Fig 6).67 For women who are at high risk and also have a contraindication to magnetic resonance imaging, whole-breast ultrasonography or molecular breast imaging, if available, may be an appropriate alternative. Additional studies are warranted to evaluate optimal supplemental screening strategies, although we suspect that the strategy will likely require a personalized approach based on risk assessment.

References
The coupling of diagnostic and therapeutic radiopharmaceuticals is important for the treatment of osteoblastic skeletal metastases.

Irena Orlov. Tiny asteroids. Digital on canvas, 40" × 60".

**Skeletal Scintigraphy**

Jaime L. Montilla-Soler, MD, and Rikesh Makanji, MD

**Background:** Skeletal scintigraphy remains a valuable tool in the initial and subsequent evaluation of the skeletal system in patients with a diagnosis of primary or metastatic neoplasms.

**Methods:** We discuss radiopharmaceuticals, nuclear medicine imaging techniques, and current as well as future oncological applications in the adult population. Pertinent literature was reviewed to describe the advantages and limitations of available technologies for the evaluation of skeletal metastatic disease. Evaluation of primary and metastatic skeletal disease using nuclear medicine and positron emission tomography techniques is discussed.

**Results:** Skeletal scintigraphy provides valuable information in the initial evaluation for the presence of osteoblastic skeletal metastases. Incremental advances on available radiopharmaceuticals (fludeoxyglucose F 18, sodium fluoride F 18), coupled with advances in imaging techniques and imaging devices (single photon emission computed tomography/computed tomography, positron emission tomography/computed tomography, positron emission tomography/magnetic resonance imaging), have had a significant impact on sensitivity, specificity, and accuracy rates for the detection of skeletal metastases.

**Conclusions:** Skeletal scintigraphy has a significant role in the initial diagnosis, staging, restaging, and treatment monitoring of patients with cancer and primary skeletal or metastatic disease. The coupling of diagnostic and therapeutic nuclear medicine agents in the setting of osteoblastic skeletal metastases is a valuable tool for the treatment for certain cancer types, including prostate cancer, and may become more widely used to treat other histologies as more data on other tumor types (eg, breast cancer, osteosarcoma) become available.

**Introduction**

Techniques in nuclear medicine remain a mainstay of the initial evaluation and staging of cancer as well as during restaging and treatment monitoring. Advanced imaging techniques such as single photon emission computed tomography (SPECT) and SPECT with computed tomography (CT) offer improved rates of sensitivity, specificity, and accuracy. Use of radiopharmaceuticals for positron emission tomography (PET) integrated with CT or magnetic resonance imaging (MRI) further increase the rate of diagnostic accuracy in this rapidly evolving technology. Thus, the coupling of diagnostic and therapeutic radiopharmaceuticals is important for the treatment of osteoblastic skeletal metastases.

**Skeletal System**

The skeletal system is dynamic and subject to internal and external stresses to which it must adapt. It is con-
structured of inorganic calcium hydroxyapatite crystal, an organic collagen matrix, and blood vessels. Normally, a constant balance exists in bone deposition by osteoblasts and bone resorption by osteoclasts.

Radiopharmaceuticals
Pharmaceuticals incorporate chemical compounds into the skeletal inorganic matrix. Ideally, they must be affordable, easy to produce, and stable; they must be rapidly absorbed by the desired target tissue; be cleared by nontarget tissue; limited in the amount of radiation they deposit into the body; and they must have favorable imaging characteristics. Radiopharmaceuticals used for diagnostic imaging are either $\gamma$- or positron-emitting. During their production, the active carrier (biologically active drug) and the radioactive compound (radionuclide) chemically combine to form the radiopharmaceutical agent.

For several decades, radiopharmaceuticals compounded with the radioactive tracer technetium Tc 99m were the most commonly utilized in clinical practice. Such examples include methylene diphosphonate (MDP) and hydroxymethylene diphosphonate (HMDP). The nonradioactive agents are stored at a local radiopharmacy, whereas the radioactive agent (eg, technetium Tc 99m) is produced from a generator system. Technetium Tc 99m is produced as the intermediate decay step for molybdenum 99 (half-life of 66 hours), which is produced by the fission of uranium 235. Technetium Tc 99m (half-life of 6 hours) then decays to its stable counterpart (half-life of 212,000 years).

Quality-control measures help to ensure these agents are safely produced and handled, and that their intended behavior is preserved for diagnostic imaging. Colloid formation from excess alumina in the technetium Tc 99m generation process will manifest as increased uptake in the liver and reticuloendothelial system. Subsequent production errors may include incomplete labeling of the pharmaceutical agent, which can cause an altered distribution in the body. Unlabeled “free” technetium Tc 99m increases radiotracer localization in several organs (eg, stomach, salivary glands, thyroid gland, kidneys).

After the intravenous administration of technetium Tc 99m MDP or HMDP, the bone rapidly extracts the radiopharmaceutical agent. The distribution of the radiopharmaceutical agent may depend on regional blood flow, but it is generally dependent on osteogenic activity. Areas of active bone turnover, such as areas of formation or repair, have relative higher uptake levels than areas of mature, undisturbed bone. Although peak bone uptake (approximately 50% of dose administered) occurs at approximately 1 hour after injection, the peak target-to-background occurs 6 hours after injection — by which time the tracer is nearly one-half decayed. Typically, skeletal scintigrams with technetium Tc 99m MDP or HMDP are imaged 3 to 4 hours after the intravenous radiotracer is administered to balance the target-to-background ratio with the rate of radioactive decay, in conjunction with the radiation dose as low as reasonably achievable.

Technetium Tc 99m MDP or HMDP binds to skeletal bone by chemisorption in the hydroxyapatite mineral bone matrix. However, areas of amorphous calcium phosphate will also bind to technetium Tc 99m MDP or HMDP. For clinical purposes, the typical dose range of technetium Tc 99m MDP/HMDP is 20 to 30 mCi (740–1110 MBq), and the surface of the bone receives the highest dose (estimated at 0.23 rad/mCi [0.063 mGy/MBq]).

Primary or metastatic skeletal neoplasms may have increased binding of sodium fluoride F 18 upon their initial presentation. Sodium fluoride F 18 is a positron emitter with a half-life of 110 minutes. The US Food and Drug Administration approved this agent for intravenous use in 1972. Clinical interest was again stimulated in 1993. Use of PET/CT is now widespread, and sodium fluoride F 18 is manufactured and distributed across the country. The affinity of sodium fluoride F 18 for osteoblastic processes is nearly 100%. It also has a nearly 100% first-pass extraction fraction from the blood pool. It localizes via chemisorption, forming fluorapatite in areas of actively mineralizing bone. Diagnostic imaging can be obtained after 30 to 60 minutes of intravenous administration. Because it is a positron emitter, multiplanar tomography can be obtained with prior and current-generation positron-imaging devices. The Society of Nuclear Medicine and Molecular Imaging has published guidelines for its use.

Clinically, the typical dose range of sodium fluoride F 18 is 5 to 10 mCi (185–370 MBq), and the organ receiving the highest dose is the urinary bladder (estimated at 0.81 rad/mCi [0.22 mGy/MBq]). Because of its favorable characteristics, sodium fluoride F 18 can be administered at a lower dose than technetium Tc 99m, thereby maintaining safety despite a higher level of exposure to energy radiation. Providing the patient with adequate hydration before its administration and allowing the patient to frequently void are important for minimizing the radiation dose (Fig 1).

Imaging Protocols
Technetium Tc99m Compounds
Imaging protocols can be tailored to the clinical question being addressed. Dynamic imaging (blood flow phase, blood pool, soft-tissue phase) after the administration of radiopharmaceuticals can be performed. Tailoring may be useful in certain clinical scenarios, such as infection, trauma, the loosening of hardware, chronic regional pain syndrome, and in the assessment of...
bone-graft viability. The entire skeletal system should be imaged. Imaging can be obtained in a single, continuous pass from multiple projections, or as numerous “spot” images until the entire skeleton is imaged.

**Sodium Fluoride F 18**

Due to the high extraction fraction and shorter half-life of sodium fluoride F 18, lower absolute specific activity of this radiopharmaceutical can be administered relative to other bone-seeking compounds. In addition, imaging can be obtained sooner, usually 30 to 90 minutes after intravenous administration. In general, imaging of the entire skeleton is obtained per established protocols for each specific device (PET, PET/CT, PET/MRI) in a tomographic fashion for subsequent, multiplanar reconstruction.

**Imaging Devices**

**Gamma Camera**

The gamma camera system is available in several configurations; the basic design has been available for many years. Its configurations are based on the number of detector “heads” utilized, which include single-, dual-, and triple-head configurations. Planar imaging (2-dimensional) is the most commonly utilized. Continuous-acquisition, whole-body anterior and posterior imaging can be obtained by allowing the detector(s) head(s) to remain stationary while the patient lies still in a supine position on the camera bed, which moves at a slow rate. Alternatively, static (spot) imaging of specific body sections can be obtained by allowing the detector(s) and the patient to remain stationary for a set amount of time or a set amount of radiotracer-detected events (counts). Commonly, physicians may combine anterior and posterior whole-body imaging with complementary, static imaging from alternate projections to achieve maximal skeletal coverage. These scans are then displayed using uniform window/level settings or can be archived for later interpretation and review.

**Single Photon Emission Computed Tomography**

The gamma camera systems can generate multiplanar (3-dimensional) imaging by recording radiotracer emission events while rotating the detector heads around a patient. This technique is known as SPECT. The patient remains stationary, usually in a supine position, while the detector(s) head(s) rotate around him or her. The rotation can be set as a fixed or variable rotation and is defined by its radius. The detector(s) head(s) record radiotracer emission events of the patient from multiple projection steps that will be reconstructed at a later time in multiple planes. These steps can be defined by time, counts, or both time and counts. The amount of steps taken to generate a single image can also be adjusted. To image an area larger

![Fig 1A–B. — Imaging of the same patient. (A) Technetium Tc 99m hydroxymethylene diphosphonate whole-body planar scintigraphy. (B) Sodium fluoride F 18 positron emission tomography/computed tomography.](image-url)
than the coverage size of the detector head(s) (eg, the entire body), multiple, sequential series of tomography must be obtained, which can take longer when compared with the time it takes to obtain whole-body planar imaging. Typically, these examinations are performed at dedicated computer workstations with software that can reconstruct these data in multiple planes and are optimized for display and interpretation.

**Single Photon Emission Computed Tomography/Computed Tomography**

Camera systems combining SPECT capabilities with radiological CT have been available since the early 2000s. These gamma camera systems benefit from the added anatomical localization offered by imaging inline acquisition and registration. For the technology to work, the patient must lie still on the imaging table while the detector head(s) record the radiotracer-emission events. CT is obtained while the patient continues to remain still in the same position; the data are subsequently registered. The order in which SPECT or CT is acquired can be tailored to the specific scenario evaluated. Low-dose CT can be performed for attenuation correction and image registration purpose, or it can be performed with diagnostic-quality CT parameters, similar to stand-alone CT scanners, for diagnostic purposes.

Similar to SPECT, the imaging data are usually exported to dedicated workstations with software capable of multiplanar reconstruction and display. These workstations can combine data from both SPECT and CT to generate co-registered scans. These are usually displayed with the CT data as background gray-scale imaging and the SPECT data displayed as color overlay. In general, both image sets can be independently reviewed. Technological developments have made it possible to normalize data from SPECT based on attenuation correction parameters obtained from CT, with corrections made for patient weight and height and administered dose-decay correction calculations, thus enabling the calculation of standardized uptake values, similar to those that have been available with PET for many years. The quantitative analysis of abnormality detection is now possible and it is quite promising; however, the value of such analyses has yet to be determined.

**Positron Emission Tomography, Positron Emission Tomography/Computed Tomography, and Positron Emission Tomography/Magnetic Resonance Imaging**

The design of PET scanners varies due to the gamma camera system designs: The detectors are static, and so is the patient. The most commonly used design has a full ring of detectors that can be several rows deep. The radiotracer emissions — in this case, positrons — are recorded as the emitted positrons decay by emitting a pair of photons in nearly opposite directions (~180 degrees). The detection events recorded by the detector ring are filtered based on a set time gap (electronic collimation) that allows the computerized system to count these recorded events as being true or false. When these events are recorded as being true, the origin of the positron decay is plotted in space and recorded to generate an image. Many of these true events need to be recorded to generate a diagnostic imaging map so that the radiopharmaceutical decay is accurate. The imaging table with the patient will move in and out of the detector ring to generate a whole-body map. Tomographic images are then reconstructed in multiple planes for interpretation.

To use the PET data, corrections must be made based on the attenuation of the photons by the body as well as the rate of radiotracer decay. Therefore, an attenuation map of the patient must be generated and decay correction factors applied. The height and weight of the patient must also be recorded for these calculations. The attenuation correction map can be generated in several ways. Historically, an external radiation source was used to record the transmission of radiation through the patient (called transmission imaging), which was then used to generate an attenuation correction map, subsequently applying this information to generate the attenuation-corrected PET imaging. However, since the development of the PET/CT hybrid system, the attenuation correction map of CT replaced the transmission attenuation map while also delivering the benefit of having co-registered anatomical CT imaging for precise lesion localization. CT used for attenuation correction can be obtained as a lower dose or as a diagnostic-quality dose. Other diagnostic parameters such breath-holding, the administration of intravenous or oral contrast, and multiphasic vascular enhancement imaging, can be performed using these systems. However, such a discussion is beyond the scope of this article.

Available hybrid PET/MRI systems offer the advantage of the simultaneous acquisition of data from both PET and MRI while also delivering less total radiation exposure to the patient, because MRI replaces CT for image registration, attenuation correction, and precise lesion localization. Other advantages include its soft-tissue contrast resolution, functional MRI capabilities, and clear advantages in neurological, gastrointestinal, and musculoskeletal imaging. However, MRI has disadvantages, including its limited performance for attenuation correction mapping when evaluating structures such as cortical bone (which usually does not generate a magnetic resonance signal); its susceptibility to patient motion; additional time needed to obtain imaging if the machine is in diagnostic mode (multiple sequences are obtained); and its significant cost. At the time of publi-
cation, PET/MRI is not reimbursed by the US Centers of Medicare & Medicaid Services as a single modality.

**Indications**

Most skeletal scintigrams performed in clinical practice are for the evaluation of skeletal metastatic disease in patients with diagnosed neoplastic disease. The most common primary neoplastic processes evaluated for skeletal metastatic disease in adults include breast, prostate, and lung cancers, which are also the leading cancers diagnosed and the leading causes of cancer-related death in American adults.6

Skeletal scintigraphy plays a primary role in the evaluation and management of cancer. The technology is sensitive for detecting skeletal abnormalities, providing the benefit of whole-body evaluation, with multiplanar capabilities such as fusion capabilities with CT using SPECT/CT devices. Up to 75% of patients diagnosed with a malignancy who present with pain will have evidence of skeletal metastatic disease when evaluated by a clinician. Moreover, a significant number of asymptomatic patients with cancer will have evidence of skeletal metastatic disease on scintigraphic examinations.7

Most skeletal metastases are distributed throughout the axial skeletal system, within the red marrow, as well as the proximal appendicular skeleton such as the humerus and femur. As skeletal metastases grow and erode the cortical bone, the reparative process begins and increased osteoblastic activity ensues, increasing the detection rate of radiotracers, which, notably, localize to the areas of attempted bone deposition, not the tumor lytic process itself. Purely osteoblastic metastases can be identified as areas of increased uptake. However, the detection level of purely lytic metastatic lesions is decreased until a pathological fracture is present or the bony destruction is such that osteoblastic activity secondarily occurs. Mild changes (5%–10%) in bony turnover can be detected with this technology, whereas approximately 50% mineralization loss is needed for radiographical detection.8 Prostate and breast cancers are examples of traditionally mostly osteoblastic metastatic processes, whereas renal cell carcinoma, multiple myeloma, and thyroid carcinoma are examples typical of lytic metastatic processes. Some tumors have a mixed lytic/blastic presentation such as lung and esophageal cancers.

Sensitivity of skeletal scintigraphy is also affected by the imaging technique utilized. The sensitivity rate of planar skeletal scintigraphy is reported to be between 70% and 90%; however, the sensitivity rate of additional tomographic evaluation, such as SPECT and SPECT/CT, can be as high as 95% in select series.8

Patients with widespread, metastatic skeletal disease who undergo treatment and imaging during the early phases of therapy may demonstrate “flare phenomenon.” This scenario usually occurs early during therapy, when skeletal scintigraphy shows suspected progression of disease based on the numerous new lesions identified, sometimes concordant with worsening symptoms (most commonly pain). However, on follow-up skeletal scintigraphy, lesions regress in uptake (usually 4–6 months after treatment) concordant with the resolution of symptoms as well as increased sclerosis of the metastatic lesions usually identified on CT.

![Fig 2. — Widespread, metastatic skeletal disease on superscan.](image-url)
With regard to skeletal metastases, sodium fluoride F 18 is commonly used in the setting of breast, prostate, and lung cancers. Bone is the most common site of breast cancer metastases, reaching an incidence of up to 85% in advanced cases.4 Schirrmeister et al9 compared sodium fluoride F 18 PET with skeletal scintigraphy and SPECT for use in breast and lung cancers and found that sodium fluoride F 18 PET detected 64 bone metastases in 17 patients compared with 29 metastases detected in 11 patients with skeletal scintigraphy. Damle et al10 studied 72 histologically proven cases of invasive ductal carcinoma and found that sodium fluoride F 18 PET/CT had the highest rates of sensitivity (100%) and accuracy (91.67%) but lower rates of specificity (75%) when compared with fludeoxyglucose F 18 PET/CT (100%; Fig 3).

Bone is a common site of metastatic disease after lymph nodes in patients with prostate cancer. Even-Sapir et al11 found that sensitivity and specificity rates for detecting bone metastases were 70% and 57% for bone scintigraphy, 92% and 82% for bone SPECT, 100% and 62% for sodium fluoride F 18 PET, and 100% and 100% for sodium fluoride F 18 PET/CT, respectively. They concluded that sodium fluoride F 18 PET/CT is a sensitive and specific imaging modality for detecting bone metastases in prostate cancer (Fig 4).4,11

Exclusion of bone metastases is important in non–small-cell lung cancer because the disease may be curable by surgery.4,9,12 Sodium fluoride F 18 PET/CT has been shown to have a higher rate of accuracy in the evaluation of bone metastases in lung cancer when compared with bone scintigraphy alone or bone SPECT/CT.4,13 Krüger et al14 compared fludeoxyglucose F 18 PET/CT with sodium fluoride F 18 PET and bone scintigraphy with regard to bone metastases in lung cancer. Concordant bone metastases were found on fludeoxyglucose F 18 PET/CT and sodium fluoride F 18 PET in 13 of 18 patients.14 Sodium fluoride F 18 PET detected bone metastases in 4 of the study patients who had false-negative findings on fludeoxyglucose F 18 PET/CT.4,14

Therapeutic agents that target osteoblastic metastases include strontium Sr 89, samarium Sm 153, and radium Ra 223. Traditionally, diagnostic skeletal scintigraphy was used in the initial evaluation of patients with osteoblastic metastases. The purpose of pretreatment imaging is for patient selection and to determine the burden of osteoblastic disease. Using a diagnostic imaging radiotracer in combination with a therapeutic radiotracer is not new, as it has been a model for the treatment of thyroid cancer. The coupling of diagnostic and therapeutic nuclear medicine agents for the management and treatment of osteoblastic metastases has served as a model for other diagnostic and therapeutic radiopharmaceutical combinations in other disease therapies (eg, lymphoma, neuroendocrine tumors).

Fig 3A–B. — (A) Routine evaluation with planar bone scintigraphy in a patient with breast cancer. No evidence can be seen of osteoblastic metastases. (B) Fludeoxyglucose F 18 positron emission tomography/computed tomography shows metabolically active, widespread metastatic disease involving the skeletal system.
However, further discussion is beyond the scope of this publication, but such an example is illustrated in Fig 5.

**Sodium Fluoride F 18 Positron Emission Tomography/Computed Tomography in Primary Skeletal Malignancies**

Primary bone tumors are rare neoplasms that can occur in children and young adults, accounting for 5% and 0.2% of malignancies, respectively. A role may exist for sodium fluoride F 18 PET/CT with regard to grading, staging, and evaluating response to therapy in such primary skeletal malignancies.

Osteosarcoma is the most common malignant primary bone tumor, accounting for 35% of bone tumors; its incidence peaks in the second decade of life. The literature is limited regarding the use of sodium fluoride F 18 PET/CT for the management of osteosarcomas. However, preliminary findings have been reported in small studies. For example, Hoh et al evaluated 13 patients with malignant bone lesions, 4 of which were confirmed to represent osteosarcoma. Patients with untreated osteosarcoma demonstrated the highest tumor-to-normal bone activity ratios compared with the other malignant lesions, and, in 1 study patient, the activity was reduced following the use of chemotherapy and immunotherapy. Although research is still needed, these findings suggest that quantitative sodium fluoride F 18 PET/CT may have some utility in monitoring therapeutic response. Increased uptake has also been shown in patients with proven pulmonary metastatic disease related to osteosarcoma. CT of the chest is the standard imaging modality for staging/restaging purposes; however, when compared with fludeoxyglucose F 18, sodium fluoride F 18 PET/CT may have added utility because pulmonary metastases due to osteosarcoma and Ewing sarcoma tend not to be fludeoxyglucose F 18 avid, regardless of their size.

Ewing sarcoma is the third most common malignant bone tumor, accounting for 16% of cases. Most cases are diagnosed within the first or second decades of life; increasing age is associated with a poor prognosis. The bones of the chest wall, the long bones of the lower extremities, and the pelvis are commonly involved, with metastasis routinely involving other bones and the lungs. In most cases, imaging involves CT of the chest and technetium Tc 99m MDP bone scintigraphy to evaluate for metastasis. Fludeoxyglucose F 18 PET can identify the extent of disease, although its role in the workup of Ewing sarcoma is unclear. No research studies are evaluating the use of sodium fluoride F 18 PET/CT in Ewing sarcoma, although Mosci et al have shown that such lesions have intense uptake. Thus, additional research is needed to define the potential role of sodium fluoride F 18 PET/CT in Ewing sarcoma.
Multiple myeloma (MM) is a neoplastic proliferation of plasma cells in the bone marrow, most commonly affecting elderly persons. Workup for suspected MM includes a radiographical bone survey, bone marrow aspiration, and biopsy. Radiographically, MM typically presents as small lytic lesions and commonly involves the vertebrae, ribs, skull, and pelvis. Technetium Tc 99m MDP scintigraphy is not commonly performed secondary to lack of uptake in the lytic lesions. Research is being conducted regarding the use of sodium fluoride F 18 PET/CT in MM, and preliminary results indicate that the potential for quantitation may provide benefit compared with traditional bone scintigraphy.

**Positron Emission Tomography/Magnetic Resonance Imaging in Skeletal Metastatic Disease**

The success of PET/CT in clinical practice has yielded an interest and need for research using other advanced, hybrid imaging modalities such as PET/MRI. Initially, PET/MRI fusion was retrospectively performed and limited to brain imaging. However, technological advancements have led to the ability to incorporate a full-fledged PET scanner into the MRI gantry.

A small, prospective study reported a higher rate of accuracy for whole-body MRI (91%) than for fludeoxyglucose F 18 PET/CT (78%) in detecting skeletal metastases. The rates of sensitivity were 94% for MRI and 78% for fludeoxyglucose F 18 PET/CT, with similar specificity rates noted (76% and 80%, respectively). The improved rate of sensitivity of MRI may have been related to the size of the lesions, which may have gone undetected on fludeoxyglucose F 18 PET and CT. The smallest detectable bone metastasis was 2 mm on MRI compared with 5 mm on fludeoxyglucose F 18 PET/CT.

Thus, additional research is necessary, but it may be likely that PET/MRI will improve the detection of bone metastases; thus, there is interest in it as an imaging method because it could exceed certain capabilities of PET/CT.

---

**Fig 5A–B.** — Patient with prostate cancer and skeletal metastases. (A) Diagnostic skeletal scintigraphy and (B) therapeutic skeletal scintigraphy. HDAP = hydroxymethylene diphosphonate.
Data regarding integrated PET/MRI for staging malignant primary bone tumors are lacking. However, although PET/MRI may not improve rates of accuracy over MRI alone in evaluating the primary tumor, Buchbender et al\textsuperscript{24} propose that a role may exist for whole-body PET/MRI as a staging examination. They also suggest that the PET component of the examination may help guide biopsies and maximize the rate of accuracy for staging and grading.\textsuperscript{24} A potential advantage of integrated PET/MRI in malignant primary bone tumors is the ability of MRI to accurately locally stage the tumor, with PET serving as a sensitive, metabolic, whole-body staging examination.\textsuperscript{24}

In a retrospective review of 117 patients with sarcoma, Tateishi et al\textsuperscript{25} found that fludeoxyglucose F 18 PET/CT had sensitivity and specificity rates of 88\% and 97\%, respectively, and it was significantly more accurate for nodal staging in malignant bone tumors than conventional staging modalities (MRI of the primary tumor and whole-body CT).\textsuperscript{24} Therefore, PET/MRI may have similar utility in detecting lymph-node metastases from malignant bone tumors.\textsuperscript{24} MRI and fludeoxyglucose F 18 PET/CT have also been shown to have utility in restaging and evaluating therapeutic response in patients with primary skeletal malignancies.\textsuperscript{24} Combining the 2 modalities with PET/MRI offers an exciting opportunity for additional research on this topic.

**Fig 6A–C.** — Extraskeletal osteosarcoma in a patient. (A) Radiography of the chest shows a large, right pleural effusion with resultant compressive atelectasis. (B) Technetium Tc 99m hydroxymethylene diphosphonate whole-body planar scintigraphy reveals osteoblastic masses within the right chest, right lower abdomen, and left pelvis. Osteoblastic skeletal lesions are also observed. (C) Contrast-enhanced computed tomography shows a multilocular, partially calcified right chest and right pelvic masses. A partially calcified left pelvic periureteral mass and skeletal sclerotic metastases were also present (not shown).
Conclusions
Skeletal scintigraphy provides valuable information in the initial evaluation of the presence of osteoblastic skeletal metastases. Incremental advances in the use of radiopharmaceuticals (fluodeoxyglucose F 18, sodium fluoride F 18), coupled with advances in imaging techniques and imaging devices (single photon emission computed tomography/computed tomography, positron emission tomography/computed tomography, positron emission tomography/magnetic resonance imaging), have had a significant impact in rates of sensitivity, specificity, and accuracy for detecting skeletal metastases. These advances directly impact disease management and patient outcomes. The coupling of diagnostic and therapeutic nuclear medicine agents in the setting of osteoblastic skeletal metastases is a valuable tool for the treatment for certain cancer types (eg, prostate cancer) and may become more widely used to treat other histologies as more data on other tumor types (eg, breast cancer, osteosarcoma) become available.

References
The role of cardiac MRI is growing in the management of cardiotoxicity associated with therapies used to treat cancer.

Cardiac Magnetic Resonance Imaging in Oncology

Daniel Jeong, MD, Aarti Patel, MD, Christopher J. François, MD, Kenneth L. Gage, MD, PhD, and Michael G. Fradley, MD

Background: Cardiac magnetic resonance imaging (MRI) is emerging as an important diagnostic modality in the management of cardiovascular-related dysfunction in oncological diseases. Advances in imaging techniques have enhanced the detection and evaluation of cardiac masses; meanwhile, innovative applications have created a growing role for cardiac MRI for the management of cardiotoxicity caused by cancer therapies. Methods: An overview is provided of the clinical indications and technical considerations of cardiac MRI. Its role in the evaluation of cardiac masses and cardiac function is reviewed, and novel sequences are discussed that are giving rise to future directions in cardio-oncology research. A review of the literature was also performed, focusing on cardiac MRI findings associated with cardiac dysfunction related to cancer treatment. Results: Cardiac MRI can be used to differentiate benign and malignant primary cardiac tumors, metastatic disease, and pseudotumors with high spatial and temporal resolution. Cardiac MRI can also be used to detect the early and long-term effects of cardiotoxicity related to cancer therapy. This is accomplished through a multiparametric approach that uses conventional bright blood, dark blood, and postcontrast sequences while also considering the applicability of newer T1 and T2 mapping sequences and other emerging techniques. Conclusions: Cardio-oncology programs have an expanding presence in the multidisciplinary approach of cancer care. Consequently, knowledge of cardiac MRI and its potential applications is critical to the success of contemporary cancer diagnostics and cancer management.

Introduction
Cardiac magnetic resonance imaging (MRI) is emerging as an important diagnostic modality in the management of cardiovascular-related dysfunction in oncological diseases. With survival rates becoming longer in patients with cancer and in those with chronic cardiovascular disease, new strategies are being developed to manage the increasing overlap between these groups of patients.1 Cardio-oncology programs have an expanding presence in the multidisciplinary approach to cancer care. Thus, knowledge of cardiac MRI and its potential applications is important to the success of contemporary oncological diagnosis and management.

Expert consensus published in 2010 on cardiac MRI includes several important indications related to oncological evaluation and monitoring.2 Cardiac MRI may be used to characterize tissue within cardiac masses and may aid in the early differentiation be-
quences.2,5 Cine bright-blood imaging sequences are opti-
mized for assessing congenital heart disease without
exposing these children to ionizing radiation.

Cardiac MRI can assess a range of parameters and
provides advantages over other imaging modalities.
Most pulse sequences of cardiac MRI can achieve spa-
tial resolutions of $1 \times 1 \times 3$ mm voxel size and temporal
resolutions of 20- to 40-millisecond frame rates with cine
sequences (Table).2,7,8 In addition, studies have shown
high reproducibility rates and low variance of quantita-
tive measures of cardiac MRI across different observ-
ers, scanners, and institutions.2,9 Although a description
of the underlying physics and components of pulse se-
quences for imaging are beyond the scope of this article,
sequences of cardiac MRI can generally be categorized
into bright blood (gradient echo-based or steady-state
free precession [SSFP] acquisition) or dark blood (in-
version recovery or spin echo acquisition) imaging se-
quences.2,5 Cine bright-blood imaging sequences are opti-
timally used to assess cardiac function, ventricular mass
and volume, myocardial perfusion, and blood flow.2,5
Dark-blood imaging sequences, including T1-weighted,
T2-weighted, and gadolinium-enhanced sequences, are
used to assess cardiac and tumor morphology.10,11 Stan-
dard cardiac MRI takes approximately 1 hour at 1.5 T or
3 T and involves localizers, cine SSFP left ventricular (LV)
short- and long-axis (2-, 3-, and 4-chamber) views, and
postcontrast delayed viability imaging.12 In oncological
imaging, T2-weighted, fast-spin echo or inversion re-
covery gradient echo and T1-weighted fast-spin echo se-
quences allow further lesion characterization.2,13,14 When
lesions involve the right ventricle (RV), axial cine SSFP
will offer RV structure and function evaluation. First-pass
arterial perfusion offers vascularity evaluation of the sus-
pected tissue. Refer to the Table for indications of each
sequence of cardiac MRI.7

Compared with imaging modalities — including fludeoxyglucose F 18 positron emission tomography,
thallium Tl 201, single-photon emission computed
tomography (CT), CT alone, and echocardiography —
cardiac MRI allows the qualitative and quantitative as-
essment of cardiac anatomy, function, perfusion, and
tissue characteristics in a single examination.2 It avoids
exposing patients to ionizing radiation, radioactive iso-
topes, or iodinated contrast with highly reproducible,
noninvasive imaging that has significant advantages
over alternative imaging modalities.2,5 Cardiac MRI
also offers superior tissue characterization, with high
spatial and temporal resolution and multiplanar imag-
ing with a larger field of view, that can be performed
in patients of various body habitus.2,5,10,13

Limitations of cardiac MRI include the time neces-
sary for the examination, reactions to contrast media,
and its cost.15 The need for breath holds and electro-
cardiographical gating can also reduce image quality,
particulary in patients with poor pulmonary reserve
or in the presence of arrhythmias.10,13 Patients who
have claustrophobia and those with non–MRI-compat-
tible medical devices may be unable to undergo cardi-
ac MRI.14 Cardiac MRI also has limited abilities for the
detection of calcium in the coronary arteries; thus, it
should be used in conjunction with other modalities if
the presence of calcium is being investigated.10

Evaluation of Cardiac Masses
Cardiac masses can be categorized as primary cardiac
tumors, secondary or metastatic cardiac tumors, intra-
cavitary thrombus, or cardiac pseudotumors.2 Primary
cardiac tumors are rare and typically benign, whereas
metastatic masses are approximately 40 times more
prevalent than primary cardiac tumors.10,13,15 Cardiac
MRI allows for accurate tissue characterization and lo-
calization of cardiac masses, and it can be used to help
the health care professional determine the extent of
involvement and functional impact of the mass.10,13,15
In a study evaluating 59 patients with cardiac mass-
es, Zhu et al16 reported 96% accuracy in differentiat-
ing benign from malignant tumors and 100% accura-
cy in differentiating neoplasms from pseudotumors
when using cardiac MRI compared with pathological
examination. Hoffman et al3 showed that character-
istics on MRI, including location, tissue composition,
and associated pleural or pericardial effusions, have
a diagnostic accuracy of 0.92 (area under curve) for
diagnosing a cardiac or paracardiac mass as malign-
ant. The superior tissue characterization of cardiac
MRI can inform clinical decision-making and help to
risk stratify patients for surgical resection, chemo-
therapy, or observation. Cardiac masses are best characterized using T1- and T2-weighted fast-spin echo in addition to multiplanar cine SSFP for LV and RV structure and function. First-pass perfusion imaging through the mass provides the clinician with real-time evaluation of regional tissue perfusion, whereas late, gadolinium-enhanced imaging has added sensitivity for the

<table>
<thead>
<tr>
<th>Sequence</th>
<th>Indication</th>
<th>Approximate Spatial Resolution</th>
<th>Temporal Resolution</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cine SSFP</td>
<td>Structural and functional evaluation</td>
<td>1.4–1.8 mm²</td>
<td>≤ 50 ms</td>
<td>Bright-blood sequence used to assess cardiac function and effect of tumor on cardiac function</td>
</tr>
<tr>
<td>Inversion recovery</td>
<td>Late gadolinium enhancement</td>
<td>1.4–1.8 mm²</td>
<td>NA</td>
<td>Used to identify areas of myocardial fibrosis or infiltration Phase sensitive and black-blood preparation versions potentially more robust</td>
</tr>
<tr>
<td>T2-weighted, double-inversion recovery</td>
<td>Tissue characterization</td>
<td>1.4–1.8 mm²</td>
<td>NA</td>
<td>Black-blood sequence used to characterize masses and detect the presence of water or edema</td>
</tr>
<tr>
<td>T2-weighted, triple-inversion recovery</td>
<td>Cardiomyopathy evaluation Myocardial strain</td>
<td>1.3 × 2.0 mm</td>
<td>≤ 50 ms</td>
<td>Used to assess regional wall motion, adherence of masses to the pericardium, constrictive pericarditis</td>
</tr>
<tr>
<td>Phase-contrast flow</td>
<td>Congenital disease Valvular disease</td>
<td>—</td>
<td>≤ 50 ms</td>
<td>Analysis planes must be prospectively prescribed</td>
</tr>
<tr>
<td>T2*</td>
<td>Cardiac iron quantification</td>
<td>1.6–3.0 mm²</td>
<td>NA</td>
<td>Repeated blood transfusions, primary hemochromatosis</td>
</tr>
<tr>
<td>T1-weighted</td>
<td>Tissue characterization</td>
<td>—</td>
<td>NA</td>
<td>Black-blood sequence used to characterize masses Can be performed with fat saturation Melanoma metastases are inherently hyperintense on T1-weighted imaging</td>
</tr>
<tr>
<td>First-pass arterial perfusion</td>
<td>Tissue characterization</td>
<td>1.8 × 1.8 × 8.0 mm</td>
<td>—</td>
<td>Saturation recovery sequence used to assess perfusion and early enhancement of masses Can also be used to evaluate for myocardial ischemia</td>
</tr>
<tr>
<td>Contrast-enhanced MRA</td>
<td>MRA</td>
<td>1.3 × 1.8 × 2.0 mm</td>
<td>NA</td>
<td>Timing of image acquisition based on vascular territory of interest (ie, pulmonary arteries for pulmonary embolism, aorta for acute aortic syndrome)</td>
</tr>
<tr>
<td>T1 mapping</td>
<td>Native T1 and extracellular volume quantification</td>
<td>2.1 × 1.1 × 8.0 mm</td>
<td>—</td>
<td>Used in myocardial characterization</td>
</tr>
<tr>
<td>T2 mapping</td>
<td>T2 signal can be altered by myocardial infarction or myocarditis</td>
<td>2.6 × 2.1 × 8.0 mm</td>
<td>—</td>
<td>Limited utility because T2 relaxation sensitive to mild infections and large interpatient variability</td>
</tr>
<tr>
<td>3D cine SSFP single-breath hold</td>
<td>Single breath-hold 3D cine short-axis sequence (&lt;22 sec) vs &gt; 8.5 min standard 2D cine SSFP, including pauses</td>
<td>2.0 × 2.0 mm in-plane</td>
<td>36–70 ms³</td>
<td>Could have a role in cardiotoxicity left ventricular evaluation Shorter time, no radiation exposure compared with MUGA</td>
</tr>
<tr>
<td>4D flow magnetic resonance</td>
<td>Advanced multiplanar flow analysis and visualization</td>
<td>1.3 mm isotropic⁵</td>
<td>—</td>
<td>Allows retrospective phase-contrast analysis</td>
</tr>
<tr>
<td>CMR/FDG PET fusion</td>
<td>Evaluation of myocardial perfusion imaging, localization, and differentiation of tumors</td>
<td>CMR: 1.4–1.8 mm² PET: 5–8 mm²</td>
<td>≤ 50 ms</td>
<td>—</td>
</tr>
</tbody>
</table>

⁴Depends on body habitus and scanner prescription.
⁵Based on heart rate.
³Using phase contrast vastly undersampled isotropic projection reconstruction.
²D = 2-dimensional, 3D = 3-dimensional, 4D = 4-dimensional, CMR = cardiac magnetic resonance, FDG = fludeoxyglucose F 18, MRA = magnetic resonance angiography, MUGA = multigated acquisition, NA = not applicable, PET = positron emission tomography, SSFP = steady-state free precession.
evaluation of soft-tissue enhancement. Additional techniques, such as myocardial tagging utilizing radiofrequency prepulses, can be used to evaluate secondary myocardial dysfunction or strain potentially arising from large or invasive masses.

**Benign Primary Cardiac Tumors**

*Myxoma:* Myxomas are the most common type of benign cardiac tumor, typically presenting between the fourth and seventh decades of life with a classic triad of cardiac obstructive symptoms, embolic events, and constitutional symptoms such as fever, weight loss, and dyspnea. Most myxomas are solitary masses found in the left atrium, and they often arise from the interatrial septum. These masses appear heterogeneous, containing myxomatous tissue originating from primitive mesenchymal cells with mucoid and other elements. Myxomatous tissue is hypointense relative to myocardium on T1-weighted imaging. Depending on the degree of associated fibrous tissue, myxomas can have a heterogeneous, T2-weighted appearance. Areas of intratumoral hemorrhage may be hypointense or hyperintense. Cine bright-blood imaging sequences reveal characteristic mobility associated with myxomas, with the masses typically hyperintense relative to the myocardium and hypointense or isointense relative to the blood pool on SSFP. Myxomas demonstrate heterogeneous enhancement and calcify approximately 50% of the time when found in the right atrium.

*Papillary Fibroelastoma:* Papillary fibroelastomas are benign endocardial lesions that predominantly affect cardiac valves. These are the second most common benign primary cardiac tumor and account for 75% of all cardiac valvular tumors. Although these lesions are generally asymptomatic, tumor fragments or surface thrombus can result in embolic events leading to stroke, pulmonary embolism, or myocardial infarction. Papillary fibroelastomas are typically small (< 1.5 cm), mobile, pedunculated masses arising from valve leaflets or the endocardium. They demonstrate a hypointense signal on SSFP and T2-weighted sequences due to their high fibrous content; however, this can make differentiating fibroelastomas from thrombus difficult. In certain cases, valvular location, papillary contour, and small...
size may offer support in diagnosing fibroelastomas. When they are large in size, fibroelastomas can result in turbulent flow, which can be observed on cine SSFP.

**Lipoma:** Typically, lipomas are incidentally discovered, and they occur across a wide range of ages. They have a homogeneous appearance with encapsulated tissue that is hyperintense on T1-weighted imaging and less hyperintense on T2-weighted imaging. Lipomas demonstrate signal intensity similar to subcutaneous or mediastinal fat on fat-saturated imaging and do not show enhancement after the administration of contrast. These lesions usually arise from the epicardial surface, but they can extend to the pericardial region; they do not warrant intervention if the patient is asymptomatic. Rarely, however, giant lipomas can lead to symptomatic obstruction that warrants resection — this is particularly true if the pericardial space is involved.

**Rhabdomyoma:** Rhabdomyomas are the most common benign cardiac tumor in children and are usually asymptomatic; however, they are often associated with tuberous sclerosis. Most cases of rhabdomyomas present with multiple masses predominately found in the ventricles. Rhabdomyomas can extend into the ventricular cavities and cause obstruction; however, most remain asymptomatic and spontaneously regress by 4 years of age. These masses appear isointense to hyperintense relative to the myocardium on T1-weighted imaging and hyperintense on T2-weighted imaging, without enhancement after the administration of gadolinium contrast.

**Fibroma:** Fibromas are the second most common congenital cardiac tumor seen in infants and children, with clinical presentations ranging from asymptomatic to heart failure and ventricular arrhythmias. Typically, fibromas are located within the ventricular walls, but they can be seen in the atria, particularly when associated with polyposis syndromes. On T1-weighted imaging, these masses typically appear as solitary masses that have a T1-weighted isointense or hypointense signal, whereas they characteristically appear homogeneously hypointense on T2-weighted imaging. Following the administration of gadolinium contrast, fibromas do not enhance during perfusion but will show intense enhancement on late gadolinium-enhanced imaging.

**Hemangioma:** Cardiac hemangiomas present in a wide variety of ages, often with dyspnea on exertion;
Fig 3A–F. — (A) Long-axis, 4-chamber, and (B) axial steady-state free precession, bright-blood imaging show a lobulated mass arising from the lateral right atrial wall. (C) T2 spectral presaturation with inversion-recovery axial, dark-blood imaging demonstrates heterogeneous, T2 hyperintensity in the mass. (D) T1 axial, precontrast, fat-saturated imaging demonstrates an isointense to mildly increased T1 signal within the mass. (E) Early and (F) later dynamic, first-pass perfusion imaging show peripheral rim enhancement of the mass. Increased T1 signal within a mass is a distinguishing feature of melanoma metastases, the diagnosis in this case.

Fig 4A–F. — Prior to anticoagulation, (A) axial- and (B) short-axis SSFP, bright-blood imaging demonstrate a well-defined, low-signal structure in the right atrium (arrow). (C) T2 spectral presaturation with inversion-recovery axial, dark-blood imaging shows low signal within the structure. (D) Short-axis, late gadolinium-enhanced imaging shows no enhancement, thus supporting the diagnosis of right atrial thrombus. (E) Axial- and (F) short-axis SSFP imaging after 3 months of anticoagulation show complete resolution of the structure, thus confirming the diagnosis of treated right atrial thrombus. SSFP = steady-state free precession.
however, they can also be asymptomatic.\textsuperscript{28,29} Hemangiomas appear heterogeneous, with isointensity or hypointensity on T1-weighted imaging and are typically hyperintense on T2-weighted imaging.\textsuperscript{30,31} Following intravenous contrast, a heterogeneous-enhancement pattern has been reported.\textsuperscript{3} Cardiac hemangiomas have also been described as having flow voids on T2-weighted imaging with calcifications best seen on CT.\textsuperscript{32}

**Malignant Primary Cardiac Tumors**

Findings suggestive of primary malignant or metastatic cardiac tumors include a diameter of more than 5 cm, invasive behavior with irregular borders, right-sided or pericardial involvement, tissue heterogeneity on T1- and T2-weighted imaging, a broad base of attachment, enhancement after the administration of gadolinium contrast, and associated hemorrhagic pericardial or pleural effusions.\textsuperscript{10,13,15,16,33}

**Angiosarcoma:** Among primary cardiac malignancies, cardiac angiosarcoma is the most common in adults.\textsuperscript{34} Angiosarcomas are often found in the right atrium, but they are usually metastatic at the time of presentation.\textsuperscript{34,35} Clinically, patients present with symptoms related to right-sided heart failure, hemorrhagic pericardial effusions, and tamponade.\textsuperscript{10,13,15} These tumors appear as a large, heterogeneous, broad-based mass with mixed signal intensity on T1-weighted imaging and a predominantly hyperintense signal on T2-weighted imaging.\textsuperscript{35,36} Following the administration of gadolinium, these tumors are typically heterogeneous with marked surface enhancement and central areas of necrosis on SSFP, they are predominantly hyperintense relative to the myocardium.\textsuperscript{37} In addition, the postcontrast appearance of cardiac angiosarcomas has, rarely, been described as having a “sun-ray” configuration of enhancement when extensive pericardial involvement is present; the “rays” are radially oriented, enhancing lines that extend from epicardium to the pericardium separated by nonenhancing pericardial regions.\textsuperscript{38,39} Fig 1 demonstrates the typical features of primary cardiac angiosarcoma.

**Rhabdomyosarcoma:** Rhabdomyosarcoma is the most common primary cardiac malignancy in children.\textsuperscript{40} Symptoms of heart failure may be present, and the tumors may involve multiple sites such as the valves without any definite chamber predominance.\textsuperscript{40} These tumors appear as an infiltrative mass with irregular margins isointense relative to the myocardium on T1-weighted imaging.\textsuperscript{41} After the administration of contrast, these masses typically show homogeneous enhancement, although areas of hypointense necrosis may be observed within the tumor.\textsuperscript{10,41}

**Other Sarcomas:** Other malignant primary cardiac tumors are usually sarcomatous in origin, and they may include undifferentiated sarcomas, leiomyosarcomas, fibrosarcomas, liposarcomas, and osteosarcomas.\textsuperscript{13,35} These tumors often present in adults in the fourth or fifth decade, and they commonly arise from the left atrium.\textsuperscript{29,42} Appearances on cardiac MRI may be heterogeneous on T1- and T2-weighted imaging, with variable contrast enhancement depending on their composition and the presence of necrosis or hemorrhage.\textsuperscript{10,43}

**Lymphoma:** Primary cardiac lymphomas are rare and have a poor prognosis; they often present with rapidly worsening heart failure, obstructive symptoms, or arrhythmias.\textsuperscript{44} Typically, lymphomas are of the non-Hodgkin B-cell type and found in the right atrium.
however, they may invade other cardiac chambers or the pericardium.44,45 Primary cardiac lymphomas are often characterized by multiple, infiltrative nodular masses that are isointense relative to the myocardium on T1-weighted imaging and heterogeneously hyperintense on T2-weighted imaging.46 They can also demonstrate diffuse pericardial infiltration with an associated hemorrhagic pericardial effusion.10,13 Following the administration of gadolinium contrast, they show heterogeneous enhancement with areas of low enhancement centrally relative to the periphery.10,46

**Metastatic Cardiac Tumors**

Metastatic cardiac tumors are significantly more common than primary cardiac malignancies.47 Autopsy studies have shown that known malignant neoplasms also have cardiac metastases in 10% to 12% of cases.13,48-50 The neoplasms that most commonly metastasize to the heart include melanoma, bronchogenic carcinoma, lymphoma, leukemia, breast carcinoma, and esophageal carcinoma.10,33,50,51 Metastatic disease may spread to the heart by direct invasion or via hematological, retrograde lymphatic, or transvenous spread.10,13,15,50 The pericardium is most often involved, although one-third of patients with metastatic cardiac involvement will die due to pericardial tamponade, congestive heart failure, or coronary artery invasion.10,13,15 Patients may present with dyspnea, angina, obstructive symptoms, or arrhythmia.10 Although metastatic lesions in the heart do not have exclusive appearances on cardiac MRI, they generally demonstrate low T1- and high T2-weighted signal with variable enhancement patterns (Fig 2).10,13,15 However, melanoma is an exception, because it has a high T1-weighted signal due to the presence of paramagnetic melanin (Fig 3).52 Metastatic lesions may demonstrate necrosis with peripheral enhancement. In patients with diffuse metastatic disease that also involves skeletal muscle, thoracic lesions may be useful to include in the examination.

**Thrombus**

Cardiac MRI may be used to characterize cardiac masses and can help the health care profes-

sional differentiate true cardiac tumors from thrombus. Thrombus more commonly occurs in the left atrium — especially in the setting of atrial fibrillation or dysfunctional left ventricles — and is often misinterpreted as atrial myxoma.10,13 Acute thrombus appears as intermediate to hyperintense on T1- and T2-weighted imaging.13,50 Subacute thrombus appears hyperintense on T1-weighted imaging with areas of hypointensity on T2-weighted imaging.10,53 Chronic thrombus appears hypointense on T1- and T2-weighted imaging (Fig 4).53 Although mild surface enhancement has been reported with organized thrombus, thrombus does not typically enhance, whereas true cardiac tumors often enhance following the administration of gadolinium contrast due to the presence of tumoral vascularity.50,53,54

**Cardiac Pseudotumors**

Cardiac pseudotumors include anatomical structures such as prominent eustachian valves, the Chiari network, crista terminalis, and lipomatous interatrial septum that may mimic true cardiac tumors but can
be distinguished by cardiac MRI.\textsuperscript{2,10,13,15} The Chiari network is an embryological remnant of mobile, fenestrated, fibrous threads commonly attached to the right atrial wall.\textsuperscript{5,5} The crista terminalis is a fibromuscular ridge separating the posterior right atrium and the trabeculated right atrial appendage (Fig 5).\textsuperscript{5,5} Lipomatous hypertrophy is characterized by hyperplasia of cardiac adipose tissue and can sometimes be mistaken for lipomas due to the similarities in fat content.\textsuperscript{13} Lipomatous hypertrophy is nonencapsulated and typically involves the limbus of the fossa ovalis with sparing of the fossa ovalis, thus creating a characteristic, bilobed, dumb-bell shape on cardiac MRI without enhancement and with a homogeneous, hyperintense signal on T1-weighted imaging.\textsuperscript{13,53} Lipomatous hypertrophy can take an atypical form with nodular fatty deposition along the coronary sinus or lateral right atrial wall that can mimic masses on echocardiography (Fig 6).

**Infiltrative Cardiomyopathies in Oncology**

Infiltrative cardiomyopathies are characterized by the deposition of abnormal substances within myocardial tissue leading to cardiac dysfunction.\textsuperscript{5,5} Additional cardiac abnormalities can arise, including ventricular wall thickening, chamber dilatation, and conduction disruption, which can lead to heart failure and arrhythmia.\textsuperscript{5,5} Cardiac amyloidosis and cardiac iron deposition are important infiltrative cardiomyopathies, which are encountered more frequently in patients with cancer.\textsuperscript{6,56} Although endomyocardial biopsy is the gold standard for diagnosing certain infiltrative cardiomyopathies, such as amyloidosis, typical features on cardiac MRI with a noncardiac tissue sample positive for amyloidosis can infer the diagnosis in cases where endomyocardial biopsy samples are not easily obtained.\textsuperscript{57} Moreover, the sensitivity rate of biopsies may be limited in early cardiac iron overload, which can have an uneven patchy distribution, and increases the utility for quantitative cardiac MRI in the diagnosis of cardiac iron overload.\textsuperscript{58}

Amyloidosis is a heterogenous group of deposition diseases resulting in the extracellular accumulation of abnormal fibrillar protein deposits. Whereas cardiac MRI or echocardiography can show concentric LV wall thickening with biaxial enlargement suggestive of nonspecific, underlying restrictive cardiomyopathy, cardiac MRI classically demonstrates circumferential, ventricular, late gadolinium enhancement with a subendocardial or transmural pattern more specific for amyloidosis (Fig 7).\textsuperscript{59} In addition, abnormal gadolinium kinetics seen particularly with amyloidosis leads to difficulty in myocardial nulling on late gadolinium-enhanced imaging. T1-mapping research has shown the expansion of extracellular volume fraction related to amyloid deposition and possible fibrosis.\textsuperscript{60}

Cardiac iron overload is a leading cause of morbidity and mortality in patients receiving repeat blood transfusions and can be seen in certain patients with cancer.\textsuperscript{6,61} Patients who are transfusion dependent receive approximately 20 times the normal physiological iron intake.\textsuperscript{6} Excess iron is initially taken up by the reticuloendothelial system; however, once overwhelmed, iron is deposited into other organs such as the liver, spleen, and heart. Serum iron, transferrin, and ferritin levels show some correlation with liver iron levels but not with cardiac iron levels.\textsuperscript{62} In addition, liver iron
stores do not reliably correlate with cardiac iron stores. Echocardiography cannot be used to directly detect iron overload, but it can detect secondary cardiac injury. Endomyocardial biopsy also offers iron quantification, but this procedure is prone to sampling error due to possible patchy iron deposition in early disease.

Cardiac MRI offers a reliable, noninvasive biomarker to evaluate cardiac iron stores. T2* cardiac MRI allows quantification of cardiac iron level with a normal value of 52 ± 16 milliseconds at 1.5 Tesla. R2* is the inverse signal sequence of T2* and allows for a more accurate quantification of iron overload in severe disease, in which a brighter R2* signal corresponds to iron overload (Fig 8). Regions of interest on T2*/R2* maps should be drawn over the interventricular septum to avoid susceptibility from the adjacent lung; susceptibility correction techniques have helped keep consistent measurements. Although early cardiac iron overload may present with restrictive cardiomyopathy, progressive disease can result in dilated cardiomyopathy with systolic dysfunction. When T2* drops below 20 milliseconds due to cardiac iron overload, the LV ejection fraction (LVEF) has been shown to decrease with an associated increased mortality rate.

**Evaluation of Cardiac Function and Cardiotoxicity**

Although cardiac MRI has become a decisive modality for identifying and diagnosing cardiac masses, it also has a growing role in monitoring cardiac function in patients with cancer, especially in the setting of cardiotoxicity related to radiotherapy and chemotherapy. Although no universally accepted definition exists, an expert consensus statement from the American Society of Echocardiography and the European Association of Cardiovascular Imaging published in 2014 defined cardiac dysfunction related to use of cancer therapeutics as a decrease in LVEF of more than 10%, to a value below 53%, and confirmed by repeat cardiac imaging performed 2 to 3 weeks later. However, cardiovascular effects of chemotherapeutic agents may range from hypertension to arrhythmias and to ventricular dysfunction. The timing and severity of cardiac dysfunction associated with use of cancer therapeutics depend on the agent, dosing, and patient-related factors.

Among chemotherapeutic agents, anthracyclines were first recognized in the 1960s to cause irreversible cardiotoxicity, including cardiomyopathy and heart failure. Tyrosine kinase inhibitors such as erb-B2–positive targeted therapies and vascular endothelial growth factor inhibitors are often associated with reversible cardiotoxicity; in addition, irreversible dysfunction can also occur. Fluorouracil, taxanes, and methotrexate have been associated with myocardial ischemia and arrhythmia, and alkylating agents such as cyclophosphamide has been linked to heart failure, myopericarditis, and arrhythmia. Radiotherapy to the mediastinum with a cumulative dose of more than 30 Gy and a daily fractioning of more than 2 Gy may contribute to restrictive cardiomyopathy, accelerated atherosclerosis, valvular dysfunction, and pericardial effusion or constriction.

Using cardiac MRI, the earliest findings of cardiotoxicity can be seen within weeks of chemotherapy in the form of myocardial edema and decreased LVEF, which can be asymptomatic. LV short-axis, T2-weighted imaging will demonstrate an abnormal,
hyperintense myocardial signal in the setting of edema. T2-weighted signal ratios of myocardium to skeletal muscle have been proposed to detect edema that is not visually apparent.71 Chronic cardiotoxicity related to chemotherapy can present with further decreased LVEF, myocardial fibrosis, and a decreased LV mass index seen months to years following the use of chemotherapy.71 In addition, Ylanen et al72 showed that both RV and LV function can be decreased in the absence of focal myocardial fibrosis in long-term survivors of childhood cancer treated with anthracyclines, which raises the possibility of interdependence of the RV and LV with regard to anthracycline cardiotoxicity.

A pilot study of 22 patients by Wassmuth et al73 demonstrated that the use of early myocardial gadolinium contrast enhancement on fast-spin echo predicted a significant loss of ejection fraction at 28 days after anthracycline therapy (Fig 9). Myocardial fibrosis is also a common finding on cardiac MRI in patients with anthracycline-induced cardiac dysfunction.74 Jordan et al74 showed that changes in T1-weighted signal intensity could serve as an early marker of anthracycline-related subclinical injury, and Drafts et al75 showed low to moderate doses of anthracycline-based chemotherapy were associated with subclinical abnormalities of cardiac function. In a study of 114 adult survivors of childhood cancer who received anthracycline therapy, Armstrong et al76 found that 2-dimensional (2D) echocardiography had a sensitivity rate of 25% and a false-negative rate of 75% for detection of ejection fraction less than 50%. Given the increased sensitivity rate of cardiac MRI, Heck et al77 incorporated cardiac MRI to follow LV function in patients with breast cancer who were treated with adjuvant cardiotoxic chemotherapy and prophylactic angiotensin-receptor blockers or beta blockers. They found a higher detection rate of cardiac dysfunction by cardiac MRI compared with echocardiography, suggesting that cardiac MRI should be considered for survivors with an ejection fraction between 50% and 59% for more comprehensive cardiac assessment.1,76,77 Early radiation-related injury can present as myocarditis or pericarditis, whereas late radiation-related effects can manifest as coronary artery disease, myocardial fibrosis, restrictive cardiomyopathy, and pericardial effusions.35 A case of constrictive pericarditis following radiotherapy for esophageal cancer is shown in Fig 10.

**Future Directions**

Cardiac MRI has become an important tool in the evaluation of cardiac tissue and function, and further developments will continue to advance the role of cardiac MRI in the diagnosis and management of cardio-oncological diseases. Three-dimensional (3D) cine SSFP imaging allows LV functional analysis during 1 breath hold, which would reduce the short-axis LV series to 22 seconds from 8.5 minutes using 2D cine SSFP without sacrificing clinically significant imaging quality.7 Combination positron emission tomography/MRI is promising for evaluating myocardial perfusion as well as in the localization and differentiation of select tumors.13

In addition to monitoring ventricular dysfunction, via T1-mapping techniques, cardiac MRI may be used to evaluate myocardial fibrosis sometimes seen in chemotherapy-induced cardiomyopathies and restrictive cardiomyopathies.
cardiomyopathy.\textsuperscript{1,33} T1 mapping and postcontrast extracellular volume can be used to quantify edema in acute coronary syndromes and the myocardial deposition of T1-altering substances, including amyloid, lipid, or protein.\textsuperscript{78} T2 mapping is a new technique based on a bright-blood T2-prepped SSFP sequence, which allows the quantification of myocardial T2 relaxation times. However, T2 mapping is limited by large interindividual variability of myocardial T2 relaxation times and relative rates of sensitivity to minor disturbances, including the common cold.\textsuperscript{79,80} Kubler et al\textsuperscript{81} showed how T1 and T2 mapping can be applied to characterize tissue within cardiac myxomas. Future studies may show an increasing role of T1 and T2 mapping in cardiac MRI for other oncological applications.

Four-dimensional flow MRI allows for the advanced evaluation of blood flow in the heart where blood flow velocities can be retrospectively quantified in any plane, and flow can be visualized in streamlines, resolved path lines, or vector graphs.\textsuperscript{82} Four-dimensional flow MRI could have an increasing role in scenarios in which cardiac or great vessel blood flow is compromised by a tumor. However, more studies are needed to determine the added benefits of these emerging cardiac MRI sequences in the management of cardio-oncological disease.

Conclusions

Imaging advances in cardiac magnetic resonance techniques have improved the rate of detection and evaluation of cardiac masses. In addition, novel applications have created a role for cardiac magnetic resonance imaging (MRI) in the management of cardiovascular-related dysfunction seen in oncological disease. Cardio-oncology is a growing field in the management of cancer. Therefore, use of cardiac MRI — in conjunction with other imaging modalities — and a multidisciplinary approach are both crucial to the contemporary model of cancer care. Knowledge of cardiac MRI and its applications will help health care professionals deliver the best care possible to their patients with cancer.

References

9. Gandy SJ, Waugh SA, Nicholas RS, et al. Comparison of the repro-


Diffusion-weighted, spectroscopy, and in- and out-of-phase imaging are expanding the role of MRI for characterizing musculoskeletal tumors.

Conventional Modalities and Novel, Emerging Imaging Techniques for Musculoskeletal Tumors

Meera Raghavan, MD

Background: Imaging of musculoskeletal tumors requires a multimodality approach and includes radiography, computed tomography (CT), and magnetic resonance imaging (MRI).

Methods: Topics related to primary bone and soft-tissue tumors are reviewed. The fundamental imaging principles are discussed as well as the applications of emerging imaging modalities.

Results: MRI is the preferred technique for the evaluation of musculoskeletal tumors, whereas other imaging modalities play a complementary role. Radiography is indicated as the first-line imaging modality in bone and soft-tissue tumors, whereas CT is the preferred modality for evaluating cortical osseous lesions or calcifications and in patients with contraindications to MRI. Positron emission tomography (PET)/CT and PET/MRI are helpful in identifying the glucose metabolism of the lesion. Ultrasonography is the most useful for biopsy guidance and can aid in differentiating cystic from solid masses and identifying vascularity. Novel modalities, such as diffusion-weighted imaging, spectroscopy, and habitat imaging, show promise in increasing diagnostic accuracy and affecting treatment strategies.

Conclusions: Conventional modalities and emerging, novel imaging techniques can provide noninvasive methods to diagnose and evaluate musculoskeletal tumors.

Introduction

The imaging evaluation of musculoskeletal tumors involves a multimodality approach. Each modality provides different diagnostic information. The patient's history, physical examination findings, and location of the abnormality will determine the type of imaging modality. The initial evaluation of bone and soft-tissue tumors is typically performed with plain radiography, followed by a cross-sectional modality such as computed tomography (CT) or magnetic resonance imaging (MRI). Nuclear medicine scintigraphy, ultrasonography, and positron emission tomography (PET) may also be performed in conjunction with or after the initial assessment. MRI is the technique of choice for the imaging assessment of soft-tissue tumors, whereas CT or MRI can be used to determine the extent of disease in bone tumors.

Novel techniques such as diffusion-weighted MRI, spectroscopy, and chemical shift are expanding the role of MRI in the characterization of musculoskeletal tumors. MRI-defined "habitats" in sarcoma provide another novel and evolving method to characterize and quantify features on MRI so as to provide prognostic and therapeutic information.
Conventional Modalities

Plain Radiography

Plain radiography remains the first-line choice of imaging modality for the initial evaluation of a bone lesion following clinical examination. Radiographs can be obtained quickly, easily, and at low cost. The differential diagnosis of many primary bone tumors is based on radiographic features. By combining radiographic features, such as lesion location, size, matrix, margin, and periosteal reaction, with patient age, sex, and clinical symptoms, the health care professional can effectively narrow the differential diagnosis to a small number of possibilities (Fig 1). The bone lesion can be classified as nonaggressive or aggressive from its radiographic appearance. A classic, nonaggressive bone lesion may not require subsequent imaging or treatment unless further anatomical information is required and surgical intervention is considered. Conversely, radiography can provide information about a lesion that helps determine appropriate further imaging with CT or MRI and useful clinical information about the potential fracture risk of the lesion. If multiple lesions are present on radiography, then the differential diagnosis will change to include other diagnoses such as metastatic disease or myeloma.

Radiographs are indicated in the workup of a soft-tissue mass. Radiographs should be inspected for tissue plane distortion, lucent areas — which might indicate fat — bony remodeling, and soft-tissue calcifications or mineralization. For example, a peripherally mineralized mass that arises following a clear history of trauma supports the diagnosis of myositis ossificans. Phleboliths in a soft-tissue mass support the diagnosis of a benign vascular lesion (Fig 2), whereas the presence of fat suggests a lipomatous mass (Fig 3).

The utility of radiographs alone in the evaluation of soft-tissue masses has been supplanted by MRI. Radiography does not obviate the need for cross-sectional evaluation and should be considered complementary to MRI and CT.

Findings on radiography can also be used to tailor cross-sectional imaging. For example, if metal density is noted, then sequences that would normally be performed with fat saturation can be altered to short tau-inversion recovery imaging to mitigate artifacts. If tumor involvement of the adjacent bone is seen, then further cross-sectional evaluation can be performed with CT because it is more useful than other modalities in the evaluation of cortical bone. Results on radiography may also suggest that the process is articular or juxta-articular (eg, synovial chondromatosis, tumor calcinosis); in that case, the imaging planes or sequences that optimize the specific joint can be performed.

Ultrasonography

Ultrasonography can be complementary to MRI or CT in the initial evaluation of soft-tissue masses. In general, it is widely available, portable, is associated with low cost, and can be performed without ionizing radiation. In particular, ultrasonography can be used for the initial evaluation of soft-tissue masses in patients with contraindications to MRI. Sonography can confirm the presence of the mass, characterizing it as solid or cystic, and assess its dynamic features such as compressibility and vascularity. Perhaps one of the most widely used applications of ultrasonography is imaging-guided intervention. Ultrasonography can be used to guide a minimally invasive technique to guide the placement of the needle during biopsy into an area of solid tissue.

In a prospective study of 358 patients, ultrasonogra-

Fig 1A–F.—Radiographic evaluation of osseous lesions in (A–D) aggressive and (E–F) benign bone tumors. (A) Anteroposterior view of the shoulder in a patient aged 13 years with Ewing sarcoma. Shown is a permeative, lytic lesion with a wide zone of transition in the proximal humerus with a pathological fracture. Shown is a lamellate or layered periosteal reaction (black arrows), which is commonly seen in Ewing sarcoma and is suggestive of an aggressive lesion. (B) Frontal view of a femur in a patient aged 18 years with a dense, periosteal reaction in the femoral cortex with ossific matrix mineralization in the soft tissue of the thigh. These findings are consistent with osteosarcoma. (C) Frontal view of a tibia in a patient aged 13 years with an aggressive, sunburst periosteal reaction and an ossific sclerotic lesion in the proximal tibia consistent with osteosarcoma. (D) Frontal view of a femur in a patient aged 70 years with a lytic lesion with a wide zone of transition in the distal femur with stippled and curvilinear mineralized matrix (white arrowhead) suggestive of a cartilaginous lesion. Deeper cortical involvement and periosteal reaction (red arrow) were suggestive of a focally aggressive malignancy (chondrosarcoma). (E) Distal femur (white asterisk) compatible with nonossifying fibroma. (F) Lateral view of an elbow in a patient aged 18 years who was in pain. A dense, continuous solid periosteal reaction in the ulna was benign (red arrows) and had central lucency, the findings of which were compatible with osteoid osteoma. Subtle central calcification can be seen within the lucent lesion, reflecting calcification within the nidus, which was the inciting fibrovascular lesion.
phy was found to be an effective tool for triaging patients with soft-tissue masses. Nearly 80% of lesions were characterized as benign based on ultrasonographic features; on further follow-up (clinical, MRI, or both), none of these patients had a malignant tumor. Of those lesions evaluated by MRI for suspicious or indeterminate findings on ultrasonography (large mass, deep-seated, painful solid components, or vascularity), fewer than 2% were histologically malignant at surgery. By contrast, a small study of soft-tissue tumors showed that 23% of the 43 patients studied were incorrectly diagnosed following initial findings on ultrasonography. A delay in diagnosis was observed (≤ 6 months) in 7 patients (5 with malignant tumors), and the most common error was interpreting a solid tumor as hematoma. These studies highlight the utility and pitfalls of ultrasonography. Although it is a useful tool in evaluating patients with soft-tissue masses and for use in guiding biopsy, ultrasonography is not routinely performed in clinical practice as an initial imaging study, nor does its use preclude the need for additional cross-sectional imaging evaluation.

Because of the inability of sound waves to penetrate bone, little role exists for ultrasonography in the evaluation of bone lesions.

**Nuclear Medicine**

Radionuclide skeletal scintigraphy uses technetium-labeled diphosphonates, which adsorb to the crystalline structure of hydroxyapatite. These tracers accumulate in areas of osteoblast activity, thus indicating areas of bone perfusion and bone turnover. Skeletal scintigraphy is a cost-effective, whole-body imaging modality for the evaluation of multifocal or disseminated osseous disease (Fig 4). Fludeoxyglucose F 18 (FDG) is the most commonly utilized radionuclide for PET. FDG-PET is a functional imaging technique that assesses tissue metabolism using radioisotopes that undergo positron emission de-
FDG is a glucose analogue transported into the cell; however, once it is phosphorylated, it does not undergo further metabolism and becomes trapped. Fluorine F 18 then decays, producing 2 coincident positrons that can be used to produce the image. Glucose metabolism can be quantified by measuring maximum standardized uptake value. A caveat to using PET/CT in musculoskeletal applications is the considerable overlap of standardized uptake values in benign and malignant soft-tissue and bone lesions. In addition, non-neoplastic conditions (e.g., inflammatory processes, trauma) can also result in abnormal uptake, mimicking malignancy and reducing the specificity of PET/CT.

PET/CT has been investigated for biopsy guidance, staging, and treatment response. Typically, MRI of the primary lesion is performed; therefore, PET/CT is used for the detection of metastatic disease. The lung is the predominant site of metastatic disease from soft-tissue sarcoma, and it is unclear how well PET can detect metastases not already identified by CT of the chest. In several studies on the initial staging of soft-tissue sarcoma in adults using PET/CT, fewer than 5% of patients were upstaged as a result of PET/CT, and few patients had the management of their disease changed as a result. In a study of pediatric patients, FDG PET/CT was equally effective in identifying primary tumors (100%) compared with conventional imaging (CT and MRI) and was superior in the identification of metastatic lymph nodes (25% vs 95%) and bone metastasis (57% vs 90%). PET/CT was also found to have diagnostic benefit in the detection of bone metastases in osteosarcoma and pediatric Ewing sarcoma, but it was less sensitive compared with conventional CT in the detection of lung nodules (Fig 5). This finding underscores the importance of CT of the chest in the staging workup of soft-tissue and bone sarcomas. The utility of PET/CT beyond diagnostic CT of the chest for the initial and subsequent follow up of sarcomas is unclear. However, it may have added value in certain sarcomas (rhabdomyosarcoma, clear cell, epithelioid) in which the pattern of spread includes nonpulmonary sites, such as bone, retroperitoneum, and lymph nodes.

Although the role of FDG-PET/CT is unclear in the initial diagnosis and staging of soft-tissue sarcoma, it can be used to assess therapeutic response early during treatment. Post-treatment changes measured by the FDG avidity of the tumor are an indicator of the effectiveness of the therapy. Earlier biochemical changes in a tumor can enable clinicians to evaluate therapeutic effectivenss earlier than conventional anatomical imaging. In particular, sarcomas are challenging because an increase in size often does not indicate poor response to therapy. Often, preoperative radiotherapy causes hemorrhage or necrosis leading to tumor enlargement. An increase in tumor size (≤ 20%) observed after radiotherapy but prior to surgery has not been associated with worse outcomes. PET/CT can also be used to guide biopsy. Soft-tissue sarcomas are often heterogenous on MRI, with areas of necrosis or myxoid components. If these areas are sampled, then the tumor may be inappropriately downgraded. PET/CT can assist in targeting hypermetabolic areas that can increase the diagnostic yield of sampling (Fig 6). However, the evidence for the use of PET for guidance during biopsy is based on a small number of studies, so
the routine use of PET to guide biopsy in real time is
not routinely performed.26

More specifically, novel radiopharmaceuticals for
use with PET, such as proliferation markers (fluoro-
deoxythymidine F 18), bone-seeking agents (sodium
fluoride F 18), amino-acid tracers (methionine C 11,
fluoroethyltyrosine F 18), or biomarkers of neoangio-
genesis (galacto-RGD F 18), are not routinely used in
clinical practice. However, they can potentially eluci-
date the underlying biological mechanisms of muscu-
loskeletal tumors and, with future research, possibly
contribute additional information to the grading, treat-
ment monitoring, and post-therapy assessment.27

Applications for PET/MRI continue to grow in
clinical practice.17 The literature on PET/MRI is not yet
available for all tumors, but PET/MRI may be of benefit
in staging and assessing treatment response in bone
and soft-tissue sarcomas.17 In general, PET/MRI may be
indicated in malignancies that require high soft-tissue
contrast for visualization, and it will be of utility in the
pediatric population because radiation exposure can
be reduced.17,28

**Computed Tomography**

When the radiographic features of a bone lesion are
indeterminate or aggressive, cross-sectional imaging is
usually obtained. Because of its superior ability to visu-
alize bony detail and evaluate cortical bone, CT is often
the modality used to evaluate tumors located within
the periosteal or cortical regions (eg, osteoid osteoma;
Fig 7).3 CT can better demonstrate subtle mineraliza-
ton or calcification that may not be appreciated on ra-
diography.4 Evaluation of flat bones and small bones
of the hands and feet are also better evaluated with CT
(Fig 8).4 Due to the complex anatomy in the spine and
pelvis, CT may also be a preferred modality or used in
adjunct to MRI.4 CT may also be the most appropriate
imaging modality for patients who are obese, patients
with pacemakers, and when MRI is not feasible.1

Earlier literature comparing MRI and CT for the
evaluation of bone tumors showed that MRI was su-
perior for initial staging.4,29-31 Zimmer et al30 and Ho-
geboom et al30 studied features of bone tumors such as
cortical destruction and involvement of marrow, soft
tissue, joints, and neurovascular structure on CT and
MRI.4 Both studies showed superiority of CT for evalu-
ating cortical bone involvement, but MRI better demon-
strated neuromuscular, and joint and compartmental
involvement, as well as intramedullary extent.29,30
Both studies also favored MRI if both CT and MRI were
available.29,30 One group demonstrated no statistical
difference between CT and MRI in the evaluation of
the extent of tumor involvement in 183 patients with
primary bone tumors (Fig 9).1,4,31

CT is useful in evaluating mineralized matrix and
bone changes related to soft-tissue sarcoma.32 It can

![Fig 7A–C. — CT evaluation of cortical lesions. (A) Radiography of the
humerus and (B) coronal CT show a benign, smooth, continuous, solid,
periosteal reaction along the medial cortex. (C) Axial CT demonstrates
a cortical-based lucency in the cortex compatible with osteoid osteoma.
The benign periosteal reaction was produced by inflammation caused by
osteoid osteoma. CT = computed tomography.](image)

![Fig 8A–C. — CT evaluation of the small bones in the feet. (A) Oblique
view of the foot shows a lucent lesion with a sclerotic center con-
firmed by (B) long-axis and (C) axial CT. CT demonstrates a lucent
lesion consistent with osteoid osteoma as well as the calcified fibro-
vascular nidus, which is the inciting lesion. CT also shows the dis-
ruption of the cortical bone that was not observed on radiography.
CT = computed tomography.](image)

![Fig 9A–C. — (A) Lateral radiography of the tibia. (B) Sagittal T1-weight-
ed MRI. (C) Sagittal-reconstruction CT in a boy aged 15 years with left
tibial adamantinoma. Radiographs, CT, and MRI all show the eccentric,
cortical-based location and extent of the lesion with an intact cortex.
CT = computed tomography, MRI = magnetic resonance imaging.](image)
be helpful in distinguishing soft-tissue sarcoma from myositis ossificans — a distinction that can be difficult on MRI, as both can have nonspecific features on T1- and T2-weighted imaging — because CT can delineate the zonal pattern of mineralization characteristic of myositis ossificans.32

**Magnetic Resonance Imaging**

Evaluation of bone tumors using MRI can help clinicians identify the extraosseous component, if present, and the compartmental location can be well evaluated — both are important factors in the preoperative evaluation. In addition, a diagnosis other than a tumor (e.g., radiographically occult fracture, osteonecrosis) may be elucidated on MRI.35 It is important to remember that radiography plays an important and complementary role in the evaluation of bone tumors. Most bone lesions (malignant and benign) have high T1 and T2 relaxation times, producing nonspecific low T1 and high T2 signals.2 This fact makes the rendering of a particular histological diagnosis all the more difficult when evaluated in the absence of radiography. In-phase and out-of-phase (also known as opposed) imaging can be useful in the evaluation of bone lesions, particularly in delineating red marrow hyperplasia from metastatic disease.

In general, MRI has replaced CT as the imaging modality of choice in the evaluation of soft-tissue masses.1 Based on the findings of 133 soft-tissue tumors, one group found that MRI and contrast-enhanced CT were comparable when determining tumor size and involvement of surrounding structures.1,31 However, in clinical practice, MRI is the preferred imaging modality for the detection, evaluation, assessment, staging, and follow up of soft-tissue tumors.

The advantages of MRI include establishing a differential diagnosis of the lesion, precise compartmental localization, and assessment of neuromuscular and joint involvement. In addition, MRI can be used to visualize the entire compartment, which can demonstrate metastatic lymphadenopathy — seen only in certain sarcomas (Fig 10). MRI is excellent at delineating soft-tissue lesions, and a specific diagnosis can be obtained in many instances by evaluating lesion signal intensity, location, growth pattern, and other unique intrinsic properties.35 Unless a specific diagnosis can be made, the lesion should be considered indeterminate and then biopsied in close consultation with an orthopedic oncologist.

Unless it is contraindicated, contrast should be administered when evaluating soft-tissue tumors. Contrast enhancement delineates areas of necrosis within the lesion and allows differentiation of myxoid material from fluid foci (Fig 11). Myxoid tissue is a gelatinous material comprised of glycosaminoglycans, and it is commonly seen in soft-tissue sarcomas.34 Myxomatous stroma demonstrates mild enhancement, which is in contrast to cystic areas or necrosis that does not enhance.

Oftentimes, the degree of enhancement is visually equivocal. In these cases, subtraction sequences can be used. Precontrast, T1-weighted images are subtracted from the postcontrast T1-weighted sequences by software to yield areas of true enhancement (Fig 12). The utility of gadolinium in imaging bone tumors is controversial; nevertheless, the pattern and degree of contrast enhancement can be useful, particularly when evaluating for extraosseous extension.

**Important Features:** The location, size, and signal features of a lesion should be assessed. In general, heterogeneous signal is seen in sarcomas, including areas of mixed tissue, necrosis, or hemorrhage. If areas of intralesional fat or calcification are observed, or the mass is arising from a nerve, then the differential diagnosis can be appropriately narrowed as a lipomatous or nerve sheath tumor, respectively. The

---

**Fig 10A–B.** — MRI detection of lymphadenopathy. (A) Axial, post–contrast MRI of the thigh demonstrates a large, posterior, compartment mass with peripheral enhancement consistent with leiomyosarcoma proven by biopsy. (B) Axial MRI of the ipsilateral inguinal region demonstrates an enlarged, enhancing lymph node compatible with metastatic disease. With the exception of certain histological subtypes, nodal metastatic disease is not commonly seen in soft-tissue sarcomas. MRI = magnetic resonance imaging.

**Fig 11A–C.** — Heterogenous soft-tissue sarcoma. (A) Axial T1-weighted, (B) T2-weighted, and (C) post–contrast MRI of a thigh with malignant myxoid liposarcoma. High T2-signal areas throughout the mass represent myxoid stroma, a gelatinous material comprised of glycosaminoglycans, commonly seen in soft-tissue sarcoma. Myxomatous stroma demonstrates mild enhancement; this is in contrast to cystic areas or necrosis, neither of which enhance on MRI. MRI = magnetic resonance imaging.
presence of areas of low signal on multiple sequences can suggest the presence of fibrous tissue.

The high soft-tissue contrast of MRI enables the clinician to assess the relationship between the tumor and neurovascular bundle (Fig 13). If the contact between the tumor and the adjacent neurovascular structures exceeds 180 degrees, then encasement should be suspected.35

Direct osseous involvement by soft-tissue sarcoma rarely occurs, but the clinician should still evaluate for it because its presence has been shown to correlate with disease-related mortality.32,36 Osseous invasion of the medullary cavity can be assessed on MRI by signal changes in the normal fat-containing marrow (see Fig 13). Cortical involvement may be more difficult to detect on MRI due to the low signal of cortical bone on all sequences; in these cases, CT can be used as an adjunct imaging modality.

Typically, a rim of low signal surrounding the tumor can be seen in sarcomas. Malignant tumors push away normal tissue around them as they enlarge; therefore, sarcomas do not infiltrate the anatomical compartments and fascial borders until late in their course. Local growth of soft-tissue sarcoma occurs in a radial fashion, compressing surrounding fibrous connective tissue, which, in combination with associated inflammatory reaction, forms a “pseudocapsule” around the tumor (Fig 14).33,37

Another important feature to assess is the presence of peritumoral high T2 or fluid signal changes that can be seen in benign and malignant tumors.37 This may be due to the increased water content in the tissues, known as peritumoral edema (see Fig 14).38 Typically, areas of peritumoral edema enhance, and they have been attributed to microscopic tumors, inflammatory reactions, vascular congestion and hyperperfusion, or edema.38 In a study by White et al,38 malignant cells were histologically identified in tissue beyond the tumor margin in 10 out of 15 cases. Identification of malignant cells beyond the margin of the tumor necessitates treatment modifications, such as extension of the radiation field or repeated resection to reduce the risk of local recurrence.

In addition to the initial staging of primary soft-tissue and bone tumors, MRI is the preferred modality for the evaluation of locally recurrent disease.17,37 Surgical and radiation changes can produce abnormal signals related to fibrosis, edema, and metallic susceptibility artifact, thus making imaging...
interpretation complex. Postoperative fluid collections or seromas can complicate the detection of recurrent disease, which most often presents with enhancing nodules in the tumor bed (Fig 15). However, enhancing mural nodules within seromas may not necessarily represent recurrent disease and should be followed up. Another common finding is treatment-related changes of the bone marrow, which can be difficult to differentiate from tumor. T1-weighted sequences and chemical-shift MRI can be useful tools for delineating changes in bone marrow from neoplasms.

**Novel Techniques**

**Chemical Shift and In- and Out-of-Phase Magnetic Resonance Imaging**

In-phase and out-of-phase (opposed) MRI allows the clinician to detect the presence of fat in lesions, so this imaging modality may be useful for delineating whether a signal abnormality seen in the marrow is likely caused by red marrow hyperplasia or a marrow-replacing process. Normal yellow marrow has a high fat content with a hyperintense signal on non-fat-suppressed T1 sequences. Normal bone marrow is rich in both fat and water, but their relative amounts is the main factor affecting signal intensity of marrow on MRI. When both fat and water are present in the same voxel, this combination results in the suppression of signal intensity on out-of-phase imaging. Marrow-replacing processes result in a lower T1 signal and lack of suppression of signal intensity on out-of-phase imaging (Fig 16). Hematopoietic or red marrow can produce focal areas of decreased T1 signal, thus mimicking a marrow-replacing lesion. Red marrow also contains fat — albeit less when compared with yellow marrow — and, therefore, can be differentiated from true lesions by chemical shift MRI. A technique described by Costa et al involves drawing regions of interest of equal size over the abnormal areas on both the in-phase and out-of-phase imaging. The signal intensity ratio of the marrow on the out-of-phase and in-phase imaging is calculated. A signal intensity ratio below 0.80 is typical of a non-neoplastic process. A study by Zajick et al showed that a 20% decrease in signal intensity on the out-of-phase images from the in-phase images was a reliable feature for distinguishing benign from malignant bone marrow in the spine. Although using a signal intensity ratio higher than 0.80 has been proposed to identify neoplastic lesions, chemical shift MRI has not been consistently shown to differentiate malignant from benign tumors.

**Diffusion-Weighted Magnetic Resonance Imaging**

Diffusion-weighted is a noncontrast, functional MRI technique that has been investigated for the characterization of tumors throughout the body. The signal intensity of diffusion-weighted MRI relies on the Brownian motion, or the microscopic motion of water molecules within tissues. The apparent diffusion coefficient (ADC) is a quantitative measure of Brownian motion. In highly cellular environments, free diffusion of water is restricted, resulting in low ADCs. Acellular tissue (ie, necrosis) allows free diffusion in all directions, resulting in high ADCs. Areas of restricted diffusion (ie, because of high cel-

---

Fig 15. — MRI detection of recurrent disease. Axial, postcontrast MRI in a patient with resected, high-grade sarcoma undergoing surveillance. Areas of diffuse enhancement (white arrowheads) are consistent with postoperative change and scarring. However, 2 solid, enhancing nodules adjacent to the humeral head (red arrows) reflect recurrent disease. MRI = magnetic resonance imaging.

Fig 16. — Chemical shift MRI. Coronal postcontrast MRI shows a metastatic lesion in the humerus. In- and opposed-phase axial imaging show no signal decrease, indicating that no fat-containing voxels can be found in the lesion, thereby suggesting this patient has a malignant lesion. MRI = magnetic resonance imaging.

Images courtesy of Laura M. Fayad, MD, Johns Hopkins Medicine, Baltimore, Maryland.
lularity) have higher signal intensity on diffusion-weighted MRI but lower signal intensity on ADC maps (Fig 17).12,43 The ADC value for a specific region of interest is calculated by plotting the change in signal of the region as it varies with different diffusion gradient strengths (b values).50

Diffusion-weighted MRI has been used to better evaluate treatment response in patients with sarcoma receiving chemotherapy.13,49 However, the literature shows variable results in the ability of diffusion-weighted MRI to distinguish between benign and malignant soft-tissue masses.49,51 A study by Subhawong et al49 determined that a threshold mean ADC of 2.5 provided a 100% specificity rate for predicting a cyst and ruling out a solid tumor. Demehri et al52 demonstrated the ability of a minimum ADC to differentiate benign from malignant peripheral nerve sheath tumors.

Few studies have examined the utility of diffusion-weighted MRI in the evaluation of bone lesions; however, a study by Ahlawat et al47 determined the minimum ADC threshold of 0.9 \times 10^{-3} \text{ mm}^2/\text{second} and 1.4 \times 10^{-3} \text{ mm}^2/\text{second} (mean ADC) for differentiating benign and malignant histology (see Fig 17). A study of patients with osteosarcoma suggests that change in ADC may be useful in assessing response to chemotherapy and can differentiate areas of granulation tissue and scarring from viable cellular tumor.50,53

Although it is not routinely used, diffusion-weighted MRI is an unenhanced method that may provide helpful clinical information, and it can be used in situations in which intravenous contrast cannot be administered due to contraindications or patient refusal.

**Proton Magnetic Resonance Spectroscopy**

Proton magnetic resonance spectroscopy is a technique used to characterize tumors based on their molecular properties; similar to diffusion-weighted MRI, it can be performed without intravenous contrast.54 The metabolic “footprint” of a lesion is determined based on the signal of water, lipids, and various metabolite content.54 Choline-containing compounds are constituents of cell membrane phospholipids and are a reflection of cell-membrane turnover. Therefore, the presence of a spectroscopic choline peak is suggestive of malignancy.54,56 The presence of a choline peak is supportive of malignancy, although some metabolically active benign tumors and abscesses may also have a choline peak.

Magnetic resonance spectroscopy is not widely used in clinical practice for musculoskeletal applications, but it shows promise in the noncontrast magnetic resonance evaluation of bone and soft-tissue lesions.

**Habitat Imaging**

Several groups have been working on the quantitative evaluation of tumor subregions in the setting of soft-tissue sarcoma.57-61 Utilizing several computer-aided techniques, including clustering algorithms and texture-feature analyses, one group noninvasively evaluated tumor subregions, or “habitats,” to better elucidate the heterogeneity of soft-tissue sarcoma. T1-weighted, gadolinium-enhanced, and fluid-sensitive pretreatment MRI was analyzed in the extremities of patients with soft-tissue sarcoma.57 Segmentation based on the pixel signal intensity was performed, followed by an analysis within each distinctive subregion to predict metastatic disease and histological necrosis.57 From this analysis, habitat maps were derived based on combinations of pixel intensity combinations from the 2 sequences, demonstrating distinct, spatial intratumoral subregions (Fig 18). The yellow-color habitat map corresponds to a high T1, postcontrast/low, T2 signal (inferred as high vascularity and cellularity), which was both predictive and prognostic. The yellow subregion correlated with decreased overall survival (P = .03) and, if present in more than 18% of the tumor slice, is predictive for the development of metastatic or locally recurrent disease. Based on texture-feature analysis, pretreatment MRI predicted that the rate of metastatic development in patients with soft-tissue sarcoma was 72.4%.61 Continued investigation into the change in habitats on pre- and post-treatment MRI is also being conducted.62 Habitat imaging is an evolving area of study that may be useful for more accurately assessing prognosis and tailoring personalized therapies.57

**Conclusions**

Progress has been made in the imaging evaluation of musculoskeletal tumors. Detecting lesions on mag-
Fig 18A–F. — Habitat imaging in a patient aged 48 years with high-grade, undifferentiated sarcoma in the left thigh. (A, D) Axial, contrast-enhanced, (B, E) T2-weighted, fat-suppressed, and (C, F) habit color mapping obtained following computed tumor segmentation. Panels A to C show pre-treatment MRI. Panels D to F show post-treatment MRI. The color maps illustrate distinct, intratumoral subregions, or habitats, derived from pixel signal intensities. The degree of spatial heterogeneity within the tumor is better delineated on the habitat color map. Note the change in distribution and size of the habitats between pre- and post-contrast color maps. The yellow subregion comprises more than 18% of the tumor pretreatment color map in panel C, thus inferring a poor prognosis. This patient had metastatic disease to the lungs and died less than 1 year after diagnosis. MRI = magnetic resonance imaging.

magnetic resonance imaging has improved the ability of clinicians to differentiate normal anatomical variants from true lesions and to characterize these lesions; additional advances and the development of novel techniques will continue to enhance this ability. Other conventional imaging modalities continue to play an integral and complementary role in the evaluation of musculoskeletal tumors. Habitat imaging that uses magnetic resonance imaging can identify and quantify tumor heterogeneity and provide health care professionals with useful clinical and prognostic information that can shape personalized and adaptive therapeutic regimens.

References

44. Kransdorf MJ, Murphy MD. Soft tissue tumors: post-treatment im-


Advanced HNSCC requires multimodal imaging for appropriate, multidisciplinary treatment planning and follow up.

Multimodal Imaging of Head and Neck Squamous Cell Carcinoma
Kenneth L. Gage, MD, PhD, Kerry Thomas, MD, Daniel Jeong, MD, Dexter G. Stallworth, MD, and John A. Arrington, MD

Background: The role of imaging in the staging, treatment planning, and ongoing surveillance of patients with head and neck squamous cell carcinoma (HNSCC) continues to evolve. Changes in patient demographics, treatment paradigms, and technology present opportunities and challenges for the management of HNSCC.

Methods: The general indications and usage of standard and multimodal cross-sectional imaging in the evaluation and management of HNSCC are reviewed, with an emphasis on incorporating them into treatment pathways. Emerging imaging technologies and methods with a potential near-term impact on HNSCC are discussed.

Results: In general, the complex, multidisciplinary approach to the treatment of advanced HNSCC requires multimodal imaging for adequate treatment planning and follow up. Early-stage disease can often be managed with clinical and endoscopic examinations and a single, cross-sectional imaging modality (eg, computed tomography, magnetic resonance imaging).

Conclusions: Although generalized treatment pathways and guidelines do exist, the literature is rapidly advancing and new radiotracers and evaluation methods are expected to alter both imaging and treatment recommendations in the years to come.

Background
In the United States, head and neck cancers are expected to account for 3.7% (63,030 new cases) of all cancers diagnosed in 2017.1 In that same year, an estimated 13,360 Americans will die as a result of tumors involving the oral cavity, pharynx, and larynx.1 The worldwide incidence of new cases of head and neck cancers is estimated to be greater by an order of magnitude, with 686,000 new cases diagnosed and 375,000 related deaths.2 Head and neck cancers encompass a broad range of tumor histologies and locations. However, more than 90% of head and neck cancers are squamous cell carcinomas, arising from the upper aerodigestive tract and frequently involving the oral cavity, oropharynx, hypopharynx, and larynx.2 Although the overall rate of new cases of oropharyngeal cancer in the United States has been stable or decreasing, cases linked to human papillomavirus (HPV) continue to rise, altering the demographics and presentation of new cases of head and neck squamous cell carcinoma (HNSCC).3

Because of its low contribution to the overall cancer incidence in the United States, the true impact of HNSCC on public health may be under-represented.1 No widely accepted screening test exists for HNSCC,

From the Diagnostic Imaging and Interventional Radiology Program (KLG, KT, DJ, DGS, JAA), H. Lee Moffitt Cancer Center & Research Institute, and the Departments of Oncologic Sciences (JAA) and Radiology (JAA), University of South Florida College of Medicine, Tampa, Florida.

Address correspondence to John A. Arrington, MD, Moffitt Cancer Center, 12902 Magnolia Drive, WCB-RAD MD/OPI, Tampa, FL 33612. E-mail: John.Arrington@Moffitt.org
Submitted November 10, 2016; accepted March 28, 2017.

No significant relationships exist between the authors and the companies/organizations whose products or services may be referenced in this article.
and many patients present with advanced-stage disease, requiring disfiguring surgery, chemoradiotherapy, or both. Both timely diagnosis and accurate staging of HNSCC are critical to avoid under- or overtreatment and to minimize mortality and morbidity. Thus, the objective of this review is to summarize the role of imaging in the management of HNSCC throughout the continuum of care while also providing clinical examples highlighting the strengths and weaknesses of each imaging modality (magnetic resonance imaging [MRI], contrast-enhanced computed tomography [CT], and positron emission tomography [PET]/CT).

**Role of Imaging**

Since the introduction of CT and MRI, the role of imaging in HNSCC has grown. The widespread application of fludeoxyglucose F 18 (18F-FDG) positron emission tomography (PET) in the late 1990s added a functional metabolic component to imaging, with the subsequent fusion of functional (PET) and anatomical (CT) imaging in the combined modality of PET/CT resulting in further improvements in disease management. Continued technological progress and the broadening applications further increase the role of diagnostic imaging in the evaluation and management of HNSCC. PET/CT, contrast-enhanced CT, and MRI have well-defined strengths and weaknesses and, therefore, play complementary roles in the evaluation and treatment planning of HNSCC. However, no single imaging modality can accurately diagnose, stage, and provide long-term surveillance of HNSCC.

**Initial Staging**

Accurate initial staging is critical to the establishment of prognosis, treatment selection, and the management of HNSCC. Guidelines issued by the American Joint Commission on Cancer represent the standard for HNSCC staging and require detection and precise delineation of the patient’s primary tumor (T), cervical nodal involvement (N), and distant metastases (M) for classifying patients, a process known as TNM staging. These guidelines provide separate staging criteria based on the mucosal site of origin, separating patients into those with cancers of the lip and oral cavity, pharynx, and larynx. The resulting prognostic stage groupings range from stages I to IV and also include substages.

In general, diagnostic imaging complements the clinical evaluation of the primary tumor and regional cervical lymph nodes and can be used to detect metastases and second primary tumors in patients with HNSCC. Following an initial clinical examination and endoscopy of the upper aerodigestive tract with biopsy, staging is refined with diagnostic imaging and finalized with the pathological evaluation of cervical lymph nodes from nodal dissection, if performed.

**Primary Site**

The extent of mucosal involvement by the primary tumor is best documented through clinical and endoscopic examinations, whereas imaging is obtained to evaluate submucosal and deep, soft-tissue extension as well as osseous, cartilaginous, or skull-base involvement.

The location of the primary site of disease can influence the selection of modalities for initial imaging assessment. For example, MRI is often the preferred imaging modality for evaluating the oral cavity, especially the anterior tongue, retromolar trigone, and the floor of the mouth, in which dental hardware and beam-hardening artifact can limit the usefulness of CT. MRI provides superior soft-tissue contrast and allows the detection of suspicious changes in bone marrow, aiding in the evaluation of the adjacent mandible and other osseous structures when tumor invasion is suspected. MRI is considered the best imaging modality for assessing perineural tumor spread, intracranial and orbital extension (Fig 2), nasopharyngeal carcinoma, and marrow involvement.

However, the superior, soft-tissue contrast provided by MRI of the head and neck is not without its own limitations. The intense inflammatory response surrounding some lesions highlighted with contrast-enhanced MRI can lead to difficulties in determining the true extent of disease, thus complicating treatment approaches and radiation fields (Fig 3). In some cases, the true lesion burden is better delineated with functional techniques such as PET/CT. In addition, the relative scarcity of excitable protons in the osseous matrix results in minimal signal from cortical bone, which may limit the detection

![Fig 1A–D](image-url) — A man aged 63 years with an infiltrating, destructive mass involving the right mandible from right retromolar trigone squamous cell carcinoma. (A) Axial, contrast-enhanced CT reveals the limited lesion visibility from beam-hardening artifact on CT, even from primarily left-sided dental hardware. (B) Coronal imaging allow improved visualization of the mandibular destruction; however, contrast-enhanced, T1-weighted, fat-suppressed imaging (B and D) provides better representation of the true extent of soft-tissue involvement in this case. CT = computed tomography.
and accurate characterization of osseous destruction on MRI (Fig 4). In these cases, diagnostic CT is often considered the best imaging modality for lesion assessment.

**Locoregional and Nodal Disease**

The most important factor that affects prognosis is cervical nodal status, and an accurate assessment is critical to the treatment plan and choice of therapy. Patients with cervical nodal metastasis, distant metastasis, or both types of metastases have worse prognoses and decreased 5-year survival rates when compared with those without metastatic disease. The importance of nodal status for overall prognosis and management is such that debate remains as to when elective neck dissections or irradiation should be performed, with a 20% or greater risk of occult, microscopic nodal disease often used as a threshold for prophylactic treatment. Imaging detection (or exclusion) of clinically occult nodal metastasis, distant metastasis, or both types of metastases may alter the treatment plan, thus reducing rates of unnecessary surgery and therapy as well as associated morbidity and cost.

Diagnostic imaging adds to the clinical evaluation of cervical nodal involvement by detecting clinically occult nodal metastases and identifying morphological features of clinical importance (Fig 5), such as the presence of extracapsular nodal extension, vascular encase-
ment, and “matted” lymphadenopathy (loss of the fat plane between ≥ 3 adjacent lymph nodes with extracapsular tissue). In general, contrast-enhanced CT and MRI are superior for detecting nodal anatomic features and provide an excellent anatomical road map for surgical planning; PET/CT demonstrates excellent overall sensitivity for the presence of nodal metastatic disease.

The detection of small, nonclustering nodal metastases can be challenging when using anatomical imaging approaches such as CT or MRI. Criteria have been established for the assessment of cervical lymph nodes using both modalities; these criteria attempt to balance the sensitivity and specificity of various nodal features, with size being the dominant component. Of course, size is not the single imaging feature of interest, and the high spatial resolution and standard use of contrast for both CT and MRI provide improved anatomical definition, which readily reveals suspicious morphological features such as those previously described. The rising prevalence of HPV-positive status in patients with HNSCC has led to an increase in patients presenting with cystic lymph-node metastases, which can be difficult to appreciate on PET/CT due to the minimal metabolic activity in the cystic component but are easily visualized on contrast-enhanced CT and MRI (Fig 6).12

Although PET/CT has superior overall accuracy for the detection of nodal metastases, the absolute physical limitations of the imaging technology can result in false-negative results for nodes measuring less than 1 cm. In addition, the nonspecific nature of hypermetabolic activity can confound PET/CT interpretation. Elevated concentrations of 18F-FDG can occur in post-treatment infection and localized inflammation but are also observed during the initial staging process. Oftentimes, PET/CT does not adequately delineate deep soft-tissue extension or osseous involvement, and therefore may not provide an adequate anatomical road map for surgical and treatment planning. High-resolution, cross-sectional imaging with contrast-enhanced CT or MRI provides the anatomical details and soft-tissue contrast necessary for therapy.

**Distant Metastatic Disease**

Distant metastases are estimated to be extant in 10% to 15% of patients at the time of HNSCC presentation and can profoundly alter treatment. In such cases, localized surgery and radiotherapy with curative intent are abandoned and management directed toward a palliative, systemic approach.

Screening for metastatic disease at the time of the initial diagnosis is a generally well accepted use of PET/CT for the initial evaluation of advanced head and neck cancers, with PET/CT demonstrating superior sensitivity for the detection of distant metastases as well as second primary cancers. In patients for whom PET/CT is unavailable or not clearly indicated, those with HNSCC and higher-stage lesions will still often receive imaging beyond the anatomical limitations of the head and neck. In general, head and neck cancers tend to have distant metastases to the lungs, with nasopharyngeal carcinoma proving to be the exception with osseous metastases. In these instances, patients will often undergo dedicated, contrast-enhanced CT of the chest due to the increased risk of metastatic disease.

**Challenges**

Despite the approaches for initial TNM staging, several questions remain as to the most appropriate approach for evaluating patients with less-common clinical presentations such as occult primary lesions and those presenting without palpable cervical adenopathy.

**Cancer of Unknown Primary:** Patients with HNSCC can present with cervical adenopathy from an occult primary lesion despite thorough clinical or endoscopic evaluation, a situation termed carcinoma of unknown primary (CUP). Historically, CUP was a rare presentation of patients with HNSCC, especially as the use of multimodal imaging became widespread. However, the increasing prevalence of HPV-positive disease has led to an increase in CUP, possibly due to the tendency of these tumors to have increased nodal disease burden with small or occult primary lesions.
PET/CT has been shown to have superior sensitivity compared with contrast-enhanced CT and combined CT/MRI for the detection of occult primary lesions, with the added advantage of its ability to detect distant metastatic disease and synchronous second malignancies (Fig 7). In addition, PET/CT can locate infraclavicular sites of primary disease when primary head and neck cancer is not the source of adenopathy, and it has been recommended for the workup of patients when standard clinical and imaging approaches are unable to identify a primary site of disease.

Management of “true” CUP remains challenging, with panendoscopy, tonsillectomy, and “blind” biopsies of lymphoid tissue advocated as possible approaches to identify occult primary lesions when diagnostic imaging is unable to provide a potential target.

Clinically Negative Neck: Patients can present with symptomatic primary lesions without palpable nodal metastatic disease, a situation termed clinically negative neck (staged cN0 in the TNM staging system). These cases are diagnostically challenging because the nodal status of the patient is of primary importance for disease prognosis and management.

Use of PET/CT for the evaluation of the clinically negative neck is controversial, especially for early-stage disease: Historical studies have been unable to discern a significant advantage of PET or PET/CT over more traditional, cross-sectional imaging such as contrast-enhanced CT and MRI. One meta-analysis found similar diagnostic accuracy rates between MRI, CT, PET, and ultrasonography for the detection of occult disease in the setting of a clinically negative neck. However, data from Roh et al, who conducted a prospective clinical trial, found PET/CT to have superior sensitivity for the detection of clinically occult, cervical metastatic disease compared with CT/MRI (71% vs 50%), a finding that highlights the importance of the improved anatomical localization seen in the combined PET/CT approach. Although it is an active area of research, PET/CT may be reaching the point where certain neck dissections may be avoided or — at the very least — minimized, thus resulting in decreased associated costs and morbidity.

Second Primary Malignancies: Patients with HNSCC are at significant risk of second (synchronous) or metachronous primary malignancies, which can present at the initial diagnosis, during treatment, and at follow-up visits; these malignancies are estimated to occur in approximately 12% of cases. Presumably, these tumors are multifactorial in origin, with environmental factors (eg, use of tobacco, alcohol), infectious agents (eg, Epstein–Barr virus, HPV), and location of the primary lesion potentially playing a role in determining where and how frequently these lesions occur.

The impact of second primary malignancies on overall patient survival is significant. Approximately 75% of patients with HNSCC and second primary cancers will have those second primary cancers outside of the head and neck region, primarily involving the lungs. Therefore, it is imperative that infraclavicular imaging (contrast-enhanced CT of the chest, whole-body PET/CT, or whole-body MRI) be pursued for select patients.

Whole-body imaging is the standard approach for PET/CT in patients with HNSCC, unlike the limited field of view used for MRI and CT imaging. The extended anatomical field of PET/CT provides an advantage for detecting both distant metastatic disease and second primary malignancies outside of the head and neck, with pooled sensitivity and specificity rates estimated to be 88.8% and 95.1%, respectively. Whole-body MRI offers the potential to detect metastatic disease and second primary malignancies without the need for ionizing radiation; however, comparative studies in the pretreatment setting found no statistical difference between PET/CT and whole-body MRI.

Residual or Recurrent Disease
Patients with HNSCC who receive treatment may be cured of disease, harbor residual neoplasms at treatment sites, experience locally recurrent disease, or develop distant metastatic disease or new second primary malignancies (local or distant). Evaluation of these patients requires an approach that accounts for the sta-
tistical likelihood of local and distant disease and appropriately leverages imaging.

Detection of malignant disease (residual, recurrent, or second primary malignancies) in the treated head and neck can be challenging. Soft-tissue changes and anatomical disfigurement seen after surgery, chemotherapy, radiotherapy, or all 3 courses of management can distort the intricate anatomy of the head and neck, thereby limiting sensitivity for detecting residual or recurrent disease. PET/CT has been suggested as the best modality for assessment of the post-treatment or altered neck, although appropriate timing of follow-up PET/CT imaging (generally 12 weeks after treatment) is required to minimize false-positive findings from residual, treatment-related hypermetabolic activity (Fig 8).\textsuperscript{34} PET/CT with iodinated intravenous contrast has several diagnostic advantages but is not routinely used at most institutions.\textsuperscript{35}

In addition to the challenge of detecting locoregional failure on follow-up examination, patients with HNSCC may be at significant risk for distant metastatic disease and remote primary cancers, especially patients with higher-stage malignancies.\textsuperscript{14} PET/CT was found to have high sensitivity and specificity rates (92% and 95%, respectively) for detecting distant metastatic disease in patients suspected of having recurrent HNSCC (Fig 9).\textsuperscript{36} Protocols for whole-body MRI have also been used and compared with PET/CT for the evaluation of HNSCC in the post-treatment setting; however, superiority was not demonstrated of either modality, although a trend was observed toward greater diagnostic accuracy with PET/CT.\textsuperscript{37}

**Emerging Applications**

**Prognostic Evaluation With Functional Imaging**

Several efforts have been published regarding the use of quantitative \textsuperscript{18}F-FDG PET/CT measures as prognostic factors for head and neck cancers.\textsuperscript{38} These quantitative measures include the mean, max, and peak of the standardized uptake value, total glycolytic volume, and many others.\textsuperscript{39}

Despite the search to associate individual quantitative, continuous variables with clinically significant prognostic outcomes, studies have indicated that there is value in more qualitative assessments such as the visual pattern of metabolic activity.\textsuperscript{38,40,41} For example, qualitative metrics by Koyasu et al\textsuperscript{38} characterized lesions as having ring-shaped (ie, central decreased activity) vs sphere-shaped distributions of \textsuperscript{18}F-FDG and demonstrated a robust prediction of outcomes in their cohort. Mathematically characterizing these qualitative measures is the focus of the field of radiomics, an area of study that has had some success in head and neck cancers.

**Fig 8A–C.** — Imaging in a man aged 52 years with head and neck squamous cell carcinoma negative for human papillomavirus. (A) Beam-hardening effect from dental hardware limits evaluation of the oropharynx and adjacent structures on contrast-enhanced CT. (B) Combined PET/CT is less affected by beam hardening and reveals nonspecific, diffuse activity post partial glossectomy. (C) Repeat imaging several months later reveals more focal, intense, radiotracer accumulation in the posterior and anterior tongue and floor of the mouth, subsequently determined to be recurrent disease. CT = computed tomography, PET = positron emission tomography.

**Fig 9A–D.** — A woman aged 55 years with recurrent squamous cell carcinoma of the right maxillary sinus, negative for human papillomavirus and Epstein–Barr virus (same patient seen in Fig 3), now involving the pterygoids and mandible. (A) Maximum intensity projection, (B) CT, (C) \textsuperscript{18}F-FDG PET, and (D) \textsuperscript{18}F-FDG PET/CT imaging reveal evidence of numerous, distant pulmonary metastases. \textsuperscript{18}F-FDG = fludeoxyglucose F 18, CT = computed tomography, PET = positron emission tomography.
cancers and can potentially offer a more generalizable, systematic approach.40,41

**New Radiotracers**

Use of PET/CT has traditionally focused on 18F-FDG, a positron-emitting radiotracer that follows the initial steps of glucose metabolism and takes advantage of the propensity of malignant cells to preferentially utilize aerobic glycolysis as an energy source, the so-called Warburg effect.42 There is an increasing assortment of radiotracers targeting alternate pathways (fluorothymidine F 18, cellular proliferation), receptor targets, and tumor environmental conditions (fluoromisonidazole F 18, tumor hypoxia) that may prove useful for further characterizing HNSCC in patients.43-45

**Discussion**

The medical literature outlines well-defined roles for the various imaging modalities for the evaluation, management, and surveillance of HNSCC. Although these roles are generally accepted by multidisciplinary clinical services, variability exists between institutions regarding which imaging modality or modalities are useful for specific clinical situations. Surgeon and radiologist preference, availability, cost, health insurance coverage, and the patient’s clinical condition will impact imaging choices and utilization.

Treatment pathways developed at Moffitt Cancer Center and elsewhere provide guidance regarding the timing, frequency, and recommended protocols for the various imaging modalities used for the management of HNSCC.46 At Moffitt Cancer Center, we utilize contrast-enhanced CT as the mainstay of our cross-sectional imaging in patients with HNSCC and utilize MRI as a “problem solver” or in specific clinical situations such as perineural tumor spread or intracranial or orbital extension, as well as for the evaluation of postoperative patients with abnormal findings on PET/CT and a normal clinical examination. The utilization of MRI and contrast-enhanced CT is determined by patient-specific clinical concerns and questions that need to be answered by imaging. PET/CT is initially used in patients with higher T-staged disease at Moffitt Cancer Center to identify second primary malignancies and distant metastases, as well as in the post-treatment and surveillance settings to detect treatment failure and recurrence. Patient and disease-specific factors often lead to the adjustment of pathway recommendations, which are usually addressed on a case-by-case basis during multidisciplinary tumor boards.

**Conclusions**

The functional and physiological advantages of positron emission tomography (PET)/computed tomography (CT) combined with the cross-sectional anatomical details, superior soft-tissue contrast, and osseous evaluation provided by magnetic resonance imaging (MRI) or contrast-enhanced CT result in the most comprehensive imaging evaluation of head and neck squamous cell carcinoma (HNSCC). The complete evaluation provided by combined modalities (PET/CT with or without contrast-enhanced CT or MRI) is often needed for the management of advanced (stage III/IV) HNSCC, which generally requires multidisciplinary treatment encompassing surgery, radiotherapy, and chemotherapy. Fludeoxyglucose F 18 PET/CT has become the imaging cornerstone for evaluating these patients, with the decision being whether to utilize contrast-enhanced CT or MRI for anatomical details. Early-stage cancers, on the other hand, are often adequately imaged and staged with a single modality, usually contrast-enhanced CT. Established imaging guidelines are in constant flux as new imaging paradigms, radiotracers, and therapies are introduced and evaluated, and it is expected that quantitative imaging approaches will begin to play a more important role in the management of HNSCC.

**References**


Clinicians may encounter unique challenges when evaluating the imaging response of GBMs treated with immunotherapy and checkpoint inhibitors.

Assessing Response of High-Grade Gliomas to Immune Checkpoint Inhibitors

Solmaz Sahebjam, MD, Dexter G. Stallworth, MD, Sepideh Mokhtari, MD, Nam D. Tran, MD, PhD, and John A. Arrington, MD

Background: Immunotherapeutic agents, especially checkpoint inhibitors, have emerged as the mainstay of therapy for several solid and hematological malignancies. These therapies are under investigation for the treatment of high-grade gliomas and brain metastases.

Methods: This article reviews the unique challenges encountered when evaluating changes on magnetic resonance imaging (MRI) of glioblastomas seen in response to immunotherapy and checkpoint inhibitors and how to effectively incorporate MRI findings into the response assessment of high-grade gliomas to these emerging therapies.

Results: An increase in tumor size or the appearance of new lesions on MRI may represent either an immune-mediated inflammatory response or true tumor progression, which may precede the subsequent stabilization or response of high-grade gliomas to immunotherapy. These MRI findings should not result in the mandatory cessation of immunotherapy in patients with high-grade glioma.

Conclusions: Although immunotherapy Response Assessment for Neuro-Oncology criteria have been developed to assist with response assessment of high-grade gliomas to immunotherapy and to provide guidance with treatment decisions, these criteria have not been validated in prospective clinical trials. In patients with brain tumors who are receiving immunotherapy, MRI findings suggestive of disease progression should be evaluated with caution to prevent premature discontinuation of potentially beneficial therapies. Close, clinical monitoring with appropriate short-term, follow-up imaging is often necessary, and histopathological analysis may be required in some cases to confirm disease progression before a decision on continuation of these novel therapies can accurately be made.

Introduction

Immune checkpoint inhibitors have emerged as a mainstay of treatment for a variety of advanced malignancies. Antibodies against cytotoxic T-lymphocyte-associated protein 4, programmed death 1 (PD-1), and its ligand (PD-L1) have demonstrated significant clinical benefit in several solid and hematological malignancies, and their list of approved indications is expanding.

Anti-PD-1/PD-L1 antibodies alone or in combination with ipilimumab, an anti–cytotoxic T-lymphocyte-associated protein 4 antibody, is being investigated in patients with high-grade gliomas.1,3 These
therapies are well tolerated in patients with newly diagnosed or recurrent glioblastoma (GBM). Although the clinical benefit of these antibodies in the setting of high-grade glioma is yet to be confirmed, the preliminary data from small cohorts suggest an antitumor effect and clinical benefit when these agents are used as single-agent or combination therapy.

Assessing Radiographical Findings

Initial increases in tumor size or the appearance of new lesions can precede the subsequent response of solid tumors to immunotherapeutic agents. Premature discontinuation of immunotherapy based on the initial increase in tumor burden can deprive patients of potentially beneficial treatments. To address this challenge, new guidelines for the evaluation of response to immunotherapeutic agents in solid tumors have been developed. Immune-related Response Criteria allows continuation of treatment with appropriate follow-up time points to confirm disease progression. Similar imaging findings have been observed in patients with high-grade glioma who have received immunotherapeutic agents such as immune checkpoint inhibitors. The appearance of a new lesion or the progression of existing lesions following the initiation of immunotherapy can represent either an immune-mediated inflammatory response or true tumor progression. It is often difficult to differentiate tumor growth from treatment changes on imaging within the first 6 months after the initiation of immunotherapy. An effective immune response may take time to develop, and brain tumors may initially progress after the initiation of immunotherapy. Therefore, an increase in tumor burden does not necessarily preclude subsequent clinical benefit, and delayed effective, immune response may result in subsequent stabilization or regression of the tumor. Differentiating high-grade gliomas that initially progress after immunotherapy but will subsequently respond from those tumors that will not respond is a critical challenge. Furthermore, in some cases, the appearance of new lesions or the increase in size of the enhancing lesions can be the result of immune-related responses rather than tumor growth. Hence, response criteria specific for GBMs treated with immunotherapies, such as checkpoint inhibitors, is critical to prevent the premature termination of these therapies.

To accurately assess the imaging changes of high-grade glial tumors and GBMs to immunotherapy, a historical perspective and an understanding of the evolution of imaging response assessment in neuro-oncology is helpful. Macdonald, Response Evaluation Criteria In Solid Tumors, and World Health Organization criteria assess the imaging response of brain tumors to the direct antitumoral effect of cytotoxic therapy with either single or bidimensional measurements of the contrast-enhancing component of the tumor. Macdonald criteria were developed for computed tomography prior to the advent of magnetic resonance imaging, which is now standard of care for evaluating the imaging response of high-grade gliomas to therapy. Macdonald criteria incorporate the changes in bidimensional tumor measurements with clinical assessment and steroid dose for the response assessment of high-grade gliomas such as GBM to therapy.

Bidimensional measurements of the contrast-enhancing component of a GBM is not always an accurate assessment of the overall extent of the tumor, and measurable change in the contrast-enhancing portion of a GBM does not always represent an accurate assessment of response to therapy. Rather than being an accurate surrogate of GBM response to therapy, change in contrast enhancement reflects changes in the vascular permeability of the brain and tumor to contrast agents and can be seen with nontumoral, treatment-related changes such as ischemia, inflammation, acute and delayed radiation effects, and tumor growth.

Now that novel agents with different mechanisms of actions are being investigated, the response assessment of imaging changes is more complex because of treatment-related imaging findings that mimic tumor growth (pseudoprogression) and treatment-related imaging findings that mimic tumor response (pseudorresponse). Limiting the imaging response assessment of GBMs to bidimensional measurements of enhancing tumors and not incorporating the assessment of the nonenhancing portion of GBMs is a significant limitation of the Macdonald criteria. To adequately address the unique imaging challenges of GBM and provide guidance in distinguishing tumor growth from treatment-related responses, changes in response-assessment criteria were necessary.

Response Assessment in Neuro-Oncology (RANO) criteria published in 2010 were a collaborative effort to update and standardize response criteria for high-grade gliomas and replace the Macdonald criteria. RANO imaging criteria incorporate fluid-attenuated inversion recovery (FLAIR) with the bidimensional measurements of the enhancing portion of the GBM obtained on contrast-enhanced, T1-weighted imaging. By incorporating FLAIR signal changes into the imaging response assessment of GBM, RANO criteria allow the assessment of the nonenhancing component of the GBM as well as associated vasogenic edema and help distinguish treatment-related changes from true tumoral changes. RANO criteria give specific clinical and imaging findings required for the diagnosis of disease progression. Imaging findings that meet RANO criteria for tumor progression include:

- Development of new lesions outside the radiation field
- ≥ 25% increase in the sum of perpendicular diameters of enhancing lesions
- Substantial worsening of T2-weighted FLAIR signal changes

Critical to the RANO criteria is the guidance in assessing treatment-related imaging changes and distinguishing these changes from tumor growth or tumor progression.
regression. Changes in bidimensional measurements of the enhancing component of a GBM can reflect nontumoral changes or treatment-related effects and do not always accurately assess response to therapy. Pseudoprogression represents imaging changes related to treatment effects and not true tumor progression. The imaging changes of pseudoprogression include increasing measurable enhancement of a lesion associated with increasing FLAIR signal changes and can be seen in patients with GBM in the first 3 months following postoperative radiotherapy and temozolomide (Fig 1).

RANO criteria require that progressive disease not be diagnosed within 3 months of the completion of therapy with radiation and temozolomide unless there is new enhancement outside of the radiation field or the patient has clinically declined. Although RANO criteria require the cessation of therapy when there is either clinical or imaging evidence of progressive disease, they do allow continuation of therapy in patients who demonstrate progressive imaging findings of an unclear etiology. Temozolomide should not be stopped in these patients until progressive changes are confirmed on follow-up imaging and as long as the patient remains clinically stable. Pseudoresponse, seen as decreasing le-
sion enhancement associated with increasing FLAIR signal changes, represents tumor growth that mimics the response of GBM to therapy. This can be seen in patients receiving antiangiogenic therapy, including therapy with bevacizumab. Tumor progression can be diagnosed per RANO criteria in these patients by the substantial worsening of FLAIR signal changes, even if there is stable or decreasing enhancement (Fig 2).

New and additional challenges are encountered when evaluating the imaging changes of high-grade gliomas in response to immunotherapy. Correctly assessing new or progressive lesions that occur during immunotherapy is critical, because early, progressive imaging findings may not preclude subsequent response to therapy and overall benefit. Changes in contrast enhancement and FLAIR signal remain the cornerstone of the imaging response assessment for GBM and high-grade glial tumors to immunotherapy. When GBMs demonstrate a decrease in measurable enhancement and a decrease in FLAIR signal changes after the initiation of immunotherapy, the diagnosis of positive response to therapy can confidently be made. When GBMs demonstrate an increase in measurable enhancement confirmed on subsequent follow-up imaging, the diagnosis of disease progression can also be made (Fig 3). Although advanced imaging

Fig 2A–D.— Pseudoresponse. (A, C) Axial FLAIR and (B, D) contrast-enhanced, T1-weighted images obtained at baseline (A, B) and after initiation of antiangiogenic therapy (C, D). (C, D) Post-treatment imaging demonstrates a significant increase in FLAIR signal changes (green arrows), with the areas of enhancement (red arrows) either remaining stable or decreasing. The substantial increase seen in FLAIR signal changes allows the diagnosis of disease progression to be made without progression of the enhancing tumor. FLAIR = fluid-attenuated inversion recovery.
Fig 3A–D. — Response to immunotherapy in combination with bevacizumab followed by progression. (A) Axial contrast-enhanced, T1-weighted images at baseline and surveillance examinations obtained at 6-week intervals following initiation of pembrolizumab and bevacizumab (B–D). (B) The 6-week, post-treatment imaging demonstrates an interval decrease in enhancement of the tumor following therapy. A decrease was observed in the enhancing tumor in both the superficial (red arrows) and deep anterior tumor margins (green arrows). (C) The 12-week, post-treatment imaging demonstrates increasing enhancement along the deep anterior tumor margin (green arrows) that continued to progress on (D) 18-week, post-treatment imaging, thus documenting disease progression. The superficial portion of the glioblastoma remained stable and did not progress (red arrows).

Fig 4A–F. — Response to immunotherapy in combination with bevacizumab. (A, D) Axial perfusion cerebral blood volume, (B, E) contrast-enhanced, T1-weighted, and (C, F) fluid-attenuated inversion recovery images are shown at baseline (A–C) and at 6 weeks following initiation of immunotherapy and bevacizumab (D–F). Post-treatment examination demonstrates an interval response to therapy with a decrease in perfusion (red arrows) and enhancement (green arrows) of the glioblastoma as well as a decrease in associated vasogenic edema (yellow arrows).
techniques, including perfusion imaging, are not part of the formal RANO or immunotherapy Response Assessment in Neuro-Oncology (iRANO) criteria for the response assessment of GBMs to immunotherapy, they can be helpful in distinguishing treatment effects from tumor growth. Perfusion imaging can estimate and evaluate changes in cerebral blood volume (CBV) and cerebral blood flow in tumors and can be helpful in distinguishing progressive enhancement related to tumor growth from progressive enhancement resulting from treatment effects. Enhancement related to tumor growth typically demonstrates increased perfusion and elevated CBV, whereas enhancement related to treatment-related changes or necrosis usually demonstrates decreased perfusion and decreased CBV. GBMs treated with immunotherapy in combination with bevacizumab will typically demonstrate an interval decrease in measurable enhancement and FLAIR signal changes, as well as decreased CBV on perfusion imaging (Fig 4).

Although RANO criteria allow for the continuation of therapy in patients with progressive imaging changes of unclear etiology, they do not permit the continuation of treatment after there is imaging evidence of disease progression. To allow patients with initial progression of imaging findings after the initiation of immunotherapy who meet the RANO criteria of progression of disease to continue therapy and potentially receive delayed or long-term clinical benefit, new guidelines and the iRANO criteria were developed.6 iRANO criteria integrate the immune-related Response Criteria concept of confirmation of radiographical progression with the RANO guidelines, defining complete response, partial response, stable disease, and progressive disease, and they allow the continuation of immunotherapy, such as immune checkpoint inhibitors, in patients who show early imaging progression within the first 6 months of initiating therapy until progression is confirmed on subsequent imaging and as long as the patient remains clinically stable (Fig 5).6 The progressive imaging findings are expected to stabilize or improve within 3 months in patients who will

![Fig 5A–F. — Initial progression of imaging findings following initiation of immunotherapy. (A, D) Axial fluid-attenuated inversion recovery, (B, E) contrast-enhanced, T1-weighted, and (C, F) sagittal contrast-enhanced, T1-weighted (C, F) images at baseline (A–C) and 6 weeks following initiation of immunotherapy (D–F). Post-treatment magnetic resonance imaging obtained 6 weeks following the initiation of immunotherapy demonstrated an interval increase in the enhancing lesion and associated vasogenic edema. By Response Assessment in Neuro-Oncology criteria, there is imaging evidence of disease progression, and therapy would have to be terminated. However, because imaging was obtained within 6 months of the initiation of immunotherapy, immunotherapy Response Assessment in Neuro-Oncology criteria allow therapy to continue until progression is confirmed on follow-up examination.](image-url)
receive long-term clinical benefit. To clarify whether the progressive imaging findings represent tumor progression or treatment-related changes, follow-up imaging is typically obtained 3 months after the initial imaging evidence of progressive disease. It is noteworthy that iRANO criteria have yet to be validated in prospective clinical trials and clinical cohorts.

Conclusions
Response assessment of patients with glioblastomas treated with checkpoint inhibitors is challenging. Although immune-related Response Criteria and Response Assessment in Neuro-Oncology criteria were developed to assist with response assessment to immunotherapy and provide guidance with treatment decisions, Response Assessment in Neuro-Oncology criteria have not been validated in prospective clinical trials in assessing the response of high-grade gliomas treated with checkpoint inhibitors. Close clinical monitoring, short-term imaging follow up, and, in some cases, histopathological analysis may be required to prevent the premature discontinuation of potentially beneficial therapies.

References
Background: Aspiration can occur in patients of any age group, but it can be prevented. The primary population at risk is made up of survivors of cancer because of their increased risk of mucositis, mucosal atrophy, and dysphagia associated with chemotherapy, radiotherapy, and the disease process itself. The rate of incidence of aspiration cannot be quantified, because minor cases of aspiration often go unreported. Sequelae ensuing from aspirations can include pneumonia, end-stage kidney disease, dialysis, and death.

Methods: Analyses of cost, decision-tree modeling, and cost effectiveness were performed to compare a hypothetical, interventional model based on best practices with usual (standard) care. A societal perspective was used as the economic viewpoint. Direct costs, caregiver time, and market values for wages were estimated for the 2 interventions. Effectiveness values for the cost-effectiveness and decision-tree analyses were obtained from the literature. The incremental–cost-effectiveness ratio was calculated and used to compare the intervention with usual care.

Results: The interventional method was more costly but more effective than usual care. A sensitivity analysis considered the uncertainty of event probability (aspiration vs no aspiration). The interventional protocol for aspiration reduction continued to be more cost effective than usual care.

Conclusions: Aspiration takes a financial toll on all facets of healthcare, including on nurses, skilled nursing facilities, patients, their families, and insurers, among others. Implementing guidelines that describe best practices for aspiration appears to be a cost-effective strategy for reducing aspirations among cancer survivors — especially elderly patients — who live in skilled nursing facilities.

Introduction

Aspiration can affect every age group, so all patients are at risk; although aspiration can be prevented, because of the toxic effects of chemotherapy and radiotherapy, the cancer disease process, mucositis, dysphagia, aging, and mucosal atrophy, elderly cancer survivors are especially at risk.1,2 Aspiration occurs when a patient chokes and the resulting food, medication, liquid, emesis, or low pH gastric fluid escapes into the lung.1,3 Aspiration can also occur during anesthesia, while patients are being treated in intensive care units, and in the trauma setting.1 Of greater public health significance is the unidentified or unnoticed, minor aspiration cases that occur and can lead to pneumonia. Thus, the incidence rate of new cases of aspiration is difficult to quantify.1

A wide range of outcomes is possible with aspiration. The severity of complications of aspiration depends on the patient’s health status and follow-up care, such as hospitalization and ventilator intubation, that may be necessary. Aspiration can result in aspiration-associated pneumonia (bacterial colonization of the lung), acute lung injury, or acute respiratory distress syndrome.2 Furthermore, aspiration can result in respiratory failure, organ failure, dialysis, need for transfusions, and unnecessary hospitalization stays and procedural expenditures for health care organizations.3 Aspiration can be avoided by using guidelines to prevent choking, especially in cancer survivors already at risk.4

Aspiration has a major influence on the expenditures of health care organizations, whose staff may care for elderly cancer survivors.5 Medicare does not reimburse health care organizations for hospital-associated infections and preventable hospitalizations.5 In 2012, the national mean inpatient costs for aspiration totaled $13,542, with an average hospital stay of 7 days.4 This cost of care included treating aspiration, but it did not include costs related to the treatment of complications (eg, hospital-acquired pneumonia).5 Patients insured by Medicare have the highest incidence of aspiration and inpatient hospitalizations.6 Some of these cases may be preventable while patients reside in skilled nursing facilities. It is worth noting that aspiration is the second leading cause of hospital transfer, mortality, and infection in long-term care facilities.7
In this study, guidelines and best practices for nursing recommended by the American Association for Critical-Care Nurses (AACN) to reduce aspiration risk, hospital-associated infections, and unnecessary expenditures from aspiration was compared with usual (standard) care. This was performed via cost analysis and then by using cost-effectiveness and decision-tree analyses to compare the 2 methods, known hereafter as the intervention and usual care models. Using the interventional protocol, registered nurses are trained to identify and remedy risks of aspiration-associated pneumonia using the decision model. However, administrators of skilled nursing facilities may prefer to allocate their nurses’ time toward patient care, rather than implementing an optional, interventional protocol to help reduce aspiration risk. Thus, usual care was used as an alternative. In the usual care model, nurses rely on their experience, with no special training, to prevent aspirations.

Methodology
This study did not require Institutional Review Board approval because only published literature and publicly available data were used.

Study Design
Cost-effectiveness analysis was used in this study as a form of economic evaluation, which values costs and outcomes. Thus, cost-effectiveness analysis compares costs in relation to a natural unit, such as years of lives saved or number of cases prevented; by contrast, cost-utility analysis uses concerns, such as quality of life or classic utility values, as the outcome. In this study, cost-effectiveness analysis performed uses the natural unit of the number of aspirations averted. In addition, using aspiration — rather than using a utility — as an end point becomes relevant with recent trends toward bundled payments, because payers are beginning to reimburse only for a single disease, outcome, or condition regardless of procedures performed for additional complications.

A decision-analytic model was used to evaluate the costs per aspiration averted in a prospective cohort of skilled nursing facility residents. Several forms of decision analysis exist, including Markov models and decision trees. Markov modeling evaluates long-term effects and uses “health states.” In Markov models, the disease process of the patient is modeled, and a patient is expected to be in a health state at a given time. However, the Markov model has disadvantages and, in this case, may not be ideal due the Markovian assumption involved (memory-less model).

Decision trees linearize the decision process and provide an overview of the logical flow of each pathway. Decision trees are easy-to-follow pathways and use relevant probabilities for each decision and are more appropriate for a state of short-term analyses. Because the time period evaluated in this study is 1 year, a decision tree was used for the cost-effectiveness analysis, which did not require the creation of health states. In addition, a decision tree structured and represented the decision at hand for skilled nursing facilities, ie, which treatment pathway was more cost effective at preventing the episode of aspiration in elderly cancer survivors.

Fig 1 is a diagrammatic representation of the deci-
sion tree used for the cost-effectiveness analysis. The payoffs included costs incurred by health care professionals, patients, and caregivers for the skilled nursing facilities, as well as effectiveness and outcomes, and were the number of aspirations averted over the time period of 1 year. Using the decision tree, the incremental–cost-effectiveness ratio was calculated for the intervention (the aspiration risk-reduction protocol training program) compared with the usual care models. A sensitivity analysis of the cost effectiveness of these interventions was performed based on a range of estimates for the effectiveness of the training program and the direct and indirect costs of aspirations.

Data from the literature were used for this study, as per common practice in decision-analysis studies. The alternatives were modeled with a decision tree that incorporated parameters from the literature, allowing decision makers to understand the impact of each direct and indirect cost. Specifically, effectiveness data (rates of aspirations/gastroesophageal reflux) were garnered from systematic reviews and practical trials. Effectiveness data were gathered from a systematic review that included a randomized controlled trial, a quasiexperimental study, and an observational study. Each article used a different time period for evaluating aspiration rates, and these values were converted to 1-year probabilities. In addition, effectiveness data were obtained from a published article that implemented an aspiration risk-reduction program concerning head of bed elevation, feeding tube insertion and placement, and gastric volume.

This cost-effectiveness modeling study utilized microcosting from the societal perspective to measure direct and indirect medical costs, patient productivity, informal caregiver time, and family time for visits. Direct and indirect costs were estimated for both the intervention (best care) and control arm (usual care) of the study. Training costs were estimated for supplies, training materials, facility use, and implementation. Recruitment costs were not included because these interventions were modeled to take place within the skilled nursing facilities.

The cost of an aspiration was estimated as the average provider cost of an aspiration case in 2012. There is no interventional cost for usual care, whereas training costs are included for the interventional program. Patient productivity costs were excluded from the model, because the residents of skilled nursing facilities were assumed to have no productivity or work output. Time spent by family caregivers was estimated to be 20 minutes of travel time each way (job salary lost) to visit the patient affected by the adverse effects of aspirations. Most caregivers (74%) lived approximately 20 minutes away from their care recipient, and 76% of caregivers visited their care recipient at least once a week.

### Table 1. — Parameter Estimates

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Base Case</th>
<th>Low</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>0.46</td>
<td>0.28</td>
<td>0.52</td>
</tr>
<tr>
<td>(Aspiration Risk-Reduction)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Probability of no aspiration</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Aspiration averted</td>
<td>68.4</td>
<td>56.6</td>
<td>1460.0</td>
</tr>
<tr>
<td>Cases of aspiration</td>
<td>30.10</td>
<td>22.80</td>
<td>34.80</td>
</tr>
<tr>
<td>Usual Care</td>
<td>0.20</td>
<td>0.11</td>
<td>0.48</td>
</tr>
<tr>
<td>Probability of no aspiration</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Aspiration averted</td>
<td>59.30</td>
<td>10.95</td>
<td>842.31</td>
</tr>
<tr>
<td>Cases of aspiration</td>
<td>35.30</td>
<td>31.90</td>
<td>73.90</td>
</tr>
</tbody>
</table>

Data from references 12, 13, and 15.

### Table 2. — Direct Costs Per Patient

<table>
<thead>
<tr>
<th>Variable</th>
<th>Estimate, $ (range)*</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Training and materials</td>
<td>62 (50–186)</td>
<td>Assumption</td>
</tr>
<tr>
<td>Aspiration</td>
<td>13,542 (7,014–24,334)</td>
<td>Inpatient aspiration costs</td>
</tr>
</tbody>
</table>

*Ranges include costs of aspiration by payer, age, sex, location, and facility size subgroups.

Data from reference 6.
Integrating the direct and indirect costs indicates that the average costs of an aspiration are $11,425.75 while receiving usual care in a skilled nursing facility setting compared with the average costs of $7,774.35 using the interventional model. Overall, this cost analysis indicates that the interventional program was less expensive than usual care.

**Results**

Table 3 lists the results of the cost-effectiveness analysis. The interventional protocol is more cost effective. It dominated usual care because it was more effective, had lower costs, and incurred savings.

The sensitivity analysis considered the uncertainty of event probability (aspiration/no aspiration). The 1- and 2-way deterministic sensitivity analyses indicate similar results. The interventional training program was more effective and less costly at all levels of the parameters. The results of the 2-way deterministic sensitivity analysis are presented in Fig 2. When all of the parameters (effectiveness) were simultaneously varied, the interventional protocol continued to dominate the usual care at most probabilities of effectiveness.

A Tornado diagram indicates the variables with the greatest impact on the incremental–cost-effectiveness ratio (Fig 3). The number of aspirations averted using the interventional program resulted in the greatest impact on the incremental–cost-effectiveness ratio; this indicates a need for information. The probability of no aspirations with the interventional program has a significant impact of the cost effectiveness of the intervention.

**Discussion**

Aspiration takes a financial toll on skilled nursing facilities, patients and their families, and insurers. Need exists to reduce the rate of aspirations as well as to assess the cost effectiveness of current interventions. In this study, the interventional model, which was based on the aspiration risk-reduction protocol recommended by the AACN, was compared with usual care in elderly cancer survivors. The incremental–cost-effectiveness ratio for usual care was

**Table 3. — Cost-Effectiveness Analysis**

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Cost, $</th>
<th>Incremental Cost, $</th>
<th>Effect</th>
<th>Incremental Effect</th>
<th>Incremental Cost-Effectiveness Ratio</th>
<th>Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interventional (aspiration risk-reduction)</td>
<td>7,774.35</td>
<td>—</td>
<td>43.78</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Usual care</td>
<td>11,425.70</td>
<td>3,651.35</td>
<td>37.38</td>
<td>−6.40</td>
<td>−580.88</td>
<td>Dominated</td>
</tr>
</tbody>
</table>

Fig 2. — Results of the sensitivity analysis for probabilities of the interventional (aspiration risk-reduction protocol) and usual care models (net benefit, willingness to pay = 12,000.00). The red sector of the diagram indicates the worst-case scenario for the interventional program and the best-case scenario for the usual care program.
$11,425.70 per aspiration averted. The interventional training for front-line nurses regarding head of bed elevation and aspiration was less expensive and was effective at preventing aspirations. The average person resides in a skilled nursing facility for 3 years, and it is likely that a cancer survivor will accrue more comorbidities that will extend that stay another year. Thus, in the long term, skilled nursing facilities with residents who have survived cancer are likely to have reduced costs if their staff implements a best practice program now. The interventional protocol dominated the usual care protocol, confirming that the usual care regimen used in many skilled nursing facilities is expensive and less effective at preventing aspirations.4,13

When all parameters were simultaneously varied, sensitivity analyses indicated that the interventional program was the most cost effective at nearly all probabilities of effectiveness. The magnitude of the probability of no aspirations (ie, effectiveness) of such a best practice program was the most significant factor impacting the results of the cost-effectiveness analysis.

In the medical literature, patients with cancer and survivors of cancer alike are at higher risk for dysphagia, aspiration, and related consequences than their counterparts.18,19 Chemotherapy and radiotherapy are major risk factors for increasing dysphagia, which can lead to aspiration, and patients with head and neck cancers are at a higher risk for dysphagia.20 For example, in a cohort of 3,513 elderly patients with head and neck cancers who were treated with chemoradiotherapy, 801 (24%) had an aspiration and related pneumonia.18 In the setting of head and neck cancers, aspiration-related pneumonia also results in increased mortality by 42%.18

Head of bed elevation has been shown to have a major impact on the prevention of aspiration, health care–associated infections, and ventilator-associated pneumonia.4,12-15 Evidence-based, clinical practice guidelines indicate that keeping head of bed elevation at a 30- to 45-degree angle reduces the probability of aspiration, especially in patients receiving enteral tube feeding.4,12-15 Similar findings have been reported by the Institute for Clinical Systems Improvement.21 The Institute of Healthcare Improvement has recommended a series of aspiration risk-reduction interventions, known as the ventilator bundle, that include head of bed elevation greater than 45 degrees, sedation to reduce extubation, and prophylaxes for peptic ulcer and deep venous thrombosis.22

Although other studies have evaluated the effectiveness and viability of head of bed evaluation interventions in nursing homes, a dearth of evidence exists regarding the cost effectiveness of aspiration-reduction interventions, nor have rigorous cost analyses been performed.12,13 I am not aware of any published cost analyses of aspiration reduction interventions prior to this study.

This study has several limitations. Because it was not feasible to obtain large sample sizes in skilled nursing facilities, many of the values used are from published studies with smaller sample sizes.12,13 In addition, skilled nursing facilities have relatively high dropout rates. Due to the 1-year time frame, follow-up costs were not included in the cost analysis. The variability in the number of aspirations parameter may partially be accounted for in the differences in measurements previously published elsewhere.12,13

Future research should include total parental nutrition and other nutrition methods in cancer care, as well as alternative methods for reducing aspiration in elderly cancer survivors residing in skilled nursing facilities as comparison for cost-effectiveness analyses. In addition, more empirical work on the feasibility and costs of aspiration-related interventions would be useful, as would research to help standardize the use of aspiration intervention-related outcome measures such as aspirations.
per 100 bed days, gastric residual volume, pepsin positive reactions, and probability of aspiration. In addition, aspiration-reduction interventions should be evaluated along with other conditions (eg, bedsores, oral health interventions) and guidelines for cancer survivors, as this should increase the value of training.19

Conclusions
These results demonstrate the cost effectiveness of the intervention protocol relative to usual care.4 Hopefully, these results will encourage administrators at skilled nursing facilities to consider implementing aspiration risk-reduction protocols for their elderly residents who have survived cancer.

Acknowledgment: I would like to thank Drs Lairson and Swint for their initial review of this article.

References

Background: The definition of fever is flexible and depends on the clinical context. Fever is frequently observed in patients with cancer.

Methods: Infectious and noninfectious causes of fever in patients with various oncological and hematological malignancies and the usefulness of biomarkers are discussed.

Results: To treat patients in a timely manner and to minimize morbidity and mortality, it is paramount that health care professionals determine the cause of fever. The usefulness of biomarkers in febrile patients with cancer continues to be controversial.

Conclusions: Fever is frequently seen in patients with cancer and can be associated with a variety of infectious and noninfectious causes. The utility of acute-phase reactants, such as erythrocyte sedimentation rate, C-reactive protein, and procalcitonin, along with a nonsteroidal anti-inflammatory drug challenge should be further evaluated as adjunct tools for the workup of fever in patients with cancer.

Introduction

A human's normal body temperature is 37 °C, although this value can change depending on the time of day and the method of measurement used.1 Defining fever is a somewhat arbitrary process because, as the body's temperature is lowered, the rate of sensitivity increases and the rate of specificity decreases.1 Thus, the American College of Critical Care Medicine and the Infectious Diseases Society of America has defined fever as a body temperature of at least 38.3 °C.1,2 For the purposes of this article, we will adhere to this widely accepted definition, although it is worth noting that it is reasonable to use a lower temperature to define fever in patients whose immune systems are compromised.1,2

Fever is frequently seen in patients with cancer and can be associated with a variety of infectious and noninfectious causes. To treat patients in a timely manner and to minimize morbidity and mortality, it is paramount that health care professionals determine the cause of fever. Infections are a principle source of fever in patients with oncological disorders and should be initially considered in both neutropenic and non-neutropenic patients.3 Possible noninfectious causes of fever include alterations of oral mucosa leading to mucositis, certain medication use, blood transfusions, radiation, endocrine disturbances, surgery, and tumor fever.5,6 Moreover, cancer has been reported as the cause of fever in 15% to 20% of patients with fever of unknown origin (FUO).5

Neoplastic Fever

Neoplastic fever, also known as tumor fever, is a diagnosis of exclusion, because no clinical features are consistently present to distinguish it from other causes of fever. Malignancies commonly associated with fever include Hodgkin and non-Hodgkin lymphomas, soft-tissue sarcoma, acute or chronic leukemia, and renal cell carcinoma; however, most types of cancer and benign tumors, such as atrial myxoma, can induce pyrexia.3,5,6 The most common symptoms that occur with neoplastic fever are diaphoresis and rubor but less often include chills/rigor. By contrast, infectious fevers tend to present with warmth, diaphoresis, and chills reflective of peripheral vasodilation. Hypotension and tachycardia commonly accompany systemic infections caused by gram-negative organisms secondary to the production of lipopolysaccharide.5 Pel-Ebstein fever, a stereotypical, noninfectious fever, has been associated with Hodgkin lymphoma and presents in a cyclical pattern of several days of fever followed by afebrile episodes of similar duration, usually 1 to 2 weeks.6 Use of aspirin and acetylamphenophen allow for defervescence in patients with infectious fever, whereas other nonsteroidal anti-inflammatory drugs (NSAIDs) like naproxen have greater efficacy in neoplastic fever.5

Many attempts have been made to pinpoint and describe the underlying mechanism of tumor fever; however, the full mechanism is still unclear. Pyrogens have been isolated in both the tissue and urine of pa-
tients with cancer presenting with tumor fever. Evidence support exists for pyrogen release from tumor cells in vitro. Known primary cytokines released by tumor cells leading to fever production are tumor necrosis factor α, interleukins 1 and 6, and interferon; however, these cytokines are produced during both infection and neoplastic fevers. Pyrogens stimulate the anterior preoptic nuclei of the hypothalamus, leading to the induction of prostaglandin E2 production and an elevated body temperature. The mechanism of release of these substances has been postulated to be from tumor necrosis, bone marrow necrosis, or another unknown mechanism; however, a thorough and exact mechanism for the pathophysiology of tumor fever remains unknown.

A retrospective, observational study by Liaw et al attempted to identify patterns in vital signs in patients with neoplastic fever. Of the 150 patients diagnosed with neoplastic fever, 60% were asymptomatic until fever was recorded in the hospital. The most common daily peak temperatures were between 38 and 38.9 °C in 103 of patients; of those exhibiting intermittent fevers, once-daily spike patterns were seen in 72% of patients, and 93% of patients showed no change in baseline heart rate except during the fever period. A complete and sustained defervescence within 24 hours of administering naproxen was seen in 87%, a partial response in 10%, and a failure to defervesce in 3% of study patients.

The usefulness of naproxen and other NSAIDs to differentiate neoplastic from non-neoplastic fever in patients with cancer was first described in 1984 by Chang and Gross. These authors described a complete and sustained resolution of fever within 24 hours after the administration of naproxen in 14 of 15 patients with neoplastic fever and none of the 5 patients with fever secondary to infection. Several published articles support the use of the naproxen challenge to differentiate neoplastic from non-neoplastic fever in patients with cancer whose previous workup for infection was negative. By contrast, the usefulness of NSAIDs in unselected patients with FUO does not appear to reliably differentiate neoplastic fever from other causes, thus leading health care professionals to exercise caution when using NSAIDs in this setting.

**Drug-Induced Fever**

Patel and Gallagher define drug-induced fever as a “febrile response coinciding temporally with the administration of a drug in the absence of underlying conditions that can be responsible for the fever.” A unique feature of drug-induced fever is the abatement of pyrexia once the offending agent is withdrawn and has been renally or hepatically cleared. The true incidence of drug-induced fever in patients with cancer is unknown, because this type of fever remains a diagnosis of exclusion, similar to that of tumor fever. One study reported select medication use as the cause of fever in up to 18% of patients with cancer who had noninfectious fevers. It is important for clinicians to consider drug-induced fever in patients with no other identifiable causes for fever in order to prevent the inappropriate and escalating use of antibiotics and use of expensive diagnostic tests. One study found that an episode of drug-induced fever prolongs the length of hospital stay by nearly 9 days, prompting an average of 5 blood culture draws, 3 radiological studies, and use of unnecessary antibiotics.

Drug-induced fever can present in a variety of patterns and degrees of pyrexia. Patients may appear “inappropriately well,” with relative bradycardia and are frequently unaware of the fevers. Other clinical features of drug-induced fever include rash, peripheral eosinophilia, an elevated erythrocyte sedimentation rate, and mild transaminitis. The mechanisms by which drugs can induce fever are divided into 5 categories: altered thermal regulation, mode of administration, pharmacological action, idiosyncrasy, and hypersensitivity. Hypersensitivity is the most common mechanism of drug-induced fever and may be mediated by humoral response.

The onset of drug-induced fever can vary and depends on the specific agent; it can occur at any point in therapy. However, the average time of 7 to 10 days is the median time between the start of the causative therapy and onset of fever. Antimicrobials and antineoplastics have been reported to have the shortest interval between the initiation of therapy and onset of fever. Antineoplastics have a mean onset of 6.0 days compared with 7.8 days in antimicrobials. In addition, no single patient population has consistently been identified to be at an increased risk for drug-induced fever.

Many agents can cause fever, but certain medications are more commonly associated with inducing fever. Antimicrobials, anticonvulsants, bisphosphonates, immunosuppressants, and antineoplastic agents are among the most common agents to induce fevers and are also frequently used in patients with cancer. Bleomycin, chlorambucil, cisplatin, daunorubicin, hydroxyurea, vincristine, and 6-mercaptopurine, among others, can induce fever. Some agents may be more likely to be accompanied by pyrexia than others, so clinicians should be aware of fever as an adverse event of these agents. In patients with hematological malignancies, the use of cladribine has been associated with fever in nearly 70% of cases. Gemcitabine, an agent widely used in the management of solid tumors such as pancreatic, breast, ovarian, and lung cancers, as well as relapsed or refractory lymphomas, induces fever in 20% to 40% of patients. From observational data at our institution (Moffitt Cancer Center, Tampa, FL), on-
set of fever is seen within 24 hours after the infusion of gemcitabine (but most commonly in 6–12 hours).

Antithymocyte globulin is an immunosuppressant used as treatment and prophylaxis of acute organ rejection during transplantation; in the setting of allogeneic hematopoietic stem cell transplantation (HSCT), antithymocyte globulin is also used to prevent graft-vs-host disease, particularly in those with aplastic anemia. In phase 3 clinical trials, fever was reported in more than 60% of participants and 51% in postmarketing surveillance among patients receiving antithymocyte globulin. Other commonly used immunosuppressants such as azathioprine, mycophenolate mofetil, and sirolimus may also induce fever after their prolonged use.

Monoclonal antibodies were first introduced into practice in the late 1980s when the US Food and Drug Administration approved muromonab for treatment of acute organ rejection. Since then, a variety of monoclonal antibodies exist for use in several nonmalignant and malignant diseases. Alemtuzumab, ipilimumab, ofatumumab, and rituximab are some of the medications in clinical use for the treatment of cancer and graft-vs-host disease. Because monoclonal antibodies are used for the management of hematological and solid-tumor malignancies, clinicians must be aware of the potential adverse events (eg, drug-induced fever) of these agents. Incidence rates of fever vary among monoclonal antibodies, from fewer than 1% in fully human-derived panitumumab to as high as 60% in rituximab, a genetically engineered, chimeric murine/human monoclonal antibody.

Supportive care is instrumental in ensuring optimal outcomes in patients with cancer. This includes administration of antiemetics, bisphosphonates, antimicrobials, and colony-stimulating factors for the management of chemotherapy-induced gastrointestinal, infectious, and hematological toxicities. The package inserts for filgrastim and sargramostim report that fever occurs as an adverse event in 12% and 80% of people receiving the drug, respectively, thus making these agents a frequent source of induced fever in patients with cancer.

We conducted a retrospective chart review of 162 patients at Moffitt Cancer Center with acute myelogenous leukemia who received induction chemotherapy with cytarabine and an anthracycline (7 + 3) followed by filgrastim (n = 28) or sargramostim (n = 134). The data revealed that fever occurred in 0% of patients receiving filgrastim and in 7% of those receiving sargramostim; however, these results were not statistically significant.

Bisphosphonates, including zoledronic acid and pamidronate, are frequently used for the treatment of hypercalcemia and osteolytic bone metastases in patients with malignancy. Data indicate that 21% of patients receiving intravenous administration of zoledronic acid had fever compared with between 15% and 30% of those receiving pamidronate.

Per guidelines from the Infectious Diseases Society of America, fever in the setting of neutropenia warrants use of aggressive antimicrobials in patients at high risk. Choice of therapy depends on multiple factors but traditionally includes ceftazidime, piperacillin/tazobactam, and meropenem. However, these agents can also be associated with persistence of fever, and they should not be overlooked as the cause of new or ongoing pyrexia in patients with cancer, even in the absence of neutropenia. Beta lactams are used in cancer treatment to manage fever. In 1 study, fever induced by β lactams and piperacillin occurred in 13% and 17% of treated patients, respectively. Eosinophilia was observed in 25% of patients with drug-induced fever secondary to β lactams, and 29% of febrile patients had rash. Case reports of fever secondary to acyclovir, amphotericin B, minocycline, nitrofurantoin, trimethoprim/sulfamethoxazole, and vancomycin use have been also documented in the literature and should be considered in patients with cancer who are receiving these agents.

**Other Noninfectious Causes of Fever**

Similar to patients without malignancies, fever in patients with cancer can be due to venous thromboembolism. Patients with active disease and malignancies are at increased risk for de novo venous thrombosis; the most common include adenocarcinomas of the breast, lung, prostate, alimentary tract, and kidneys. Nonbacterial thrombotic endocarditis, also known as marantic endocarditis, is a manifestation of hypercoagulability in patients with cancer, particularly adenocarcinoma. The phenomenon results in sterile vegetations that typically occur on the mitral or aortic valves of these patients. Other factors predisposing patients with cancer to venous thromboembolism include occlusion by tumor or lymphadenopathy and chemotherapy-induced endothelial injury. Clinicians should be aware of the risk of venous thromboembolism in patients with cancer, thus considering the condition in the differential diagnosis in a febrile patient with cancer.

Guidelines for the evaluation of new-onset fever in adults who are critically ill outline several noninfectious causes of fever that can occur in the oncological population. Fever related to noninfectious, inflammatory states can be associated with any organ (eg, worsening of inflammation after acute myocardial infarction in the setting of Dressler syndrome). Several other etiologies of inflammation associated with noninfectious fever include adrenal insufficiency, gout, intracranial bleeding, pancreatitis, pulmonary infarction, stroke, thyroid storm, and tumor lysis syndrome, among many others not listed here.
A host of symptoms (eg, fever) can be observed in patients with cancer during the neutrophil recovery and after they have undergone cytotoxic chemotherapy. Overproduction of proinflammatory cytokines is the mechanism thought to be responsible for the febrile syndrome. For patients undergoing HSCT, these clinical manifestations can be observed prior to, during, or immediately following neutrophil engraftment (leading to the terms pre- and peri-engraftment fever). The full presentation of these syndromes is beyond the scope of this article, but all of them include fever as part of the presentation with concomitant rash and, oftentimes, pulmonary findings. For clinicians caring for such patients, it is crucial to consider engraftment fever in the differential diagnosis of a febrile patient undergoing HSCT.

Usefulness of Biomarkers

To differentiate between noninfectious and infectious causes of fever, several acute-phase reactants (procalcitonin, C-reactive protein, erythrocyte sedimentation rate) have utility in patients without cancer. The usefulness of biomarkers in febrile patients with cancer is controversial, but some evidence suggests that procalcitonin can discriminate between different causes of fever. Inflammatory conditions, infections, and cancer can induce the synthesis of C-reactive protein and increase the erythrocyte sedimentation rate; thus, their discriminatory ability between neoplastic and infectious fever in patients with cancer is limited.

Procalcitonin is a prohormone of calcitonin and is produced by a variety of tissues in response to inflammation and infections caused by fungi, bacteria, and parasites. In patients with cancer, scant evidence exists regarding the use of procalcitonin levels to discern between infection or acute-phase reaction due to drug use or presence of a tumor. Penel et al analyzed 245 cases of fever in 155 patients with solid-tumor malignancies. Of the 95 patients with infection, 19 had procalcitonin levels above 2 ng/mL; thus, the researchers concluded that procalcitonin failed to discriminate infection. In another study of patients with white blood cell counts below 1000/µL, procalcitonin levels did not rise above 2 ng/mL in those with sepsis or severe sepsis, whereas white blood cell counts above 1000/µL resulted median procalcitonin levels of 4.1 ng/mL and 45.0 ng/mL, respectively. Procalcitonin has several limitations to its use as a marker of sepsis and infection. In the absence of bacterial infection, elevated levels of procalcitonin can occur during extremely high times of stress or during systemic inflammation without an infectious etiology. For example, the stress of labor, acute graft-vs-host disease, and several types of immunotherapy, among many other causative conditions, may cause false-positive procalcitonin levels. Additional data are needed to assess the role and cutoff values of procalcitonin in febrile neutropenic and non-neutropenic patients with cancer. Moreover, serial procalcitonin levels should be obtained to establish a trend, because baseline levels may be elevated in patients with cancer.

Conclusions

Fever is common in patients with cancer and is associated with several types of infectious and noninfectious causes. Although infection remains the main etiology of fever in patients with cancer, noninfectious causes should also be considered following the negative results of a thorough workup for infection. Neoplastic fever, drug-induced fever, and venous thromboembolism are all important causes of fever in patients with hematological and solid-tumor malignancies. The usefulness of acute-phase reactants, such as erythrocyte sedimentation rate, C-reactive protein, and procalcitonin, along with a nonsteroidal anti-inflammatory drug challenge should be further evaluated as adjunct tools for the workup of fever in patients with cancer.

References


Primary Adrenal Angiosarcoma: A Rare and Potentially Misdiagnosed Tumor

Ariel Grajales-Cruz, MD, Francis Baco-Viera, MD, Ernesto Rivé-Mora, MD, Carlos Ramírez-Tanchez, MD, David Tasso, MD, Norma Arroyo-Portela, MD, Elizabeth Calderón, MD, Ilean Joan Padua-Octaviani, MD, and William Cáceres-Perkins, MD

Summary: A man aged 69 years presented with acute right flank pain secondary to a hemorrhagic large adrenal tumor. En bloc resection was performed to repair the inferior vena cava. Immunoperoxidase levels in the tumor were positive for factor VIII and CD31 and negative for S100, protein Melan-A, CD34, synaptophysin, chromogranin, desmin, muscle specific actin, ETFA (EMA), KRT20 (CK20), CDX2, TTF1, LNPEP (PLAP), inhibin, α-fetoprotein, CD30, hepatocyte paraffin, and aberrant expression of cytokeratin 7 and pankeratin. The pathological diagnosis was consistent with adrenal angiosarcoma. Obtaining appropriate immunoperoxidase stains and multidisciplinary evaluation helped make the diagnosis of this rare adrenal tumor and determine its management. The patient had an uneventful postoperative course and completed 4 cycles of adjuvant chemotherapy with doxorubicin/ifosfamide and adequately tolerated the treatment. However, positive surgical margins were found, so he was referred to radiation oncology specialists for possible adjuvant radiotherapy to the surgical bed. Weeks after the first initiation of therapy, the patient presented to the emergency department complaining of shortness of breath, fatigue, and generalized weakness for 3 days. He was admitted and found to have new-onset anemia and a new-onset, large, right pleural effusion. Thoracentesis performed showed sanguinolent fluid that, after microscopic evaluation, was suggestive of recurrent malignancy. Thoracic aortography performed with subselective catheterization to several arteries (right bronchial, right phrenic, and right renal arteries) did not show any active bleeding. However, the right inferior intercostal and adrenal arteries were presumed to be the reason for the bleeding event, so they were embolized until stasis. The patient remained hemodynamically unstable but eventually experienced multiorgan failure. In spite of aggressive measures, he died 10 days after admission to the hospital.

Background

Adrenal masses are incidentally found on computed tomography (CT) of the abdomen (so-called “incidentalomas”) approximately 4% of the time and in 8% in autopsy series.1 Up to 80% are benign adenomas.2 Patients in whom a high suspicion of malignancy exists due to the clinical picture or the presence of clinically evident overt adrenal disease are excluded from the definition of incidentaloma and should be thoroughly evaluated. It is important to distinguish benign from malignant processes, especially differentiating functioning vs nonfunctioning tumors.1 Patients with benign adenomas can be clinically followed, whereas patients with entities such as adrenocortical carcinoma, pheochromocytoma, primary aldosteronism, and cortisol-producing tumors (Cushing syndrome), will require surgical evaluation.1 In 2002, a consensus of the National Institutes of Health recommended excision in all masses larger than 6.0 cm and to observe clinical judgement in those between 4 and 6 cm in size.1,3 All adrenal masses larger than 1.0 cm in size (excluding myelolipomas, hemorrhages, and cysts) should undergo thorough clinical, radiological, and hormonal testing at the patient’s initial presentation to distinguish malignant and hyperfunctioning masses from benign masses. Those that are hyperfunctional or indicative of malignancy (attenuation value < 10 HU by CT) should be evaluated for surgical removal. Percutaneous adrenal biopsy has high false-negative rates and puts patients at risk for complications.4 The only role this procedure plays is confirmation of metastatic disease in patients with known cancer or confirmation of the diagnosis of adrenal cortical carcinoma when resection is not feasible.5

Angiosarcomas make up less than 1% of soft-tissue sarcomas; they are malignant tumors that arise from the endothelium of blood vessels and, in addition to soft tissue, commonly occur in the breast, skin, spleen, bone, and liver.6,7 The survival rate at 5 years is 24% to 31%.6,7 Twenty-two cases of adrenal angiosarcomas
in the medical literature (English language alone) have been reported.\(^7\)

Pathological diagnosis is difficult because the aberrant expression of cytokeratin (CK) can lead physicians to misdiagnose metastatic carcinoma of the adrenal gland.\(^7\) Immunohistochemical staining for vascular markers with CD34, FLI1, CD31, factor VIII, and CD34 are necessary for the diagnosis.\(^7\)

In 1988, Kareti et al.\(^8\) described the first case of adrenal angiosarcoma in a 54-year-old man with long-term left upper quadrant pain. Although angiosarcomas are generally aggressive, long-term survival has been recorded.\(^9\) Adrenalectomy is the only treatment available, but the benefits of resection, the role of adjuvant radiotherapy, and the timing of radiotherapy have not yet been determined.

**Case Report**

A US veteran aged 69 years with a medical history significant for controlled hypertension and diabetes mellitus (diagnosed in 2003) presented to the emergency department in May 2015 due to acute right flank pain. He explained that he had been having vague discomfort for the last 2 months and recently acute-onset, right flank pain several hours before his presentation. He said that the pain did not resolve with bed rest and acetaminophen. He rated the pain as being an 8 on a scale of 0 to 10 in intensity (with 10 being the worst), and it radiated to his right inguinal area and worsened upon ambulation. In the past 2 months, he had been unintentionally losing weight. He denied flushing, dizziness, bouts of hypertension, nervousness, palpatations, diarrhea, nausea/vomiting, change in bowel habits, diaphoresis, headache, or any other complaints. He was employed as a driver and denied any occupational exposure to toxic substances. He also denied any use of alcohol or tobacco. He had no personal or family history of cancer.

On physical examination, he was alert, oriented, cooperative, and was in acute pain. His blood pressure was 145/74 mm Hg (no postural changes) and his pulse was 100 beats/minute (regular). His lungs were clear, no murmur was heard, and visceromegaly was absent. He had right-sided abdominal pain on deep palpation but experienced no rebound tenderness. Peristalsis was adequate. Findings on the neurological examination were unremarkable. Electrocardiography was obtained, the findings of which revealed sinus tachycardia.

Abdominal CT was performed and showed a right adrenal mass lesion 16.4 × 9.1 × 9.5 cm in size with adjacent retroperitoneal hematoma, reaching the right kidney and right renal vein. The mass had attenuation values higher than the liver (39 HU). He had no intra-abdominal adenopathy (Fig 1). The Table includes a list of the laboratory values obtained.

The patient’s pain improved after he was treated with analgesics. After negative findings following a workup for a hyperfunctioning tumor, he underwent exploratory laparotomy in June 2015 because of the size of the lesion and its radiographical appearance as well as the manifestations of unintentional weight loss and pain. During exploratory laparotomy, a large, right adrenal mass was found that rounded the inferior vena cava, with preserved right kidney artery and vein. En bloc resection was performed to repair the inferior vena cava.

Findings on pathology were consistent with a right hemorrhagic mass 10.0 cm in size with positive margins and associated hematoma and mitosis (Fig 2A). Results on immunohistochemistry were positive for factor VIII and CD31 (Fig 2B) and negative for S100, protein Melan-A, CD34, synaptophysin, chromogranin,
desmin, muscle specific actin, ETFA (EMA), KRT20 (CK20), CDX2, TTF1, LNPEP (PLAP), inhibin, α-fetoprotein, CD30, hepatocyte paraffin, and aberrant expression of cytokeratin 7 and pankeratin (Fig 2C).

Results from the immunoperoxidase study excluded melanoma, pheochromocytoma, adrenal cortical carcinoma, and metastases with a pulmonary, gastrointestinal, liver, and germ cell origin. The final pathological diagnosis was a cystic, malignant, epithelioid, mesenchymal neoplasm consistent with adrenal angiosarcoma (Figs 2D and 2E).

The patient had an uneventful postoperative course and completed 4 cycles of adjuvant chemotherapy with doxorubicin/ifosfamide with adequate tolerance. Positron emission tomography/CT performed 3 and 6 months after surgical resection did not identify any significant fluorideoxyglucose-avid lesions. Positive surgical margins were found, so he was referred to radiation oncology specialists for possible adjuvant radiotherapy to the surgical bed. Thoracic and abdominopelvic CT performed 1 year following the resection did not show any evidence of disease recurrence. He was then evaluated again by radiation oncology specialists and consented to undergo adjuvant radiotherapy.

Some weeks after the initiation of therapy, the patient presented to the emergency department complaining of shortness of breath, fatigue, and generalized weakness with a duration of 3 days. He was admitted to the hospital and was found to have new-onset anemia. Results on CT revealed a large-sized, right pleural effusion (Fig 3). Thoracentesis performed described sanguinolent fluid that, after microscopic evaluation, was suggestive of malignant recurrence. Thoracic aortography was performed with subselective catheterization to several arteries (right bronchial, right phrenic, and right renal) and did not show any active bleeding. However, the right inferior intercostal and adrenal arteries were suspected to be the cause of the bleeding event, so they were embo-
lized until stasis. The patient remained hemodynamically unstable, but he experienced multiorgan failure. Despite undertaking aggressive measures, he died 10 days after his admission to the hospital.

**Discussion**

Diagnosing primary angiosarcomas of the adrenal gland can be challenging to the clinician because of the rarity of these soft-tissue sarcomas.\(^7\) Few cases have been reported (22 in the English-language literature between 1988 and 2013), and most have been single-case reports.\(^7,10\) The largest series (9 cases) comes from Wenig et al.\(^10\) of the Armed Forces Institute of Pathology.

The etiology of adrenal angiosarcoma is unknown, but it has been associated with exposure to arsenic-containing insecticides.\(^11\) Another report concerns a person aged 68 years who was employed at a factory and had been exposed to vinyl chloride for 15 years.\(^12\) No case, including ours, had a history of multiple endocrine neoplasia syndrome.\(^11,12\) Our patient also had no known history of toxic exposure.

Adrenal angiosarcoma occurs more frequently in men in the sixth and seventh decades of life than in younger men or women of any age.\(^13\) The most commonly reported symptom is pain combined with the finding of an abdominal mass.\(^13\)

None of the reported cases had hyperfunctioning tumors.\(^11,12\) Tumors ranged in size from 5 to 10 cm and were solid to cystic in appearance, similar to our case.\(^11,12\) Initial microscopic examination of nearly all relevant cases in the medical literature revealed an epithelioid appearance.\(^7\) Most immunohistochemical findings were positive for keratins, making it difficult to confirm our diagnosis. Obtaining a wide immunohistochemical panel is required for a successful pathological diagnosis.\(^14\)

Adrenal angiosarcomas are high-grade tumors that have the capacity to infiltrate and metastasize to distant organs.\(^7\) The data are limited in the use of adjuvant therapy after surgical resection.\(^7\) Surgical eradication appears to have a good outcome in more than 50% of patients.\(^14\) Due to their aggressive biology, use of adjuvant therapy for the management of adrenal angiosarcomas has been advised.\(^12\) For example, Rodriguez-Pinilla et al.\(^12\) reported in 2002 on 5 cases with disease that had metastasized to the bone, liver, lung, and pleura.

Diagnosing primary angiosarcomas of the adrenal gland is made difficult for pathologists and other health care professionals for several reasons. Necrosis and hemorrhage associated with cystic changes make it challenging to identify the primary focus.\(^7\) In addition, other neoplasias, including pheochromocytomas and cortical adenomas, have been associated with cystic components.\(^7\) Thus, an experienced clinician must pay detailed attention to the gross specimen and take into account identification of the solid component of the angiosarcoma.\(^7\) By contrast to most angiosarcomas with a histological vasoformative pattern, most primary adrenal gland angiosarcomas have a solid epithelioid pattern.\(^15\) Positive immunoreactivity to cytokeratins, a marker of epithelial tumors, can lead to an incorrect diagnosis of metastatic epithelial tumor. For a definitive diagnosis, in addition to the clinical and radiographical presentation, the pathologist must perform a wide immunohistochemistry panel to establish the diagnosis. A definitive diagnosis also requires immunohistochemical staining for vascular markers such as CD31, CD34, FLI1, and factor VIII.\(^3\)

**Conclusions**

Our case report illustrates the need for multidisciplinary evaluation by clinicians, radiologists, surgeons, and pathologists in order to diagnose primary adrenal angiosarcomas and provide these patients with adequate therapy. Surgical excision is the treatment of choice. The irregular, histological attributes of these angiosarcomas, as well as their low incidence rate,\(^1\) can lead to an incorrect diagnosis. The diagnosis should be confirmed by immunohistochemistry panels after clinical suspicion is prompted by the patient's clinical and radiographical presentation.

**References**

NUT Midline Carcinoma: A Rare Malignancy
Sameer Al Diffalha, MD, Nidal Al Aukla, MD, Saleh Hasan, Shohreh Dickinson, MD, and Farah Khalil, MD

Summary: Nuclear protein of the testis (NUT) midline carcinoma can present in the head, neck, and mediastinum. In general, it presents in young adult men and has a poor prognosis. We report on a case of NUT midline carcinoma of the mediastinum in a man 27 years of age without any prior malignancy. Due to the location of the tumor, mediastinal lymphoma and germ cell tumor were initially considered; however, immunohistochemistry was performed using NUT antibody that revealed it to be NUT midline carcinoma. Although guidelines exist for squamous cell carcinoma of the head, neck, and mediastinum, no such specific guidelines are available for NUT midline carcinoma, which looks morphologically similar to squamous cell carcinoma but behaves more aggressively and carries a poor prognosis.

Background
Nuclear protein of the testis (NUT) midline carcinoma is a rare, aggressive, and fatal carcinoma that most often occurs in the midline of the body, which includes the head, neck, and mediastinum. It is characterized by undifferentiated morphological features immunoreactive to NUT and defined by NUT rearrangement. It is a rare subtype of squamous cell carcinoma. Previous reports cite an identical chromosomal translocation, suggesting that NUT midline carcinoma is also known as carcinoma with chromosomal translocation 15:19. NUT encodes a protein at the chromosome 15 breakpoint that demonstrates testis-restricted expression and nuclear localization signals. This type of carcinoma typically affects young adults (median, 15 years of age). In general, NUT midline carcinoma is restricted to the mediastinum, head, and neck areas, but rare cases have also involved gynecological structures.

Case Report
A man 27 years of age who had never smoked presented with cough and hemoptysis. Initially, he presented at an urgent care clinic where radiography of his chest was obtained, the results of which were concerning for mediastinal mass and lymphadenopathy (Fig 1A). The patient later developed severe headaches and facial swelling and flushing. He was diagnosed with a mediastinal mass, and his health care team also suspected that he might have superior vena cava syndrome; therefore, he was referred to the H. Lee Moffitt Cancer Center & Research Institute (Tampa, FL) for further workup.

Computed tomography (CT) of his chest was performed and showed a large mediastinal mass and lymphadenopathy (Fig 1B–C). CT of his abdomen and pelvis revealed a right adrenal nodule 3.0 cm in size that appeared to be adrenal adenoma. Findings on ultrasonography of his scrotum and testicles were unremarkable.

Based on these findings, we suspected that the large mediastinal mass in the patient was either a germ cell tumor or lymphoma.

Fiberoptic bronchoscopy, bronchoalveolar lavage, and biopsies of the tumor in the left main stem bronchus were performed. The results showed diffusely thickened mucosa throughout the right bronchial tree and left main stem bronchus. The tumor extended into and moderately obstructed the left upper lobar bronchus, extending into and severely obstructing the left lower lobar bronchus. Specimens taken from the biopsies of the left main stem bronchus were sent for frozen section analysis. They were interpreted as a poorly differentiated malignant neoplasm. The final pathology results were deferred to permanent sections to perform the necessary immunohistochemistry (IHC) and flow-cytometry studies.

Papanicolaou smear and Romanowsky-stained slides showed cellular, loosely cohesive, and isolated cells (Fig 2A–B). The cells were 3 times larger in diameter than that of a small lymphocyte. The nuclei were round to oval in shape and had slightly irregular contours; some cells had prominent nucleoli. The
nuclear chromatin was dense and finely granular in most of the cells, and vesicular open chromatin was observed in occasional cells. No overt keratinization or dyskeratosis was seen. Glandular structures were not observed.

His case was initially determined to be a germ cell tumor of the mediastinum. Another small tissue fragment was submitted for lymphoma workup. Ancillary studies were performed on the tissue obtained from biopsy of the left main stem bronchus, fragments of which showed squamous mucosa with invasive, malignant, epithelioid cells in a background of extensive necrosis, acute inflammation, and reactive changes. Small foci of the tumor showed vague squamous features (Fig 2C–F).

Immunoperoxidase stains were performed and revealed that the tumor cells were strongly reactive for pankeratin (AEI/AE3/CAM5.2), p40, and cytokera-
tins 5 and 6 (Fig 3A–B). Triple stain for PIN4 (AMACR, CK903, p63) showed the tumor cells strongly positive for p63. The tumor cells were nonreactive for CD45, CD20, placental alkaline phosphatase, Sal-like protein 4, glypican 3, α-fetoprotein, c-Kit (CD117), endosomal membrane protein, synaptophysin, CHG, and Wilms tumor 1, thus excluding lymphoma and germ cell tumor from the differential diagnosis. The morphological and immunoperoxidase findings were suggestive of a malignant tumor with squamous differentiation.

Based on the tumor histomorphological findings of the poorly differentiated carcinoma, the location of the tumor, and the patient’s age, NUT midline carcinoma was added to the differential diagnosis. Additional testing for NUT IHC was positive (see Fig 3). Thus, a diagnosis of NUT midline carcinoma was made.

The patient was also experiencing left temporal/retro-orbital and back pain, which necessitated additional radiological studies. Magnetic resonance imaging of the brain revealed bony metastatic disease involving the left greater wing of the sphenoid, the lateral wall of the left orbit, and the floor of the left middle cranial fossa with minimal intracranial, extradural tumor extension. Imaging findings also showed lytic lesions in the thoracic and lumbar spine. The patient received chemotherapy (carboplatin/paclitaxel) along with radiation to the mediastinum (30 Gy in 10 fractions) and sphenoid/skull base (30 Gy in 5 fractions).

The patient underwent left temporals biopsy, the findings of which revealed metastatic squamous carcinoma. In situ hybridization testing for high-risk human papillomavirus (types 16, 18, 31, 33, and 51) was positive, indicating the presence of at least 1 of the high-risk types. Targeted, next-generation sequencing was also performed. A gene panel showed no clinically relevant results. He was enrolled in a phase 1 clinical trial. While participating in the trial, he had initial, significant resolution of diffuse bone metastases; however, positron emission tomography/CT for staging purposes showed bone disease progression.

The patient eventually developed thrombocytopenia and spontaneous tension pneumothorax without evidence of pulmonary embolism seen on CT of the chest. He was started on vancomycin, cefepime, and levofloxacin; in addition, his dose of steroids was increased. However, the patient acutely decompensated; he developed pericardial effusion, which continued to worsen, and he was exhibiting early signs of tamponade.

The health care team discussed the long-term goals of care with the patient and his family, who together decided to pursue comfort measures alone. He was then given patient-controlled analgesia (hydromorphone). Due to increasing breakthrough agitation, the patient was prescribed intravenous lorazepam. Following a discussion with the supportive care team, his family decided to pursue palliative sedation and intravenous phenobarbital. Five months after undergoing the diagnostic biopsy, the patient died.

Discussion

NUT midline carcinoma is a rare and aggressive carcinoma that usually presents as widely metastatic and unresectable disease.1 The mean survival rate is approximately 9 months.7-11 Typically, it affects boys aged 15 years, but it may present in older persons.1,7,12,13 The majority of cases occur in the midline of the body, including the head, neck, and the mediastinum.1 It may involve the nostrils, epiglottis, orbits, sinuses, bladder, and the right iliac bone.8,15

Sixty-two cases have been reported of NUT midline carcinoma; of those, only 2 have presented in gynecological structures.6 Unlike most solid tumors,
NUT midline carcinomas are not classified according to tissue or site of origin; instead, they are genetically defined.1,6 NUT was initially described in 1991. Its symbol comes from the protein coded at the chromosome 15 breakpoint.2,3,5

The undifferentiated morphological features of NUT midline carcinoma are immunoreactive to NUT and are defined by rearrangement involving the NUT locus at 15q14. This generates a specific fusion transcript with a member of the bromodomain-containing family, such as BRD4, which is located on chromosome 19p13.1. It is also known as carcinoma with chromosomal translocation 15:19.1

In approximately two-thirds of NUT midline carcinoma cases, NUT was discovered to structure a steady fusion oncogene with BRD4, creating chimeric genes that encode BRD–NUT fusion proteins.3 The other one-third of cases of NUT midline carcinomas in which NUT was fused with an unidentified oncogene were designated as a NUT-variant carcinoma other than BRD4.5

Historically, a diagnosis of NUT midline carcinoma was made by showing NUT rearrangement by dual color, split-apart fluorescence in situ hybridization, or by demonstration of a BRD4–NUT fusion transcript by reverse transcriptase polymerase chain reaction. Haack et al6 reported this by developing a particular monoclonal antibody against recombinant NUT protein that had a sensitivity rate of 87%, a specificity rate of 100%, and a positive predictive value of nearly 100%.

Histological findings are not diagnostic for NUT midline carcinoma. The morphological findings generally consist of poorly differentiated carcinoma or squamous cell carcinoma not broadly known to most pathologists.2,4 Occasionally, it has been classified as other tumors (eg, thymic carcinoma).5 Similarly in our patient, the original differential diagnosis was broad; however, because the diagnosis was initially thought to be a germ cell tumor or lymphoma, the specimen from the biopsy was first assigned to the genitourinary pathologist who did an extensive workup. We also consulted with a thoracic pathologist, who suggested NUT midline carcinoma given the findings on morphology, the patient's clinical history, and the location of the tumor. Based on these findings, additional immunostains were performed to check for squamous differentiation. NUT IHC showed clear reactivity within the tumor cells. NUT IHC can detect NUT in NUT midline carcinoma, the expression of which in normal, mature adult tissue is restricted to the testis.

Because incidence rates and published data are lacking, no standardized treatment exists for NUT midline carcinoma. It is an aggressive, fatal disease that is unresponsive to aggressive chemoradiotherapy.3,14 Its median survival is 9 months, ranging from 28 to 96 weeks depending on the molecular characteristics of the tumor.2,11

In the absence of optimal treatment, platinum-based and lymphoma-type regimens have been used.3,15 In a large series by Bauer et al16 no differences were seen in progression-free and overall survival rates by patient age, sex, histology findings, type of translocation, or lymph-node involvement. The 1- and 2-year rates of progression-free survival among 25 adults were both 4%, whereas the overall survival rates were 16% and 5% at 1 and 2 years, respectively.16 In this series, large resection and radiotherapy delivered early appeared to be associated with improved progression-free survival and overall survival rates.16

Balla et al6 reported on a 10-year old boy with NUT midline carcinoma. They used a histone deacetylase inhibitor to treat the patient for 5 weeks, who had an objective clinical response before toxicities limited its continued use. The patient's disease recurred, and he died 11 months after the initial diagnosis.5

Looking toward the future, targeted therapeutic approaches are being developed, such as direct-acting bromodomain inhibitors and histone deacetylase inhibitors.10,16 For more information on current trials of NUT midline carcinoma, please visit www.nmcregistry.org/clinicaltrial.html.

Conclusions

Nuclear protein of the testis midline carcinoma is an aggressive and usually fatal disease that should be considered in the differential diagnosis of midline poorly differentiated carcinoma in a young male. Optimal surgery and radiotherapy regimens are improving the rates of progression-free and overall survival, and advances are taking place in our understanding of the specific translocation in the pathogenesis of the disease. In the future, targeted therapy could lead to better treatment options for this aggressive and rare cancer.

References


CD4-Positive T-Cell Large Granular Lymphocytosis Mimicking Sézary Syndrome in a Patient With Mycosis Fungoides

Ling Zhang, MD, Magali Van den Bergh, MD, and Lubomir Sokol, MD, PhD

Summary: A white woman aged 65 years presented with a macular, nonscaly, nonpruritic, erythematous lesion on her right breast. Test results revealed histological features similar to lichenoid dermatitis and early-phase primary cutaneous T-cell lymphoma with a subtype of mycosis fungoides (MF). Despite topical therapy with steroids, her skin disease continued to progress, so she underwent polymerase chain reaction and gene mutation testing. Two missense mutations were detected. The overall findings supported a diagnosis of co-occurring, CD4-positive large granular lymphocytosis and stage IA MF. The patient continued to receive topical steroids and maintenance phototherapy, and her skin lesions completely resolved after 14 weeks of therapy. Approximately 5 years after her initial presentation, she was free of symptoms, cytopenia, and no skin lesions were present. CD4-positive, large granular lymphocytosis was persistent. This patient case — to our knowledge, the first of its kind — posed dilemmas of a diagnostic and therapeutic nature. Correctly staging the lymphoma helped to aid the diagnosis and can help prevent patients similar to the one in this case from receiving unnecessary therapy.

Introduction

CD4-positive T-cell large granular lymphocytosis is an entity distinguished from conventional, CD8-positive T-cell large granular lymphocytic leukemia (LGLL). LGLL is frequently associated with sustained cytopenia, autoimmunity, splenomegaly, and recurrent mucocutaneous infections; and it has immunophenotypical positivity for CD3, CD8, CD57, and T-cell receptor αβ. Other rare immunophenotypic variants (eg, T-cell receptor γδ) have also been reported. By contrast, CD4-positive large granular lymphocytosis is a clonal T-cell lymphoproliferative disorder often associated with various neoplastic or autoimmune disorders or emerging from an iatrogenic immunotherapy. Given the aberrant expression of “pan” T-cell markers in addition to CD57, including positivity for CD3, positivity for CD4, dim positivity and negativity for CD8, CD7-positive subset, CD56-negative subset, and positivity for T-cell receptor αβ, such a population could be misinterpreted as another mature T-cell lymphoma, especially when the patient lacks a clear clinical history or a clinical investigation is incomplete.

Herein, we discuss a clinical scenario that, to our knowledge, is the first such case report of sustained, CD4-positive large granular lymphocytosis occurring in a patient with stage IA mycosis fungoides (MF) that posed diagnostic and treatment dilemmas.

Case Report

A 65-year-old white woman initially noted a macular, nonscaly, nonpruritic, erythematous lesion on her right breast. The lesion subsequently became more papular in appearance, and several additional maculopapular lesions emerged on her back and abdomen. Findings on shave biopsy of the lesion on her back showed histological features similar to lichenoid dermatitis and early-phase primary cutaneous T-cell lymphoma with an MF subtype.

Findings on staging positron emission tomography were normal. Complete blood count showed a white blood cell count of 11.9 × 10^9/µL and an absolute lymphocyte count of 5535/µL (45%). A brief flow cytometry panel was performed on peripheral blood mononuclear cells and identified a partial loss of CD26 antigen on T-cell lymphocytes and aberrant expression of CD57 of uncertain clinical significance. Staging bone marrow biopsy showed a small population of T cells (15%) with a similar phenotype.

Findings on shave biopsy of another skin lesion located on her shin revealed atypical lymphoid cells with cerebriform nuclei in the epidermis, thus suggesting a diagnosis of MF.

Peripheral blood flow cytometry revealed a distinct population of T cells positive for CD4, dimly positive for CD7, and negative for CD26 comprising approximately 61% of the gated lymphocytes with an ab-
solute count of abnormal lymphocytes of 3544/µL. The lymphoid cells also expressed CD56, CD57, and T-cell receptor αβ, but they lacked positivity for CD16, CD25, CD30, HLA-DR, and T-cell receptor γδ (Fig 1). Examination of peripheral blood film showed that the majority of lymphocytes were large granular lymphocytes (Fig 2A–B). Serological test results for HIV and human T-cell lymphotropic virus were negative. Although atypical lymphoid cells with classic cerebriform nuclei were absent, differential diagnoses should include Sézary syndrome, reactive T-cell lymphocytosis, T-cell LGLL, peripheral T-cell lymphoma (leukemic phase), and blastic plasmacytoid dendritic cell neoplasm.

The patient was treated with topical steroids. After 4 months, the skin disease progressed, with patch disease and similar morphology and immunophenotype noted (Fig 2C–D). Repeat flow cytometry performed on her peripheral blood showed a population of atypical T cells (absolute count > 2000/µL) with unchanged immunophenotype.

Polymerase chain reaction (PCR) was used to identify the clonal TCR rearrangement. To target T-cell receptors in the Dβ, Jβ, Jγ, Vβ, and Vγ regions, PCR amplification was performed in 5 multiplex PCR tubes.
with primers, after which the products were detected and separated using capillary gel electrophoresis on a genetic analyzer. Clonal TCR rearrangement was identified at peaks at 249.85 and 298.53, and clonal TCR γ rearrangement was visualized at peaks at 209.12 and 175.46 (Fig 3). Karyotyping performed on peripheral blood revealed a normal female karyotype.

Gene mutation testing was performed with the
NexCourse Complete (Genoptix, Carlsbad, CA) assay. This type of assay interrogates 173 genes known to be recurrently mutated in cancers, including T- and B-cell lymphoproliferative disorders (sequencing depth of 500 × coverage).6 The results showed no pathologically significant mutations (Fig 4), including the absence of STAT3 and STAT5B, which are frequently mutated in T-cell LGLL.6 Two missense mutations, CCNE1 112G>A, p.R374Q with 52% allele frequency and RAD21 1811A>G, p.K604R with 49% allele frequency, were detected. In our experience, both of these mutations have rarely been reported, and their clinical significance is uncertain.

The overall findings supported a diagnosis of CD4-positive large granular lymphocytosis — rather than Sézary syndrome — occurring simultaneously with advanced-stage MF.

The patient continued to receive topical steroids and then was switched to narrowband ultraviolet B phototherapy when new skin lesions developed. After 14 weeks of phototherapy, her skin lesions completely resolved. Subsequently, she continued receiving maintenance phototherapy. At her last follow-up visit approximately 5 years after her initial presentation, she had persistent, circulating CD4-positive T-cell large granular lymphocytosis (4460/µL) without any symptoms or cytopenia. No skin lesions were present.

Discussion

CD4-positive T-helper cells are a subtype of lymphocytes, major histocompatibility complex class 2 restricted, that play a key role in adaptive immunity. Of note, most cases of peripheral cell lymphoma originate from CD4-positive T cells.7 By contrast to CD4-positive mature lymphomas, CD4-positive large granular lymphocytosis is a laboratory finding with good clinical outcomes. The entity is considered rather to be a reactive than a neoplastic process and it has been found to be paraneoplastic, yet with an uncertain pathogenesis.2,5 In our experience, certain medication use, cytokine release, and immune dysregulation in response to an underlying primary neoplasm could trigger increased production of CD4-positive T lymphocytes.

Garrido et al8 showed the coexistence of the T-cell receptor Vβ repertoire (eg, positive for T-cell receptor Vβ13.1, HLA-DRB1*0701), suggesting that CD4-positive large granular lymphocytosis may originate from an antigen-driven, clonal T-cell stimulation. It is contro-
versial as to whether CD4-positive large granular lymphocytosis with a benign course should be considered to be a variant of T-cell LGLL. STAT5B mutation is also frequently detected in CD4-variant T-cell LGLL, a finding that could be useful for subcategorizing the entity.9 Regardless, in our experience, the mainstay of treatment for CD4-variant T-cell LGLL is observation alone.

STAT5B mutations were not detected in our patient after targeted gene sequencing (see Fig 4), a finding that could be attributed to different technologies used for testing. Of note, Andersson et al9 used an exome-sequencing platform for detecting STAT5B mutation on sorted CD4-positive or CD4-positive/CD8-positive cells and used CD4-negative fractions as a control with higher sensitivity and specificity rates.

In our patient, lack of generalized lymphadenopathy diminished the likelihood of peripheral blood involvement by CD4-positive peripheral T-cell lymphoma, not otherwise specified.7 Blastic plasmacytoid dendritic cell neoplasm dually expresses CD4/CD56 that could mimic CD4-positive large granular lymphocytosis. However, blastic plasmacytoid dendritic cell neoplasm also co-expresses CD123, TCL1, or CD303 (BDCA2) and shows blastoid cytological features; these were negative in our patient.

Abnormal CD4-positive T-cell proliferation that coexisted with MF in our patient raised suspicion for Sézary syndrome as the diagnosis, because both cutaneous and peripheral circulating abnormal T cells shared a similar phenotype: CD4 positivity with loss of CD7 and CD26.11 However, these CD4-positive cells also express CD57 and CD56, thus mitigating a diagnosis of Sézary syndrome. Furthermore, the patient never presented with the classic skin manifestations associated with Sézary syndrome (eg, exfoliative erythroderma).

Conclusions

The patient in our case had an unusual clinical presentation with concurrent stage IA mycosis fungoides and sustained, CD4-positive large granular lymphocytosis. An accurate diagnosis can aid clinicians in correctly staging lymphoma and can help prevent patients similar to ours from receiving unnecessary therapy.

References


