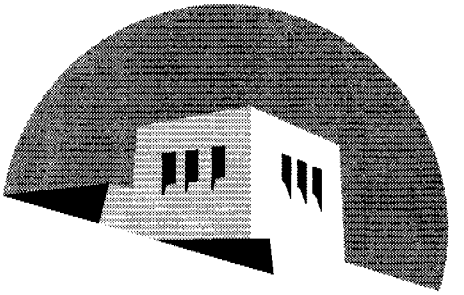

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Correspondence Continuing Education Courses for Nuclear Pharmacists and Nuclear Medicine Professionals

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Breast Cancer Diagnosis and Treatment

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BREAST CANCER DIAGNOSIS AND TREATMENT

STATEMENT OF OBJECTIVES

The primary purpose of this lesson is to increase the reader's knowledge and understanding of the diagnosis and treatment of breast cancer.

Upon completion of this continuing education unit, the reader should be able to:

1. Identify risk factors for the development of breast cancer.
2. Describe the current recommendations for breast cancer screening.
3. List the different types of biopsy techniques available for non-palpable breast cancer.
4. Discuss the advantages and limitations of nuclear medicine imaging of breast cancer.
5. Compare and contrast the radiopharmaceuticals utilized for breast cancer imaging.
6. Describe breast cancer staging using the TNM classification.
7. List the treatment for patients with non-invasive and invasive breast cancer.
8. Explain the role of sentinel lymph node biopsy in breast cancer surgery.
9. Describe the role of adjuvant therapy in breast cancer treatment.

COURSE OUTLINE

I. INTRODUCTION

II. PATHOPHYSIOLOGY

A. Histopathology

B. Etiology and Risk Factors

III. DIAGNOSTIC STUDIES

A. Mammography

B. Ultrasound

C. Magnetic Resonance Imaging (MRI)

D. Nuclear Medicine Imaging

V. STAGING

V. TREATMENT

A. Non-invasive cancer

B. Invasive cancer

VI. SUMMARY

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INTRODUCTION

Cancer of the breast remains a significant health issue despite recent advances resulting in earlier diagnosis and management. Although it is primarily a disease of older women, it can affect any age group and is characterized as having a wide variation in its clinical course. The treatment of breast cancer has evolved over the last several decades due to the results of well-controlled clinical trials and the development of promising new drugs, and should serve as an example for evaluating new treatments for other malignancies.

To understand the impact of early detection on breast cancer morbidity and mortality in the United States, it is important to look at how breast cancer trends have changed over time. All of the statistics that follow are compiled from estimates published by National Cancer Institute (NCI) Surveillance, Epidemiology and End Results (SEER) Program, 1998 [1] and from Vital Statistics of the United States, 1998.[2] Breast cancer remains the leading cause of estimated new cancer cases in the United States. In 1999 breast cancer accounted for 29% of all new cancer cases as compared to lung and bronchus cancer estimated at 13%.[1] Women of all ages have a one in eight chance (12.5%) of developing breast cancer at some point in their lifetime, with a peak incidence of 6.8% (1 in 15) between the ages of 60 and 79. Once the data have been tabulated, it is predicted that 176,300 new cases of invasive cancer will be reported for 1999: 1,300 in men and 175,000 in women. It also is estimated that there will be 43,700 breast cancer deaths with 400 in men and 43,300 in women in 1999.[3] For the period of 1993 to 1995, breast cancer continued to have an age-related trend. However, that trend is reversed when predicting cancer related deaths in 1999, with lung and bronchus cancer predicted to account for 25% of cancer deaths in 1999 while breast cancer is predicted in 16% of cancer deaths.[4]

According to race and ethnicity, the incidence of breast cancer per 100,000 women during 1990-1995 was highest in white women (113.2), followed by black women (99.0), Asian/Pacific island women (71.4), Hispanic women (69.3), and finally Native American women (31.9).[1] The mortality rate is highest among black women at 31.5 (per 100,000), followed by white women (26.0), Hispanic women (15.3), Native American women (11.7), and Asian/Pacific island women (11.6).[2]

The variation in the incidence of breast cancer between races may be related to factors such as differences in diet, socioeconomic status, heredity patterns and other culturally linked traits. The differences in mortality seen between races may be due to the stage at which breast cancer is diagnosed. For the period of 1980 to 1994, 62% of breast cancer cases in white females were detected at a localized stage, compared with only 50% in black women. During this same period of time, breast cancer was detected at a regional phase in 29% of white women compared to 35% in black women, and distant metastases were present in 6% of white women as compared with 9% in black women. These data suggest that breast cancer is detected earlier and at a less advanced stage in white women than in their black counterparts.

The trend toward a reduction in breast cancer mortality in some countries, and in the United States in particular, is encouraging. This decreased mortality rate is due in part to concerted efforts at patient and professional education advocating the importance of early detection in conjunction with the widespread availability of high-quality, low-cost screening programs. More women are being screened than ever before, resulting in earlier detection of breast cancer at a more curable stage. Early detection remains the primary opportunity to catch breast cancer in its most treatable phase. Improved diagnosis and better staging techniques will continue to have a positive impact on mortality rates. A major goal in breast cancer diagnosis is the ability to distinguish between benign and malignant lesions. Emerging diagnostic modalities are being developed as a way to supplement mammography screening.

PATHOPHYSIOLOGY

Primary tumors of the breast are classified as invasive or non-invasive, depending upon whether the tumor cells have violated the basement membrane of the mammary ducts.
Non-invasive lesions include ductal carcinoma in situ (DCIS), or lobular carcinoma in situ (LCIS), depending on the cell of origin. Ductal carcinoma is the most common type of invasive breast malignancy, arising from the epithelial cells that line the mammary ducts.

Histopathology

There are several subtypes of invasive *ductal* carcinoma including tubular, medullary, papillary, and colloid (mucinous). Invasive *lobular* carcinoma accounts for 3-4% of invasive breast cancers and originates from the mammary lobules. Theses malignancies have a unique histologic appearance characterized by small cells in a linear arrangement (Indian-file) with a tendency to proliferate around ducts and lobules (targeted growth).

Etiology and Risk Factors

While the etiology of breast cancer remains uncertain, genetics, hormones, and dietary factors probably play a significant role in carcinogenesis. There continues to be extensive ongoing research evaluating the role of risk factors for breast cancer, however these findings have not yet translated into major clinical advances in early detection. Major risk factors include a personal history of breast cancer, a first degree relative with breast cancer, and biopsy proven proliferative breast disease. Minor risk factors include precocious menarche, primagravida > 30 years of age, and exogenous hormone (estrogen) use. These risk factors are useful in assessing overall risk and should be discussed with patients to help individualize their follow-up. While a personal history of breast cancer is the strongest risk factor, a first-degree relative with breast cancer places the patient up to 3 times greater risk than that of the general population. True hereditary breast cancer is present in only 5-10% of all breast cancer cases, while the sporadic (non-hereditary) type accounts for more than 80%. A previous breast biopsy showing proliferative breast disease places the patient at increased risk, especially if atypical hyperplasia is present. The relative risk for developing breast cancer is 1.6 for proliferative disease without atypia and 4.4 if atypia is present. Patients with atypia and a family history have a relative risk of 8.9, which approaches the risk of patients with in situ carcinoma.[5]

With the discovery of the hereditary breast cancer genes BRCA-1 and BRCA-2, an individual patient's risk of developing breast cancer can be assessed. Unfortunately, the vast majority of non-hereditary cases of breast cancer do not involve BRCA-1 and 2 mutations. A major advance in the prevention of breast cancer through the use of the anti-estrogen tamoxifen was recently reported.[6] Women with a 5-year breast cancer risk of greater than 1.7 (using the Gail risk model) were enrolled into

The double-blinded Breast Cancer Prevention Trial and randomized to receive tamoxifen (20 mg per day) or placebo for 5 years. Tamoxifen use reduced the development of breast cancer by 45% in high-risk women. This reduction in risk was seen in both premenopausal and postmenopausal women and was most pronounced in those women with LCIS (lobular carcinoma in situ) and atypical hyperplasia found on a previous biopsy. There was a slight increase in endometrial cancer and deep venous thrombosis in the tamoxifen group, which has dampened enthusiasm. The number of breast cancers prevented was much greater than the frequency of endometrial cancers attributed to the use of tamoxifen. The STAR Trial will compare tamoxifen to raloxifene, a selective estrogen receptor modulator (SERM) in reducing breast cancer onset. Newer SERMs, such as raloxifene, may provide similar benefit in preventing breast cancer without the potential toxicities.

DIAGNOSTIC STUDIES

The differential diagnosis of a palpable breast mass includes a fibroadenoma, which is more common in the younger age group (20-30's), and fibrocystic mastopathy, seen in premenopausal and perimenopausal women. Other masses, such as cysts, lipomas, adenosis tumors, phylloide tumors (benign and malignant), and papillomas can present as palpable lesions. Most nonpalpable mammographically detected masses/densities are cysts, however, fibroadenomas, papillomas, radial scars, and benign lymph nodes are often seen. Certain microcalcifications can be a sign of malignancy. Adenosis and fibrocystic changes account for most benign biopsies.

Most patients with breast cancer will present with a palpable mass or mammographic abnormality. Because mammographic screening has been shown to be effective in reducing breast cancer mortality in postmenopausal women, it has become widely used as a screening tool in addition to breast self exam and examination by a physician.[7-9]

The American Cancer Society guidelines for screening include monthly breast self-exam after age 20, baseline mammogram at age 35 if there is a family history for breast cancer, and a mammogram annually for women over 40. Additionally, professional physical examination of the breasts should be performed every 3 years between the ages of 20 and 40, and annually thereafter. These are only guidelines and individual patients may require modification based on risk factor analysis. With the inception of new screening programs and the use of these guidelines, earlier and smaller tumors are being diagnosed. This allows for more conservative breast surgery to be performed and may result in improved survival.

Mammography

Mammography remains the most effective method of detecting breast tumors early, when the disease is most successfully treated. According to the U.S. Public Health Service, widespread screening of women over 50, followed by prompt treatment when required, can reduce breast cancer deaths by as much as 30%.[10] Mammography has a high sensitivity (ability to detect cancer when it is indeed present) and can visualize 85% to 90% of breast cancers in women over 50. It also can discover a tumor up to two years before a malignancy can be felt.[11]

Despite its many successes, mammography is not unequivocal; although its sensitivity is 85%, it is limited in its specificity (ability to correctly identify a woman who does not have breast cancer) with ranges reported from as low as 30% in some studies -- to highs of 65%[12-14] to 80% in other studies.[15]

In particular, mammography is less sensitive and less specific in younger women who tend to have denser breast tissue (nearly 70% of the breast is comprised of dense tissue in young women). Mammography is also less sensitive and less specific in older women with denser breasts (i.e. hormone replacement therapy), and in women who have undergone breast surgery or radiation therapy. Dense

breast tissue is an important consideration because it can compromise mammographic results by obscuring underlying tumors. As many as 25% of women have radiographically dense breasts[16], and this number is much higher in women under the age of 50.

Some studies report mammography is associated with relatively high false-negative rates[17-19], with as many as 40% of cases going undetected with mammography alone, particularly in young premenopausal women because of the confounding factor of dense breasts. Furthermore, mammography, in many cases, may be unable to accurately identify the type of lesion, requiring biopsy or further investigation. In addition, mammography has a relatively low positive predictive value ranging between 20% and 30%. The predictive value of mammography is calculated by dividing the total number of true cancers, verified histologically, by the total number of tests thought to be positive for breast cancer.[20] In fact, only one in every four to six biopsies will reveal breast cancer, which means that as many as 75% of biopsies are performed for benign lesions and therefore unnecessary. Suspicious findings with mammography are the primary cause of unnecessary biopsy. There continues to be a need for a breast cancer imaging technique that is highly sensitive, highly specific, relatively noninvasive, offers a high predictive value, and is cost effective. Several potential candidates for this "ultimate breast cancer imaging modality" are discussed in the sections that follow. Since none of these techniques is without its drawbacks the search will continue until one can be found.

Mammographic abnormalities, which are suggestive of malignancy, are characterized as either masses or microcalcifications, and classified according to the BIRADS System as category 0-5 with 5 being highly suspicious. If a mass is present on mammography, it can usually be determined whether a mass is cystic or solid with an ultrasound examination of the mass; often these two technologies complement one another. Biopsy is warranted if a mass does not meet the sonographic criteria for a simple cyst, or if microcalcifications are present on mammogram. Stereotactic or ultrasound-guided core needle biopsy and wire localization surgical biopsy are both acceptable biopsy methods. Core biopsy, done under fluoroscopy, has the advantage of being less "invasive" than a needle-localization surgical biopsy, but it should be emphasized that adequate sampling of the suspicious lesion is required. If atypia is present on a stereotactic biopsy, an open biopsy is necessary to rule out a malignancy.[11]

As previously mentioned, mammography does have its limitations. With the exception of examination of mammographically classic lesions such as calcified fibroadenomas, lipomas, fat necrosis and spiculated carcinomas, mammography is not "diagnostic" and should not be used alone to reliably differentiate between benign and malignant lesions.[21] The only definitive means of confirmation of a suspicious lesion seen on mammography is either excisional, fine-needle aspiration or stereotactic core biopsy for the provision of tissue to the pathologist. However, cancerous tissue is only found in 25% of the estimated 700,000 biopsies completed in the United States each year. This results in an estimated 525,000 unnecessary biopsies, which leads to increased health care costs and the pain and inconvenience of an invasive medical procedure.

Complementary modalities such as ultrasound, Doppler ultrasound, computed tomography (CT), MRI, and digital mammography have been employed to improve the sensitivity (detection) and specificity (distinguishing benign from malignant). Unfortunately, the sensitivity of these procedures is too low to replace mammography as a screening device, and these procedures have variable rates of specificity. Although the use of these procedures is becoming more common as a complementary procedure, there is still a need for a diagnostic procedure with greater specificity.

Ultrasound

Although its usefulness as a screening device is limited, ultrasound has proven to be valuable as an adjunct to conventional mammography. This is particularly true in the evaluation of radiographically dense breasts and as a supplement to mammography due to mammography's low-positive predictive value and its inability to reduce unnecessary biopsies. Originally, ultrasound was dismissed as a useful screening technique because of its inability to detect occult malignancies in women with normal mammographies and clinical exams. In retrospect, many of the problems associated with the use of ultrasound were operator dependent. However, there have been substantial improvements in ultrasound technology, particularly with the advent of high frequency, hand-held devices leading to its use in a number of difficult-to-evaluate patients as described below in **Table 1**.

Table 1. Conditions for Which Ultrasound Has Demonstrated Diagnostic Efficacy in Breast Disease.

- Differentiating cysts from solid masses (palpable or non-palpable).
- Imaging of women with a palpable mass who are less than 25 years old.
- Evaluating a palpable mass that is occult with mammography.
- Providing imaging guidance for core-needle biopsy and cyst aspiration.
- Evaluating ruptured silicone breast implants.
- Evaluating abscesses.

These new devices offer the advantage of enhanced spatial resolution in a real-time environment.[22] It is impossible to consistently image microcalcifications using ultrasound only. Furthermore, there is significant overlap in the morphologic characteristics of benign versus malignant lesions with ultrasound. As a result, many palpable lesions are biopsied despite negative ultrasonographic findings. The management of nonpalpable lesions is based upon their appearance with ultrasound.

Ultrasound is extremely operator dependent. It is essential that all of the breast and surrounding tissue be imaged to adequately identify and evaluate any lesions. The length of time required to conduct an adequate ultrasound examination of the breast is also extremely operator dependent. In some cases, skilled sonographers can perform an adequate ultrasound examination of the breast in as few as 90 seconds; other less experienced operators may require as long as 9 minutes to accomplish an examination. It is difficult to know whether the entire breast and surrounding tissue has been imaged adequately when considering the time involved to perform the ultrasound.[23]

Magnetic Resonance Imaging

Over the past 15 years, there have been numerous technologic advances in magnetic resonance imaging (MRI) of the breast. The introduction of intravenous, gadolinium-based contrast agents, the development of dedicated breast surface coils, and introduction of

standard imaging sequences have improved MRI imaging of the breast. Today, MRI imaging of the breast generally is performed with a dedicated coil that permits simultaneous imaging of both breasts. However, MRI techniques vary between institutions (eg, dosage of interventional agents and timing of imaging) leading to a lack of standardized data regarding the potential usefulness of MRI in breast imaging.[22]

Magnetic resonance imaging permits visualization of breast lesions because these lesions are usually enhanced following the administration of intravenous contrast agents. This phenomenon is due to the hypervascularity of growing tumors and increased uptake of contrast media by these lesions. However, enhancement of non-malignant lesions and even normal breast tissue (particularly at certain times during the menstrual cycle), also may occur with MRI resulting in false-positive results.[24] A variety of factors has been considered in an effort to distinguish benign from malignant tumors with MRI. For example, time-intensity curves have been developed in an attempt to understand the actual enhancement dynamics of a breast mass as it is visualized with MRI over time.

Patterns of enhancement that occur in benign versus malignant lesions also have been studied.[25,26] The use of morphologic features has been considered as a possible means to identify malignant tumors. Unfortunately, there is a substantial overlap between the characteristics of benign and malignant lesions detected with MRI. Although MRI demonstrates high sensitivity in the detection of breast cancer, its specificity remains rather low.

MRI can successfully identify additional foci of breast cancer not evident with mammography or clinical examination.[27] In addition, MRI is more accurate than mammography in evaluating the actual size of a malignancy. This may be useful in selecting a more appropriate treatment protocol for some patients. For example, confirmation of a small primary lesion may warrant a change in the surgical approach from a mastectomy to a lumpectomy. At the other end of the spectrum, identification of additional foci of breast cancer may preclude a planned lumpectomy and require consideration of other treatment options such as chemotherapy. MRI evaluation can provide important information in the follow up of women who have undergone breast conservation or chemotherapy in whom mammographic findings are inconclusive. It also is possible to use MRI to identify primary breast cancer in patients with metastatic axillary adenopathy in whom previous mammography and clinical examination yielded normal results.

In the future, it is predicted that MRI will become a useful biopsy-guidance technique. However, this will require that MRI-guided biopsy is possible in lesions detected with MRI or its usefulness will be limited. Furthermore, small, dedicated and low-cost MRI breast imaging systems must become commercially available if MRI is to play a substantial role in the future diagnosis of breast cancer. If not, the high cost of MRI will continue to limit its widespread use.

Nuclear Medicine Imaging

Mechanisms of Action

Over the years, two approaches have been used to image soft tissue tumors. The first approach utilizes a function of normal tissue not shared by malignant tissue and thus uptake of the radiopharmaceutical is excluded from the cancer. An example of this technique is the imaging of masses in the liver using technetium Tc-99m sulfur colloid where the space-occupying lesion that replaces the normal reticuloendothelial system tissue appears as a "cold" defect in a normally "hot" background.

Imaging a "cold" defect in a "hot" organ is more difficult due to interference from radioactivity in surrounding tissue. This method of detecting tumors (indirect imaging), depends primarily on displacement of normal tissue, disruption of normal physiologic mechanisms, or identification of physiologic and biochemical

reactions to tumor growth. This mechanism of localization is inherently nonspecific and cannot distinguish between benign and malignant disorders.

Another approach utilizes a characteristic of the neoplasm not shared by normal tissue in order to localize the radiopharmaceutical in the cancer. This technique allows the tumor to be seen as an area of increased radioactivity, or "hot" spot, as in gallium Ga-67 citrate imaging of tumors such as lymphomas. In this case, the neoplastic lymph nodes will concentrate the radioactivity while normal lymph nodes will not.

Imaging a "hot" spot in a "cold" background area is more desirable than the first approach. This method of tumor detection (direct imaging) relies upon the biochemical, physiologic, or immunologic aspects of the tumor itself to localize the radiopharmaceutical.

Characteristics of Tumor Cells Pertinent to Nuclear Medicine Imaging

Localization of radiopharmaceuticals in cancer is attributed to one or more of the following properties of tumors.

1. *Increased Metabolic Activity*

The radiopharmaceutical is introduced into a tumor as a metabolic substrate, which enters the metabolic pathway of the specific tumor. An example is the use of fluorine-18 fluorodeoxyglucose (F-18 FDG) for the diagnostic imaging of colorectal, breast, brain, lung, and skin cancer. The F-18 FDG localizes in areas of increased glucose metabolism, which is common in many tumor cells. Another example involves the uptake of C-11 thymidine into certain tumor cells that demonstrate increased DNA synthesis, e.g., some lung, brain, and head and neck tumors. In addition, the mechanism of osteoneogenesis plays a major role in the localization of Tc-99m skeletal imaging agents in primary and metastatic cancer of the bone. In this example, uptake occurs at the site of reactive bone, which has a high metabolic rate as it works to replace the skeleton involved with the neoplasm.

2. *Tumor-Specific Receptors*

A tumor may be detected using radiolabeled antibodies or peptides that bind to specific tumor markers such as antigens or other receptor compounds found in vivo. Included in this category are the radiolabeled antibody compounds developed over the past few years for detection of colorectal, ovarian, lung, and prostate cancer, as well as the radiolabeled peptide compounds that bind to specific receptors found in increased concentration on the surface of some tumor cells. Areas of current investigation include radiolabeled estradiol compounds and the usefulness of FDA approved imaging agents such as indium-111 satumomab pendetide and technetium-99m arcitumomob for imaging breast cancer.

3. *Increased Tumor Blood Flow*

In order to accommodate the tremendous growth rate of tumors compared with the normal surrounding tissue, cancers lay down an intricate and complex network of blood vessels in order to bring nutrients and oxygen to the tumor cells as they grow and replicate. Increased vascularization, a common feature of many tumors, may promote tumor uptake in a variety of neoplasms, such as the localization of Ga-67 citrate in soft tissue neoplasms.

4. *Altered microvasculature*

In the ongoing effort to supply the fast growing tumor cells with nutrients and oxygen, increased vascular permeability to macromolecules is seen in tumors. This characteristic is thought to play a role in the localization of gallium Ga-67 citrate in neoplasms as transferrin bound Ga-67 is removed from the circulation and incorporated into the tumor mass. Non-specific leakage of large macromolecules may also aid in the uptake of radiolabeled antibodies and peptides, which are moved from the vascular space before binding to specific receptors, found on the tumor cell surface.

The notion of using nuclear imaging techniques in the detection of breast cancer is not new, with a variety of radiopharmaceuticals

undergoing evaluation for breast cancer imaging over the years. Nuclear medicine breast imaging or scintimammography (SMM) is primarily used as a complementary procedure to evaluate suspicious lesions detected with mammography in an attempt to avoid unnecessary biopsies or surgery.

Nuclear medicine breast imaging has a high degree of accuracy for detecting breast cancer depending on the location, size and biological characteristics of the breast cancer. The nuclear medicine breast image is especially useful when mammogram findings are difficult to interpret. This may include patients who have dense breast tissue or a history of biopsy or surgery involving the breast. **Table 2** provides a list of indications for adjunctive nuclear medicine breast imaging (in addition to the mammogram).

Table 2. Clinical Indications for Scintimammography

1. Assessment of radiographically dense breasts.
2. Assessment of scarring or architectural distortion of the breast due to previous breast surgery, radiation therapy, chemotherapy, or biopsy.
3. Assessment of breast implants (scintimammography is not affected by attenuation of silicone implants).
4. Assessment of palpable masses and normal or equivocal mammography and ultrasonography. It is not rare for patients to present with a palpable mass that is difficult to diagnosis with mammography and ultrasound alone. This is particularly true in patients with dense breasts or fibrocystic disease. These patients are often referred for biopsy or follow up mammography. Since the positive and negative predictive values for scintimammography are high in palpable lesions, scintimammography could be performed immediately after mammography. If the results are positive, biopsy is recommended.
5. Assessment of multifocal disease. Scintimammography may be useful in patients with normal or inconclusive mammography who are scheduled to undergo lumpectomy. Scintimammography can be useful in the evaluation of multifocal disease. If multifocal disease is shown to be present, a different surgical approach will be employed.
6. Evaluation of patients at high risk for breast cancer.
7. Evaluation of tumor response to chemotherapy.
8. Evaluation of metastatic axillary lymph nodes. The diagnostic accuracy of scintimammography (80% to 85%) is too low to replace axillary lymph node dissection in patients with proven invasive primary breast cancer. However, it could be useful in patients reluctant to undergo axillary node dissection if there is positive uptake. Or, on the other hand, if there is focal uptake in the breast, but no uptake in the axilla, axillary dissection may be canceled.[28]

Nuclear Imaging Agents

Thallium Tl-201 Thallous Chloride

Historically, thallium Tl-201 thallous chloride (Tl-201) scintigraphy was first used in the evaluation of myocardial perfusion. However, during the mid-1970s, Lebowitz and colleagues[29] hypothesized that Tl-201 might be useful in the imaging of tumors because of its similarity to cesium, which was known to concentrate in tumors. The idea originated from the knowledge that a number of cations were shown to have tumor affinity including Ga^{+2}, In^{+3}, Hg^{+2}, Bi^{+2}, K^{+1}, Tl^{+2}, and NH_3^{+1}. The exact mechanism by which most of these cations localize in tumors is unknown. As a group, they show poor tumor specificity with equal or greater affinity for inflammatory lesions and abscesses. Early studies demonstrated Tl-201 uptake in malignant lesions, including tumors of the brain, bone, breast and other soft tissue sarcomas.

The first documented case of carcinoma detection with Tl-201 was reported in 1976, in which a focal area of increased uptake was seen in a male patient with lung cancer who had been referred for Tl-201 evaluation of his heart.[30] In a subsequent study of 173 patients with malignant tumors and 76 with benign lesions (including 2 patients with known breast cancer), it was concluded that Tl-201 had a sensitivity of 64% and specificity of 61%.[31] In another study of 15 patients with breast cancer, uptake of Tl-201 was observed in all.[32]

The use of Tl-201 in the evaluation of malignant tumors has increased due to technical difficulties with procedures such as mammography, MRI, and CT. It may be useful in distinguishing post-operative changes related to surgery, radiation therapy or chemotherapy from tumors, recurrence of lesions, or tissue necrosis.

Technetium Tc-99m Sestamibi (Miraluma™)

Like Tl-201, technetium Tc-99m sestamibi (MIBI) also was used initially as a cardiac imaging agent. However, ^{99m}Tc-MIBI has higher energy photons and a shorter half-life than thallium, permitting the injection of doses 5 to 10 times greater than thallium. As such, images acquired with ^{99m}Tc-MIBI are of higher quality and improved resolution compared with images obtained with thallium. The results from several clinical trials suggest that the uptake of ^{99m}Tc- MIBI far exceeds Tl-201. The mean uptake of T1-201 is 80% higher in malignant cells than in normal cells; however, ^{99m}Tc-MIBI uptake in cancerous lesions is 4 times higher than Tl-201. This underscores the need to further define the role of ^{99m}Tc-MIBI in the imaging of tumors.[31,33]

One study[34] demonstrated that ^{99m}Tc-MIBI uptake was related to angiogenesis and possibly to oxidative metabolism involving increased uptake associated with elevated mitochondrial levels in tumor cells. In practice, in order to avoid the non-specific uptake of ^{99m}Tc-MIBI in benign structures, SMM should be performed:

1) Before or 7 to 10 days following fine needle aspiration;

2) From 4 to 6 weeks after a breast biopsy; or

3) At least 2-3 months after breast surgery and radiotherapy.

Questions exist regarding the optimal phase — if any — during the menstrual cycle to perform SMM. Optimal imaging positions and dosages are under investigation. At present, although standard dosages vary, the most commonly reported dose of ^{99m}Tc-MIBI is 20 mCi (740 MBq). Intravenous administration into the antecubital vein in the arm contralateral to the suspected breast lesion is recommended. This is necessary to avoid false-positive uptake in the axilla on the same side as the suspected lesion. Injection can also be made through a dorsal pedal vein if bilateral lesions are suspected or if the patient has undergone previous mastectomy.[34]

Optimal imaging position remains undetermined. Prone imaging provides improved visualization of breast tissue and can better delineate the breast contour. This is helpful in identifying the precise location of a suspected lesion. It also provides improved separation from the heart and the liver; organs that demonstrate relatively high uptake of 99mTc-MIBI, which can mask breast activity. This prone position also minimizes the distance between the breast and the camera. Furthermore, the prone position permits evaluation of all breast tissue proximal to the thoracic wall. While the prone position does offer some advantages in breast imaging, the supine position offers better localization of the primary tumor. The supine position also affords better visualization of the axillae and possible internal mammary lymph node involvement. As such, a combination of positions is preferred.[34]

In general, images are acquired over 10 minutes. Studies indicate that high quality diagnostic imaging can be accomplished in 5 to 15 minutes after the injection of ^{99m}Tc-MIBI. Timing is important, as delayed imaging can result in a premature or false-negative result. Despite the potential advantages that may be achieved with SMM, its routine use in breast cancer detection is still debated.[35]

Numerous clinical studies have been undertaken to establish the role of ^{99m}Tc-MIBI in the detection and evaluation of breast cancer. Results of these studies suggest that the sensitivity of SMM in the detection of primary breast cancer is 80% to 90%, with an average of 85%.[28]

SMM is significantly more sensitive in the detection of palpable versus nonpalpable lesions. In addition, its sensitivity for lesions less than 10 mm in diameter is low and no lesions less than 7 mm in diameter have been detected with this technique, possibly due to limitations of currently available detectors. Therefore, SMM is not recommended as a screening test for breast cancer detection. However, unlike standard mammography, its sensitivity is not affected by the density of breast tissue, and therefore may be advantageous in patients as described in **Table 2**. It may also be useful in women in whom recurrent disease is suspected, particularly if they have undergone previous surgery, chemotherapy, radiotherapy, or breast augmentation.[28]

The specificity of ^{99m}Tc-sestamibi is somewhat higher than its sensitivity, with an average of 89%. While ^{99m}Tc-sestamibi is concentrated in breast cancers, increased uptake can also take place in benign breast conditions, particularly in cases of hyperproliferative (fast growing) fibrocystic breast disease. In general, fibrocystic disease appears as a region or regions of slight-to-moderate increased uptake that is often more diffuse than localized. It is often bilateral without well-delineated margins, and a patchy pattern of uptake.[28]

Breast cancer, on the other hand, generally appears to be much more focal and is often unilateral, with relatively well-defined contours. Uptake of ^{99m}Tc-sestamibi varies from mild to intense depending on several factors, such as size, type, location, and hormonal factors. In general, a tumor to background activity ratio of greater than 1.2 to 1.4 is thought to suggest a malignant lesion. However, many benign conditions such as highly mitotic juvenile adenomas, papillomas, abscesses, local inflammation or highly proliferative breast disease can present with ratios greater than 1.5.[28]

Because it is well known that the axillary nodes are the primary drainage sites for breast, axillary node involvement is considered one of the most important prognosticators in breast cancer. Once a diagnosis of breast cancer has been made, nearly all patients with invasive and noninvasive breast cancer will undergo axillary dissection.[28]

While axillary dissection does provide important information about the staging of breast cancer, it is associated with morbidity such as arm edema (swelling), lymphostasis and infections of the ipsilateral (same side) extremity. A noninvasive way of evaluating the axillary nodes would be useful. As Taillefer[28]

describes it, numerous studies[36-46] have evaluated a variety of imaging techniques for their potential in the evaluation of possible metastatic involvement of the axillary lymph nodes. When considered together, results of these studies suggest an average sensitivity of 77% and a specificity of 89% in the detection of axillary metastases in patients with primary breast cancer. The positive predictive value was 86%; "negative" value was 84%.[28]

Technetium Tc-99m Sestamibi Case Study

Figure 1 shows four different views of a patient who received 20mCi of Tc-99m sestamibi to aid in the diagnosis of breast cancer. The patient is a 48-year-old woman who had previous breast implants in both of her breasts. The patient had noticed a lump in her left breast, which was also palpated by her physician. The presence of the silicone implant made the mammogram difficult to interpret. The SMM shows increased uptake in the mass in the left breast slightly below the silicone implant, which appears as a circular object with slightly decreased radioactivity. The mass can be seen in the anterior views near the apex of the heart. A core biopsy proved the mass to be an infiltrating ductal carcinoma.

Technetium Tc-99m Tetrofosmin (Myoview™-Nycomed Amersham)

While technetium Tc-99m tetrofosmin is not currently approved for use in the detection of breast cancer, it may offer some clinical potential. In 1996, abnormal uptake in a breast carcinoma was reported in a patient undergoing myocardial perfusion scintigraphy.[28]

Similar to ^{99m}Tc-sestamibi, ^{99m}Tc-tetrofosmin is a lipophilic cation with demonstrated uptake in tumor cells. Although its uptake in tumor cells is less than ^{99m}Tc-sestamibi, its target-to-background activity ratio is high enough to permit detection of the breast tumor. However, unlike ^{99m}Tc-sestamibi, the uptake of ^{99m}Tc-tetrofosmin is hypothesized to be less related to mitochondrial activity. However, similar to ^{99m}Tc-sestamibi, there is no

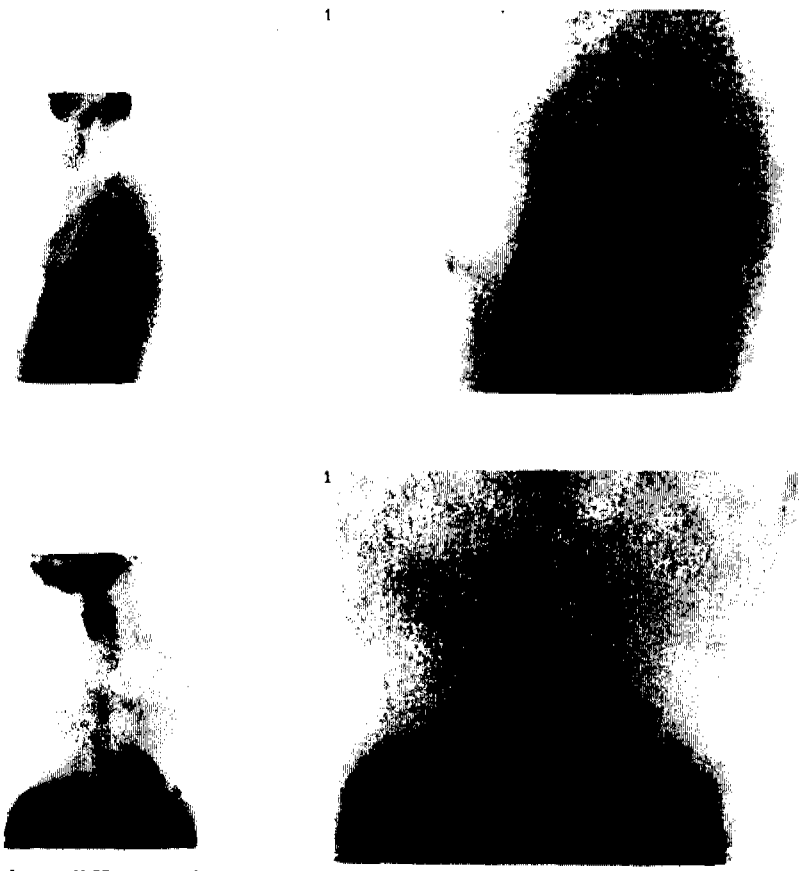

Figure 1. Shown are four different views of a 48-year-old woman who received 20mCi of Tc-99m sestamibi for detection of breast cancer. See text for more detailed information.

significant myocardial washout with ^{99m} Tc-tetrofosmin. It demonstrates faster lung and liver clearance, which may prove useful in the detection of breast tumors near these regions. However, more research is needed to establish the possible advantages of a particular radiopharmaceutical over the other.[28]

The administration, image acquisition, and analysis are virtually identical with both radiopharmaceuticals. Although data are limited, preliminary results suggest similar sensitivity as well as similar positive and negative predictive values for ^{99m}Tc-sestamibi versus ^{99m} Tc-tetrofosmin. Again, the data are limited and most studies were performed with palpable lesions (diameter greater than 1 cm). It boasts similar accuracy rates when compared with ^{99m}Tc-sestamibi in the evaluation of axillary node metastases.[28]

Sentinel Lymph Node Localization-Lymphoscintigraphy

In general, while there may be instances of complex lymphatic drainage, there often is only a single sentinel node. The notion of lymph node staging was first proposed by Morton et al[46] in the treatment of melanoma. Cabanas also proposed its use in the treatment of penile cancer.[47] In 1994 Guiliano and colleagues[48] proposed its use in breast cancer using blue dye; and Krag proposed the use of the sentinel node approach using a radiation sensitive probe a year earlier.[49]

Recent approaches involve the intramammary injection of radiotracer to visualize drainage of the tumor itself. The radiotracer is injected directly into the tumor or into surrounding tissue to identify the node(s) to first receive lymphatic drainage for that tumor. The most relevant node(s), identified by the radiotracer or blue dye are then removed and examined.

Several different techniques are used currently with variations in the injection of technetium Tc-99m sulfur colloid (filtered or unfiltered) from 1 mL to 10 mL. It is important to note that other countries may use different colloids, for example, antimony sulfide colloid is used in Australia. The essential factor is that the size range of the particle be selected in accordance with the colloid to be used.

Injection may be intratumoral, peritumoral, or subdermally over the tumor. It is not known whether injection outside the margins of the tumor will yield accurate drainage patterns. Furthermore, the intratumoral injection may pose some risk of spreading tumor cells with the drainage of the radiotracer or poor drainage in the case of solid tumors. In addition, the injection of too much or too little radiotracer can also hamper the accuracy of results --not enough can result in little to no drainage; too much can result in pooling of tracer, thereby obscuring the results. Glass and colleagues[36] recommend volumes between 3 mL and 7 mL, injected around the tumor margins to optimize visualization of drainage patterns. They note that larger volumes of radiotracer may be required in patients with large breasts. Ultrasound can be used to help pinpoint the desired site of injection. Imaging should be conducted within minutes after the injection of the radiotracer. Allowing too great an interval of time between injection and imaging can result in the mistaken identification of the sentinel node or nodes.

The preferred position for the patient is in a semi-recumbent position with the ipsilateral shoulder elevated and that arm raised over the patient's head. Imaging done with the patient in the supine position can mask the sentinel node due to scatter radiation from the injection sites. Migration of radiotracer can be hastened with the application of heat or massage at the site of injection or by elevating the venous pressure. Having the patient move the arm can also accelerate migration of the radiotracer.[36]

Once the sentinel node(s) has been identified, the first node to become radioactive, the location is then marked on the patient's skin. This method, however, is subject to patient movement and positioning, among other things. The ideal method of localization requires the use of a hand-held, radiosensitive probe that is used while the patient is in the same position that will be used during surgery. Many surgeons

use blue dye in addition to a radiotracer to provide a visual clue for excision. Once the sentinel node(s)has been identified, the node is verified using the hand-held probe to confirm that this is indeed the sentinel node. Without the use of blue dye, the surgeon must rely solely on the radiosensitive probe. If blue dye is used, identification is somewhat easier, as the sentinel node is the node that is both blue and radioactive.[36]

Sentinel node localization in the staging of breast cancer continues to gain popularity. It is a minimally invasive technique and can spare patients many of the complications associated with axillary dissection. Furthermore, it is considered very accurate in the identification of the sentinel node and is a less morbid procedure.

Applications

Because of its limited sensitivity in the detection of breast tumors less than 10 mm in size, SMM is not recommended in breast cancer screening in asymptomatic patients. Its use is reserved as a complementary diagnostic procedure to mammography when its results are suspicious as described in **Table 2**.[28] One of the primary limitations of SMM s the spatial resolution of the gamma camera. New gamma cameras dedicated for scintimammography are under development in an effort to improve spatial resolution. Another problem involves the localization of a lesion that is neither palpable nor visible with mammography but is subsequently identified using SMM. There are several approaches used to locate such a lesion but none is ideal. A skin marker can be used to identify lesion from an anterior supine view and a lateral view if possible to determine the depth of the lesion. This is a relatively gross method of localization, however. A second technique involves the use of a radionuclide-guided, stereotactic pre-biopsy needle to help locate an abnormality seen with SMM. This approach requires that a post-biopsy SMM be performed to confirm that the targeted area was indeed biopsied. A third technique requires the use of a gamma probe immediately following the injection of the radiotracer during surgery as a means to locate the lesion.[28,52]

STAGING

The staging of breast cancer relies on clinical and pathologic criteria that are helpful in both treatment and prognosis. The current staging method is the TNM system similar to the TNM system used in other malignancies (Table 3). Physical examination and histologic confirmation are essential for accurate staging; physical examination should include an estimate as to tumor size (T, tumor), relative mobility, or fixation to the underlying pectoral fascia, or skin involvement (ulceration, erythema, edema). Skin dimpling and pagetoid changes in the nipple do not indicate skin involvement unless accompanied by signs of ulceration, erythema, or edema.

Physical examination can be used to assess the axillary lymph node status (N, nodes), however it is not an accurate assessment and requires histologic evaluation of the lymph nodes obtained at the time of lumpectomy or mastectomy. A clinically "negative" axilla may contain histologically positive lymph nodes in up to 30% of patients.

Evidence of distant metastasis, (M, metastasis), should be obtained through a careful history, physical examination, along with the selective use of imaging studies. Since the most common sites of metastases are bone, lung, and liver, a chest x-ray and liver function tests are appropriate. A bone scan can be obtained, however its yield in the asymptomatic patient is extremely low. It can serve as a useful baseline study in the event that skeletal pain does develop in the follow-up period. Patients who initially present with symptoms suggestive of metastatic disease benefit from the use of selected imaging studies (i.e., CT chest, abdomen, brain).

Table 3. Staging for Breast Carcinoma/TNM System

DEFINITIONS:

PRIMARY TUMOR (T)

Tx: Primary tumor cannot be assessed

T0: No evidence of primary tumor

Tis: Carcinoma in situ

T1: Tumor 2cm or less in greatest dimension

T2: Tumor more than 2cm, but not more than 5cm in greatest dimension

T3: Tumor more than 5cm in greatest dimension

T4: Tumor of any size with direct extension to chest wall or skin

REGIONAL LYMPH NODES (N)

NX: Regional lymph nodes cannot be assessed

N0: No regional lymph node metastasis

N1: Metastasis to movable ipsilateral axillary lymph node(s)

N2: Metastasis to ipsilateral axillary lymph nodes that are fixed to one another or to other structures

N3: Metastasis to ipsilateral internal mammary lymph node(s)

DISTANT METASTASIS (M)

MX: Presence of distant metastasis cannot be assessed

M0: No distant metastasis

M1: Distant metastasis [includes metastasis to ipsilateral supraclavicular l lymph node(s)]

Fluorine F-18 Fluorodeoxyglucose (FDG)

Data suggest that many breast cancers have increased levels of metabolic activity that can be detected with fluorine F-18 fluorodeoxyglucose (FDG). Several studies have evaluated the use of FDG in the detection and diagnosis of breast cancer, reporting an increased uptake in cancers of the breast and in axillary nodes positive for cancer. The use of positron emission tomography (PET) therefore may prove useful in the staging of breast cancer and in the assessment of metastatic spread or recurrence of cancer.[35,51,52]

Early studies showed promising results boasting high sensitivities, visualizing 82% of primary breast tumors in one study[53] and 100% in another study[54], although all of the patients in the second study had primary tumors > 5 cm in diameter. Studies that are more recent report sensitivity rates ranging between 80% and 90%. Variations between these studies may be due to the patient selection process, image acquisition (length of time), primary tumor size (>1.0 cm in diameter), etc. Tumor size is particularly important since the larger the primary tumor, the more likely the chance of metastases.

Due to the overall lack of data it is impossible to accurately predict specificity and the negative prediction value of FDG. FDG may be useful when other imaging modalities are insufficient, such as in the detection of lesions in patients with silicone breast implants or in patients with radiographically dense breasts. However, the use of ^{99m} Tc-sestamibi may yield equally accurate results. Only one study[55] compared the use of FDG with ^{99m} Tc-sestamibi and both modalities yielded similar results, but the sample size (20 patients) was relatively small and the primary lesions were large with a mean diameter of 2.9 cm. As such, more data are required before an adequate comparison of FDG and ^{99m} Tc-sestamibi can be made.

One concern that is consistent with both FDG imaging and ^{99m} Tc-sestamibi is the cost of the procedure and the appropriate follow up once a lesion has been detected. Inherent in both techniques is the problem of accurate localization that is required in order to perform biopsy, lumpectomy, or surgery. Both techniques suffer from the lack of an anatomical reference that is available with modalities like mammography, ultrasound, and MRI. Until anatomic resolution of a lesion detected with PET or SPECT can be accomplished, localization after detection will remain a limitation of FDG and ^{99m}Tc-sestamibi scintimammography.[50]

FDG also has potential application in the evaluation of axillary node status. It is known that FDG has high accumulation in the axillary nodes containing metastases.[56-58] Although the sensitivities reported in these studies were higher than the specificities reported, it is thought that the use of FDG in the assessment of axillary node involvement could help to minimize false-negative findings.

Whole body FDG PET can also be used to identify metastatic breast lesions.[54,59] It may prove useful in staging and monitoring of patients undergoing chemotherapy or radiation therapy. It may also be useful in the monitoring of the effectiveness of chemotherapy in patients.[60-62] As treatment with chemotherapy progresses, the metabolic changes in breast cancer lesions can occur within 8 days following initiation of treatment, and the amount of FDG uptake in tumors can be used to assess its effectiveness. Changes in metabolic activity can occur without an appreciable change in tumor size.[60] Results from another study showed a significant decrease in FDG tumor uptake in 75% of patients (8/12) who showed a conventional response to chemotherapy. This decrease could be measured with PET within 6-13 days after chemotherapy had been initiated. Obviously, this could be particularly useful in measuring the response of breast cancer tumors in patients undergoing chemotherapy, promoting a change in the chemotherapeutic regimen if necessary. At present, FDG PET is still relatively expensive compared with other

imaging modalities and more studies are need to determine its potential cost-benefit ratio, and to verify its effectiveness in the diagnosis of breast cancer, and for perhaps its even more important potential role in the evaluation of the effectiveness of chemotherapy for some patients.[52]

Unfortunately, at present, this is an expensive procedure that involves the production of radioactive tracers with very short half-lives that must be produced in an on-site accelerator. At present, insufficient large-scale clinical trials have been conducted to demonstrate the role of PET in the imaging of breast cancer. With the advent of new imaging equipment (coincidence imaging) and the regional distribution of FDG, the cost-effectiveness of this agent will be improved.

Case Study: 51-Year-Old Woman Imaged With Fluorine F-18 Fluorodeoxyglucose

A 51-year old woman noticed a lump in the upper-outer quadrant of her right breast during self-exam after being bumped by her horse. A mammogram showed a spiculated lesion, which was followed by an excisional biopsy that revealed a 3.5cm invasive, moderately differentiated, ductal carcinoma. The patient presented for a second opinion regarding follow-up treatment.

The patient's past medical history was negative except for hormonal replacement therapy for two years since post-menopausal symptoms. Physical examination of the breasts revealed no left breast masses or axillary adenopathy. She had a well-healed biopsy scar in the upper-outer quadrant of her right breast with no other masses or axillary adenopathy on the right side. Further discussions with the patient reviewed options for treatment including mastectomy, breast conservation surgery (lumpectomy) and the need to evaluate lymph nodes.

The patient was studied with 8.2mCi of FDG with images of the brain and total body completed for staging as shown in Figures 2 and 3. Images of the chest revealed several foci of abnormally increased uptake in the right axilla and an irregular accumulation of radioactivity in the upper-outer aspect of the right breast. The remainder of the study demonstrated uptake within the brain, liver, bone marrow, kidneys, and G.I. tract. Findings were reported as consistent with a right breast malignancy with metastatic disease to the right axilla.

One week later, the patient underwent right breast lumpectomy with sentinel node biopsy and axillary dissection. During the procedure, two sentinel lymph nodes were identified in the right axilla which were both positive for metastatic carcinoma upon frozen section pathological examination. Based on this information, the patient underwent an axillary dissection removing twenty lymph nodes, which were all negative for tumor upon pathological examination. The lumpectomy tissue, which was positive on the FDG images, was found to have an invasive ductal carcinoma, Grade II/III.

TREATMENT

Non-Invasive Carcinoma

Ductal Carcinoma In Situ (DCIS)

DCIS rarely presents as a breast mass, either palpable or discovered on a mammogram. More often, it presents as a new non-palpable mammographic finding of clustered microcalcifications without an associated mass. Occasionally, it may be present (microscopic) in breast tissue surrounding a benign lesion discovered incidentally with a biopsy. By definition, DCIS is non-invasive so metastasis outside of the breast is not found unless there are areas of microinvasion that go unrecognized. Patients with DCIS are usually treated with lumpectomy followed by radiation therapy to the breast, as their lifetime risk of developing invasive cancer, in that breast, approaches 30%.[63] Although radiation has been shown to decrease the recurrence rate when instituted following complete excision with negative margins, some recent studies have shown lumpectomy alone to be sufficient treatment for certain types of DCIS, particularly those lesions that are small and low-grade.[64-65] Axillary dissection is not indicated unless an accompanying invasive cancer is

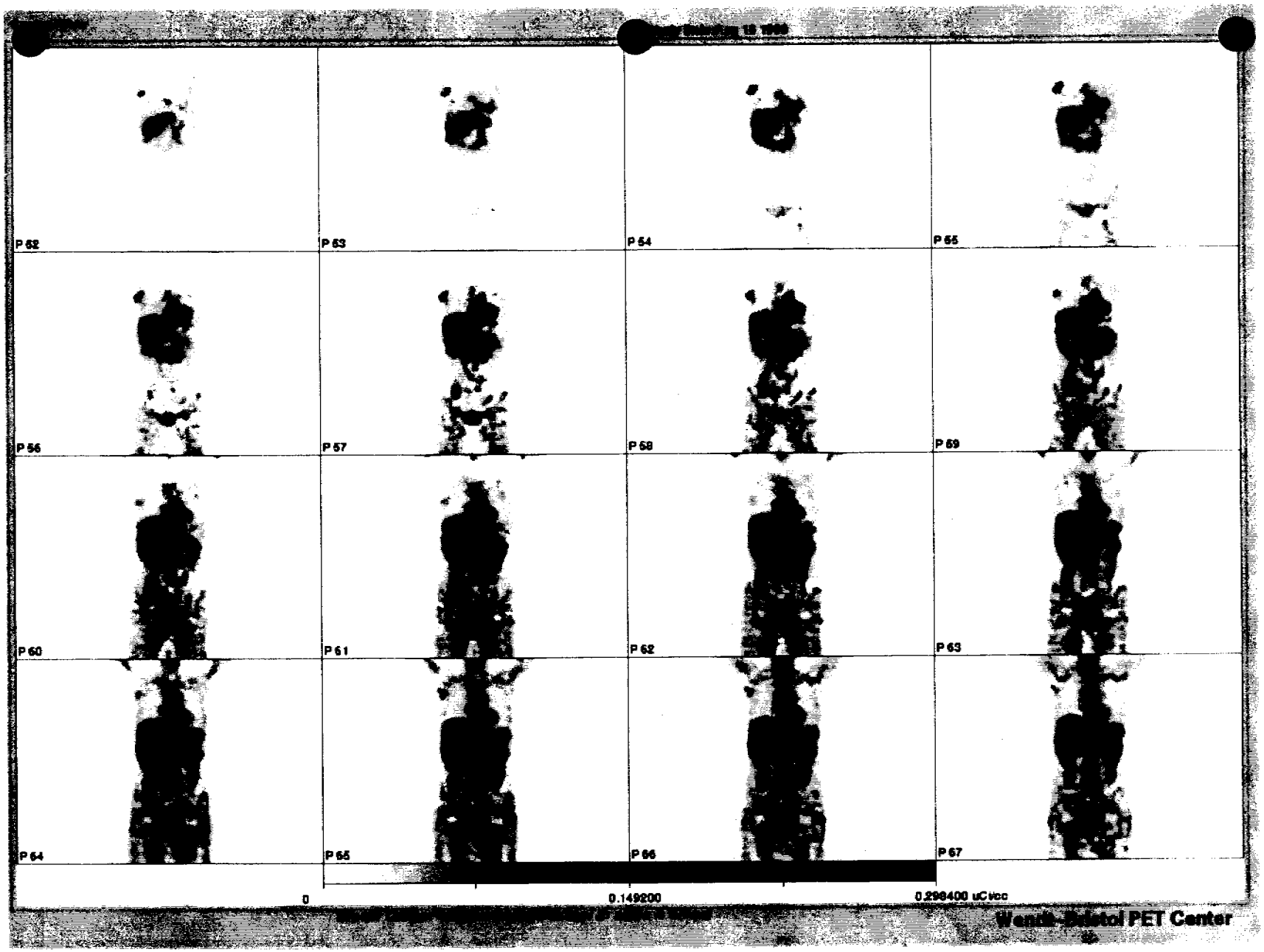

Figure 2. A case study of a 51-year-old woman with a lump in the upper-outer quadrant of her right breast. The patient was studied with 8.2mCi of FDG with images of the brain and total body completed for staging as shown in Figures 2 and 3. Images of the chest revealed several foci of abnormally increased uptake in the right axilla and an irregular accumulation of radioactivity in the upper-outer aspect of the right breast.

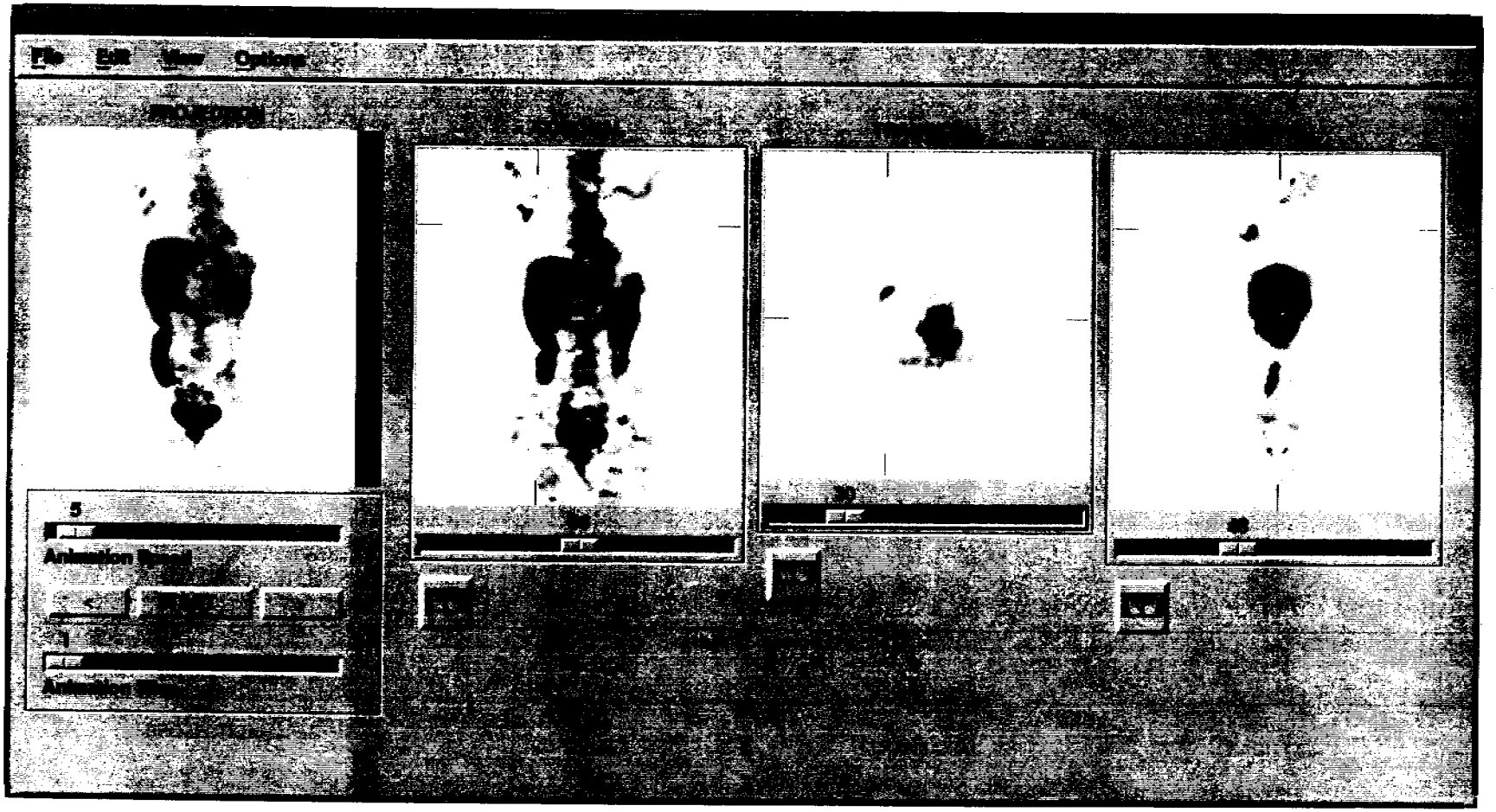

Figure 3. The remainder of the study demonstrated uptake within the brain, liver, bone marrow, kidneys, and G.I. tract. Findings were reported as consistent with a right breast malignancy with metastatic disease to the right axilla.

present. Diffuse, extensive DCIS often requires total mastectomy. Tamoxifen has been shown to reduce the rate of contralateral breast cancer by approximately 50% in patients treated with lumpectomy and radiation for DCIS.[66]

Lobular Carcinoma in Situ (LCIS)

LCIS is a diagnosis usually made coincidentally when examining breast tissue for another reason. It does not present as a mass and is not evident on mammogram. Patients with LCIS are at a lifetime risk for developing *invasive carcinoma,* in either breast, of 17-37%.[67]

Because of these factors, LCIS is not considered an early stage of breast cancer, but rather a marker for subsequent cancer development. Therefore, patients with the diagnosis of LCIS should be followed in a "high risk" clinic with frequent (6 months) exams, annual mammography, and should be considered for enrollment into breast cancer prevention trials. Tamoxifen should be strongly considered as it has been proven to reduce breast cancer risk by 45%.[6] An alternative but extreme treatment involves bilateral simple mastectomy with breast reconstruction, which can be offered to selected patients.

Invasive Carcinoma

Surgical Options

Following the diagnosis of invasive cancer, the options for treatment should be completely discussed with the patient. A surgeon, radiation therapist, and plastic surgeon should be included in the discussions; the more information provided to the patient, the better opportunity she will have to make an educated decision. The final decision should not be influenced by the specific bias of the surgeon or other physician. Surgery remains the initial treatment for AJCC Stage I, II, and some Stage III breast cancer patients. In Stage I and most Stage II cancers, the surgical options include a modified radical mastectomy or a lumpectomy with axillary dissection or sentinel node biopsy followed by breast irradiation. For large Stage II and Stage III tumors, modified radical mastectomy is the procedure of choice. Patients with advanced loco-regional disease (including inflammatory cancer) may benefit from preoperative (neoadjuvant) chemotherapy and post-operative radiation therapy.

Lumpectomy vs. Mastectomy

For early stage cancers (Stage I and II), modified radical mastectomy or lumpectomy/axillary dissection with breast irradiation should both be considered viable options. Several prospective studies have shown that these procedures both result in the same long-term survival rate, despite an increased local recurrence rate in patients treated with lumpectomy/axillary dissection.[68,69] There are several contraindications to breast conservation including multicentric cancer, previous breast or chest wall radiation, and large tumor size in relation to the breast size. Since the goal of breast-sparing surgery is to achieve an optimal cosmetic result, a lumpectomy that results in a less than desirable appearance should be avoided. Patients with small breasts are often poor candidates for lumpectomy/axillary dissection as the lumpectomy followed by radiation produces a suboptimal cosmetic result. Therefore, while no particular tumor size is an absolute contraindication, the relative breast size should be considered. Additionally, patients with large breasts are not ideal candidates because the cosmetic appearance after radiation is often poor.

If a modified radical mastectomy is chosen, immediate reconstruction can be offered to selected patients. Those with advanced loco-regional disease are not good candidates as local recurrence rates are high and post-operative radiation therapy may be necessary. Otherwise, the options for immediate reconstruction include saline tissue expanders/implants or autologous tissue transfer with a latissmus dorsi or rectus abdominus myocutaneous (TRAM) flap. Plastic surgical consultation should be obtained prior to surgery in order for the patient to make an educated decision.

Sentinel Lymph Node Biopsy

Sentinel node biopsy has recently been described as an alternative to axillary node dissection in selected women.[70] The driving force behind this new technology is the realization that most women with early stage breast cancer do not have axillary nodal metastases. However, axillary dissection is performed routinely because there is no accurate predictor of nodal metastasis. Axillary dissection can result in significant long-term morbidity such as lymphedema. As described earlier, the sentinel node is the first lymph node(s) to drain the primary tumor. If this node is histologically negative, the chance of other lymph nodes being involved is generally less than 5%. Technetium Tc-99m sulfur colloid is injected around the primary tumor and a hand-held gamma detector probe is used to identify radioactive lymph nodes during surgery. Blue dye is also used to aid in the visualization of the lymphatic pathway. For palpable breast lesions or biopsy cavities, the lymphatic mapping agent can be injected directly around the tumor site, while nonpalpable lesions should be injected using ultrasound or mammographic guidance. Although used widely, the role of routine preoperative lymphoscintigraphy has yet to be defined. Contraindications to sentinel node biopsy include palpable nodes, a tumor $\geq$ 5 cm in size, multifocal invasive carcinoma, previous extensive breast or axillary surgery, and preoperative chemotherapy. It is also essential that each surgeon perform 20-30 sentinel node biopsies followed by an axillary node dissection to validate his/her technique, as this procedure is associated with a significant learning curve. Results indicate this technique may replace routine lymph node dissection in women with clinically negative nodes. There are currently two multi-institutional trials underway that will assess sentinel node biopsy as an alternative to complete axillary lymphadenectomy.

Adjuvant Therapy

The rationale for adjuvant systemic therapy is based upon the premise that many patients with early breast cancer have undetectable metastases that, if left unaddressed, would result in recurrence. Even though these micrometastases may not be clinically detectable, their presence is suggested by the natural history of many patients treated with surgery alone. There are two forms of systemic therapy used in adjuvant therapy--chemotherapy and hormonal therapy.[71-74]

While chemotherapy can improve survival in node-positive patients, its use also may improve disease-free survival in premenopausal, node-negative breast cancer patients. However, it is important to note that this advantage, while statistically significant, is modest and may not be associated with an improvement in overall survival. Since not all node-negative patients benefit from this therapy, a tremendous amount of effort has gone into identifying "high risk" node-negative patients who might benefit. Tumor size, estrogen receptor content, DNA analysis, grade, and blood vessel invasion are several examples of prognostic indicators that are taken into consideration in assessing one's risk of recurrence. Adjuvant chemotherapy is not without toxicity, so the clinician ideally would want to treat the group that would receive the most benefit. As more of the current clinical trials are completed, treatment strategies will become more standardized. Tamoxifen is usually added to chemotherapy in receptor-positive patients.

Postmenopausal patients generally are less likely to enjoy the same benefits of chemotherapy as the premenopausal group. Thus, the adjuvant use of hormonal therapy alone in patients with estrogen or progesterone (ER/PR) positive tumors is associated with a modest but significant improvement in disease-free survival. Chemotherapy, in addition to tamoxifen, is often used in node-positive patients as determined by their performance status. The use of chemotherapy in the node-negative postmenopausal patient is more controversial. Tamoxifen has also been shown to reduce the

risk of contralateral breast cancer, which is another potential advantage.

Follow-up

Patients with early stage breast cancer should be followed for the remainder of their life, as recurrences are seen as far as 15-20 years following diagnosis. Additionally, they are at increased risk of developing a second breast cancer. Therefore, follow-up is aimed to detect recurrence, as well as screening the remaining breast tissue for malignancy. Patients should be followed at 3-month intervals for the first 2-3 years, then at 6-month intervals. Any new symptoms of bone pain, headaches, or neurological changes should prompt an immediate work-up. Otherwise, chest x-rays and liver function tests are performed at the time of follow-up. Additionally, all patients should have annual mammograms to evaluate for local recurrence or a new cancer.

Treatment of Metastatic Disease

Systemic therapy for metastatic breast cancer is aimed at improving the quality of life and, if possible, prolonging survival. Conventional therapy for metastatic disease has been shown to provide palliation to selected patients; however, a survival benefit has been difficult to document. The conventional treatment can be hormonal therapy or chemotherapy, depending upon the patient's age, severity of symptoms, and hormone status of the primary tumor. Postmenopausal patients with ER/PR positive tumors who have non-life threatening recurrences are good candidates for hormonal therapy, usually tamoxifen. In patients in whom a response to hormonal therapy is seen, but who subsequently progress, a second-line hormone therapy should be instituted, usually a progestin or aromatase inhibitor. Response rates of up to 60-70% can be expected with hormonal therapy.

Chemotherapy is generally used in younger, hormone-unresponsive women or in a patient with life-threatening metastases, where a quicker response is needed. Conventional chemotherapy consists of the same agents used in adjuvant treatment, cyclophosphamide, 5-FU, and adriamycin or methotrexate. Taxol has also shown effectiveness in this setting. Response rates range from 20-50% with an average duration of 6 months.

SUMMARY

With the increasing utilization of screening mammography and the more widespread use of breast self-examination, breast cancer patients are presenting at an earlier stage. This allows for more effective treatment and subsequently improved survival. It is hoped that with the use of genetic markers, high risk patients will be identified at an early age, allowing for more intensive screening and chemopreventive strategies.

The treatment of breast cancer has evolved from a philosophy of radical surgery to an approach that involves more aggressive local therapy combined with systemic therapy. This change has occurred secondary to the realization that breast cancer in its early stages is a local disease, but in its later stages, it is a "systemic disease" and should be treated as such. Therefore, chemotherapy and hormonal therapy play an extremely important role in the treatment of more advanced disease. The goal of surgery at any stage of the disease is to loco-regional control while achieving an acceptable cosmetic result.

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QUESTIONS

1. Which of the following can metastasize?
   a. DCIS
   b. LCIS
   c. Atypical hyperplasia
   d. Invasive ductal carcinoma

2. Which of the following is used to enhance magnetic resonance imaging (MRI) studies of the breast?
   a. Iodine
   b. Calcium
   c. Gadolinium
   d. Gold

3. Which of the following is not considered a risk factor for breast cancer?
   a. Asbestos exposure
   b. Family history of breast cancer
   c. Personal history of breast cancer
   d. History of atypical hyperplasia on a previous biopsy

4. Clinical investigations have shown that tamoxifen can reduce the incidence of breast cancer in high-risk women by which of the following percentages?
   a. 10%
   b. 20%
   c. 25%
   d. 45%

5. Which of the following is the current screening recommendation for breast cancer?
   a. Breast self-examination beginning at age 20
   b. Annual clinical breast exams beginning at age 40
   c. Annual mammography beginning at age 40
   d. All of the above

6. Of the following, which typically is not imaged with mammography?
    a. Clustered microcalcifications
    b. Masses
    c. Lymph nodes
    d. Microcalcifications associated with masses

7. Ultrasound can be used to:
    a. Determine if a mass is cancer
    b. Determine if a solid mass is benign
    c. Differentiate between a solid mass and cyst
    d. Screen women for breast cancer

8. Which of the following is true concerning the use of technetium Tc-99m sestamibi for breast cancer imaging?
    a. It can be used in women with dense breasts to detect cancer.
    b. It takes advantage of high mitochondrial activity in breast tumors.
    c. The most commonly reported dosage is 20mCi.
    d. All of the above

9. Which of the following tumor cell characteristics is not associated with the localization of technetium Tc-99m sestamibi in breast cancer?
    a. Monoclonal antibody binding to a specific tumor-associated antigen
    b. Increased metabolic activity of tumors
    c. Increased tumor blood flow
    d. Altered microvasculature within the tumor

10. Staging breast cancer:
    a. Utilizes the TNM classification
    b. Requires surgery for complete staging
    c. Requires CT and bone scan in symptomatic patients
    d. All of the above

11. Treatment of DCIS includes all of the following, except:
    a. Lumpectomy
    b. Radiation therapy
    c. Chemotherapy
    d. Mastectomy

12. Which of the following statements is most true about lobular carcinoma in situ (LCIS)?
    a. It is found frequently on mammography
    b. It is a risk factor for the subsequent development of breast cancer
    c. It is treated effectively with radiation therapy only.
    d. It is treated effectively with chemotherapy only.

13. Surgical options for invasive breast cancer include all of the following except:
    a. Lumpectomy with axillary dissection
    b. Modified radical mastectomy
    c. Lumpectomy with sentinel node biopsy
    d. Radical mastectomy

14. The diagnostic agent found in the radiopharmaceutical, Miraluma™, was originally developed for diagnostic studies involving which of the following?
    a. Hepatobiliary system imaging
    b. Lung aerosol ventilation studies
    c. Myocardial perfusion imaging
    d. Detection of *Helicobacter pylori* in the stomach

15. Contraindications to breast conservation (lumpectomy) surgery include:
    a. Palpable axillary lymph nodes
    b. Tumor size >2 centimeters
    c. Previous chest wall radiation
    d. Age >60 years

16. Breast reconstruction after mastectomy can be performed using all of the following except:
    a. TRAM flap
    b. Latissmus dorsi flap
    c. Tissue expander
    d. Allogenic breast transplant

17. The sentinel lymph node:
    a. Is always in the same location
    b. Is the first node(s) to drain the tumor
    c. Can only be 1 node
    d. Can always be found

18. Contraindications to sentinel node biopsy include:
    a. Palpable axillary lymph node(s)
    b. Tumor size >5 centimeters
    c. Multifoical invasive carcinoma
    d. All of the above

19. Which of the following radiopharmaceuticals is commonly used for sentinel lymph node biopsy?
    a. Technetium Tc-99m sestamibi
    b. Thallium Tl-201 thallous chloride
    c. Technetium Tc-99m sulfur colloid
    d. Fluorine F-18 Fluorodeoxyglucose (FDG)

20. Which of the following is thought to play the major role in the localization of fluorine F-18 FDG in breast cancer?
    a. Altered microvasculature within the tumor
    b. Increased metabolic activity within the breast mass
    c. Increased tumor blood flow
    d. Tumor specific receptor uptake

21. Which of the following is true concerning the drug tamoxifen?
    a. It is a type of anti-hormonal therapy
    b. It is an adjunct medication used to enhance nuclear medicine imaging
    c. It can be used as a substitute for surgery
    d. It is a substitute for radiation therapy

22. In addition to breast cancer, which of the following malignant lesions has demonstrated localization with thallium Tl-201 thallous chloride?
    a. Skeletal
    b. Brain
    c. Soft Tissue Sarcomas
    d. All the above

23. Which of the following sensitivities were reported in clinical investigations for the use of thallium Tl-201 thallous chloride for breast cancer imaging?
    a. 22%
    b. 41%
    c. 64%
    d. 80%

24. Which of the following is the most common cause of a breast mass in a 20-year-old patient?
    a. Cancer
    b. Fibroadenoma
    c. Lipoma
    d. Cyst

25. Which of the following radiopharmaeuticals has an FDA-approved indication for breast cancer imaging?
    a. Thallium Tl-201 thallous chloride
    b. Technetium Tc-99m tetrofosmin
    c. Technetium Tc-99m sestamibi
    d. a and b only.